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European Society of Human Reproduction & Embryology

When the engine of desire breaks down...

What should we know about sexual dysfunction, how to pick-up the problem, how to solve

EMMANUELE A. JANNINI
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University of L'Aquila, Italy
L'Aquila University School of Sexology - Coordinator

THE AIMS OF THE LESSON

- When the engine of desire breaks down
  - What the engine of desire is?
  - What should we know about sexual dysfunction: HSDD – **Definition**
  - HSDD - **Aetiologies**
- How to pick-up the problem – **diagnosis of HSDD**
- How to solve - **therapy**

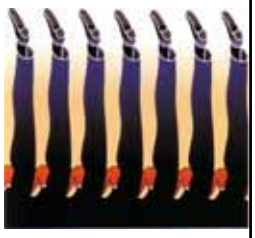
Discussing some practical aspects

What the engine of desire is?

Sex, sex, sex

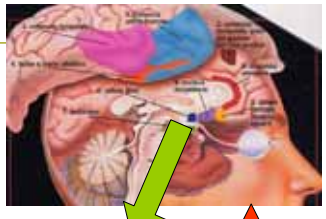
We admit that we are making sex with something which is beetween legs,

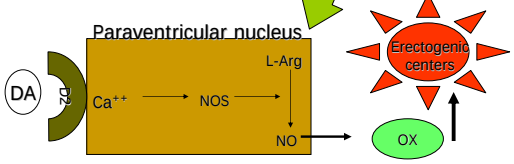
but only seldom we realize that we making sex with something which is between...



...EARS

The engine



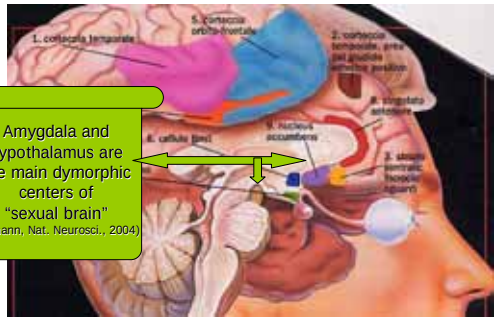


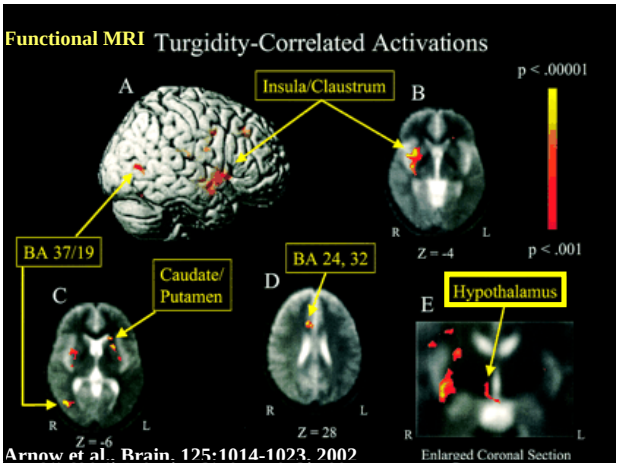
The aminergic balance

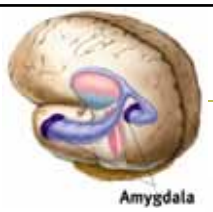
UP: DOPAMINE

DOWN: SEROTONINE

Where the brain "thinks" sex?





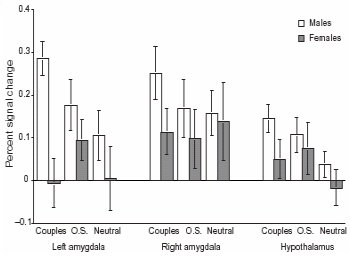


Amygdala: processing of emotional stimuli

Men and women differ in amygdala response to visual sexual stimuli

Stephan Hamann *et al.*

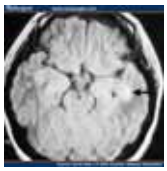
Nature Neuroscience - Published online: 7 March 2004,



Kluver-Bucy syndrome

- **bilateral amygdala damage:**
  - **"inappropriate" or "indiscriminate" sexual behaviour**
  - **Homosexuality in previous etherosexual**
  - **Exhibitionistic behavior**

  (Kluver & Bucy (1939) Arch. Neurol. Psychiatry)



4 Nature Publishing Group http

Imaging gender differences in sexual arousal

Turhan Canli & John D E Gabrieli

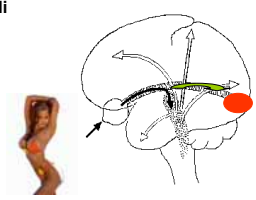
Men tend to be more interested than women in visual sexually arousing stimuli. Now we learn that when they view identical stimuli, even when women report greater arousal, the amygdala and hypothalamus are much more strongly activated in men.

