70° Congresso Nazionale

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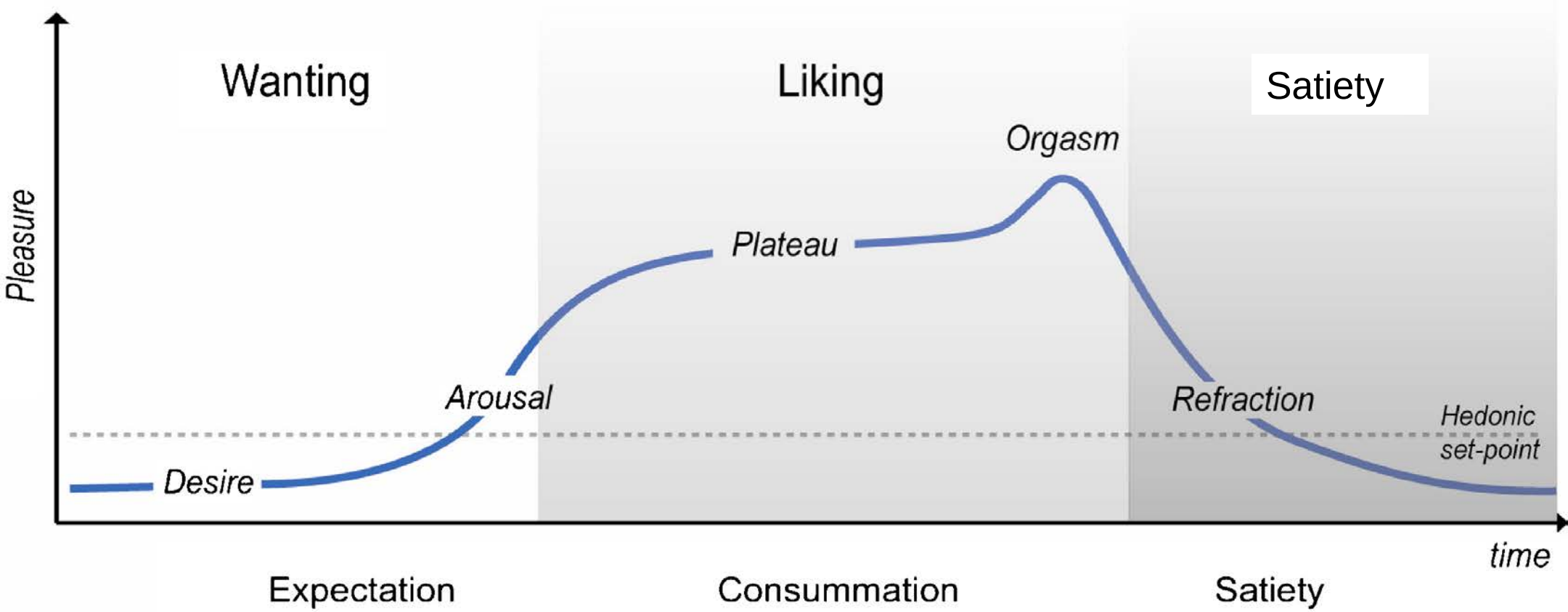
Le disfunzioni sessuali femminili

Giovanni Corona MD, PhD

Endocrinology Unit
Medical Department, Ospedale Maggiore
Bologna, Italy
jocorona@libero.it



Master EH, Johnson V. 1966

Visuospatial tasks are typically stronger in male subjects relative to female subjects

Childress et al., PlosOne 2008, 3:1506
Salonia et al., j Sex med 2010, 7:2637

Sex-related differences were due to

Women's sexual response may be triggered by a much wider variety of stimuli than men

Chivers et al., Arch Sex Behav 2010, 39: 5-56
Sergerie K et al., Neurosc and Biobehav Rev 2008; 3:811-30

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Larger amygdala response to neutral stimuli in women ➔ smaller effect size between emotional and contro stimuli

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Sergerie K et al., Neurosc and Biobehav Rev 2008; 3:811-30

Sex-related differences were due to

Influence of sex hormones and the mestrual cycle

Clayton et al., J Sex and Marital Therapy 1999, 25: 281-91
Wallen and Rupp Hormones and Behaviour 57:263-68

DISFUNZIONI SESSUALI FEMMINILI

- DISTURBO DEL DESIDERIO (HSDD)
  - DESIDERIO SESSUALE IPOATTIVO
  - AVVERSIONE SESSUALE
- DISTURBO DELL'ECCITAMENTO (FSDA)
- DISTURBO DELL'ORGASMO (FOD)
- DISTURBO CARATTERIZZATO DA DOLORE SESSUALE
  - DISPAREUNIA
  - VAGINISMO
  - DOLORE SESSUALE NON COITALE

1) DISTURBO DEL DESIDERIO

• DESIDERIO SESSUALE IPOATTIVO

Persistente o ricorrente carenza o assenza di fantasie sessuali, e/o desiderio, o recettività per l'attività sessuale, che provochi "personal distress"

✓ *E' la forma più comune di disfunzione sessuale (10-51% nella pop. generale)→aumenta prevalenza con età*
✓ *femmina/maschio: 2:1 o 3:1*
✓ *Spesso si accompagna a ridotta eccitazione ed infrequente orgasmo*
Basson R., NEJM 354:14, 2006

• AVVERSIONE SESSUALE

Persistente o ricorrente avversione fobica con evitamento del contatto con un partner sessuale, che causi "personal distress"

1) DISTURBO DEL DESIDERIO

- **DESIDERIO SESSUALE IPOATTIVO**

  Persistente o ricorrente carenza o assenza di fantasie sessuali, e/o desiderio, o recettività per l'attività sessuale, che provochi "personal distress"

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  ✓ *femmina/maschio: 2:1 o 3:1*
  ✓ *Spesso si accompagna a ridotta eccitazione ed infrequente orgasmo*
  Basson R., NEJM 354:14, 2006

An absence of desire <u>any time</u> during the sexual experience designates disorder.

Basson R et al., Revised definitions of women's sexual dysfunction. J Sex Med. 2004 Jul;1(1):40-8

Depressione

Desiderio Sessuale

Anedonia

Desiderio Sessuale

- La depressione per sé è caratterizzata da sintomi della sfera sessuale: ANEDONIA anche sessuale; ansia; svalutazione di se stessi; ricorrenti pensieri negativi (accentuazione della memoria emotiva negativa)

Distressing sexual problems in United States women revisited: prevalence after accounting for depression.

Johannes CB, Clayton AH, Odom DM, Rosen RC, Russo PA, Shifren JL, Monz BU.

Department of Pharmacoepidemiology and Risk Management, Research Triangle Institute (RTI) Health Solutions, Waltham, Massachusetts 02451, USA. cjohannes@rti.org

"About 40% of women with sexual disorder of desire, arousal, or orgasm have concurrent depression"

Importance of evaluating depression along with sexual problems

(fMRI) « attivazione cerebro-corticali a stimoli sessuali visivi

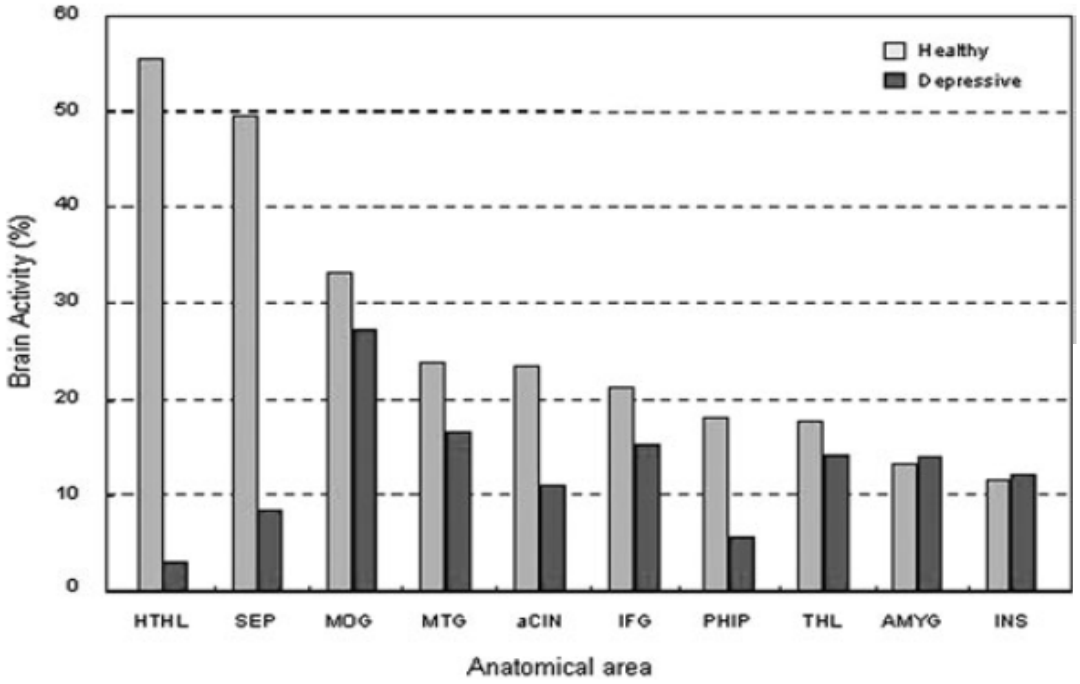

Figure 2 Comparison of the brain activities associated with sexual arousal in healthy and depressive women. HTHL: Hypothalamus, SEP: Septal area, MOG: Middle Occipital Gyrus, MTG: Middle Temporal Gyrus, aCIN: anterior Cingulate Gyrus, IFG: Inferior Frontal Gyrus, PHIP: Parahippocampal Gyrus, THL: Thalamus, AMYG: Amygdala, INS: Insula.

Yang JC et al., J Sex Med 2008, 5:602

Farmaci antidepressivi

Depressione

Desiderio Sessuale

Farmaci antidepressivi

- *Inibitori delle MAO (selegilina→seledat)*
- *Inibitori della ricaptazione delle amine (triciclici: imipramina→tofranil; clomipramina→anafranil; nortriptilina)*
- *Atipici (Bupropione: Zyban; Elontril)*
- *Inibitori della ricaptazione della serotonina : -- effetti collaterali (ipotensione, tachicardia, disturbi conduzione intramiocardica, secchezza fauci) ma ++ riduzione del desiderio sessuale*

Fluoxetina (Prozac, Fluoxerene, Fluoxetina)
Paroxetina (seroxat; sereupin, Eutimil, Daparox)
Sertralina (zoloft, Tatig)
Escitalopram (Cipralex, Entact,)
Citalopram (Elopram, Seropram)
Fluvoxamina (Maveral, Dumirox, Fevarin)

Farmaci antidepressivi

- *Inibitori delle MAO (selegilina→seledat)*
- *Inibitori della ricaptazione delle amine (triciclici: imipramina→tofranil; clomipramina→anafranil; nortriptilina)*
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Bupropione

antidepressivo atipico

Inibitore selettivo re-uptake dopamina, noradrenalina e serotonina (in misura minore)

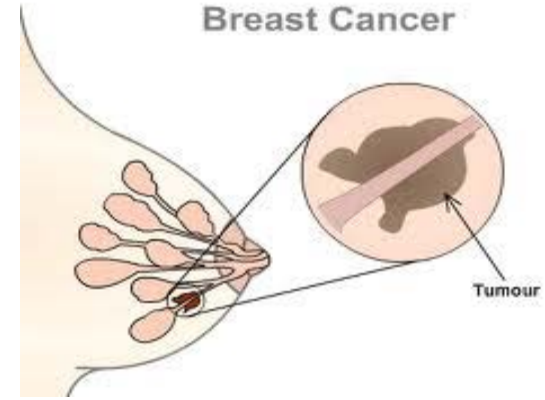
Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies.

Adult outpatients with moderate to severe DSM-IV-defined major depressive disorder (MDD) and normal sexual functioning were randomly assigned to receive bupropion XL (300-450 mg/day; N = 276), escitalopram (10-20 mg/day; N = 281), or placebo (N = 273) for up to 8 weeks in 2 identically designed, randomized, double-blind, parallel-group studies

CONCLUSIONS: Bupropion XL had a sexual tolerability profile significantly better than that of escitalopram with similar HAM-D-17 remission rates and HAM-D-17 total scores in patients with MDD

J Clin Psychiatry. 2006 May;67(5):736-46.

