

# Use of transdermal testosterone nanoemulsion in women with hypoactive sexual desire and risk assessment for tendency to aggressiveness: a double blind randomized clinical trial

Maria Eugenia C. L. Cardoso<sup>1</sup>, Ivaldo Silva<sup>2</sup>, Lucia Helena Laprano<sup>3</sup>, Marcela Furlan Margato<sup>4</sup>

<sup>1</sup>Gynecological Endocrinology Department of University of Santo Amaro, São Paulo, Brazil; <sup>2</sup>Gynecological Endocrinology Department of Federal University of São Paulo, Brazil; <sup>3</sup>Psychology Department of Federal University of São Paulo, Brazil; <sup>4</sup>Gynecological Endocrinology Department of Federal University of São Paulo, Brazil

## ABSTRACT

**Background and Purpose:** Decreased libido is a frequent and highly prevalent female complaint also in premenopause. Transdermal testosterone is one of the therapeutic options, but still lacks consensus on the effective dose or occurrence of side effects, such as behavioral changes including aggressiveness, in this age group. This study aims to evaluate the efficacy and tolerability of transdermal testosterone gel compared with a placebo in a 12-week treatment of premenopausal female sexual dysfunction.

**Methods:** Patients diagnosed with hypoactive sexual desire disorder (HSDD) at the gynecological endocrinology clinic of the Paulista Medical School were screened according to the study's inclusion and exclusion criteria. Participants (n = 52) were randomly divided into two groups, had blood samples collected, filled out the FSFI (Female Sexual Function Index) and EATA (Scale to Assess Tendency to Aggressiveness) questionnaires, and were instructed to use, daily, the treatment to which they had been randomized: placebo formulation or testosterone gel 300 mcg. The participants and researchers remained blind to the randomization until the end of the analysis of the results.

**Results:** The group using transdermal testosterone showed a significant increase in the desire (p=0.01), arousal (p=0.01), lubrication (p=0.05), orgasm (p=0.04) and satisfaction (p=0.05) subscores of the FSFI after 12 weeks of treatment. There were no significant changes in androgenic laboratory profile after the intervention (p>0.05), nor tendency-to-aggressiveness behavioral changes according to the EATA questionnaire (p=0.30).

**Conclusion:** Transdermal application of testosterone gel, 300 mcg daily, shows positive effects on sexuality, without negative effects on behavior, while keeping plasma androgen levels within the normal range.

## KEYWORDS

Sexuality; Psychogenic Sexual Dysfunctions; Behavior; Aggression; Drug Evaluation; Testosterone.

## Introduction

Hypoactive sexual desire disorder (HSDD) and difficulty in reaching orgasm are two of the most frequent female sexual complaints [1-3]. Although these symptoms worsen in postmenopause, a period in which the androgen / estrogen ratio inverts due to hypoestrogenism, there is a high prevalence of decreased libido in women in premenopause too, a phase in which there are still high levels of circulating estrogen. Therefore, the role of testosterone and its precursors in the development of these symptoms must be considered [4-7].

HSDD is characterized by absent or reduced motivation to engage in sexual activity or fantasies for at least 6 months, leading to personal suffering. It can be primary or secondary, generalized or specific, and it affects about 10% of women of reproductive age in the USA [2,8,9]. Non-sexual mental disorder, anguish in the relationship, and effects of a substance or medical condition must be ruled out as other possible causes of lack of desire [8,9].

## Article history

Received 13 Mar 2020 – Accepted 14 Apr 2020

## Contact

Maria Eugenia C. L. Cardoso; maria\_e\_clc@hotmail.com  
2491 Angelica Avenue, 9th floor, Higienópolis, São Paulo/SP, Brazil.  
Zip 01227-200

The association of HSDD with testosterone is not clear, mainly because biochemical tests do not show good sensitivity to low values, as found in female serum, due to hormonal variation during the menstrual cycle [10-15].

Even though several studies have shown that transdermal testosterone, associated or not with estrogen therapy, is one of the possible treatments for decreased sexual desire in postmenopause [10,11], there is still no consensus on its effective dose, side effects, or on whether it has positive results in terms of increasing libido in premenopause [16-24]. Some authors have also demonstrated a relationship between androgen therapy and be-

havioral changes including aggression, irrationality, mood and unstable personality [20].

