HSDD Hormone Treatment: Androgens
ISSWSH Annual Meeting 2024
Precourse

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02/22/2024
9:50 AM - 10:10 AM

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Conflict Of Interest Disclosure Statement

- Consultant
  - Dare Bioscience
  - Ms. Medicine Provider Executive Group

Objectives

- **Review the efficacy and safety of transdermal testosterone for generalized acquired hypoactive sexual desire disorder (HSDD) in postmenopausal women.**
- **Explore the choice/use of testosterone amongst HSDD POC recommended pharmacological treatment options.**
- **Discuss clinical indications, appropriate candidates, and target symptoms for treatment with off-label use of evidenced-based transdermal testosterone.**
- **Explain current clinical practice guidelines regarding preparation choice, dosing, clinical & laboratory monitoring, and follow-up when prescribing transdermal testosterone for women.**

Case Scenario – “Denise”

- **HSDD** is characterized by sexual and romantic **avoidance,** lack of **initiation,** low and changed **frequency,** and decreased **self-esteem, distress regarding not wanting** and **concern/stress** about **partner’s expectations.**
- She loves her current partner x 8 years, **positive non-sexual relationship**, which is affectionate but **strained** due to lack of interest in romantic and sexual bonding.
- Prior 20 year **combined oral contraceptive use** for contraception and acne.
- **No other contributing medical, medication, substance-related, or psychosocial factors** contributing to HSDD (based on DSDS questionnaire responses and follow-up clinical interview)
- **Total Testosterone 7.9 ng/dl (lowest quartile of reference range)**, SHBG 85 nmol/L, TSH 2.29 ml/UL

Testosterone Case Questions

- Would you recommend **off-label testosterone** for her **post-menopausal generalized, acquired HSDD**?
- How do you counsel peri-menopausal patient regarding choice of evidence-based off-label **testosterone** vs. **non-hormonal centrally-acting HSDD medication**?
- How do decide between referring for **couples sex therapy** and **testosterone**?
- Where does addressing **discrepant desire** fit into treatment plan?
- What **baseline testing** you obtain?
- What **formulation** and **dose regimen** would you recommend?
- What **monitoring** would you perform?
- How would you advise her regarding **clinical follow up** and **duration of therapy**?

Hypoactive Sexual Desire –Helen Singer Kaplan MD, PhD

- Physiology of sexual desire as yet has not been delineated precisely…governed by **neural circuits** that pass through **special centers**.
- These **circuits** are usually responsive to specific **neural transmitters**. Presumably, sexual desire originates in circuits in the **limbic brain…hypothalamus**.
- It appears that **testosterone** is necessary for the functioning of the sexual appetite **centers** in females.
- This general concept is supported by **clinical evidence** that suggests that **central nervous system depression, use of sedatives and narcotics, debilitating illness, etc. impair sex drive on a physical basis.**
- Similarly, **any illness or drug** that interferes with proper levels of **testosterone**, or with **the estrogen-testosterone ratio, can and will also diminish sexual desire**.

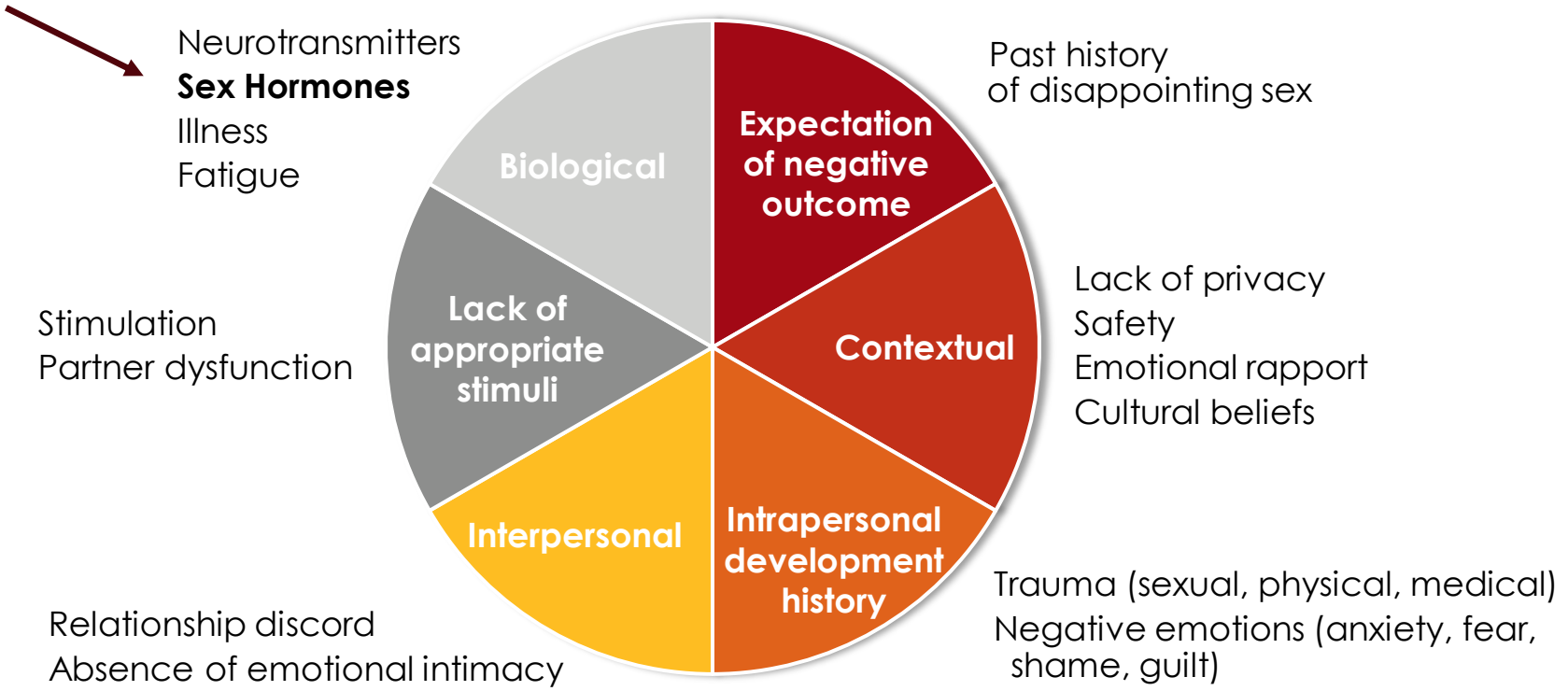
Journal of Sex & Marital Therapy, Vol. 3, No. 1, Spring 1977

Testosterone Treatment: Kaplan and Owett

- Every patient who received replacement was pleased by rapid return of her sexual feelings. **"*It's a miracle*" and "*I couldn't live without my testosterone [injections]*"**
- Fortunately, **relatively low levels of testosterone** that effectively restore and maintain female libido do not generally result in virilization of peripheral organs.
- Neurons that make up the **sexual motivation** centers of the **female brain** require only **relatively small amounts of circulating T**.
- "**Physiologically correct**" dose must result in a blood level that is high enough to **maintain sexual responsiveness** but **too low** to result in **virilization**.
- **"Therapeutic window" at which beneficial effects on female libido can be achieved without incurring unwelcome masculinizing side effects is usually attained at 1/10th of the dose that is administered to hypogonadal men.**
- ***Urged combination parenteral T replacement and psychosexual counseling***

Kaplan & Owett (1993) Journal of Sex & Marital Therapy, 19:1, 3-24.