17-item Hamilton Rating Scale for Depression (HAM-D-17) total score



The disturbances to sexual functioning frequently reported following the diagnosis and treatment of breast cancer include :
dyspareunia
fatigue
vaginal dryness
decreased sexual interest or desire
decreased sexual arousal
numbness in previously sensitive breasts
difficulty achieving orgasm
lack of sexual pleasure

Emilee and Perz Maturitas 2010, 66: 397

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Sexual Problems in Younger Women After Breast Cancer Surgery

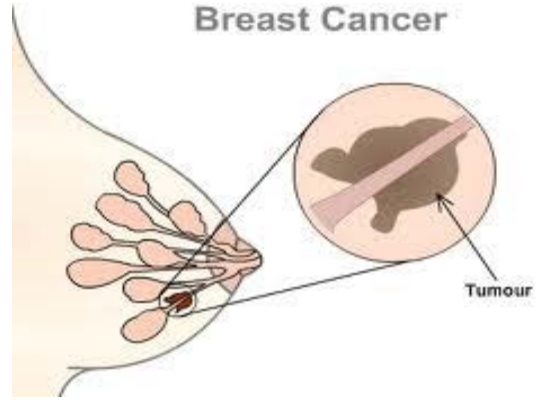
Stephanie R. Burwell, L. Douglas Case, Carolyn Kaelin, and Nancy E. Avis

Table 5. Mixed Model Results for Overall Sexual Problems

Variable	β	SE	P
Prediagnosis sexual function	0.43	0.04	< .0001
Physical well being	−.54	0.21	.0099
Social well being	−.83	0.26	.0015
Perceived sexual attractiveness	−6.89	1.02	< .0001
Radiation therapy	−5.67	2.11	.0076
Weeks since surgery*			
No current chemotherapy	0.04	0.12	.6998
Current chemotherapy	−.31	0.11	.0049
Effect of chemotherapy, weeks*			
6	10.90	3.43	.0016
12	8.75	2.73	.0015
18	6.61	2.23	.0032
24	4.47	2.06	.0307
30	2.33	2.30	.3129
36	0.18	2.85	.9491
42	−1.96	3.57	.5833
48	−4.10	4.38	.3490

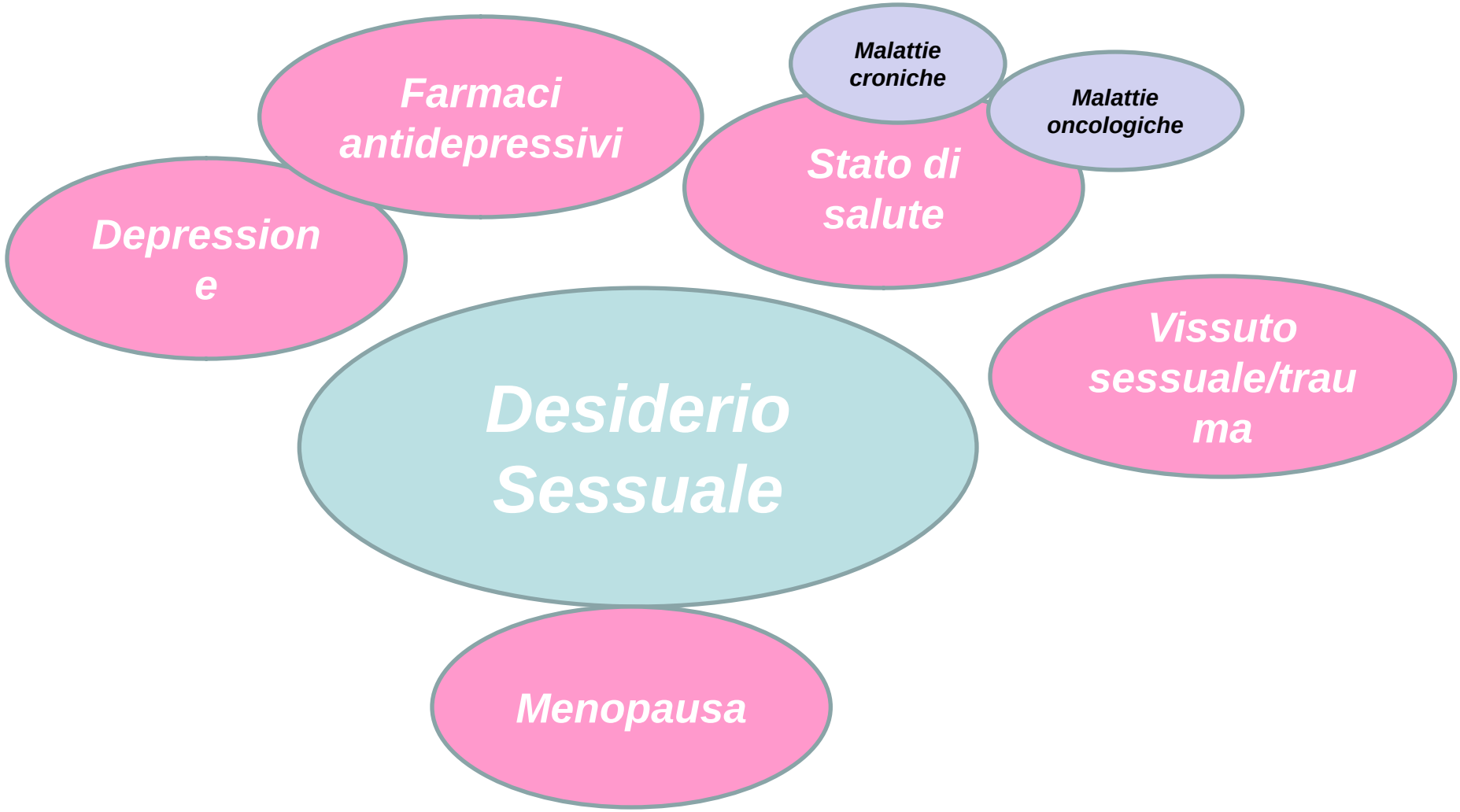
*Interaction between time and chemotherapy was significant ($P = .0238$).

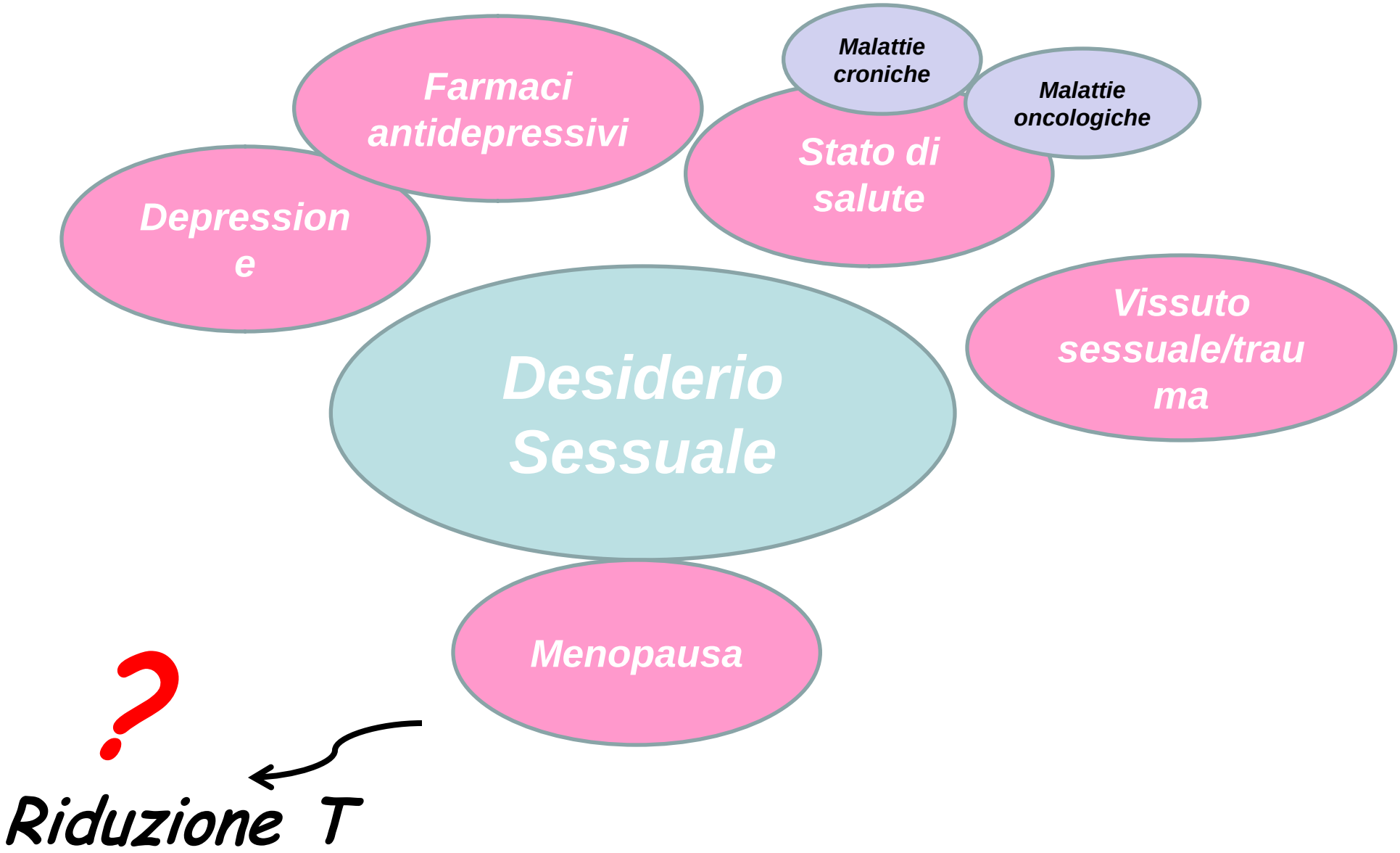
Bruwell et al., J Clin Oncol 2006, 24: 2815



The strongest consistent predictor of sexual problems after breast cancer is lower perceived sexual attractiveness

Poor body image after mastectomy (no in cases of conserving treatment or breast reconstruction)→lower rate of sexual satisfaction
Ganz et al., J Clin Oncol 1998, 16: 501


Farmaci antidepressivi
Malattie croniche
Malattie oncologiche
Depressione
Stato di salute
Desiderio Sessuale
Vissuto sessuale/trauma
Menopausa


Farmaci antidepressivi
Malattie croniche
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Stato di salute
Depressione
Desiderio Sessuale
Vissuto sessuale/trauma
Menopausa
?
Riduzione T