So far, it is known that testosterone does not determine aggression or changes in sexuality per se, and that, in parallel, it has been more associated with dominance than aggressiveness itself [25-30]. However, due to the presence of conflicting and limited data, this study seeks to better understand the role of testosterone in women with HSDD in premenopause, both in the genesis and treatment of this condition, and as regards a possible correlation with tendency-to-aggressiveness behavioral changes.

## Methods

The trial was a randomized, double-blinded, placebo-controlled study performed at the gynecological endocrinology clinic of the Paulista Medical School in São Paulo, Brazil. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and the protocol was approved by the university ethics committee. The study is registered with EnsaioClinicos.gov.br (RBR-27CQN5).

The primary objective of the study was to describe possible correlations between tendency to aggressive behavior and enhanced sexual desire in patients diagnosed with HSDD and treated with a nanostructured transdermal testosterone gel (daily dose of 300 mcg). The secondary objective was to look for associations between the use of testosterone and improved sexual desire, behavioral changes (i.e. a tendency to aggressiveness), and increased serum levels of free and total testosterone.

## Patients

It was established that to detect, within a group, a 1 percentage point increase or decrease in mean EATA (Scale to Assess Tendency to Aggressiveness) and mean FSFI (Female Sexual Function Index) scores with a power of 90% and an  $\alpha$  of 95%, a sample size of 24 participants per group was required. All data were processed using the STATA program (version 7).

Patients attending the gynecological endocrinology clinic of the Paulista Medical School, diagnosed with HSDD, aged between 18 and 45 years, with physiological menstrual cycles, steady relationships, and using contraceptive methods were screened, given a physical examination, and invited to participate in the research and sign the informed consent term. Participants with a BMI below 18 kg/m<sup>2</sup> or above 35 kg/m<sup>2</sup>, hyperandrogenic syndrome, severe clinical illness or severe depression, pregnant women, lactating women or women with a history of androgen therapy in the last 6 months were excluded from the study. Patients over 40 years old should have had a normal mammogram within the last 2 years.

## Study procedures

The participants who met the selection criteria were divided by the researcher, using the Random.org program, into two groups according to a 1:1 ratio to receive formulation A or B, provided by Evidence Soluções Farmacêuticas Ltda. The treatment consisted of one dose daily for a period of 12 weeks applied to the inner arm or thigh. The participants and the researchers

remained blind until the end of the analysis of the results, when Group A was revealed as placebo with Biolipid/B2<sup>®</sup> vehicle and Group B as testosterone 300 mcg with Biolipid/B2<sup>®</sup> vehicle after breaking the code (double-blind). As there is no standard treatment for HSDD, the patients in the placebo group were not undertreated.

Biolipid/B2<sup>®</sup> is a transdermal nanostructured drug delivery system produced exclusively by Evidence Soluções Farmacêuticas Ltda with a US patent (2013/0123221 A1). Composed of esters of cholesterol and free fatty acids, it forms a micellar structure, homogeneous and stable when in contact with the skin, and according to the skin permeation evaluation by spectroscopy, the formulation Biolipid/B2<sup>®</sup> with testosterone is available in the microcirculation within the first hour after use and remains subsequently 24 hours evaluation [29].

Symptomatic events were analyzed at the beginning and at the end of the treatment through anamnesis, physical exam and evaluation of scores obtained on the two questionnaires: the FSFI (cutoff value 26, less than that indicates a risk of developing sexual dysfunction), and EATA (cutoff value 17, more than that means a high tendency to aggressiveness), plus evaluation of laboratory samples of free testosterone, total testosterone and sex hormone-binding globulin (SHBG) sent to a partner laboratory chosen for the study (Posenato Laboratory).

At the end of the research it was expected that patients would have recovered their libido with low or no side effects. Participants who did not have increased sexual desire were invited to attend a specialized clinic to define a treatment, not necessarily with testosterone.

## Statistical methods

Data were collected through questionnaires; in addition, continuous and discrete variables were collected during the screening and follow-up exams. Data were tabulated in the Excel program (Microsoft Windows 2010). The random distribution program was Random.org.

The codes in the “code book” remained hidden until the data had been fully analyzed. All study participants, including outcome assessors, remained blind until the end of the analysis.