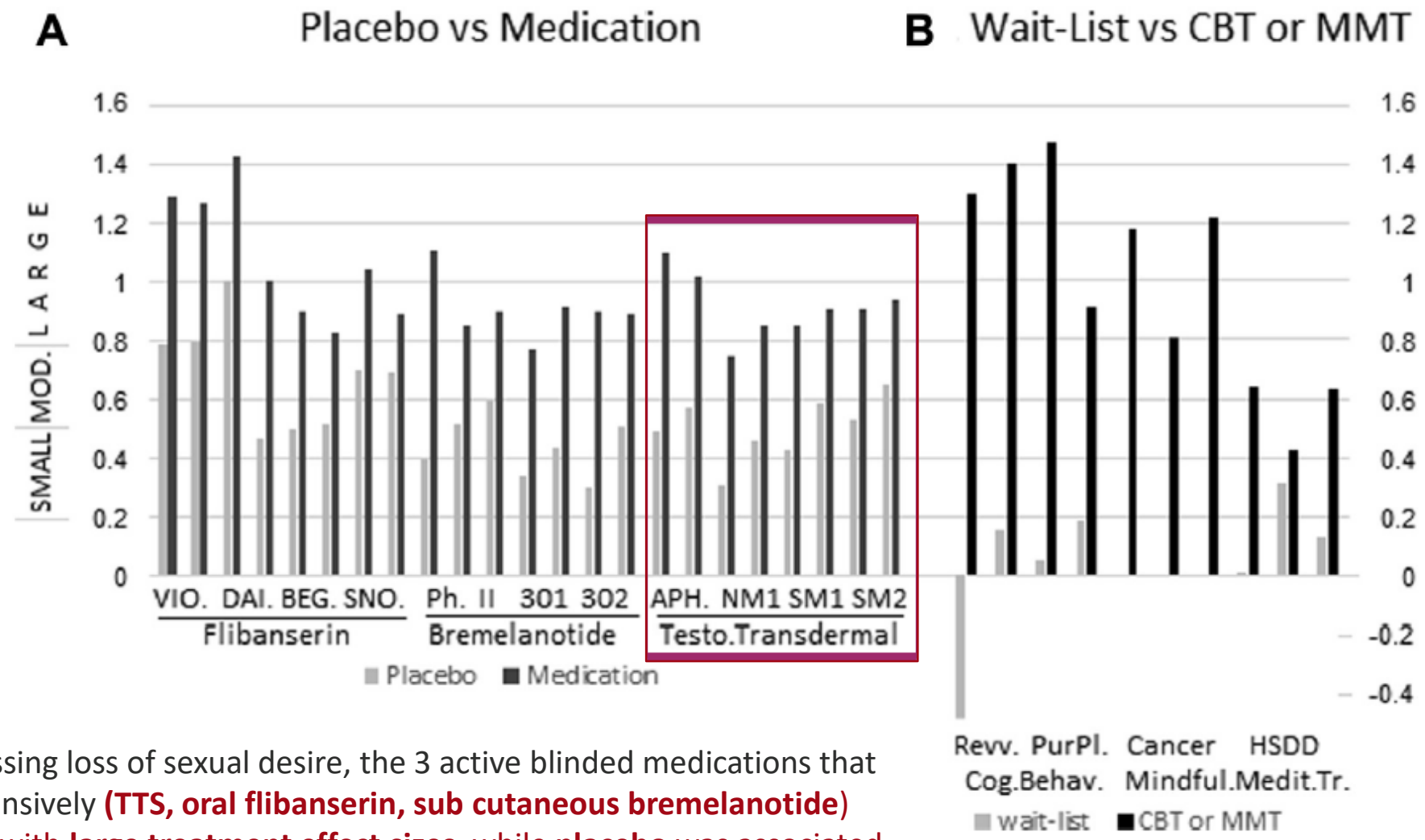
Contributors to Desire Problems



Created by: Sandra Leiblum, PhD.

Effect Size of Treatments for HSDD in Women

Pyke RE, Clayton AH. Sex Med Rev 2018;6:358-366.



In women with distressing loss of sexual desire, the 3 active blinded medications that have been tested extensively **(TTS, oral flibanserin, sub cutaneous bremelanotide)** were each associated with **large treatment effect sizes**, while **placebo** was associated with a **moderate treatment effect size.**

Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Davis SR, Baber R, Panay N, Bitzer J, Cerdas Perez S, Islam RM, Kaunitz AM, Kingsberg SA, Lambrinoudaki I, Liu J, Parish SJ, Pinkerton J, Rymer J, Simon JA, Vignozzi L & Wierman ME. **Global consensus position statement on the use of testosterone therapy for women.** ***Climacteric***, 22:5, 429-434, DOI: 10.1080/13697137.2019.1637079, September 2, 2019. **(FREE)**

Davis SR et al. ***Journal of Clinical Endocrinology and Metabolism,*** 104(10): 1-7, DOI:10.1210/jc.2019-01603, September 2019.

Davis SR et l. ***Journal of Sexual Medicine,*** 2019 Sep;16(9):1331-1337. doi: 10.1016/j.jsxm.2019.07.012.

Davis SR et al. ***Maturitas***, 2019 Jul 17. pii: S0378-5122(19)30628-0. doi: 10.1016/j.maturitas.2019.07.001.

Global Statement: Summary and Key Messages

- International panel concluded only evidence-based indication for testosterone therapy for women is for **treatment of HSDD**
- Data supports **moderate** therapeutic effect in **postmenopausal** women
- Meta-analyses shows **no severe adverse** events during **physiological testosterone use**, with caveat that women at high cardiometabolic risk were excluded from studies
- **Safety of long-term** testosterone therapy has not been established.
- Diagnosis of HSDD involves **full clinical assessment** and that other **factors contributing** to FSD must be identified and addressed before testosterone therapy is initiated…guided by available diagnostic criteria (**ISSWSH, ICD 11)**
- A blood **total testosterone** level should not be used to diagnose HSDD **(NO CUTOFF).**

Davis et al. Climacteric, Maturitas, J Sex Med, JCEM; ePub 2/9/2019.

Global Statement: Summary and Key Messages

- Treatment should only be with formulations that achieve blood concentrations of testosterone that approximate **premenopausal physiological concentrations** **[no biological rationale for higher levels]**
- As no approved female product is approved by a national regulatory body, **male formulations** can be judiciously used in **female doses** and **blood testosterone concentrations** must be monitored regularly.
- The panel recommended **against** use of **compounded testosterone**.

- *The panel highlighted the pressing need for **more research** into testosterone therapy for women and the development and **licensing of products** indicated specifically for women [does not preclude testing of any formulation].*

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

Rakibul M Islam, Robin J Bell, Sally Green, Matthew J Page, Susan R Davis

Published Online
July 25, 2019

- 46 reports of 36 randomized controlled trials of **8480 participants**
- **Testosterone significantly increased sexual function, including satisfactory sexual event frequency, desire, arousal, orgasm, and self-image, and reduced distress in postmenopausal women.**
- Associated with greater likelihood of reporting **acne** and **hair growth**
- **No serious adverse events** (breast, intermediate CV endpoints, uterus)
- Administration via **non-oral routes** (**transdermal** application) preferred because of **neutral lipid profile**.

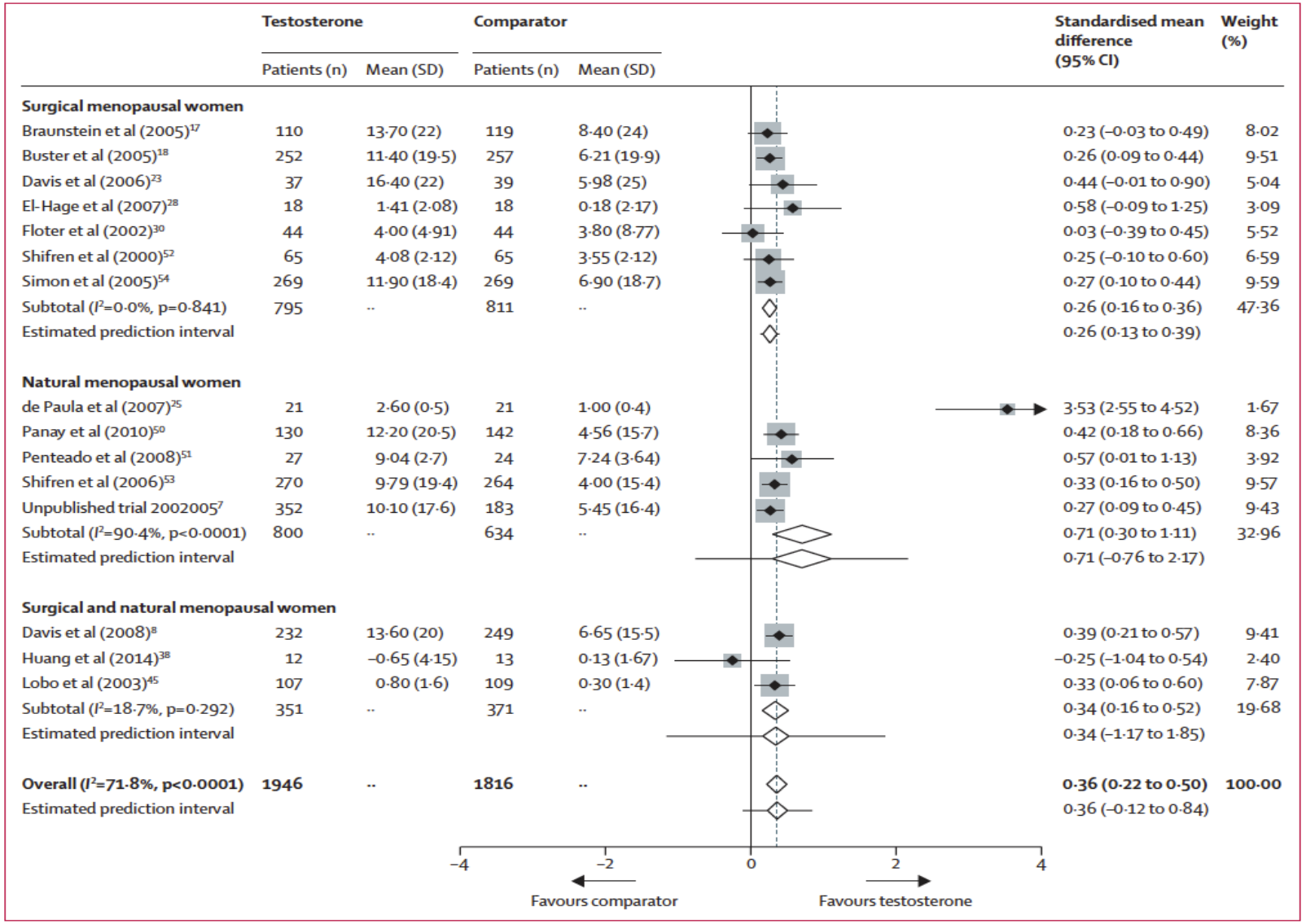
Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Climacteric, 22:5, 429-434, September 2, 2019.

Testosterone treatment of naturally or surgically postmenopausal women with HSDD, with/or without concurrent estrogen therapy:

Testosterone therapy, ***in doses that approximate physiological testosterone concentrations for premenopausal women,*** exerts a **beneficial effect on sexual function** above the effects of placebo/comparator therapy of an average of **one SSE/month**, and increases in the subdomains of **sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness**, with a **reduction** in sexual concerns including **sexual distress** (Level I, Grade A).