"A man falls in love through his eyes, a woman through her ears," wrote Woodrow

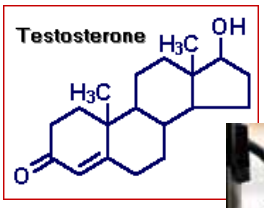
reflect sex differences in the processing of sexually arousing stimuli.

between males and females looked at the contrast in brain activation between the couples

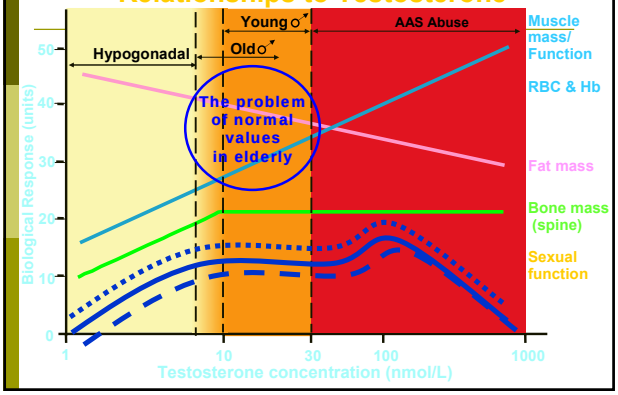
Men tend to be more interested than women in visual sexual arousing stimuli



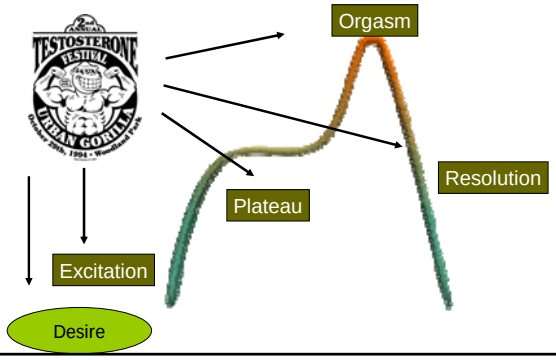
The gasoline of the engine

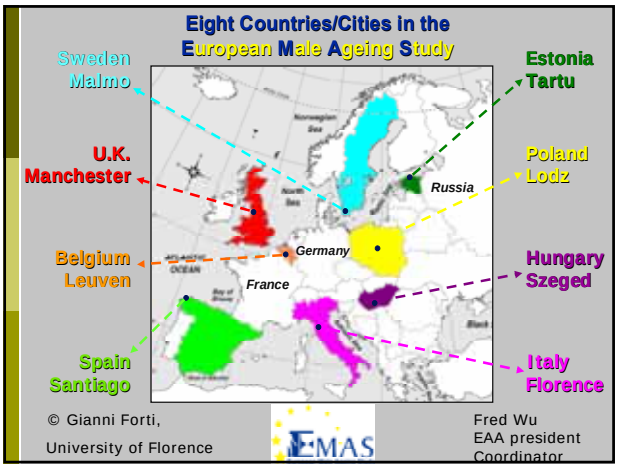


Tissue Specific Dose-Response Relationships to Testosterone



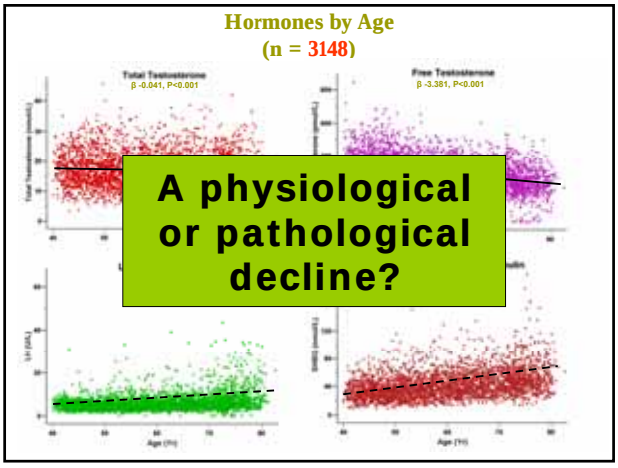
Testosterone acts at almost all levels in the *d.e.p.o.r.* system