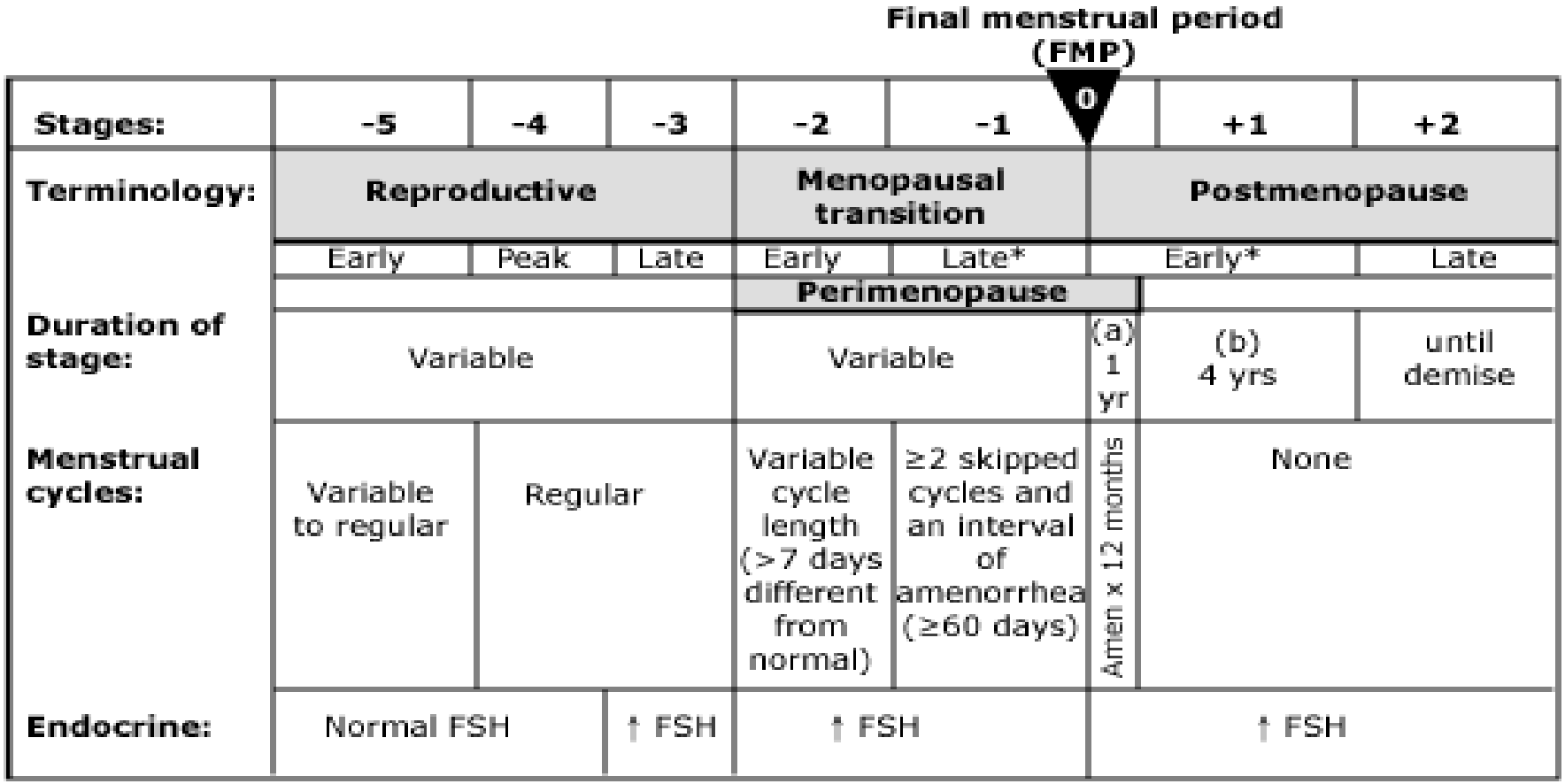
Menopause definition

According to Reproductive Aging Workshop (2001)
Menopausal transition: **it begins with variation in menstrual cycle length and an elevated serum FSH concentration and ends with the final menstrual period (not recognized until after 12 months of amenorrhea).**

Menopause: **it is defined as 12 months of amenorrhea after the final menstrual period.**

Post-menopause: **Stage +1 (early) is defined as the first five years after the final menstrual period. It is characterized by further and complete dampening of ovarian function and accelerated bone loss; many women in this stage continue to have hot flashes. Stage +2 (late) begins five years after the final menstrual period and ends with death.**

Manopausal transition: begins with variation in menstrual cycle length and an elevated serum FSH concentration and ends with the final menstrual period (not recognized until after 12 months of amenorrhea).



Soules et al., Fertil Steril. 2001;76:874.

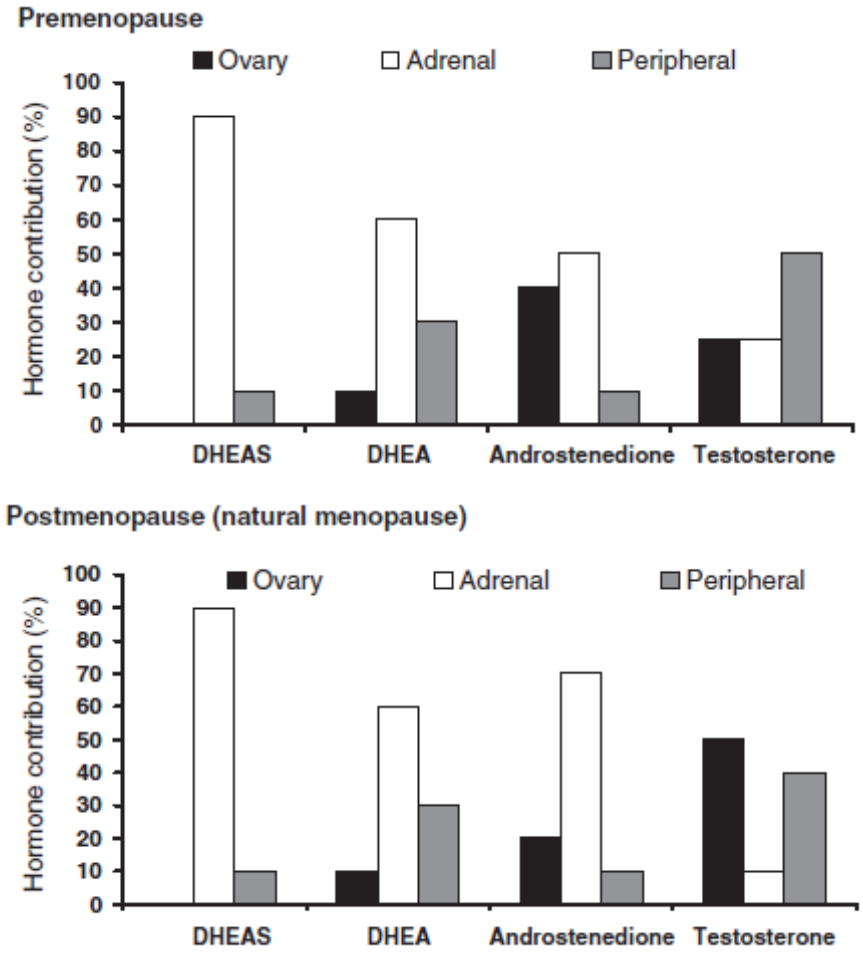
Hormone levels in relationship to menstrual period

Years from the final menstrual period	TT (nmol/L) ↔	DHEAS (μmol/L) ↔	↑ FSH (IU/L*) P<0.001	↓E_2 (pmol/L*) P<0.001	↓ Inhibin (IU/L*) P<0.001
-4	1.29	1.93	13.80	235.53	150.95
-3	1.36	1.91	16.20	219.60	131.66
-2	1.41	2.03	25.90	192.44	131.13
-1	1.42	2.00	46.85	120.72	92.83
0	1.33	1.93	74.71	62.09	79.53
1	1.29	1.89	94.22	43.60	66.59
2	1.27	1.86	98.31	36.40	60.14
3	1.27	1.90	94.46	40.28	61.08

The Melbourne Women's Midlife Health Project, a longitudinal Australian study which followed a cohor of women for 8 years,

Dennerstein et al. Fertil Steril 2005;84:174

Menopause hormonal modifications



Testosterone treatment for hypoactive sexual desire disorder

Guidelines and position statements differ quite significantly, creating a therapeutic dilemma

North American Menopause Society

"postmenopausal women with HSDD associated with distress and with no other identifiable cause may be CANDIDATE for T therapy "

Menopause. 2005 Sep-Oct;12(5):496-511

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Menopause. 2005 Sep-Oct;12(5):496-511

The Endocrine Society

"although there is evidence for short term efficacy of T treatment in selected population, generalized use of T by women IS NOT RECOMMENDED due to inadequate indications for treatment and the lack of evidence of safety in long-term studies"

Endocrine Practice Vol 12 N°3 May/June 2006

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"although there is evidence for short term efficacy of T treatment in selected population, generalized use of T by women IS NOT RECOMMENDED due to inadequate indications for treatment and the lack of evidence of safety in long-term studies"

International drug regulatory agencies

FDA

not recommend approval of the transdermal T patch for surgically menopausal women, principally because of concerns regarding the absence of information on long- term safety

Guidelines and position statements differ quite significantly, creating a therapeutic dilemma

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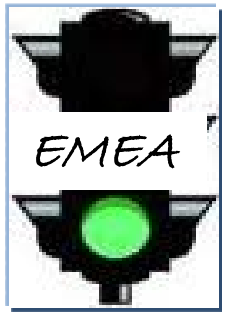
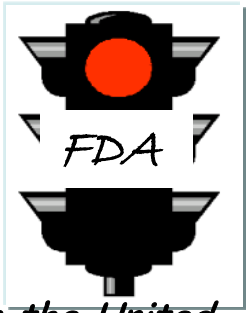




approved the Intrinsa T patch (300 mcg) in July 2006 for use in the United Kingdom and European Union for surgically menopausal women with HSDD on concurrent ET

Intrinsa era indicato per il trattamento del disturbo da desiderio sessuale ipoattivo (Hypoactive Sexual Desire Disorder, HSDD) nelle donne sottoposte a ovariectomia e isterectomia bilaterali (menopausa chirurgica) che ricevono una terapia estrogenica concomitante.

Ciascun cerotto di 28 cm^2 contiene [illegible] di testosterone e rilascia 300 microgrammi di [illegible] 24 ore.

ritirato in Europa per ragioni commerciali - ottobre 2012-

La dose giornaliera raccom[illegible]a di testosterone è di 300 microgrammi.

La dose viene raggiunta con l'applicazione del cerotto due volte la settimana, su base continuativa.

Il cerotto deve essere sostituito ogni 3-4 giorni con un nuovo cerotto. Applicare un solo cerotto alla volta

TESTOVIS IM 2F 2ML 100MG

DONNA: (come regola generale e' da evitare la somministrazione di Testovis durante il periodo mestruale). Frigidita': iniezioni da 100 mg di Testovis distanziate di 3 giorni, ripetibili dopo qualche mese. Meno-metrorragie: 1-3compresse da 10 mg al di'. Emorragie di fibromioma: iniezioni da 50 mg2 volte la settimana a cicli di 3 settimane, intervallati da una settimana. Mastodinie e mastopatie nelle sindromi dolorose congestizie: una compressa da 10 mg al giorno (5 mg nelle giovinette) nei 3 giorni precedenti la presunta comparsa dei dolori; nelle forme fibrocistiche 50 mg settimanali di Testovis. Ingorgo mammario post-partum: 3 compresse al di' per 2-3 di'.

Tostrex 2% gel

Off-label

1/3 di push (300 microgr)/die

Farmaco di fascia A.

DHEAS è l'ormone steroideo sessuale più abbondante nelle donne
E' UN ANDROGENO DI DERIVAZIONE SURRENALICA