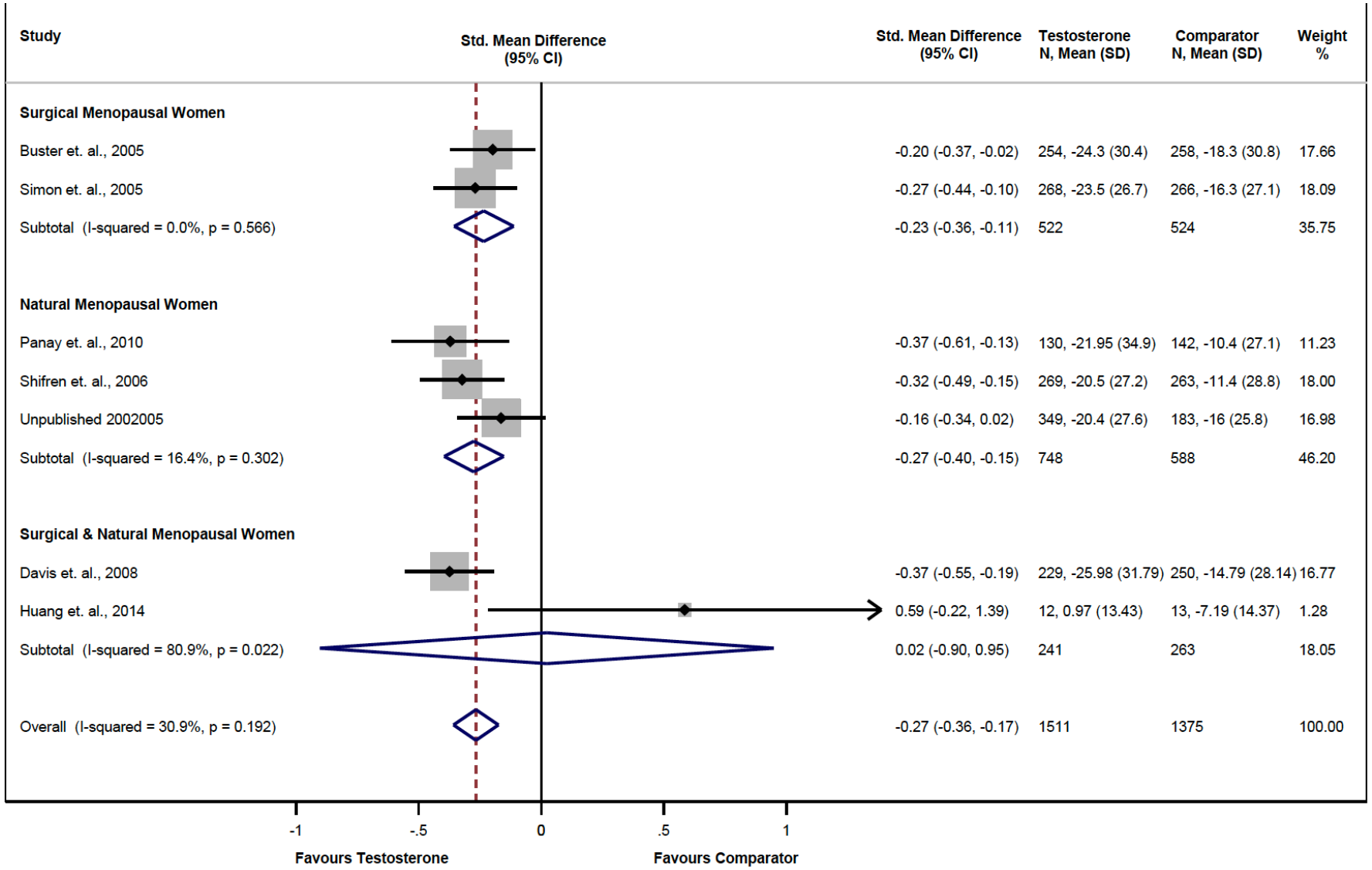
SEXUAL DESIRE Improves With Testosterone Therapy In PM Women With HSDD



	Testosterone		Comparator		Standardised mean difference (95% CI)	Weight (%)
	Patients (n)	Mean (SD)	Patients (n)	Mean (SD)		
Surgical menopausal women						
Braunstein et al (2005)[17]	110	13·70 (22)	119	8·40 (24)	0·23 (–0·03 to 0·49)	8·02
Buster et al (2005)[18]	252	11·40 (19·5)	257	6·21 (19·9)	0·26 (0·09 to 0·44)	9·51
Davis et al (2006)[23]	37	16·40 (22)	39	5·98 (25)	0·44 (–0·01 to 0·90)	5·04
El-Hage et al (2007)[28]	18	1·41 (2·08)	18	0·18 (2·17)	0·58 (–0·09 to 1·25)	3·09
Floter et al (2002)[30]	44	4·00 (4·91)	44	3·80 (8·77)	0·03 (–0·39 to 0·45)	5·52
Shifren et al (2000)[52]	65	4·08 (2·12)	65	3·55 (2·12)	0·25 (–0·10 to 0·60)	6·59
Simon et al (2005)[54]	269	11·90 (18·4)	269	6·90 (18·7)	0·27 (0·10 to 0·44)	9·59
Subtotal (I^2=0·0%, p=0·841)	795	..	811	..	0·26 (0·16 to 0·36)	47·36
Estimated prediction interval					0·26 (0·13 to 0·39)	
Natural menopausal women						
de Paula et al (2007)[25]	21	2·60 (0·5)	21	1·00 (0·4)	3·53 (2·55 to 4·52)	1·67
Panay et al (2010)[50]	130	12·20 (20·5)	142	4·56 (15·7)	0·42 (0·18 to 0·66)	8·36
Penteado et al (2008)[51]	27	9·04 (2·7)	24	7·24 (3·64)	0·57 (0·01 to 1·13)	3·92
Shifren et al (2006)[53]	270	9·79 (19·4)	264	4·00 (15·4)	0·33 (0·16 to 0·50)	9·57
Unpublished trial 2002005[7]	352	10·10 (17·6)	183	5·45 (16·4)	0·27 (0·09 to 0·45)	9·43
Subtotal (I^2=90·4%, p<0·0001)	800	..	634	..	0·71 (0·30 to 1·11)	32·96
Estimated prediction interval					0·71 (–0·76 to 2·17)	
Surgical and natural menopausal women						
Davis et al (2008)[8]	232	13·60 (20)	249	6·65 (15·5)	0·39 (0·21 to 0·57)	9·41
Huang et al (2014)[38]	12	–0·65 (4·15)	13	0·13 (1·67)	–0·25 (–1·04 to 0·54)	2·40
Lobo et al (2003)[45]	107	0·80 (1·6)	109	0·30 (1·4)	0·33 (0·06 to 0·60)	7·87
Subtotal (I^2=18·7%, p=0·292)	351	..	371	..	0·34 (0·16 to 0·52)	19·68
Estimated prediction interval					0·34 (–1·17 to 1·85)	
Overall (I^2=71·8%, p<0·0001)	**1946**	..	**1816**	..	**0·36 (0·22 to 0·50)**	**100·00**
Estimated prediction interval					0·36 (–0·12 to 0·84)	

Islam RM et al.
Lancet D&E 2019

SEXUAL DISTRESS Lessens With Testosterone Therapy In PM Women With HSDD



Islam RM et al.
Lancet D&E ePub July 25, 2019

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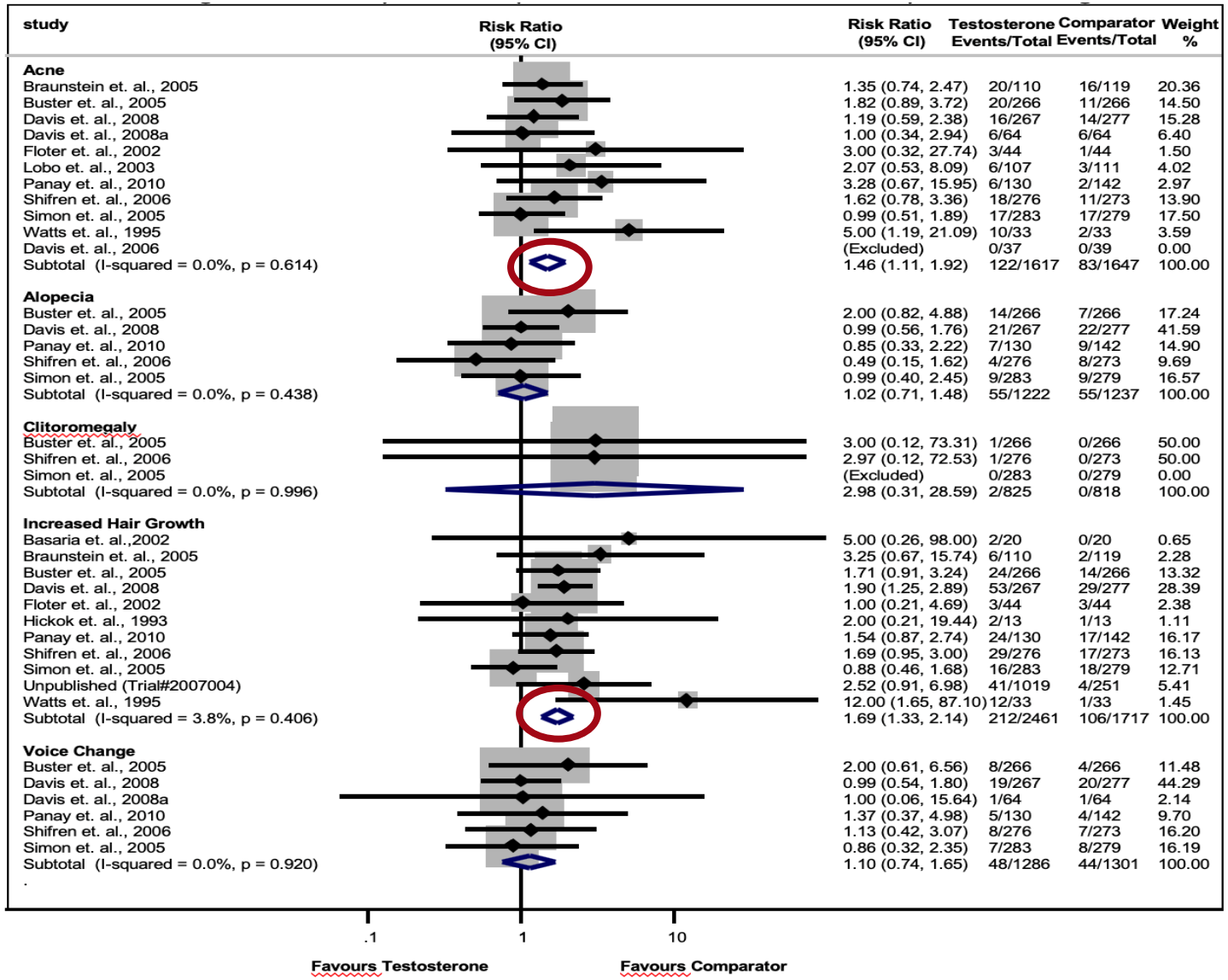
META-ANALYSIS: Testosterone vs Comparator: Androgenic Events