The statistical analysis was performed using the R program, latest version 3.6.1. Descriptive analyses of all variables of interest for the study were carried out. Numerical or continuous variables were summarized based on measures of central tendency and dispersion, in order to determine the appropriate statistical tests (parametric or non-parametric), and tests were performed to measure normality and estimate asymmetry measures.

The relationship between age and each of the variables related to the study objective was analyzed, mainly with the scores obtained in the questionnaires evaluated through correlation analysis, Student's T test or Mann-Whitney U test, taking into account the sample distribution in two groups. In the same way, Pearson's Chi Square test was performed for contingency tables according to the characteristics of the other study variables (sociodemographic data, FSFI and EATA scale scores, as well as the testosterone and SHBG values). The interpretation of the results on each of the scales was done using established international methods.

## Results

The present study was carried out at the gynecological endocrinology clinic of the Paulista Medical School from July 2018 to October 2019, when the target number of patients was reached. Initially 52 female patients were randomly divided into two groups: Group A (use of placebo) and Group B (use of transdermal testosterone nanoemulsion 300 mcg/day). Three patients were excluded for not meeting the inclusion and exclusion criteria: one with a BMI above 35 kg/m<sup>2</sup>, one with another

cause of sexual dysfunction, and one for inconsistent data. This resulted in a total of 49 participants in the study.

Baseline sociodemographic and clinical characteristics of the patients are presented in Tables 1 and 2. The groups had similar baseline characteristics.

**Table 1** Sociodemographic characteristics.

	PLACEBO 23(46.9%)	INTERVENTION 26(53.1%)	P-VALUE
Age			
Range	23-45	20-44	
Mean (SD)	32.3(5.8)	31.6(6.5)	.34*
Race N (%)			
White	8(35%)	16(62%)	
Black	4(17%)	-	
Brown	9(39%)	10(38%)	18**
Yellow	-	-	
Indigenous	1(4%)	-	
Not known	1(4%)	-	
Children			
Range	0-6	0-2	.03*
Mean (SD)	1.3(1.6)	0.7(0.8)	
Marital status N (%)			
Single	5(21.7%)	8(30.8%)	.21**
Married	12(52.2%)	12(46.2%)	
Divorced	-	1(3.9%)	
Widowed	-	-	
Cohabiting	6(26.1%)	5(19.2%)	
Professional background N (%)			
College degree	7(30.4%)	7(26.9%)	.21**
Technical	12(52.2%)	12(46.2%)	
Student	1(4.4%)	2(7.7%)	
N/A	3(13.1%)	5(19.2%)	
Religion			
Catholic	6(26.1%)	7(26.9%)	
Evangelical	9(39.1%)	10(38.5%)	.21**
Spiritist	-	-	
Atheist	1(4.3%)	1(3.8%)	
Agnostic	7(30.4%)	8(30.8%)	
Salary			
1 a 2 MW***	6(26.1%)	4(15.4%)	
3 a 4 MW***	10(43.5%)	12(46.2%)	
5 a 6 MW***	-	5(19.2%)	
7 a 8 MW***	4(17.4%)	2(7.7%)	23**
9 a 10 MW***	-	2(7.7%)	
More than 10 MW***	2(8.7%)	1(3.8%)	

\* T-Test Student; \*\*Chi-Square; \*\*\*Minimum wage in Brazil is R\$ 1.039

**Table 2** Basic characteristics of the groups.

	PLACEBO 23(46.9%)	INTERVENTION 26(53.1%)	P-VALUE
Relationship Length (months)			
Range	24-324	7-276	
Mean (SD)	121.8(77.8)	87.9(62.6%)	.05*
BMI N(%)			
Low weight	1(4.3%)	-	
Normal	8(34.8%)	10(38.5%)	.23**
Overweight	9(39.1%)	10(38.5%)	
Obesity	5(21.7%)	4(15.4%)	
Comorbidities N (%)			
Yes	6(26.1%)	12(46.2%)	1.00**
No	17(73.9%)	14(53.8%)	
Use of Medicines N(%)			
Yes	5(21.7%)	10(38.5%)	.19**
No	16(69.6%)	13(50%)	
Physical activity N(%)			
Yes	7(30.4%)	7(26.9%)	1.00**
No	16(69.6%)	19(73.1%)	
Smoking N(%)			
Yes	4(17.4%)	2(7.7%)	
No	19(82.6%)	23(88.5%)	.20**
Ex Smoker	-	1(3.8%)	
Gynecological cancer family history N (%)			
Yes	4(16.4%)	8(30.8%)	.21**
No	19(82.6%)	18(69.2%)	
Menarche (years)			
Range	8-16	8-17	.76*
Mean (SD)	12(1.8)	12.4(2)	
1st intercourse (years)			
Range	11-28	12-25	
Mean (SD)	16.7(3.7)	17.7(2.9)	.84*