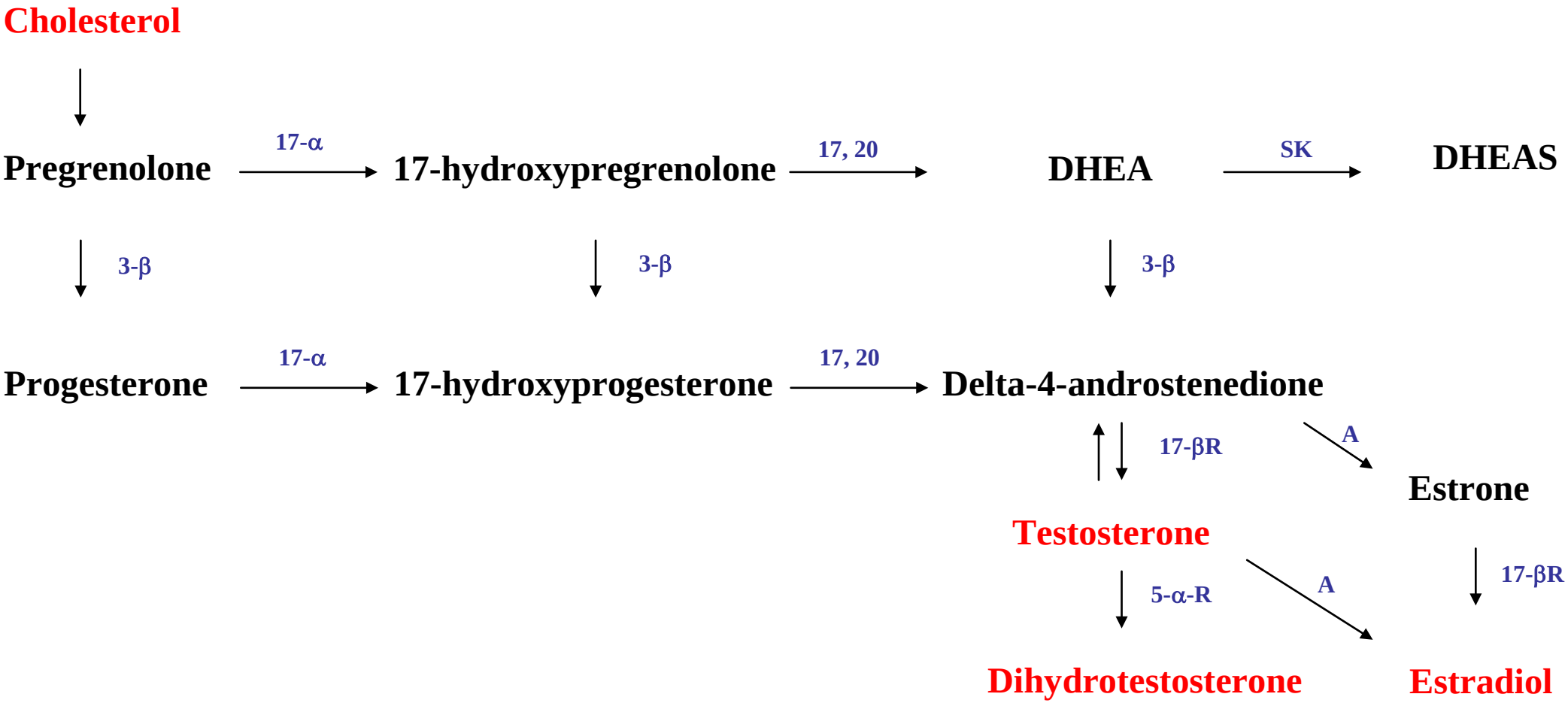
↓

DHEA: Riduzione del 70-80% con menopausa

Laughlin GA, Barrett-Connor E. Sexual dimorphism in the influence of advancing aging on adrenal hormone levels: the Rancho Bernardo study. *J Clin Endocrinol Metab.* 2000;85:3561–3568.

Per ridotta attività della 17-20 desmolasi surrenalica

Liu CH, Laughlin GA, Fischer UG, Yen SSC. Marked attenuation of ultradian and circadian rhythms of dehydroepiandrosterone in post-menopausal women: evidence for a reduced 17,20 desmolase enzy-matic activity. *J Clin Endocrinol Metab.* 1990;71:900–906.


Cholesterol
Pregrenolone
17-α
17-hydroxypregrenolone
17, 20
DHEA
SK
DHEAS
3-β
3-β
3-β
Progesterone
17-α
17-hydroxyprogesterone
17, 20
Delta-4-androstenedione
17-βR
A
Estrone
Testosterone
17-βR
5-α-R
A
Dihydrotestosterone
Estradiol

DHEAS has been implicated in a broad range of biological abnormalities including

-Obesity
-Diabetes
-Osteoporosis
-Sexual dysfunction
-Mental disorders
-Cancer

-**A relative DHEAS deficiency may contribute to the development of common age-related diseases or diminished longevity**.

SPECIAL FEATURE

Review

A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials of DHEA Treatment Effects on Quality of Life in Women with Adrenal Insufficiency

Aziz A. Alkatib, Mihaela Cosma, Mohamed B. Elamin, Dana Erickson, Brian A. Swiglo, Patricia J. Erwin, and Victor M. Montori

Conclusions: DHEA may improve, in a small and perhaps trivial manner, HRQOL and depression in women with adrenal insufficiency. There was no significant effect of DHEA on anxiety and sexual well-being. The evidence appears insufficient to support the routine use of DHEA in women with adrenal insufficiency. (*J Clin Endocrinol Metab* 94: 3676–3681, 2009)

SPECIAL FEATURE

Clinical Review

DHEA Replacement for Postmenopausal Women

Susan R. Davis, Mary Panjari, and Frank Z. Stanczyk

Conclusions: Taken together, findings from this review of the published literature of studies do not support the use of DHEA in postmenopausal women at this time. (*J Clin Endocrinol Metab* 96: 1642–1653, 2011)

Terapia HSDD:

1-Rimozione cause (relazionali, intrapsichiche, organiche: iperprl, distiroidismi, farmaci)

2- Farmaci:

- Testosterone

.Yohimbina: antagonista α2 adrenergico

Agisce potenziando il tono noradrenergico (sembra in grado di contrastare il Calo di desiderio associato a SSRI)

Clayton AH. Curr. Womens health Rep. 2002, 2:182.

Preparazione galenica: capsule da 5 mg da assumere tre volte al dì

2) DISTURBO DELL'ECCITAMENTO

- Persistente o ricorrente incapacita' ad ottenere o mantenere un sufficiente eccitamento sessuale, che causa "personal distress"

- ***COMBINATO***

- ***ECCITAZIONE MENTALE***
  (soggettiva mancanza di eccitamento)

- ***ECCITAZIONE GENITALE***
  (oggettiva mancanza di lubrificazione genitale)

Combined arousal disorder Disorder is characterized by absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation, and absent or impaired genital sexual arousal (vulval swelling and lubrication).	There is no sexual excitement in the mind and no awareness of reflexive genital vasocongestion.
Subjective arousal disorder Disorder is characterized by absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation. Vaginal lubrication and other signs of physical response still occur.	There is no sexual excitement in the mind, but there is awareness of adequate lubrication.
Genital arousal disorder Disorder is characterized by absent or impaired genital sexual arousal (minimal vulval swelling or vaginal lubrication from any type of sexual stimulation, and reduced sexual sensations when genitalia are caressed). Subjective sexual excitement still occurs from nongenital	The presence of subjective arousal (sexual excitement) from nongenital stimuli (e.g., erotica, stimulating the partner, receiving breast stimulation, kissing) is key to the AUA Foundation diagnosis.

Ridotta lubrificazione
Secchezza vaginale

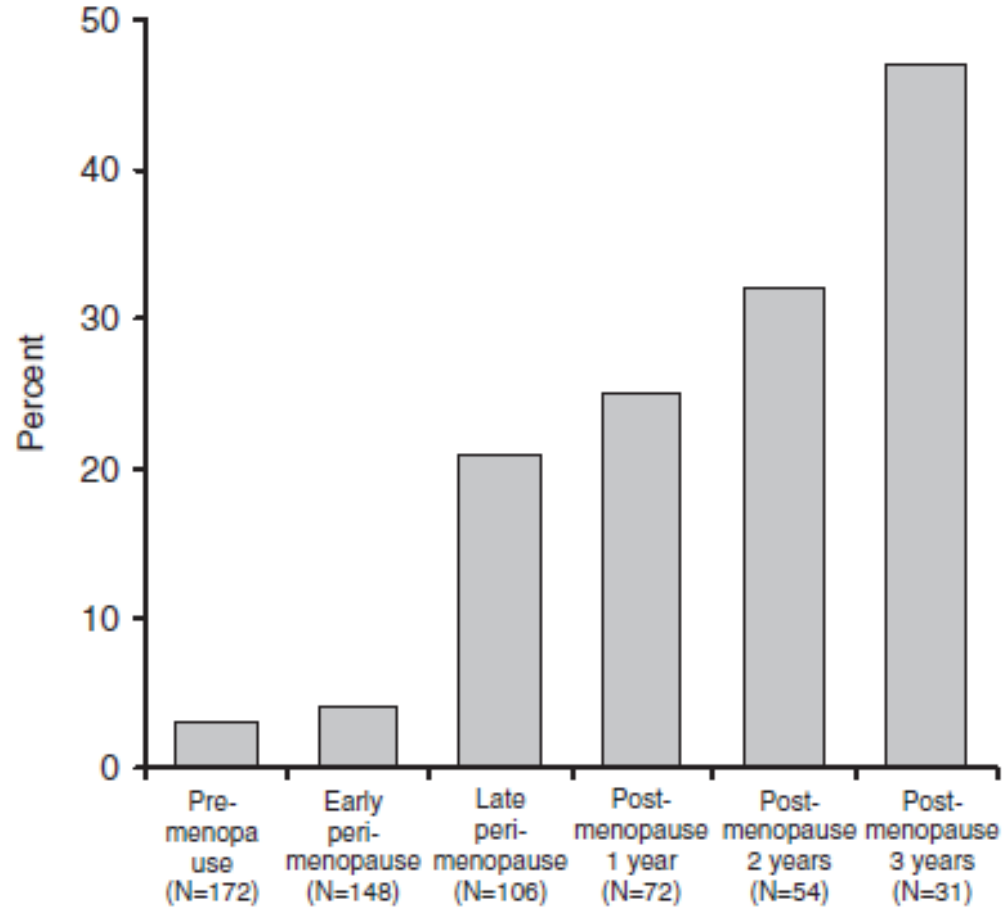
Low lubrication
Vaginal dryness

Low libido➔ low lubrication.

Estrogen deficiency.

Menopause

Lack of E2 determine an increased prevalence of vagina dryness (Graziottin et al., 2005)