ACNE

BODY HAIR GROWTH



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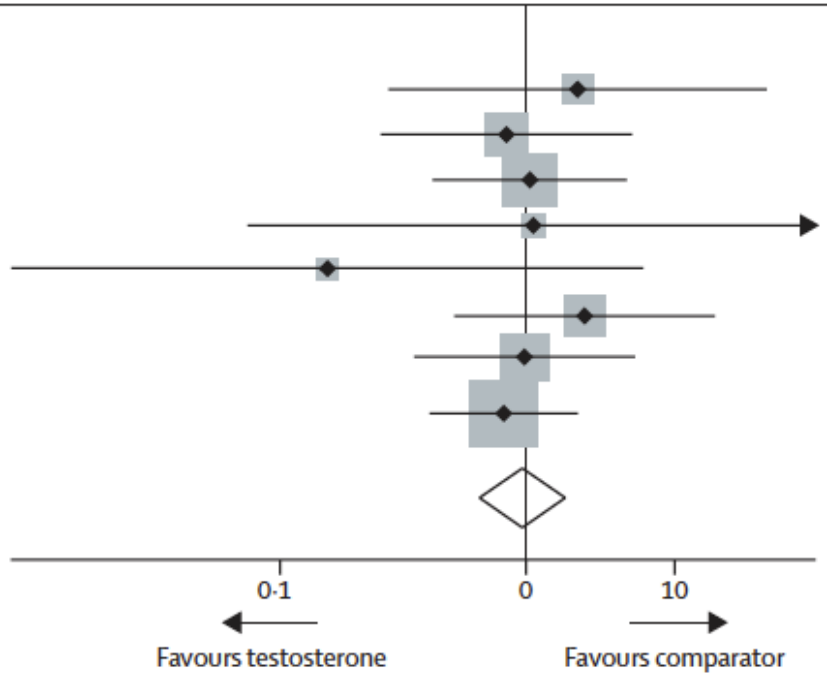
Testosterone Not Associated With Serious Adverse Events With Doses ~ Physiological Concentrations For Premenopausal Women (Level I, Grade A)

	Events/total (n/N)		Risk ratio (95% CI)	Weight (%)
	Testosterone	Comparator		
Serious adverse events				
Braunstein et al (2005)[17]	3/110	2/119	1·62 (0·28–9·53)	5·15
Buster et al (2005)[18]	5/266	6/266	0·83 (0·26–2·70)	11·70
Davis et al (2008)[8]	9/267	9/277	1·04 (0·42–2·57)	19·55
Huang et al (2014)[38]	1/14	1/15	1·07 (0·07–15·54)	2·26
Panay et al (2010)[50]	0/130	3/142	0·16 (0·01–2·99)	1·85
Shifren et al (2006)[53]	7/276	4/273	1·73 (0·51–5·85)	10·90
Simon et al (2005)[54]	7/283	7/279	0·99 (0·35–2·77)	15·08
Unpublished trial 2002005[7]	33/1019	10/251	0·81 (0·41–1·63)	33·52
Davis et al (2006)[23]	0/37	0/39	*	0·00
Subtotal (I^2=0·0%, p=0·884)	**65/2402**	**42/1661**	**0·97 (0·65–1·44)**	**100·00**



Islam RM et al Lancet D&E, 2019

Testosterone for Other Indications

Available data do not support an effect of testosterone therapy on:

- Bone loss or fracture prevention
- Cognitive function
- Lean body mass, total body fat, or muscle strength
- Psychological general wellbeing
- Prevention of any other disease

Islam RM et al.
Lancet D&E ePub July 25, 2019

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SEXUAL MEDICINE

SOCIETY REPORT

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

Sharon J. Parish, MD,[1] James A. Simon, MD,[2] Susan R. Davis, MBBS, PhD,[3] Annamaria Giraldi, MD, PhD,[4,5] Irwin Goldstein, MD,[6,7] Sue W. Goldstein, BA, CSE,[7] Noel N. Kim, PhD,[8] Sheryl A. Kingsberg, PhD,[9] Abraham Morgentaler, MD,[10] Rossella E. Nappi, MD, PhD,[11] Kwangsung Park, MD, PhD,[12] Cynthia A. Stuenkel, MD,[13] Abdulmaged M. Traish, PhD,[14] and Linda Vignozzi, MD[15,16]

J Sex Med 2021;18:849–867

*Parish SJ, *Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. ***J Womens Health*** (Larchmt). 2021 Apr;30(4):474-491.

*Parish SJ, *Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. ***Climacteric.*** 2021 Apr 1:1-18.

***Co-first authors**

ISSWSH CPG for Systemic Testosterone

- **Purpose:** To provide **specific guidelines** regarding identification of patients, laboratory testing, dosing, post-treatment monitoring, and follow-up care in the consideration of testosterone therapy for HSDD in women.

- **The Global Position Statement** was/is the **most comprehensive, evidence-based guideline to date, superseding all previous guidelines;** where guidance is not provided, **previously published guidelines** were reviewed and referenced.

- **Updated HSDD POC (in progress)** will provide any new **available efficacy and safety data** and any change in **evidenced-based management recommendations.**

*No industry funding

ISSWSH CPG for T Use: Key Messages

- **Androgens, including testosterone, are essential hormones** for development and maintenance of female sexual anatomy and physiology and **modulation of sexual behavior**.
- Testosterone has many physiological and pathophysiological actions in women, directly through its **cell specific receptor**, by **non-receptor mediated actions**, and by conversion to 5a-DHT and estrogens.
- There is **no serum testosterone level for diagnosis of** HSDD or for use as a treatment target [no **CUT OFF/POINT**].
- **Total serum testosterone concentration** is the best practical assay.

ISSWSH
International Society for the Study of Women's Sexual Health, Inc.

ISSWSH CPG for T Use: Key Messages

- Proper dosing should attain and maintain testosterone levels in the **premenopausal physiological range**.
- If an approved female formulation is not available, **one-tenth of a standard male dose of 1% *transdermal* testosterone or about 300 mcg/day** can usually achieve the normal premenopausal physiological range.
- **Compounded testosterone, pellets, IM injections, and oral formulations are not recommended.**
- Additional testing and alternative strategies may be required to assess failure to respond to typical testosterone treatment, particularly when **testosterone or SHBG levels are high**.