\* Mann-Whitney U test; \*\*Chi-square (contingency tables)

### Changes in FSFI Score

Both groups showed statistically significant increases in the total FSFI score after 12 weeks: the Placebo Group had a baseline mean score of 17.9 which rose to 24.1 after treatment, and the Intervention Group had a baseline mean score of 18.6, increasing to 24.9 after treatment. The Intervention Group showed a higher total FSFI score than the Placebo Group at the second timepoint ( $p > 0.05$ ) (Table 3). When the FSFI domains were evaluated independently, it was found that the Intervention Group obtained higher scores in most of all FSFI domains, when compared with the Placebo Group at the second timepoint, with statistical significance. (Table 3) Further, in all subdimensions of the FSFI except pain, it was observed in the Intervention Group that the

youngest patients had the highest scores, which means the lowest risk of developing sexual disorder ( $p < 0.05$ ).

### Changes in EATA score

Evaluating the mean total EATA score at the second timepoint in each group, we observed a reduction in the values after 12 weeks. The Placebo Group had a mean score of 10.9, falling to 7.6 at the second evaluation ( $p < 0.05$ ) and the Intervention Group had a mean score of 9.8 passing to 8.7 at the second evaluation ( $p > 0.05$ ). No significant differences were found between the groups in the total mean score or in the single subscale scores (Table 4).

### Laboratory analysis

With regard to the analysis of serum total testosterone (Table 5) and free testosterone (Table 6), at the second evaluation of laboratory samples the mean values of the Intervention Group were found to have increased, however there was no statistical difference between the two timepoints or between the two groups after the treatment.

Analyzing the mean values of SHBG, we observed an increase at the second evaluation in the Placebo Group compared with a decrease at this timepoint in the Intervention Group. In neither group was the change statistically significant; furthermore, no significant difference emerged when comparing the two groups (Table 7).

**Table 3** FSFI scores by domain.

	PLACEBO	P-VALUE	INTERVENTION	P-VALUE	P-VALUE-2
Desire 1					
Range	1.20-3.60		1.20-4.20		
Mean (SD)	1.19(0.69)		1.98(0.81)		
		.01*		.01*	.01**
Desire 2					
Range	1.20-5.40		1.20-6		
Mean (SD)	3.25(1.22)		2.80(1.10)		
Arousal 1					
Range	1.20-4.50		0-5.40		
Mean (SD)	2.57(0.92)		2.76(1.33)		
		.02*		.01*	.01**
Arousal 2					
Range	1.50-5.40		1.20-6		
Mean (SD)	3.69(1.30)		3.96(1.42)		
Lubrication1					
Range	1.50-5.40		0-6		
Mean (SD)	3.43(1.14)		3.43(1.43)		
		.01*		.01*	.05**
Lubrication2					
Range	1.80-6		2.70-6		
Mean (SD)	4.33(1.29)		4.58(1.06)		
Orgasm 1					
Range	1.20-5.60		0-5.60		
Mean (SD)	2.42(1.23)		2.75(1.49)		
		.01*		.01*	.04**
Orgasm 2					
Range	1.20-6		1.20-6		
Mean (SD)	3.81(1.72)		4.08(1.67)		
Satisfaction 1					
Range	1.20-6		1.60-5.20		
Mean (SD)	3.08(1.23)		3.38(1.09)		
		.01*		.01*	.05**
Satisfaction 2					
Range	1.20-6		2-6		
Mean (SD)	4.21(1.70)		4.22(1.21)		
Pain 1					
Range	1.60-6		0-6		
Mean (SD)	4.56(1.20)		4.26(1.88)		
		.26*		.05*	.03**
Pain 2					
Range	2-6		2.80-6		
Mean (SD)	4.78(1.37)		5.17(0.97)		
Total 1					
Range	9.10-28.60		3.10-29		
Mean (SD)	17.87(5.52)		18.58(6.11)		
		.01*		.01*	.43**
Total 2					
Range	10.40-32.70		14.60-34.30		
Mean (SD)	24.07(7.25)		24.93(5.84)		