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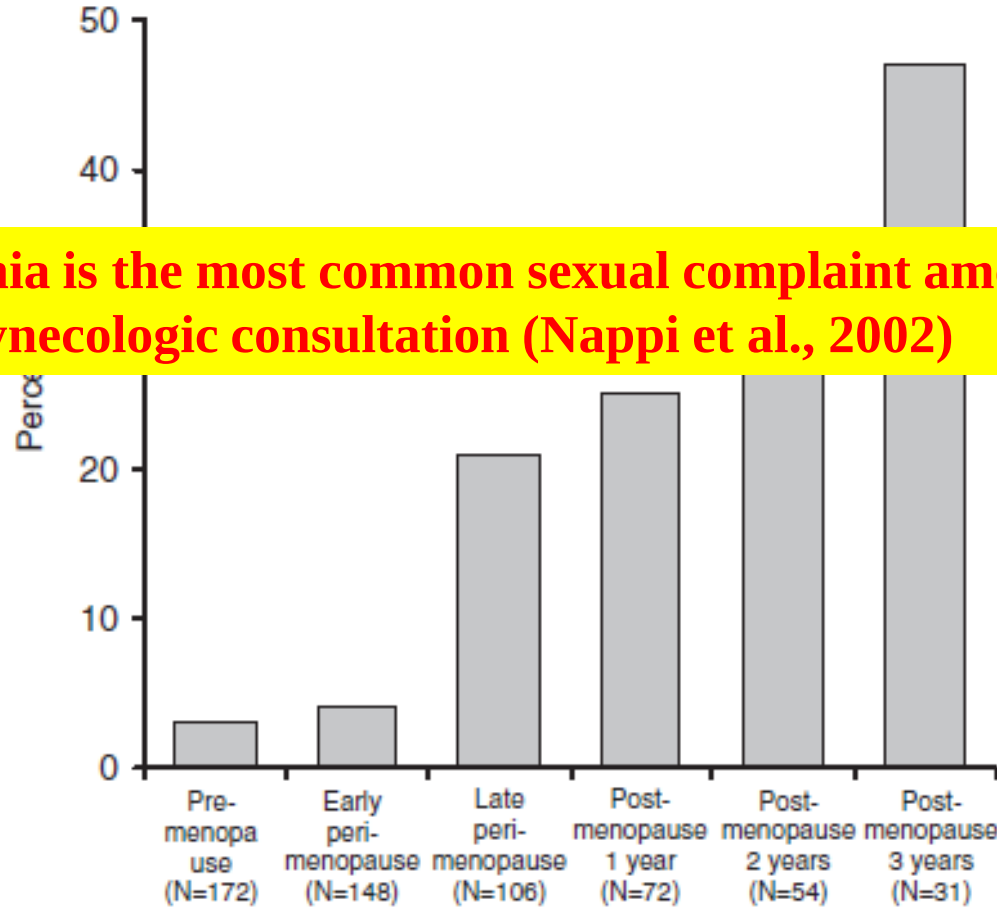
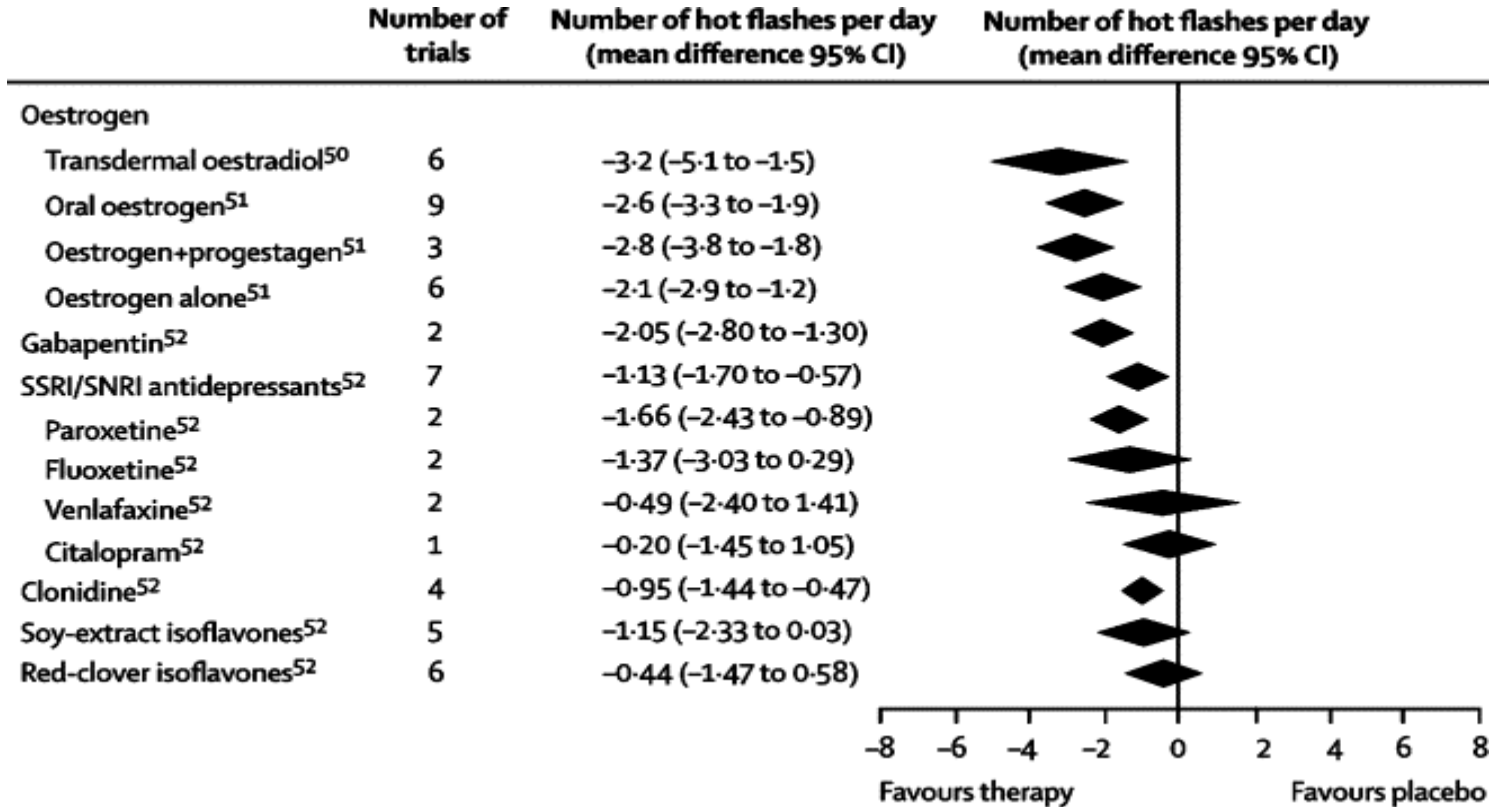


Dispareunia is the most common sexual complaint among older women seeking gynecologic consultation (Nappi et al., 2002)

Menopause

Lancet 2008; 371: 760–70 www.thelancet.com Vol 371 March 1, 2008

Heidi D Nelson



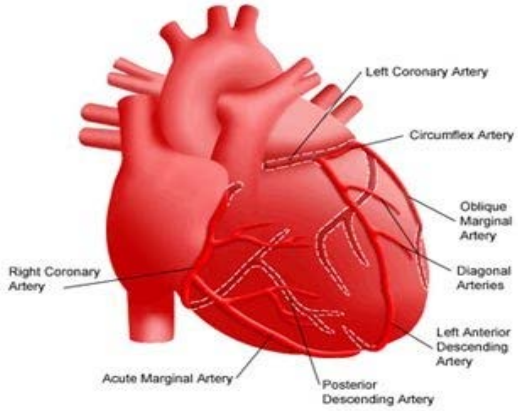
ORIGINAL CONTRIBUTION

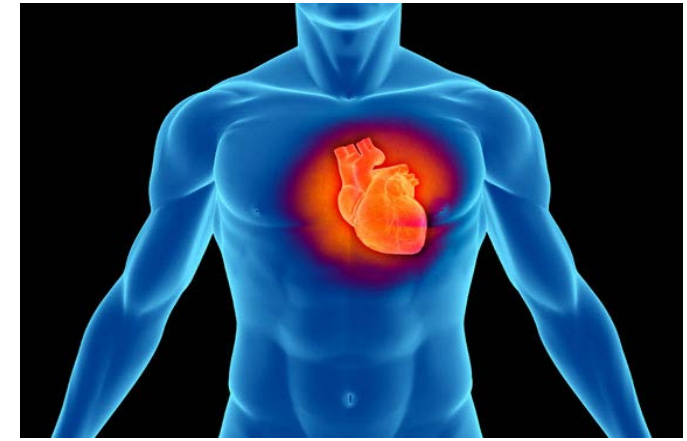
Erectile Dysfunction and Subsequent Cardiovascular Disease

Ian M. Thompson, MD
Catherine M. Tangen, DrPH
Phyllis J. Goodman, MS

Context The risk factors for cardiovascular disease and erectile dysfunction are similar.

Objective To examine the association of erectile dysfunction and subsequent cardiovascular disease.





#ED is a harbinger of CVD
#Sexual activity stimulates T

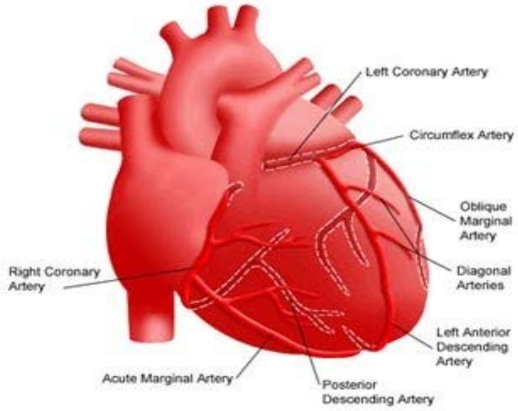
ORIGINAL CONTRIBUTION

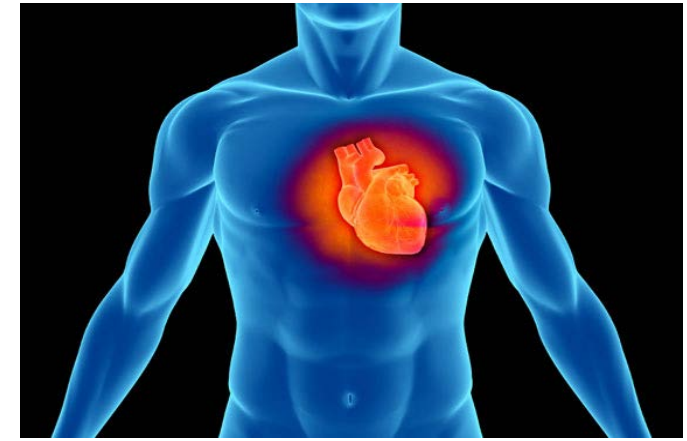
Erectile Dysfunction and Subsequent Cardiovascular Disease

Ian M. Thompson, MD
Catherine M. Tangen, DrPH
Phyllis J. Goodman, MS

Context The risk factors for cardiovascular disease and erectile dysfunction are similar.

Objective To examine the association of erectile dysfunction and subsequent cardiovascular disease.





#ED is a harbinger of CVD
#Sexual activity stimulates T

Female sexual dysfunction?

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Sexual Satisfaction and Cardiovascular Disease: The Women's Health Initiative

Jennifer S. McCall-Hosenfeld, MD, MSc,[a,b] Karen M. Freund, MD, MPH,[b] Claudine Legault, PhD,[c] Sarah A. Jaramillo, MS,[c] Barbara B. Cochrane, PhD, RN,[d] JoAnn E. Manson, MD, DrPH,[e] Nanette K. Wenger, MD,[f] Charles B. Eaton, MD, MS,[g] S. Gene McNeeley, MD,[h] Beatriz L. Rodriguez, MD, PhD,[i] Denise Bonds, MD, MPH[j]

[a]VA Boston Healthcare System, Mass; [b]Boston University, Mass; [c]Wake Forest University School of Medicine, Winston-Salem, NC; [d]University of Washington, Seattle; [e]Brigham and Women's Hospital, Boston, Mass; [f]Emory University, Atlanta, Ga; [g]Memorial Hospital of Rhode Island, Pawtucket; [h]Wayne State University, Detroit, Mich; [i]University of Hawaii, Manoa; [j]University of Virginia, Charlottesville.

Postmenopausal women aged 50 to 79 years, recruited at 40 clinical centers throughout the United States during 1994 through 1998

There were 93,676 women who participated in the observational cohort and were followed for 8-12 years

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Table 3 Odds of Prevalent Cardiovascular Disease by Sexual Satisfaction Status at Baseline (Women's Health Initiative Observational Study)

Baseline Cardiovascular Disease	OR (95% CI)	aOR (95% CI)
Myocardial infarction*	1.11 (0.94-1.31)	1.09 (0.88-1.36)
Stroke†	1.20 (0.98-1.47)	1.23 (0.99-1.52)
Coronary revascularization‡	0.89 (0.73-1.08)	0.92 (0.72-1.17)
Composite cardiovascular disease§	1.04 (0.92-1.17)	0.94 (0.78-1.11)
Peripheral arterial disease‖	1.52 (1.30-1.79)	1.44 (1.15-1.82)
Angina¶	0.98 (0.88-1.09)	0.77 (0.66-0.90)
Congestive heart failure**	0.95 (0.71-1.28)	0.93 (0.63-1.36)

No increased prevalence or incidence of cardiovascular disease among sexually active female subjects complaining of dissatisfaction with sexual activity at baseline, over 7.8 years of follow-up

CONCLUSIONS: Dissatisfaction with sexual activity was modestly associated with an increased prevalence of peripheral arterial disease, even after controlling for smoking status. However, dissatisfaction did not predict incident cardiovascular disease. Although this may represent insensitivity of the sexual satisfaction construct to measure sexual dysfunction in women, it might be due to physiological differences in sexual functioning between men and women.