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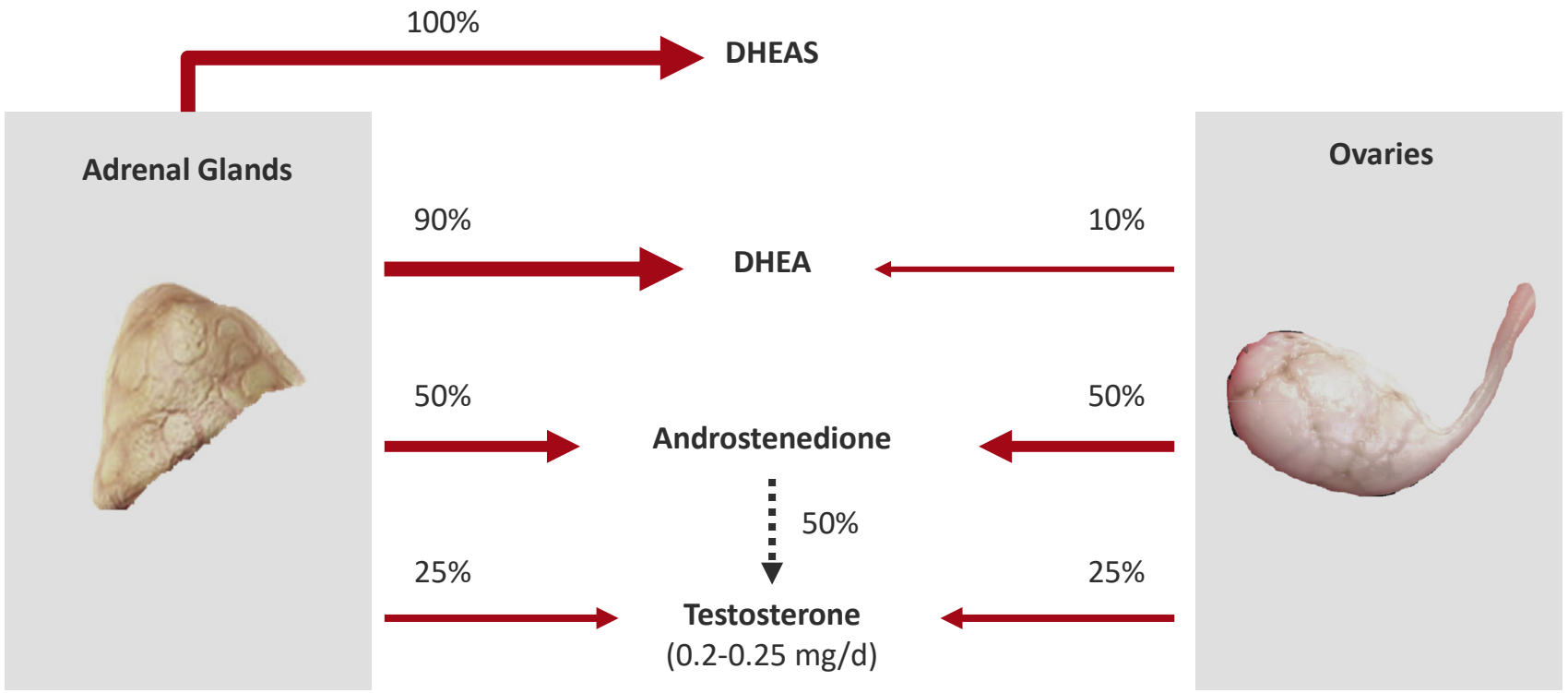
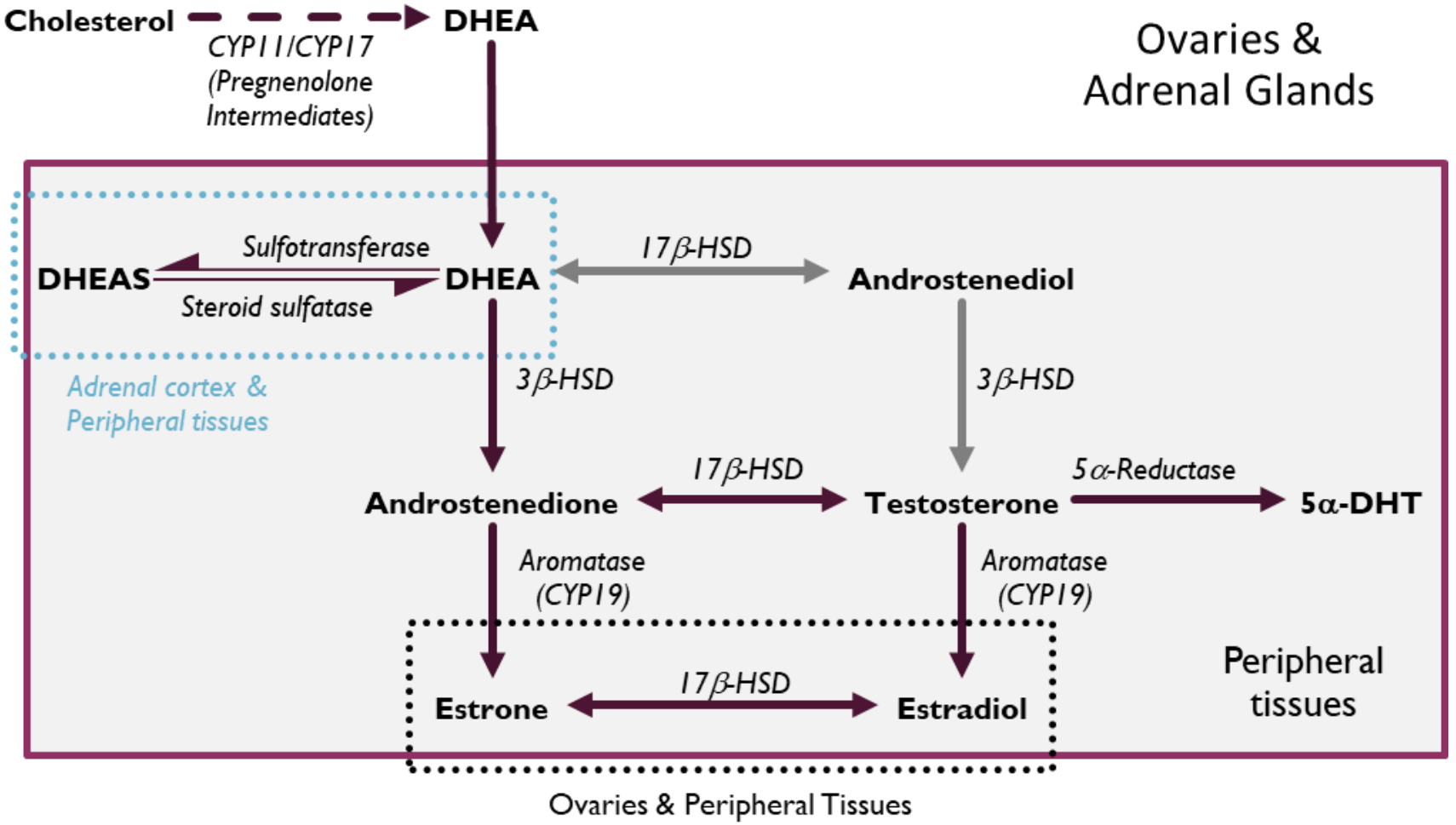
Relative Production Of Circulating Androgens In The Adrenal Glands And Ovaries



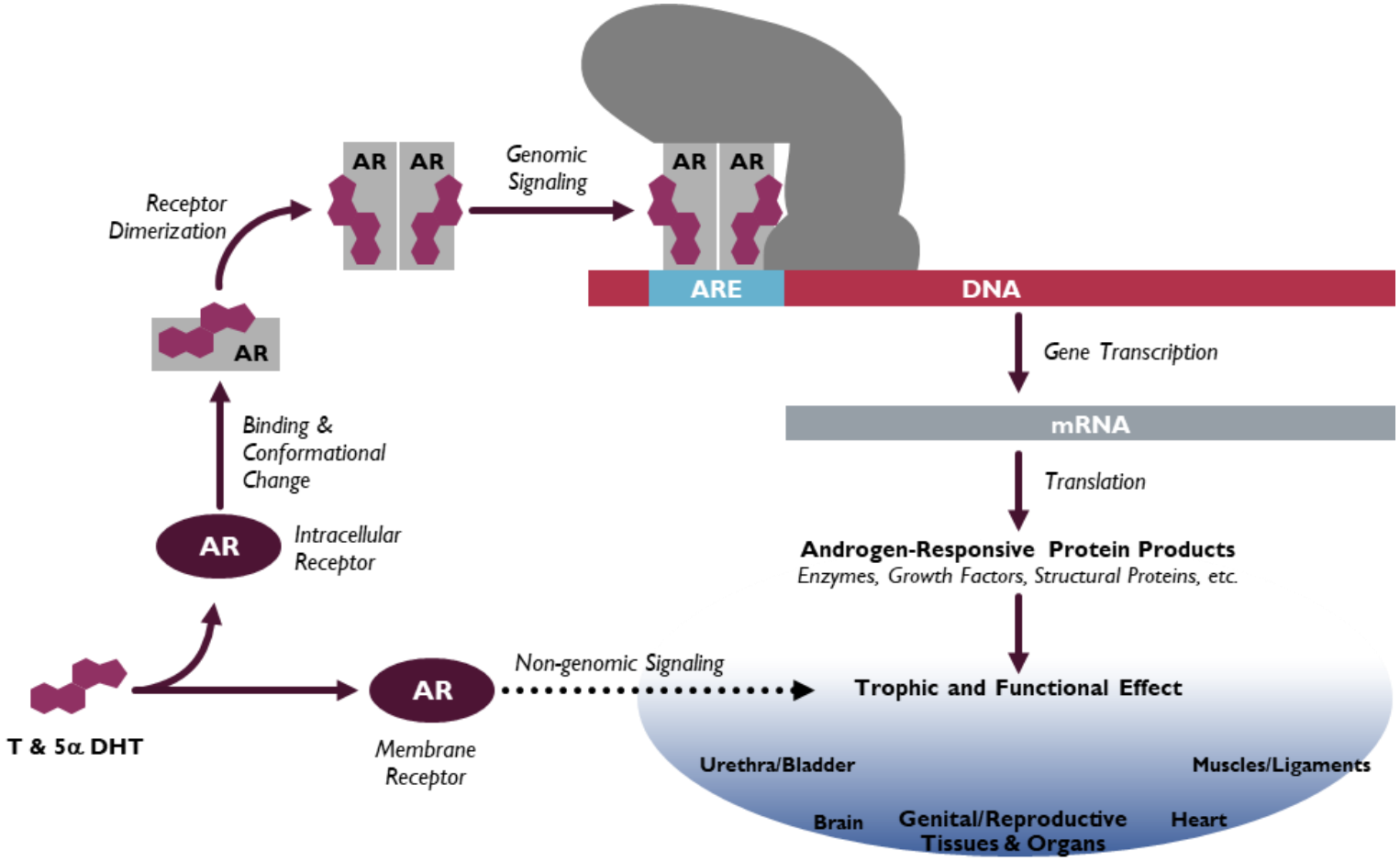
Redrawn from: Parish et al: International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Sex Med 2021;18:849-867.