\* Mann-Whitney U test; \*\* Mann-Whitney U test (comparative between groups at the second evaluation)

**Table 4** EATA scores.

AGGRESSIVENESS	PLACEBO	P-VALUE	INTERVENTION	P-VALUE	P-VALUE-2
Subscale A 1 Mean (SD)	2.78(1.51)	.76*	2.50(1.24)	.76*	.43**
Subscale A 2 Mean (SD)	2(1.83)	.01*	2.08(1.32)	.03*	
Subscale B 1 Mean (SD)	6.35(4.90)	.70*	5.73(3.13)	.70*	.25**
Subscale B 2 Mean (SD)	4.47(4.15)	.01*	5.38(4.47)	.32*	
Subscale C 1 Mean (SD)	1.74(2.32)	.61*	1.58(1.72)	.61*	.43**
Subscale C 2 Mean (SD)	1.11(2.16)	.01*	1.21(1.84)	.13*	
EATA total score 1 Mean (SD)	10.87(7.26)	.72*	9.81(4.74)	.72*	.30**
EATA total score 2 Mean (SD)	7.58(6.58)	.01*	8.67(6.51)	.09*	

\* Student's T-test; \*\* Student's T-test comparing both groups at the second evaluation.

**Table 5** Total testosterone ng / dL values time 1 and 2.

	PLACEBO	P-VALUE	INTERVENTION	P-VALUE	P-VALUE-2
Total T 1 Range Mean (SD)	20-78.3 32.9(17.4)		20-54.8 26.8(10.9)		
Total T 2 Range Mean (SD)	20-75.4 28.6(14.9)	.10*	14.8-234 43.2(52.9)	.57*	.11**

\* Mann-Whitney U test; \*\* Mann-Whitney U test (comparative between groups at the second evaluation)

**Table 6** Free testosterone ng / dL values time 1 and 2.

	PLACEBO	P-VALUE	INTERVENTION	P-VALUE	P-VALUE-2
Free T 1 Range Mean (SD)	0.1-1.2 0.43(0.3)		0.1-0.7 0.25(0.2)		
Free T 2 Range Mean (SD)	0.1-1.3 0.36(0.3)	.27*	0.1-1.7 0.35(0.3)	.29*	.54**

\* Mann-Whitney U test; \*\* Mann-Whitney U test (comparative between groups at the second evaluation)

**Table 7** SHBG nmol/mL values at timepoints 1 and 2.

	PLACEBO	P-VALUE	INTERVENTION	P-VALUE	P-VALUE-2
SHBG 1 Range Mean (SD)	14-232 79.9(61.8)		23-207 108.9(63.5)		
SHBG 2 Range Mean (SD)	18-201 86(68.2)	.13*	28-271 107.52(70.4)	.77*	.17**

\* Mann-Whitney U test; \*\* Mann-Whitney U test (comparative between groups at the second evaluation)

## Discussion

HSDD is one of the four most common forms of sexual dysfunction defined by the fifth edition of the DSM, and it is characterized by a chronic or recurrent deficit or lack of sexual desire, which causes distress and personal suffering [35].

In this study, both groups showed increased total FSFI scores after the intervention; a placebo response is in fact known to be very common in trials that use subjective patient-reported measures like this one.

Thus, a significant change above the placebo response can be taken to reflect a treatment effect, as seen in the group using testosterone, versus the Placebo Group, at the second timepoint in most of all FSFI domains, which showed statistical significance. Furthermore, this increase was even more evident in young patients.

Similar results were seen in a study by Shifren *et al.* [23] where, despite an appreciable response to the placebo, the use of testosterone 300 mcg resulted in even greater increases in the frequency of sexual activity, sexual fantasies and masturbation, with increments of two to three times from baseline. Reduced suffering and distress due to greater sexual satisfaction were also observed, reaching 20% superiority when compared with placebo [36].