CME

Cardiometabolic Risk and Female Sexual Health: The Princeton III Summary

Martin Miner, MD,* Katherine Esposito, MD, PhD,† Andre Guay, MD,‡ Piero Montorsi, MD,§ and Irwin Goldstein, MD¶

*Men's Health Center, Department of Family Medicine and Urology, Warren Alpert School of Medicine, Brown University, Providence, RI, USA; †Division of Diabetology and Metabolic Diseases, Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy; ‡Center for Sexual Function, Lahey Clinic, Peabody, MA, USA; §Department of Cardiovascular Sciences, University of Milan, Centro Cardiologico Monzino, IRCCS, Milan, Italy; ¶Sexual Medicine, Alvarado Hospital, San Diego, CA, USA

Conclusion. Female sexual health is complex: there is relative independence between subjective and objective aspects of arousal and desire, with numerous contributing factors (hormonal, psychological, interpersonal, and social). Based on limited current data, there appears to be an association between female sexual health and vascular risk factors (hypertension, hyperlipidemia, metabolic syndrome/obesity, diabetes, and coronary heart disease). More research is needed. **Miner M, Esposito K, Guay A, Montorsi P, and Goldstein I. Cardiometabolic risk and female sexual health: The Princeton III summary. J Sex Med 2012;9:641–651.**

International Journal of Impotence Research (2010) 22, 179–184

0955-9930/10
www.nature.com/ijir

Diabete mellito Tipo 2

ORIGINAL ARTICLE

Determinants of female sexual dysfunction in type 2 diabetes

K Esposito[1,2], MI Maiorino[1], G Bellastella[1], F Giugliano[1], M Romano[1] and D Giugliano[1,2]

[1]*Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy and* [2]*Artemis Group for Female Health of the Italian Society of Endocrinology, Naples, Italy*

A total of 595 t2 DM female patients

Table 3 Contribution of HbA1c and other risk factors to risk of FSD in the diabetic population (based on multivariate logistic regression)

	OR for FSD	*95% CI*	P-*value*
Age (years)	1.10	1.01–1.21	0.01
Duration of diabetes (years)	1.03	0.83–1.20	0.24
HbA1c (per 1%)	1.03	0.92–1.17	0.12
BMI (per kg m^{-2})	1.02	1.00–1.07	0.04
WHR	1.02	1.01–1.08	0.05
Obesity (yes vs no)	0.99	0.86–1.21	0.34
Metabolic syndrome (present vs absent)	1.18	1.01–1.36	0.03
Hypertension (yes vs no)	1.14	0.88–1.53	0.34
Atherogenic dyslipidemia[a] (yes vs no)	1.13	1.01–1.29	0.04
Cigarette smoking status			
Never	1.00		
Past	1.05	0.66–1.98	0.56
Current	0.98	0.81–1.59	0.35
Physical activity (per MET)	0.91	0.77–0.98	0.04
Depression (yes vs no)	1.86	1.16–2.65	0.01
Married (yes vs no)	1.59	1.09–2.18	0.03

Abbreviations: BMI, body mass index; CI, confidence interval; FSD, female sexual dysfunction; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; MET, metabolic equivalent task; OR, odds ratio; WHR, waist-to-hip ratio.
[a]HDL-cholesterol <50 mg per 100 ml and triglycerides >200 mg per 100 ml.

Depression status and marital status are the most strongly correlated with FSD.

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Sexual Dysfunction in Women With Type 1 Diabetes

Long-term findings from the DCCT/ EDIC study cohort

PAUL ENZLIN, PHD[1,2]
RAYMOND ROSEN, PHD[3,4]
MARKUS WIEGEL, PHD[3,4]
JEANETTE BROWN, MD[5]
HUNTER WESSELLS, MD[6]
PATRICIA GATCOMB, RN, CDE[7]
BRANDY RUTLEDGE, PHD[8]
KA-LING CHAN, MS[8]
PATRICIA A. CLEARY, MS[8]
THE DCCT/EDIC RESEARCH GROUP*

oxide–related mechanisms in the corpora cavernosa, have been strongly linked with the development of sexual dysfunction in men (1,4,5).

Women with diabetes have similar rates of cardiovascular and neurological

Diabete mellito Tipo 1

A large well-characterized cohort sample of women with type 1 diabetes using a validated measure of sexual function (FSFI): cross-sectional analysis of data obtained at 10-year follow-up

652 donne (età media 43 aa):

Diabetiche tipo 1

57% Riduzione desiderio
51% Riduzione orgasmo
47% Riduzione lubrificazione
38% Riduzione eccitamento
21% Dolore coitale

Analisi multivariata → FSD correla con depressione e rapp. maritali

Enzlin P et al., Diabetes Care, 2009 32(5): 780

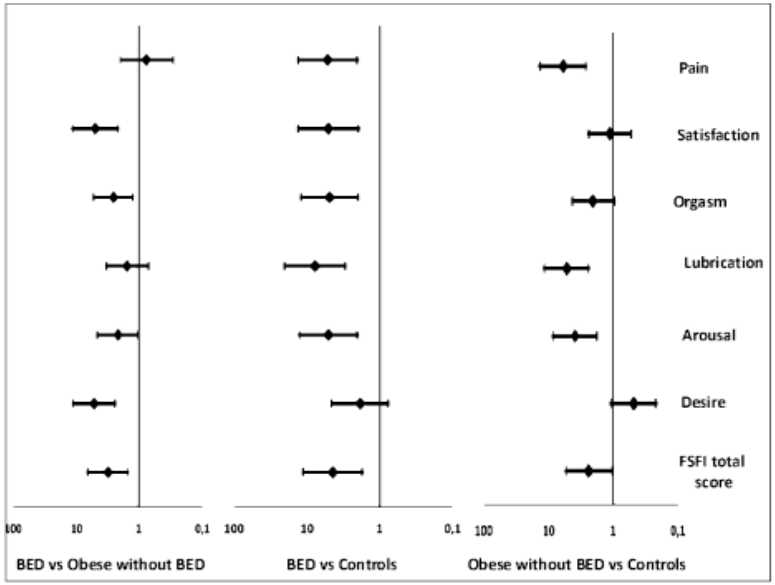
Psychosocial aspects

Sexual Function in Obese Women with and without Binge Eating Disorder

Giovanni Castellini, MD,* Edoardo Mannucci, MD,† Chiara Mazzei, DClinPsych,* Carolina Lo Sauro, MD,* Carlo Faravelli, MD,‡ Carlo M. Rotella, MD,§ Mario Maggi, MD,¶ and Valdo Ricca, MD*

*Psychiatric Unit, Department of Neuropsychiatric Sciences, Florence University School of Medicine, Firenze, Italy; †Section of Geriatric Cardiology, Department of Cardiovascular Medicine, Florence University School of Medicine, Firenze, Italy; ‡Department of Psychology, University of Florence, S. Salvi, Padiglione 16, Firenze, Italy; §Unit of Endocrinology, Department of Clinical Physiopathology, Florence University School of Medicine, Firenze, Italy; ¶Department of Clinical Physiopathology, Andrology Unit, Florence University School of Medicine, Firenze, Italy

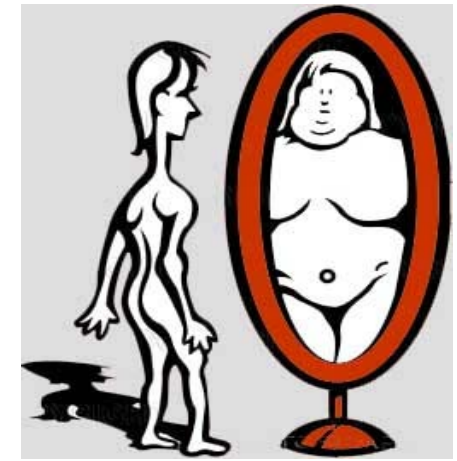
Obese women reported a lower sexual activity compared to controls



✓ *No association with BMI*

✓ *Psychopathological determinants were impulsivity,;Shape concerns, emotional eating*

Obesità



Physiological differences ***between men and women may explain the difference in the role of cardiovascular disease in sexual function.***

Low lubrication
Vaginal dryness

Low libido➔ low lubrication.

Estrogen deficiency.

Testosterone effects on female genitalia

Corpo cavernoso FEMMINILE

Term. colinergica

Nervi cavernosi

Term. adrenergica

Ach

Cellula endoteliale

PI3-chinasi

Akt

Ca^{2+}

IP3

Ca^{2+}

L-arginina

P

eNOS

O_2

NO

NO

NO

NO

NO

PGE1

Prot. G

Adenilato ciclasi

ATP

cAMP

PDE2,3,4

5'AMP

PKA

Reticolo sarcoplasmatico

K^+

$\downarrow Ca^{2+}$

Rottura cross-bridges fra actina/miosina

Ca^{2+}

Rilasciamento

PKG

NANC

L-arginina

O_2

nNOS

SGC

GTP

cGMP

PDE5

5'GMP

K^+

Ca^{2+}

Cellula muscolare liscia

stimolazione

inibizione

.....However, PDE5 inhibitors are not useful in treating Female sexual arousal disorders

In 16 studies PDE5i inconsistently improved female sexual function

Table 1 Studies examining phosphodiesterase type 5 inhibitor's efficacy in female samples

Author	Subjects	Design	Dosage	Measures	Results
Kaplan et al. (1999) [24]	Pre- and postmenopausal women with mixed sexual dysfunctions (n = 33)	Open-label, at-home, prospective study	Sildenafil 50 mg	Global efficacy, IFSF	No significant differences. Positive trend in women on hormone replacement. 7/33 clinically significant change in their sexual functioning; 7/33 clitoral hypersensitivity and discomfort using sildenafil.
Sipski et al. (2000) [14]	Premenopausal women with SCI (n = 19)	Placebo-controlled, crossover design laboratory study	Sildenafil 50 mg Placebo	Vaginal photoplethysmography, subjective arousal	Significant effects on subjective arousal. Positive trend on genital arousal.
Berman et al. (2001) [15]	Pre- and postmenopausal women with FSAD (n = 48)	Open-label study of at-home and laboratory use	Sildenafil 100 mg	Doppler ultrasonography measures of genital blood flow, vaginal pH, vaginal pressure–volume changes, and genital vibratory perception thresholds; BISF-W	Significant improvement on physio-measures of arousal; increases in sexual desire, arousal, lubrication, sensation, orgasm, satisfaction, and reduced pain during at-home phase
Caruso et al. (2001) [16]	Premenopausal women with FSAD—physiological arousal problems (n = 51)	Placebo-controlled, double-blind, crossover, at-home study	Sildenafil (25 mg, 50 mg) Placebo	PEQ assessing sexual arousal, orgasm, enjoyment, satisfaction by frequency, frequency of intercourse, and frequency of sexual fantasy, global efficacy	Significant improvements in arousal, orgasmic capacity, frequency of sexual intercourse with both doses of drug vs. placebo
Laan et al. (2002) [30]	Premenopausal women without sexual dysfunction (n = 12)	Placebo-controlled, crossover design	Sildenafil 50 mg Placebo	Vaginal photoplethysmography, subjective sexual arousal	Significant increases in vaginal vasocongestion, no differences in subjective arousal. Expectancy effect on subjective arousal
Basson et al. (2002) (Study 1) [20]	Postmenopausal women not on ERT (n = 221)	Placebo-controlled, flexible dose study	Sildenafil 25–100 mg Placebo	Validated questionnaire, event logs, global efficacy	No significant differences on any measures
Basson et al. (2002) [20] (Study 2)	Pre- and postmenopausal women with normal estrogen (n = 583)	Placebo-controlled, fixed-dose study	Sildenafil 10–100 mg, placebo	Validated questionnaire, event logs, global efficacy	No significant differences on any measures
Caruso et al. (2003) [25]	Premenopausal women without sexual dysfunction (n = 50)	Double-blind, randomized, crossover design	Sildenafil 50 mg, Placebo	PEQ items assessing sexual arousal, orgasm, enjoyment, satisfaction with frequency, frequency of intercourse, and frequency of sexual fantasy	Significant drug effects for sexual arousal, orgasm, and enjoyment
Berman et al. (2003) [26]	Premenopausal women and surgically and naturally postmenopausal women (some using HRT) with Dx of FSAD N = 92 (placebo) and 88 (sildenafil)	Double-blind, placebo controlled trial without crossover	Sildenafil 25–100 mg	FIEI, SFQ, sexual activity event log	Significant effects on genital sensation, quality of sexual activity, self-reported sexual arousal, lubrication, sexual arousal and sensation, and orgasm only for women without a secondary diagnosis of HSDD

Chivers & Rosen, J. Sex. . Med. 2010; 7:858.