Synthetic Pathways of Sex Steroids



Redrawn from: Parish et al: International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Sex Med 2021; 18:849-867.

Androgen Receptor (AR) Mechanism of Action



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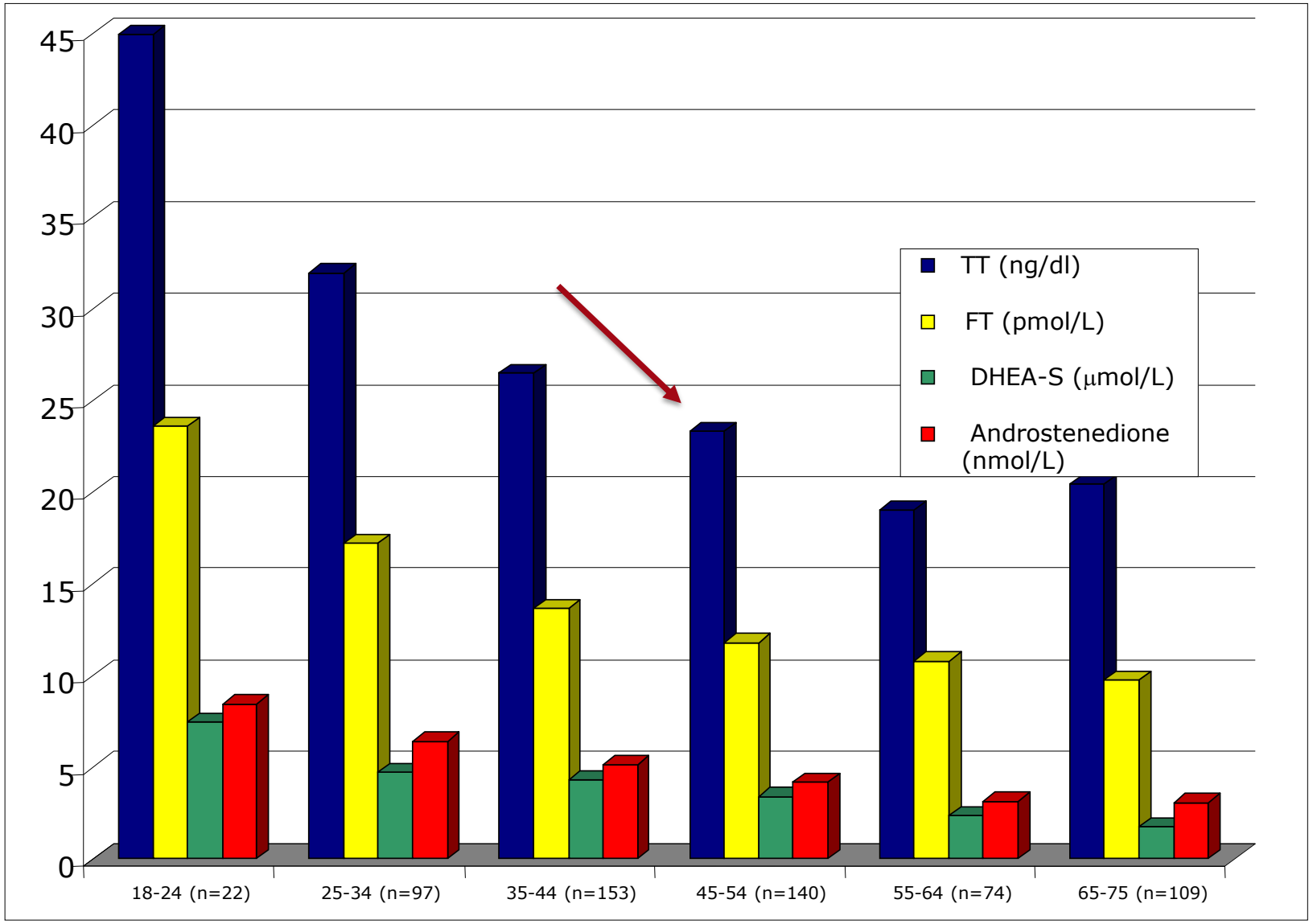
Circulating Androgen Levels AndSelf-reported Sexual Function In Women

- The physiology of androgens is complex due to their conversion in tissues and possible **intracrine metabolism** in multiple tissues.
- Androgenic effects vary according to individual variations in amount and activity of **enzymes 5-reductase and aromatase** and individual differences in **androgen-receptor response.**
- Measurement of serum testosterone does not provide **specific measure of androgen tissue exposure or action.**
- Testosterone may act **directly via the androgen receptor (AR)/non-genomic androgenic action,** or by **reduction to the more potent androgen dihydrotestosterone (DHT)** and/or aromatization to estradiol and their metabolites.

Davis et al. JAMA 2005;294:91-96.
Davis SR, Wahlin-Jacobsen S. Lancet Diabetes Endocrinol 2015; 3:980–92.

Relationship Between Age and Androgens in Women



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Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853

Incidence of HSDD Among Menopausal Women

Menopausal Status Age	Surgical (20-49 yrs)	Surgical (50-70 yrs)	Natural (50-70 yrs)
% Low desire (a)	36*	33	29
% Women with low desire classified as distressed (b)	72**	44*	33
% Total population with HSDD (a x b/100)	26*	15*	10

*p<0.05 vs. NM; **p<0.05 vs. NM and older SM

Leiblum at al. Menopause 2006;13:46-56.

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

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

*Randomized controlled trials
#Randomized cross-over trials

THE JOURNAL OF SEXUAL MEDICINE
ORIGINAL RESEARCH & REVIEWS
J Sex Med 2022;19:1778–1789

FEMALE SEXUAL FUNCTION

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

Annechien Stuursma, MD,[1,2] Lieke Lanjouw, MSc,[2] Demy L. Idema, MSc,[3] Geertruida H. de Bock, PhD,[2] and Marian J.E. Mourits, MD-PhD[1]

Testosterone Levels and FSD Diagnosis and Treatment

ISSWSH CPG Rationale for Testosterone Therapy:

Although **no testosterone serum concentration** correlates with the presence or absence of **HSDD** or its severity, there is a **loose correlation** between testosterone concentration while undergoing treatment and its **benefits** for improving sexual dysfunction.

There is **no blood level that is a treatment goal** for testosterone therapy, as serum concentrations do not predict treatment efficacy.

Main reasons to **measure** testosterone:

(1) to **exclude** women with midrange to high values (according to assay used) that suggest against androgen levels being associated with patient's symptoms

(2) to **monitor** testosterone therapy to ensure against supraphysiological values and associated androgen excess side effects

Davis, Baber, Panay et al Climacteric, Maturitas, J Sex Med, JCEM; ePub 2/9/2019.
Parish et al. J Sex Med 2021;18:849-867.

Testosterone Measurement

- ***Use TOTAL TESTOSTERONE - evidence regarding free T as biologically active fraction is lacking.**
- **Total testosterone** measured with high accuracy and reproducibility using **liquid/gas chromatography and tandem mass spectrometry** assays (LC/GC-MS/MS).
- **Direct assays** for measurement of total and free testosterone are highly unreliable in female range.
- **Direct assays** are appropriate to **exclude high baseline** concentrations and to exclude **supraphysiological concentrations** during treatment.