A placebo response similar to or only slightly less than that observed with testosterone could also be associated with the circumstance that participants wished their sex lives to be more satisfactory; it may also be due to the fact that they felt welcomed by the researchers and the research team; along the same lines, participation in the trial may have encouraged greater communication with partners [35].

In the present study, comparison of serum androgen levels between the groups at the second timepoint revealed higher values in the Intervention Group, but without the differences reaching statistical significance. Also, when we compared the Intervention Group before and after the use of testosterone, we observed increases in total testosterone and free testosterone and a decrease in SHBG, again without the differences reaching statistical significance. This same trend in hormonal profile was observed by other authors, within the same treatment period, in studies with larger numbers of participants, and similar or even higher testosterone concentrations [17,18]. This means that testosterone does not interfere negatively in laboratory tests, demonstrating safe use.

In addition, physiological free testosterone levels closer to the upper limit in the premenopause after the use of transdermal testosterone were found to be associated with an increase in the frequency of satisfactory sexual events when compared with placebo, again with good tolerability [18].

Even so, neither our study nor others with a similar design, when compared placebo users with testosterone users, showed more cases of virilization, acne, allergic reactions, androgenic alopecia or voice alterations with statistical significance [10,11,20,36]. No serious adverse effects occurred.

When evaluating the EATA scale results, the participants showed a reduction in the total score and in the subscale scores after the intervention, which indicates that use of testosterone 300 mcg was not associated with the development of behavioral

changes characterized by a tendency to aggressiveness. Trials even show improvement in depressed mood and psychological well-being when using the same formulation compared to placebo [10,11,17], probably because restoration of sexual health generates motivation and contentment, and *vice versa* [20].

Thus, as demonstrated in our research, testosterone can be used in doses low enough to improve the patient's symptoms, while keeping serum androgen values as close to the physiological levels as possible, with minimal side effects.

Therefore, it is recommended to use the transdermal route with formulations in cream, gel, or transdermal patch according to availability, avoiding use for over 6 months in unresponsive patients, or in any case for over 24 months due to lack of available safety data.

Serum testosterone levels have not yet been clearly related to sexuality, behavioral changes or aggression. Serum testosterone levels should be monitored before the start of therapy, 3-6 weeks after starting the medication, and thereafter every 6 months, or also as necessary to make sure androgen levels are close to the premenopause normal physiological range [10,11,36].

Despite several studies involving the use of testosterone to enhance desire and arousal, we have not yet been able to define the impact of this hormone on human sexuality in premenopause, as the trials differ in terms of the drug type, dosages and routes of administration, in addition to demonstrating benefits also with use of the placebo. Due to the small sample size and short patient follow-up period in this study, it is important to carry out complementary trials to gather more information on the safety and effectiveness of testosterone long-term therapy in the premenopause.

## Conclusions

The transdermal Biolipid/B2® vehicle formulation with testosterone 300 mcg was shown in a 12-week treatment period to be safe and effective for HSDD patients in the premenopause, keeping plasma androgen levels within the normal range, demonstrating positive effects on sexuality, and having no negative effects on behavior, as shown by the absence of tendency to aggressiveness.

## References

1. Laumann EO, Nicolosi A, Glasser DB, et al; GSSAB Investigators' Group. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res.* 2005;17:39-57.
2. Clayton AH, Goldstein I, Kim NN, et al. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. *Mayo Clin Proc.* 2017;93:467-87.
3. Parish SJ, Hahn SR. Hypoactive Sexual Desire Disorder: a review of epidemiology, biopsychology, diagnosis, and treatment. *Sex Med Rev.* 2016;4:103-20.
4. Lambrinouadaki I, Bouziou G, Armeni E, et al. Circulating androgens are associated with mood disturbances in young postmenopausal women. *Climacteric.* 2015;18:205-13.
5. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oopho-