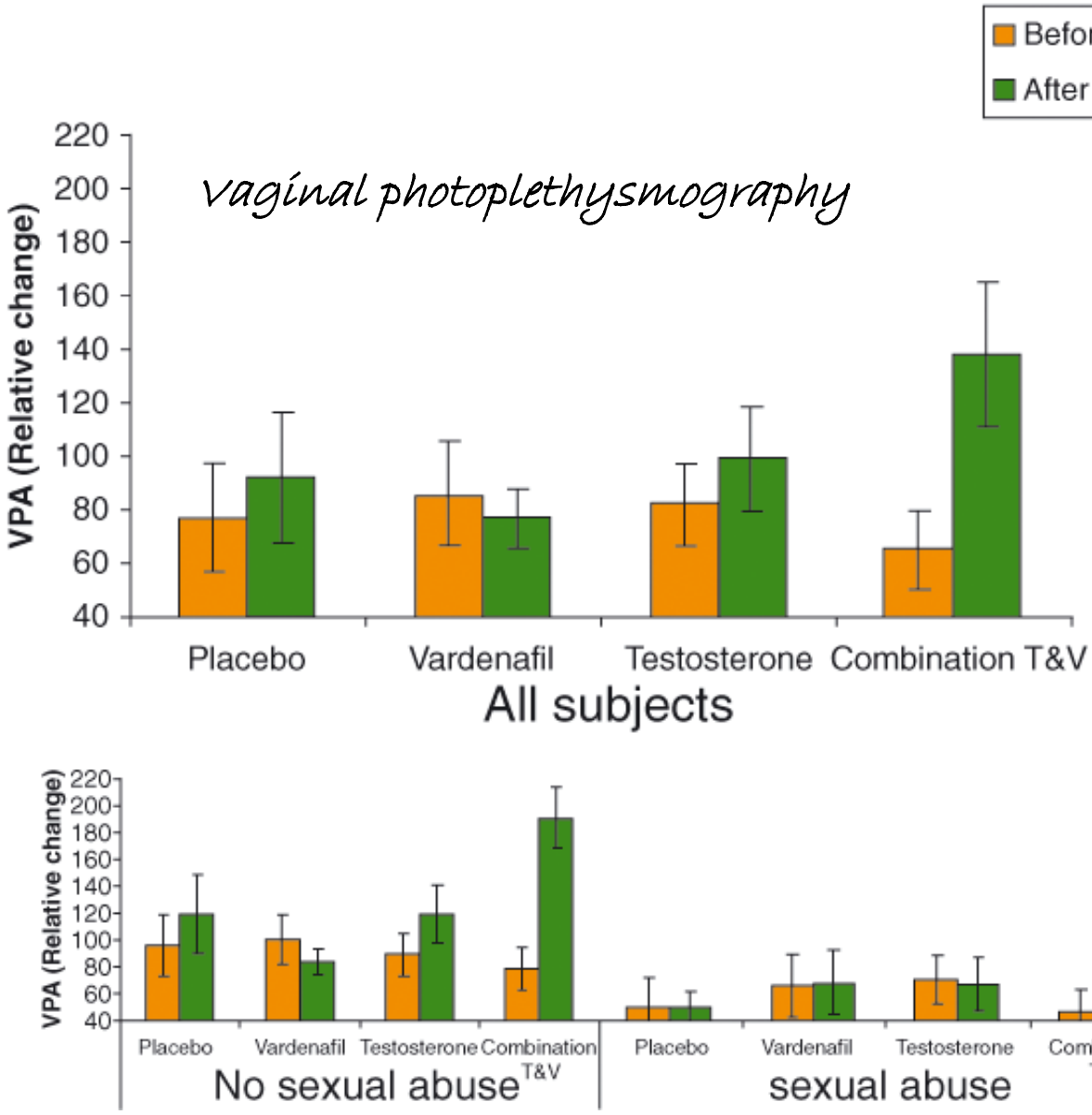
In 16 studies PDE5i inconsistently improved female sexual function

Table 1 Continued

Author	Subjects	Design	Dosage	Measures	Results
Basson and Brotto (2003) [27]	Women using ERT with Dx of acquired FSAD and impaired orgasm (n = 34). Women classified by vaginal responsiveness to visual sexual stimuli using vaginal photoplethysmography; low responders (n = 10), high responders (n = 13)	Placebo-controlled crossover design	Sildenafil 50 mg, placebo	Visual sexual stimuli, and during vibrotactile stimulation; subjective measures of perception of genital sensation and self-reported sexual arousal	Reduced latency to orgasm, increased self-reported sexual arousal and perception of genital sensation for women with low VPA responses; no effect on subjective measures of arousal. Sildenafil increased latency to orgasm for high VPA responders
dasGupta et al. (2004) [17]	Nineteen women with sexual dysfunction secondary to multiple sclerosis	Double-blind, randomized, placebo controlled, crossover design. Open label extension phase	Sildenafil 50 mg, Placebo	SFQ	Significant improvement in lubrication and genital sensation during double-blind phase; significantly improved (compared with baseline, not placebo) orgasm in open-label phase
Caruso et al. (2008) [28]	Thirty-two premenopausal Women with FSAD and type I diabetes	Placebo-controlled crossover design	Sildenafil 100 mg, placebo	Doppler ultrasonography of clitoral artery blood flow during unaroused state; PEQ	Increased clitoral blood flow; increased arousal and orgasm, reduced dyspareunia
Yang et al. (2008) [29]	Twelve women with FSAD, eight pre- and four postmenopausal	Double-blind, randomized, two-way crossover design	Sildenafil 50 mg, placebo	MRI of clitoral volume; subjective sexual arousal	Increased clitoral volume with visual sexual stimulation for half of sample; no effect on subjective arousal
Nurnberg et al. (2008) [19]	Ninety-eight women with serotonin reuptake inhibitor induced sexual dysfunction	Prospective, parallel-group, randomized, double-blind, placebo-controlled clinical trial	Flexible does between 50 and 100 mg sildenafil	Clinical Global Impression scale (CGI), Sexual Functioning Questionnaire (SFQ), Arizona Sexual Experience Scale, and the University of New Mexico Sexual Function Inventory	Symptom reduction and improvement in orgasmic functioning with sildenafil
van Der Made et al. (2009a) [31]	Thirteen women with HSDD; 5 with a history of childhood sexual abuse	Double-blind, randomized, placebo-controlled crossover design	Placebo, 10 mg vardenafil, 0.5 mg sublingual testosterone, combo of vardenafil and testosterone	Vaginal photoplethysmography, emotional Stroop task (behavioral measure of sexual attention)	Significant increase in genital response for women without history of childhood sexual abuse in testosterone and vardenafil condition
Van Der Made et al. (2009b) [32]	Twenty-eight women with HSDD and/or FSAD	Double-blind, randomized, placebo-controlled crossover design	Placebo, 10 mg Vardenafil, 0.5 mg sublingual testosterone, combo of vardenafil and testosterone	Vaginal photoplethysmography, emotional Stroop task (behavioral measure of sexual attention), contiguous assessment of vaginal sensations using a lever, post-trial self-report of subjective sexual arousal	Significant increase in genital response, post-trial self-reported genital sensations, and sexual desire for women with low attention to sexual cues (as determined by emotional Stroop pretesting)

BISF-W = Brief Index of Sexual Functioning for Women; ERT = estrogen replacement therapy; FIEI = female intervention efficacy index; FSAD = female sexual arousal disorder; HSDD = hypoactive sexual desire disorder; IFSF = Index of Female Sexual Function; MRI = magnetic resonance imaging; PEQ = Personal Experiences Questionnaire; VPA = vaginal pulse amplitude.

Chivers & Rosen, J. Sex. Med. 2010; 7:858.



Vaginal photoplethysmography

13 women with HSDD, with (n=5) or w/o (n=8) CSA tested:

1) Placebo
2) Vardenafil
3) Testosterone
4) Testosterone + vardenafil

Figure 2 Mean vaginal pulse amplitude (VPA) pre vs. postdrug in four drug conditions in all women (upper), in women without childhood sexual abuse (left, below), and with childhood sexual abuse (right, below). T&V = testosterone and vardenafil.

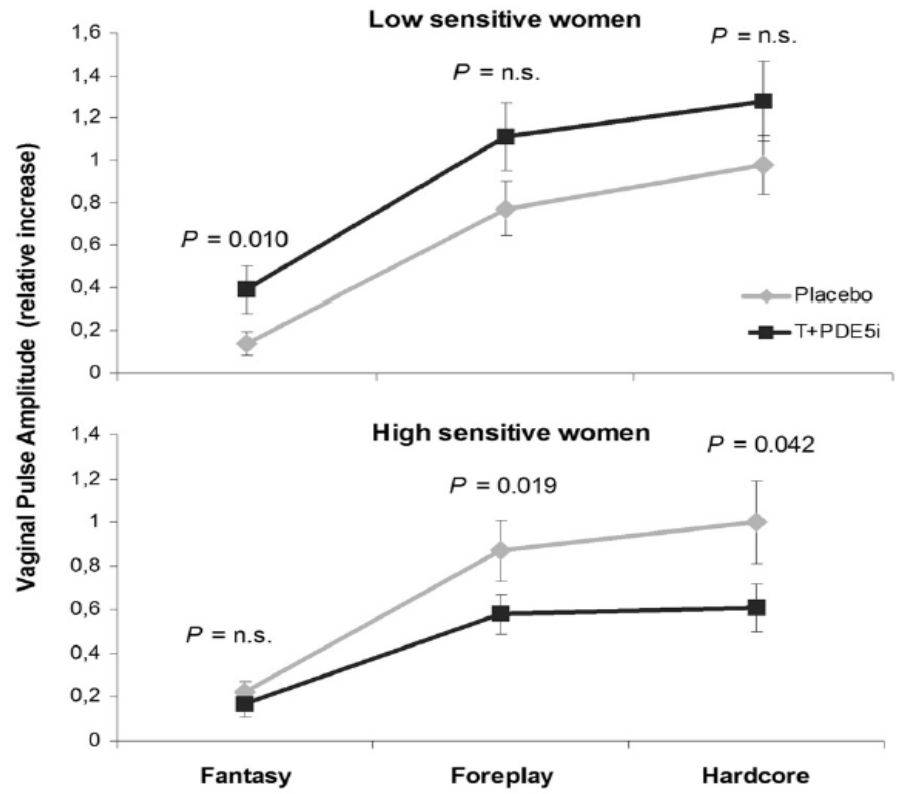
Van der Made et al., J. Sex. Med. 2009; 6:429.

Toward Personalized Sexual Medicine (Part 2): Testosterone Combined with a PDE5 Inhibitor Increases Sexual Satisfaction in Women with HSDD and FSAD, and a Low Sensitive System for Sexual Cues

Saskia Poels, MD,*† Jos Bloemers, MSc,*† Kim van Rooij, MD,*† Irwin Goldstein, MD, PhD,‡ Jeroen Gerritsen, MSc,*†¶ Diana van Ham, MSc,*† Frederiek van Mameren, MD,§ Meredith Chivers, PhD,** Walter Everaerd, PhD,†† Hans Koppeschaar, MD, PhD,* Berend Olivier, PhD,††‡ and Adriaan Tuiten, PhD*†

56 women with HSDD:

PLACEBO vs T+PDE5I



J Sex Med December 2012

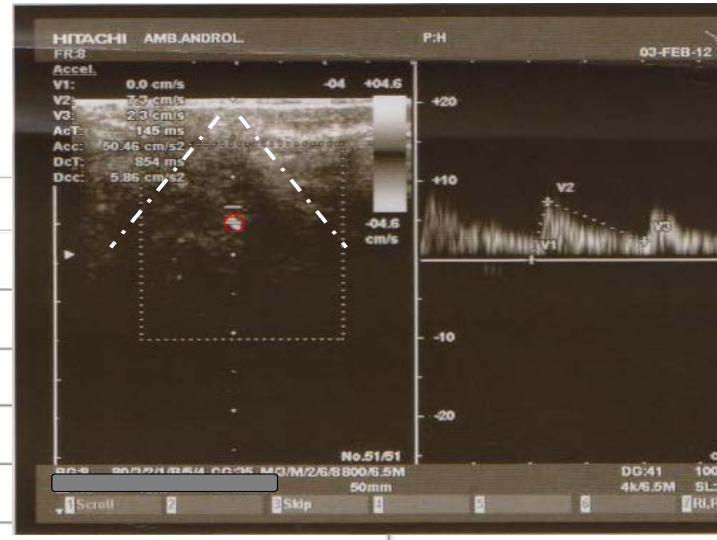
Testosterone is important for maintaining
The physiological contractile/relaxant pathways
In the (clitoris)
Smooth muscle cell