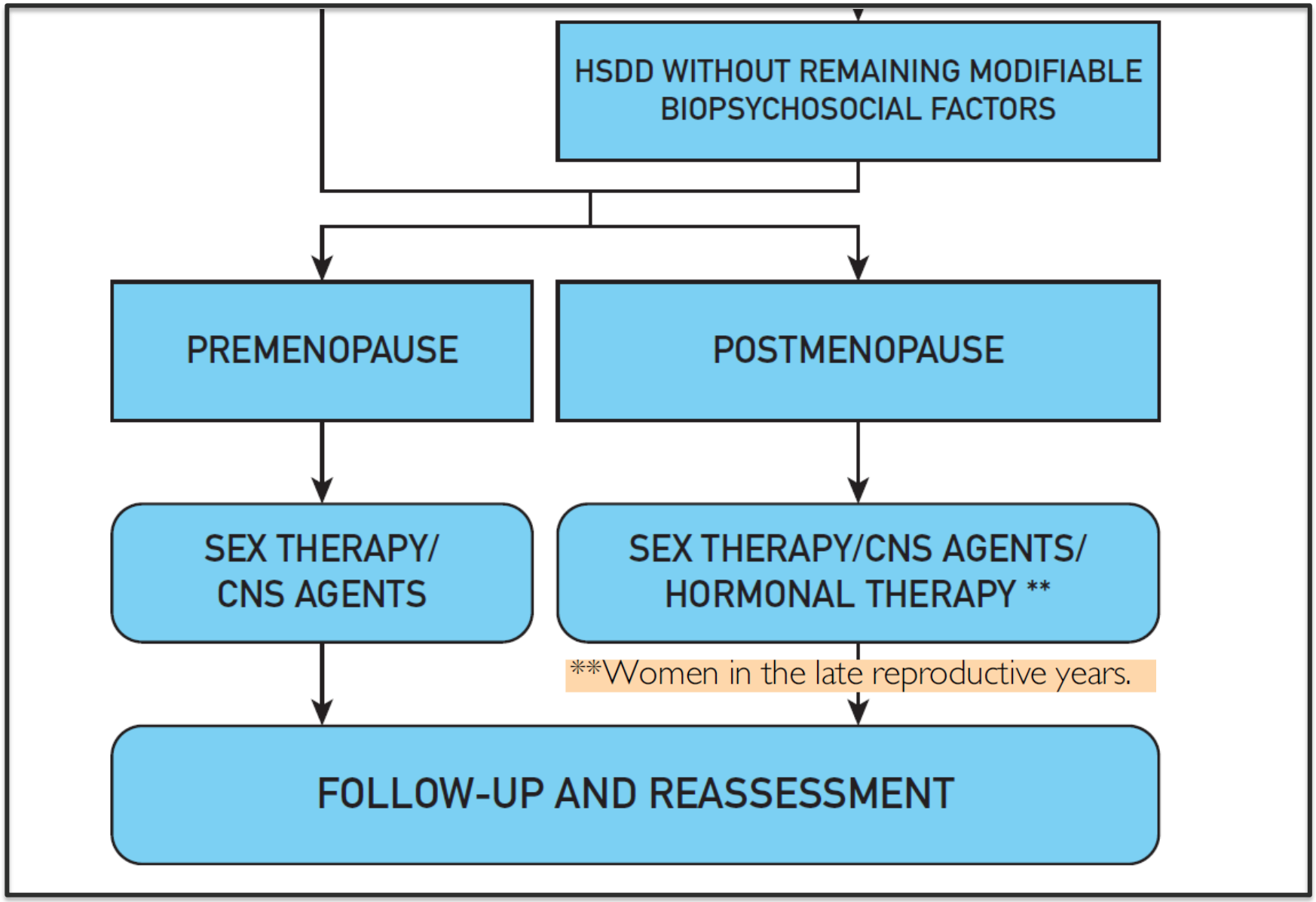
Davis et a. Climacteric, Maturitas, J Sex Med, JCEM; ePub 2/9/2019.

Treatment Recommendations Should Follow Biopsychosocial Model

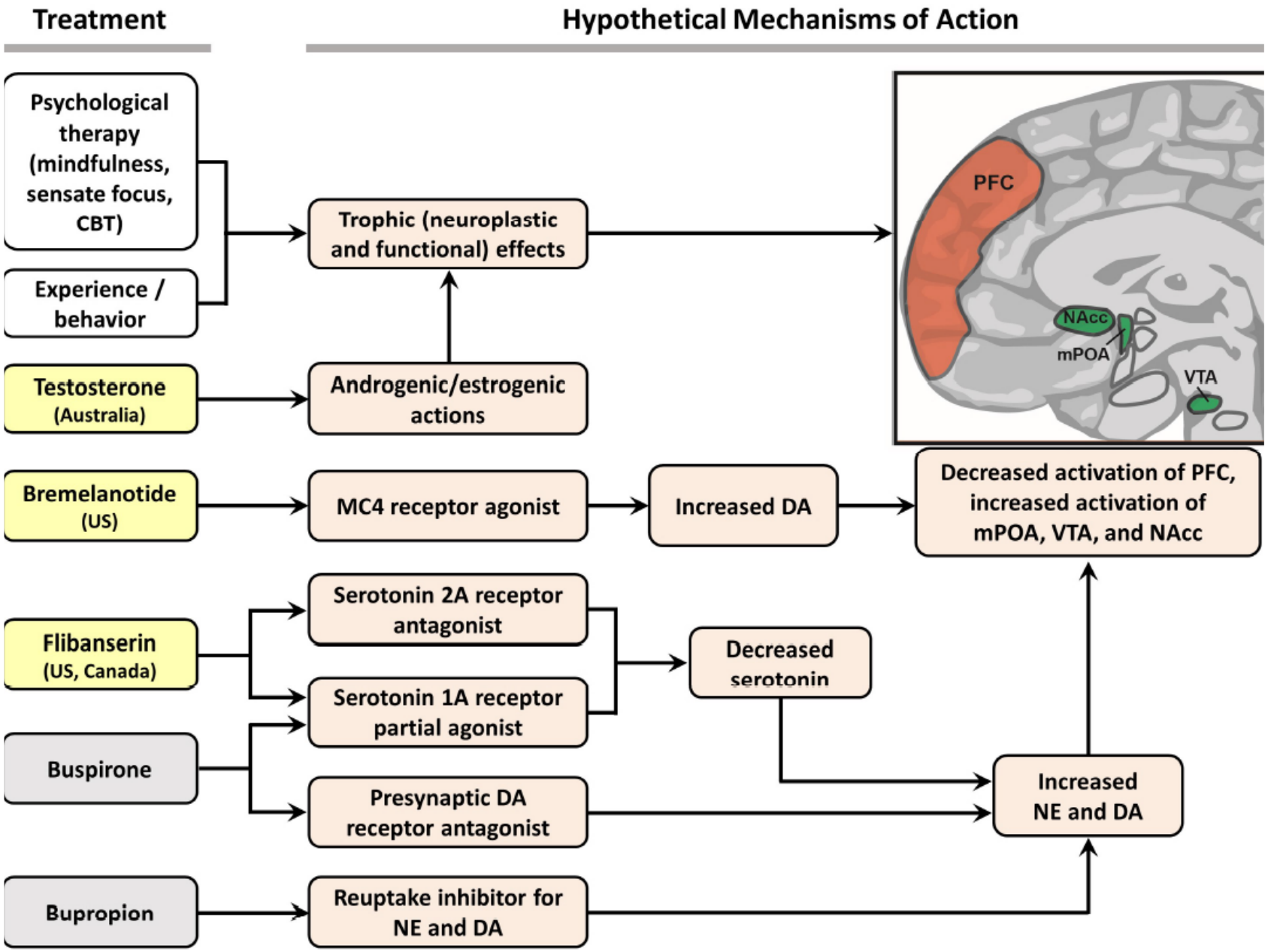
Testosterone therapy should only be initiated after a full biopsychosocial evaluation and appropriate management of other conditions that may contribute to diminished desire.

- Treatments should follow a **biopsychosocial model** and include **pharmacologic** options (hormonal and nonhormonal agents), **psychotherapy**, or multimodal treatments that combine pharmacologic with nonpharmacologic treatments.
- Even when the primary etiology is **biological**, symptoms may be maintained or exacerbated by **psychosocial and interpersonal factors** that have been the consequence of a biologically based female sexual dysfunction.
- When the etiology of **generalized, acquired HSDD** appears to be **multifactorial** without a predominant factor identified, pharmacologic treatment can be considered.
- ***Combination therapy*** *(psychological and pharmacologic therapy) may be beneficial in all circumstances.*

Davis, Baber, Panay et al Climacteric, Maturitas, J Sex Med, JCEM; ePub 2/9/2019



Clayton et al. Mayo Clin Proc. 2018;93(4):467-487.


Treatment
Hypothetical Mechanisms of Action
Psychological therapy (mindfulness, sensate focus, CBT)
Experience / behavior
Trophic (neuroplastic and functional) effects
PFC
NAcc
mPOA
VTA
Testosterone (Australia)
Androgenic/estrogenic actions
Bremelanotide (US)
MC4 receptor agonist
Increased DA
Decreased activation of PFC, increased activation of mPOA, VTA, and NAcc
Flibanserin (US, Canada)
Serotonin 2A receptor antagonist
Serotonin 1A receptor partial agonist
Decreased serotonin
Buspirone
Presynaptic DA receptor antagonist
Increased NE and DA
Bupropion
Reuptake inhibitor for NE and DA

Who to Treat

- Although the Global Position Statement endorses testosterone therapy only for postmenopausal women, the **ISSWSH POC for HSDD** and **ISSWSH T CPG** include women in the **late reproductive years**, a recommendation supported by the physiology of **decline** in androgens and **efficacy** data.

- Insufficient data to recommend use of testosterone in **premenopausal women** for treatment of sexual function, including women on COCs.
  - ***Stopping COCs is a modifiable factor.***

- Assessment and management of women with **premature ovarian insufficiency** (less than age 40 years) and **early menopause** (less than age 45 years) should be the same as for any other postmenopausal woman presenting with HSDD.

- *Transdermal testosterone has not been studied for the **FSIAD indication in any RCT/other clinical trial.***

Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.
Clayton et al. Mayo Clin Proc. 2018;93(4):467-487.

Testosterone Preparation	Daily Dose	Mode of Delivery
FDA approved male products Gel, 1% Underarm solution	**1/10 male dose** ½ cc in 5 cc syringe 0.3 cc, 4 drops	Transdermal: Back of calf, outer thigh
		Underarm
Testosterone enanthanate/cypionate	50 mg/ml 0.1 ml	IM injection into vastus lateralis thigh muscle, 27 gauge needle
Testosterone pellet	75 mg 1 pellet	Subcutaneous implantation Q4-6 months
Testosterone compounded cream 1%, meter-dosed dispenser	5 mg/day (0.5 gm)	Transdermal – arms, legs, abdomen; avoid transfer
Testosterone 1% cream (10 mg per mL), Australia	5 mg/day (0.5 ml)	Transdermal

Pinkerton et al. Endocrinol Metab Clin N Am 2021;50 139–150.