- rectomy. *J Clin Endocrinol Metab.* 2005;90:3847-53.
6. Morley JE, Perry HM 3rd. Androgens and women at the menopause and beyond. *J Gerontol A Biol Sci Med Sci.* 2003;58:M409-16.
  7. Lobo RA. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet Gynecol Surv.* 2001;56:361-76.
  8. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review. *Mayo Clin Proc.* 2017;92:114-28.
  9. Kingsberg SA, Clayton AH, Pfaus JG. The Female Sexual Response: Current Models, Neurobiological Underpinnings and Agents Currently Approved or Under Investigation for the Treatment of Hypoactive Sexual Desire Disorder. *CNS Drugs.* 2015;29:915-33.
  10. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *J Clin Endocrinol Metab.* 2019;104:4660-6.
  11. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol.* 2019;7:754-66.
  12. Aedo AR, Landgren BM, Diczfalusy E. Studies on ovarian and adrenal steroids at different phases of the menstrual cycle: II. A comparative assessment of the circadian variation in steroid and luteinizing hormone levels during the follicular, periovulatory and luteal phases. *Contraception.* 1981;23:407-24.
  13. Vermeulen A, Verdonck L. Plasma androgen levels during the menstrual cycle. *Am J Obstet Gynecol.* 1976;125:491-4.
  14. Wåhlin-Jacobsen S, Kristensen E, Pedersen AT, et al. Androgens and Psychosocial Factors Related to Sexual Dysfunctions in Premenopausal Women\*: 2016 ISSM Female Sexual Dysfunction Prize. *J Sex Med.* 2017;14:366-79.
  15. Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA.* 2005;294:91-6.
  16. van Anders SM. Testosterone and Sexual Desire in healthy women and men. *Arch Sex Behav.* 2012;41:1471-84.
  17. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause.* 2006;13:770-9.
  18. Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. *Ann Intern Med.* 2008;148:569-77.
  19. Davis SR, Moreau M, Kroll R, et al; APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med.* 2008;359:2005-17.
  20. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause.* 2003;10:390-8.
  21. Achilli C, Pundir J, Ramanathan P, Sabatini L, Hamoda H, Panay N. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil Steril.* 2017;107:475-82.e15.
  22. Layton JB, Meier CR, Sharpless JL, Stürmer T, Jick SS, Brookhart MA. Comparative Safety of Testosterone Dosage Forms. *JAMA Intern Med.* 2015;175:1187-96.
  23. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med.* 2000;343:682-8.
  24. Chudakov B, Ben Zion IZ, Belmaker RH. Transdermal testosterone gel per application for hypoactive sexual desire disorder in premenopausal women: a controlled pilot study of the effects on the Arizona sexual experiences scale for females and sexual function questionnaire. *J Sex Med.* 2007;4:204-8.
  25. van Honk J, Tuiten A, Verbaten R, et al. Correlations among salivary testosterone, mood, and selective attention to threat in humans. *Horm Behav.* 1999;36:17-24.
  26. Cunningham RL, Lumia AR, McGinnis MY. Androgen receptors, sex behavior, and aggression. *Neuroendocrinology.* 2012;96:131-40.
  27. Mehta PH, Beer J. Neural mechanisms of the testosterone-aggression relation: the role of orbitofrontal cortex. *J Cogn Neurosci.* 2010;22:2357-68.
  28. Heany SJ, van Honk J, Stein DJ, Brooks SJ. A quantitative and qualitative review of the effects of testosterone on the function and structure of the human social-emotional brain. *Metab Brain Dis.* 2016;31:157-67.
  29. Peterson CK, Harmon-Jones E. Anger and testosterone: evidence that situationally-induced anger relates to situationally-induced testosterone. *Emotion.* 2012;12:899-902.
  30. Yildirim BO, Dersken JJ. A review on the relationship between testosterone and life-course persistent antisocial behavior. *Psychiatry Res.* 2012;200:984-1010.
  31. Queiroz D, Botelho MA. Biológico, Dossie Científico. Evidence. 2012. [access June 12th of 2018]. Available at: [https://issuu.com/grupo-evidencia4/docs/dossie\\_biologico\\_deo\\_b2](https://issuu.com/grupo-evidencia4/docs/dossie_biologico_deo_b2).
  32. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther.* 2000;26:191-208.
  33. Pacagnella Rde C, Martinez EZ, Vieira EM. [Construct validity of a Portuguese version of the Female Sexual Function Index]. *Cad Saude Publica.* 2009;25:2333-44.
  34. Sisto FF. Escala para Avaliação de Tendência à Agressividade (EATA). 1st Ed. São Paulo: Casa do Psicólogo;2013.
  35. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab.* 2005;90:5226-33.
  36. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99:3489-510.