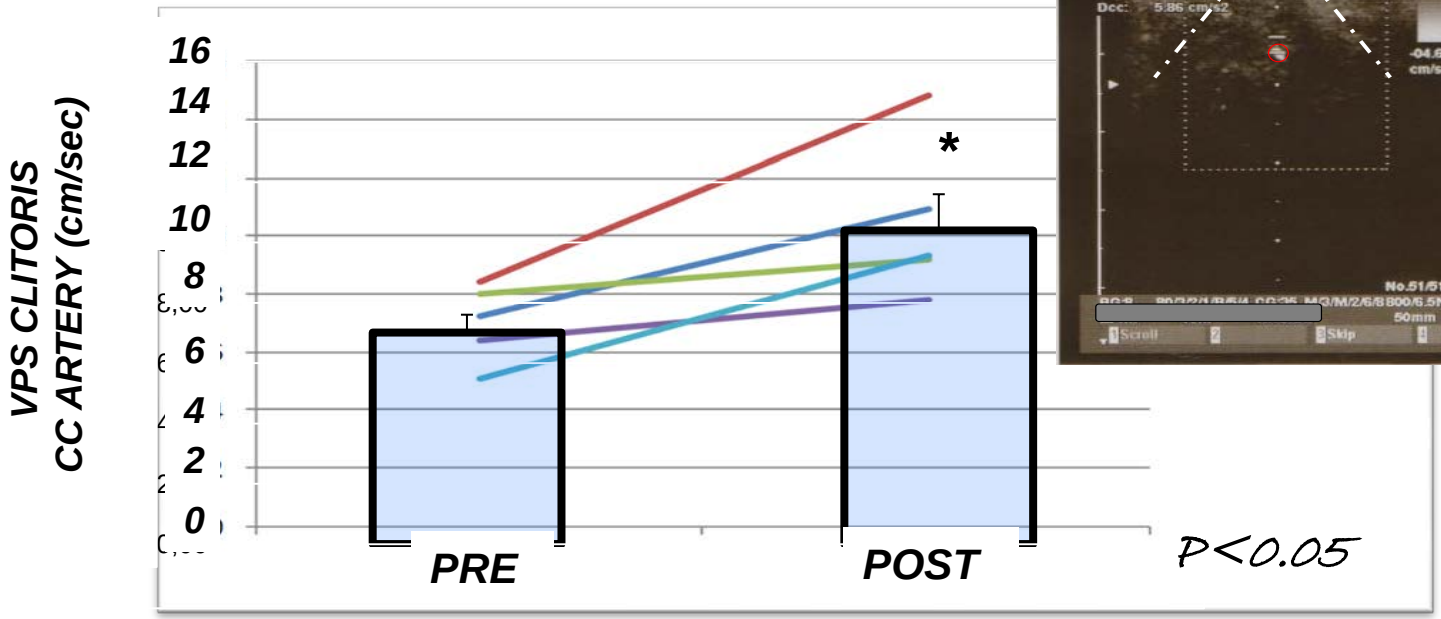
And

.....

PDE5 inhibitors efficacy

Testosterone gel (300 microgr/die) for three months





Test per campioni appaiati

		Differenze a coppie					t	df	Sig. (2-code)
		Media	Deviazione std.	Errore std. Media	Intervallo di confidenza per la differenza al 95% Inferiore	Superiore			
Coppia 1	clitoride_vps - clitoride_vpspost	-3,380000	2,154530	,963535	-6,055202	-,704798	-3,508	4	,025

3) DISTURBI DELL'ORGASMO

"Orgasm is a sensation of intense pleasure creating an altered consciousness state accompanied by pelvic striated circumvaginal musculature and uterine/anal contractions and myotonia that resolves sexually-induced vasocongestion and induces well-being/contentment."

- Persistente o ricorrente difficolta' a raggiungere l'orgasmo, nonostante un adeguato stimolo ed eccitamento, che causa "personal distress"

  - ***PRIMARIO*** *(mai raggiunto orgasmo)*
    Storia di abusi, educazione, princ. religiosi etc

  - ***SECONDARIO***
    (secondario a trauma, tx medica, deficit ormonale)

Circa 24% della popolazione femminile sessualmente attiva (18-59 aa) negli USA Meston et al., Disorders of orgasm in women J Sex Med. 2004 Jul;1(1):66-8

4) DISTURBO CARATTERIZZATO DA DOLORE SESSUALE

- **DISPAREUNIA**

persistente o ricorrente dolore genitale associato al rapporto sessuale che causa personal distress

- **VAGINISMO**

persistente o ricorrente spasmo involontario della muscolatura vaginale che impedisce la penetrazione vaginale e che causa personal distress

(il dolore può insorgere secondariamente)

DISPAREUNIA

Meta-analisi dei fattori di rischio associati a dispareunia

Factor	No of trials	No of exposed/No of women: Cases	Controls	Statistics: (O-E)	Var.	OR (99% CI)
Demographic/medical factors						
Age <50 years***	4	650/1841	2510/3683	43.1	118.1	1.44 (1.14 to 1.83)
Peri/postmenopausal status	3	394/950	962/2462	59.2	141.5	1.52 (1.22 to 1.89)
Ethnicity (black *v* not)	1	84/270	66/310	14.2	27.7	1.67 (1.02 to 2.72)
Ulcerative colitis	1	15/22	25/56	3.7	4.0	2.53 (0.70 to 9.19)
Obstetric/gynaecological factors						
Grandmultiparity	1	29/53	42/83	1.3	8.1	1.18 (0.48 to 2.91)
Previous pelvic inflammatory disease	2	42/85	243/1473	26.8	11.6	9.98 (4.69 to 21.24)
Prolapse	1	13/18	32/44	-0.1	2.6	0.98 (0.20 to 4.84)
Circumcision	2	122/161	903/1917	11.7	22.6	1.68 (0.98 to 2.88)
Abuse/psychological factors						
Physical abuse	1	8/30	14/60	0.7	3.7	1.20 (0.32 to 4.53)
Sexual abuse***	7	512/1515	1240/5108	147.5	150.5	2.67 (2.16 to 3.29)
Unsatisfactory relationship with spouse/partner	1	28/107	98/486	5.3	14.7	1.43 (0.73 to 2.80)
Anxiety	1	50/113	116/532	20.9	17.8	3.23 (1.76 to 5.94)
Depression	1	18/116	21/534	11.0	5.4	7.77 (2.56 to 23.60)

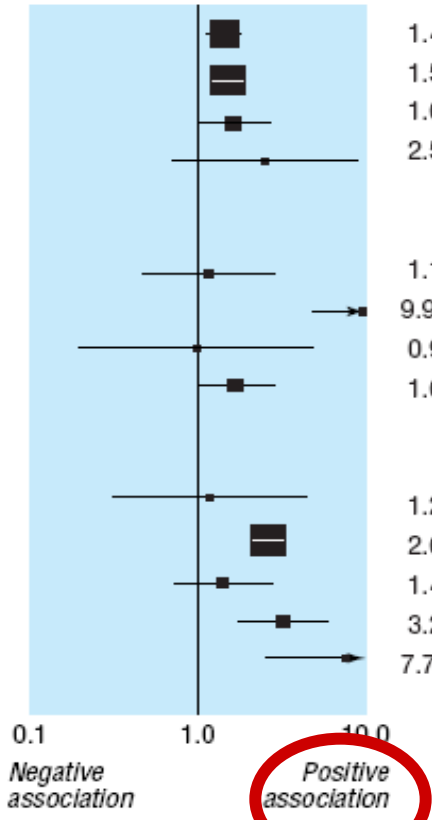


Fig 4 Meta-analysis of risk factors associated with dyspareunia (all multiple studies are heterogeneous; *** P<0.001, **P<0.01)

Latthe P et al., BMJ 2006, 332:749

Standard Operating Procedures for Female Genital Sexual Pain

Kerstin S. Fugl-Meyer, PhD,* Nina Bohm-Starke, MD, PhD,† Christina Damsted Petersen, MD, PhD,‡ Axel Fugl-Meyer, MD, PhD,§ Sharon Parish, MD,¶ and Annamaria Giraldi, MD, PhD**

*Department of Neurobiology, Care Sciences & Society, Karolinska Institutet and Department of Social Work, Karolinska University Hospital, Stockholm, Sweden; †Department of Clinical Sciences, Division of Obstetrics and Gynecology, Karolinska Institutet and Danderyd Hospital, Stockholm, Sweden; ‡Department of Gynecology and Obstetrics, Rigshospitalet University Hospital, Copenhagen, Denmark; §Department of Neuroscience, Uppsala University, Uppsala, Sweden; ¶Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA; **Department of Sexological Research, Sexological Clinic, Psychiatric Center Copenhagen, Rigshospitalet University Hospital, Copenhagen, Denmark

DOI: 10.1111/j.1743-6109.2012.02867.x

Generalized vulvodynia (GV)

The generalized form of unprovoked vulvodynia is

- Not common (mostly in post-menouse)
- usually, the pain is continuous, diffuse, and described as burning.
- the vulvar structures are of normal appearance
- sexual activity can often be performed without pain.

GV shares many features with neuropathic pain conditions and may be triggered by previous trauma or disorders of the lower back or pelvic muscles and ligaments

Gabapentin: 300mg x3 die (up to 900 mgx3die)

J Sex Med 2013;10:83–93

Standard Operating Procedures for Female Genital Sexual Pain

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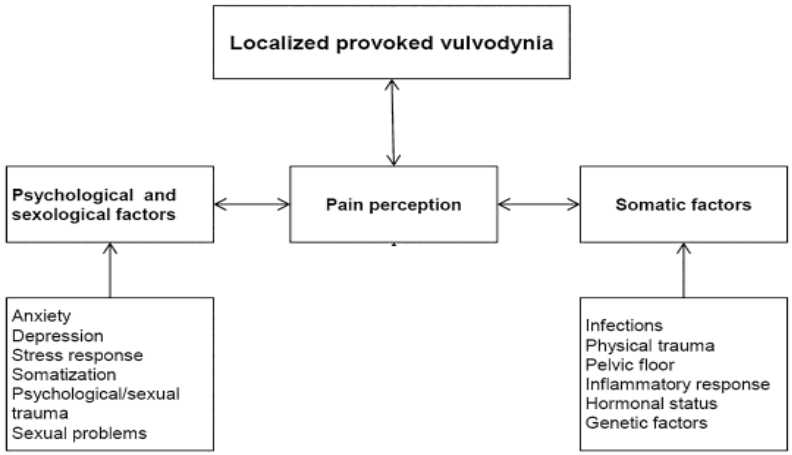

Localized provoked vulvodynia (LPV)

- is one of the most common causes of superficial GSP in premenopausal women.
- Pain is provoked by light touch of the mucosa around the vaginal opening
- vaginal penetration is always painful.

The etiology of LPV is considered multifactorial.

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- Locally applied botulinum toxin injection neither reduces pain nor improves sexual function (Petersen J Sex Medicine 2009;6:2523; LE: 1b).

Botulinum toxin, a temporary muscle paralytic, has been recommended in the treatment of vaginismus with the aim of decreasing the hypertonicity of the pelvic floor muscles. The use of botulism toxin (150 to 400 units of botulism toxin type A injected in the levator ani at three points) is an experimental intervention and no randomised controlled trials (RCTs) exist.

- Worldwide currently, tricyclic antidepressants are often used. Amitriptyline 50–75 mg at night can be tried, and women with generalized vulvodynia usually respond well. In women with LPV, the effect varies.

The use of antidepressants (tricyclics) or anti convulsants (usually carbamazepine or gabapentin) has been tried, however resolution with these drugs appears infrequent. The starting dose of amitriptyline and other tricyclic antidepressants is low (10 mg) but can be gradually increased to 40 to 60 mg daily, as tolerated (Crowley 2006)

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There are, unfortunately, very few controlled studies; and a Cochrane review [McGuire H et al., Cochrane Database Syst rev 2003, 1:CD001760] has shown that there is very limited evidence on the effect of medical treatment for vaginismus.

Nella maggior parte dei casi è PRIMITIVO
(Presente fino dall'inizio della vita sessuale)
Ma può essere anche SECONDARIO
(a Dispareunia, Avversione Sessuale acquisita, Dolore Sessuale non Coitale)

Il trattamento (oltre a terapia medica se eziologia è organica) è comportamentale e centrato sull'utilizzo di una serie di dilatatori graduali con associate tecniche di rilassamento. Vi è poi un graduale coinvolgimento del partner sotto la guida ed il controllo della donna.

Female sexual dysfunction

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La sessualità di coppia