Dosing Recommendations

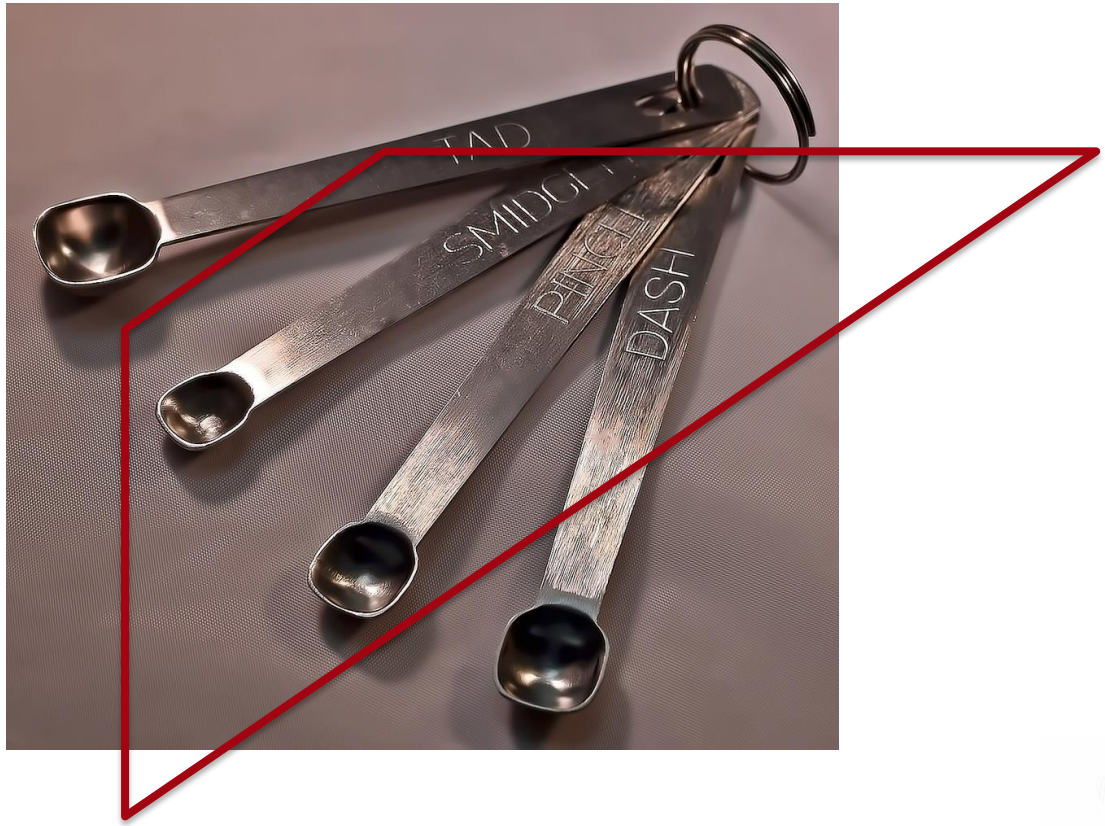
- Men use **30 tubes** or packets per month
- **1/10th** of a tube or packet/day; **3 tubes/month**
- **Resealable** tubes, room temp. (4 drops, 5cc syringe)
- Apply **gel** to **skin** surface, back of calf or thigh, upper outer thigh, or buttock (to avoid transference).
- Patients should be counseled that on average efficacy emerges **6 to 8 weeks** after initiation of therapy.
- Many women feel improvement after **4 weeks**, including reductions in distress, with maximal efficacy in **12 weeks**.

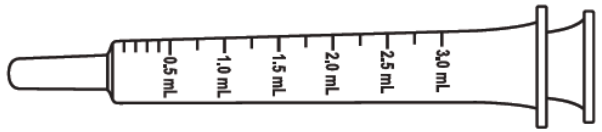
Parish et al. J Sex Med 2021;18:849-867.

FDA-Approved Male Products Dosed for Women

- **Testim**, **AndroGel 1%**, **AndroGel 1.62%**, **Fortesta**, and **Vogelxo** are brand names for medications that contain **testosterone gel**.
- **AndroGel 1%** is available in a packet.
- **AndroGel 1.62%** is available in a packet or as a pump.
- **Fortesta** is available as a pump that's applied to the thighs.
- **Vogelxo** is available in a tube, packet, and as a pump.
- Some brands are available as **generic** medications.

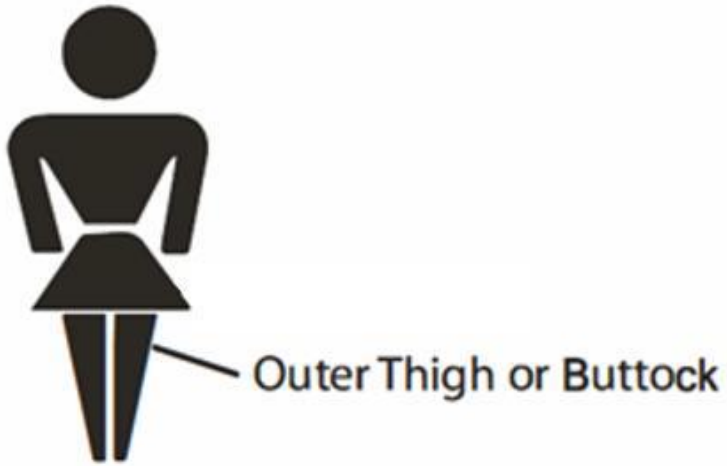
https://www.goodrx.com/testosterone/what-is#dosage





"Fill the applicator to the required dose. E.g.: a 0.5 mL dose of 5 mg testosterone to flat part of plunger level with the 0.5 mL mark."
https://www.lawleypharm.com.au/products/

http://www.rxfor.me/



Monitoring and Follow-up

- **Baseline total testosterone** should be measured before initiating therapy.
- **Repeat level** in **3–6 weeks**
- Physiological range for women aged 40-49: **Total T 27 – 38.6**
- Check T levels **6 weeks** after dose increase and **2-3 weeks** after supraphysiological level and dose decrease.
- Monitor for clinical response, assess for signs of **androgen excess**, and decrease dose if side effects occur.
- Check **serum total testosterone** level every **4-6 months** to screen for **overuse** and **androgenic consequences.**
- If no benefit by **6 months**, treatment should be **ceased**.
- If testosterone therapy results in improvement of HSDD, consider continuing for **6–12 months** and then taking a **drug holiday** to see if further treatment is required.

In most cases, **ongoing testosterone therapy is needed to maintain improvement in HSDD.*

Parish et al. J Sex Med 2021;18:849-867.
Davis et al. Climacteric, 22:5,429-434, September 2, 2019.
Guay et al. Int J Impot Res. 2004:16:112-20.

Monitoring and Follow-up

- **Measurement of SHBG and assessing free T may contribute to understanding lack of response.**
  - Women whose blood levels are in **physiologic range** and not experiencing improvement of HSDD symptoms
  - **High SHBG**: healthy women, *high dose oral estrogens, *estrogen-containing hormonal contraceptives, *untreated hyper- and hypothyroidism, thyroid replacement; **modifiable factor*
  - **SHBG** should (may) also be measured at **baseline** - women with levels greater than normal range less likely to benefit from therapy
- **Androgenic side effects** may occur despite standard dosing or normal levels of total testosterone or both.
  - May occur with **low concentrations of SHBG**, associated with **type 2 diabetes, metabolic syndrome, and/or obesity**

Parish et al. J Sex Med 2021;18:849-867.
Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.

Testosterone Clinical And Laboratory Monitoring

- Annual breast and pelvic exams
- Annual mammography
- Evaluation of abnormal bleeding
- Evaluation for **acne, hirsutism**, androgenic alopecia, voice changes, clitoromegaly
- Lipid profile, LFTs, CBC - baseline, 6 months, annually

Basson et al. J Sex Med 2010:7:314-3
Shiffren JL, Gass MLS. Menopause 2014;21:1038-1062.
Shiffren Jl. Menopause 2015;10:1147-1149.
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Other Treatment Considerations

- **Compounded "bioidentical" testosterone therapy cannot be recommended** due to the **lack of evidence for efficacy and safety**, unless an authorized equivalent preparation is not available.

- If a compounded product is needed, the compounding pharmacy should be compliant with purity of **Active Pharmaceutical Ingredients (API)** and **Good Manufacturing Practice (GMP)** to meet industry standards for quality and safety.

- **Systemic DHEA** is not associated with significant improvement in libido or sexual function in postmenopausal women with normal adrenal function and **not recommended** for women with HSDD.

- In the absence of vulvovaginal atrophy, **vaginal DHEA** has not been tested and thus cannot be recommended.

Pinkerton et al. Endocrinol Metab Clin N Am 2021;50 139–150.
Parish et al. J Sex Med 2021;18:849-867.
Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.

Key Take Home Points

- Transdermal testosterone is **moderately effective** for HSDD in late reproductive age and post-menopausal women.
- Maintain **total** testosterone levels in the **physiological premenopausal range** to diminish adverse events and optimize CNS and peripheral sexual responses.
- If an **approved female formulation** is not available, **1/10th of a standard male dose of 1% transdermal testosterone (300 mcg/day)** can usually achieve the normal premenopausal physiological range.
- **Compounded** testosterone, pellets, IM injections, and oral formulations are **not recommended.**

Parish et al. J Sex Med 2021;18:849-867.
Davis et al. Climacteric, 22:5, 429-434, September 2, 2019.