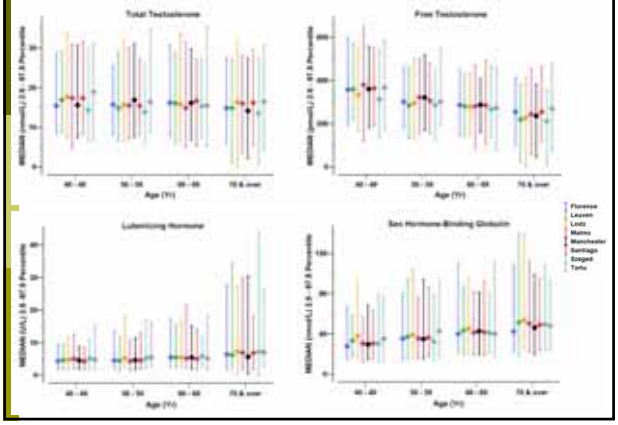


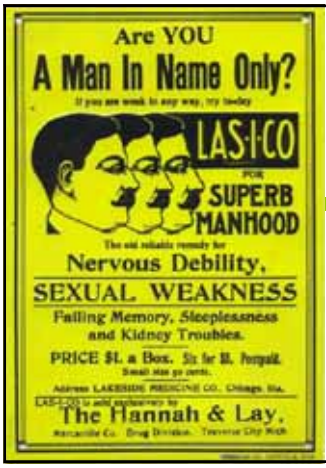
Study Design

- Longitudinal study
  - Baseline survey 2003 - 2005
  - Follow-up survey 2007-2009
- Random population sample of community-dwelling men stratified by age (40-79 yr)
- 8 countries in Europe, 400 subjects/country
- Identical instruments, standardised methods across 8 centres for anthropometric evaluation and heel ultrasound
- Questionnaires translated to local languages
- Blood samples for measurement of 18 hormones and DNA polymorphisms



Distribution of Hormones by Age and Centre





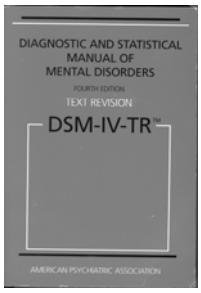
What should we know about sexual dysfunction: HSDD – **Definition**

Desire = de-sidera (lat.)

= from stars, the prevision of fecundity in infertile couples

Definition

Persistently or recurrently deficient (or absent) sexual fantasy and desire for sexual activity leading to marked distress or interpersonal difficulty

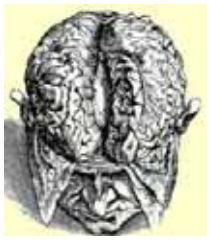


Why HSD-D?

Symptoms & signs

SIGNS & SYMPTOMS OF ANDROGEN DEFICIENCY AVAILABLE FROM MMAS

- Loss of Libido
- Erectile dysfunction
- Depression
- Lethargy
- Inability to concentrate
- Sleep disturbance
- Irritability
- Depressed Mood

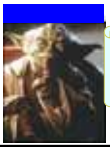


HSDD

Aetiologies

Aetiologies

- **The major causes of HSDD are:**
  1. Marital
  2. Another sexual dysfunction
  3. Depression
  4. Organic
- **Check for**
  - Systemic diseases
  - Endocrine diseases
  - Intrapsychic disorders
  - Marital problems



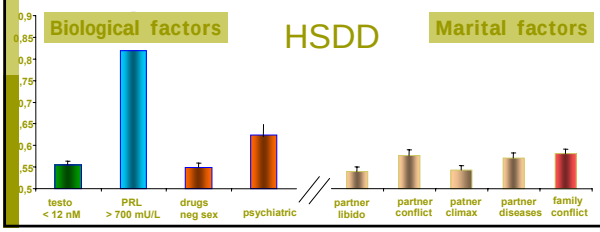
Many patients will tell you about HSDD, even if they have ED or other sexual symptoms

International Journal of Impotence Research (2003) 15, 230–220
© 2003 Nature Publishing Group All rights reserved 0955-9930/03 $25.00
www.nature.com/ijir

Structured interview on erectile dysfunction (SIEDY©): a new, multidimensional instrument for quantification of pathogenetic issues on erectile dysfunction

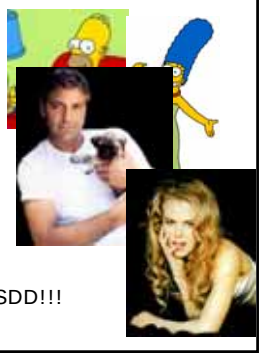
L Petrone[1], E Mannucci[2], G Corona[1], M Bartolini[3], G Forti[1], R Giommi[4] and M Maggi[1]*

[1]Andrology Unit, [2]Endocrinology Unit, [3]Radiology Units; and [4]Department of Clinical Physiopathology, University of Florence and International Institute of Sexology, Florence, Italy



Is the 'marital' HSDD a true HSD?

If the patient with this partner:



...does not desire when he/she can freely shift to this partner:

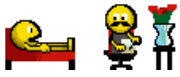
...it is a true HSDD!!!

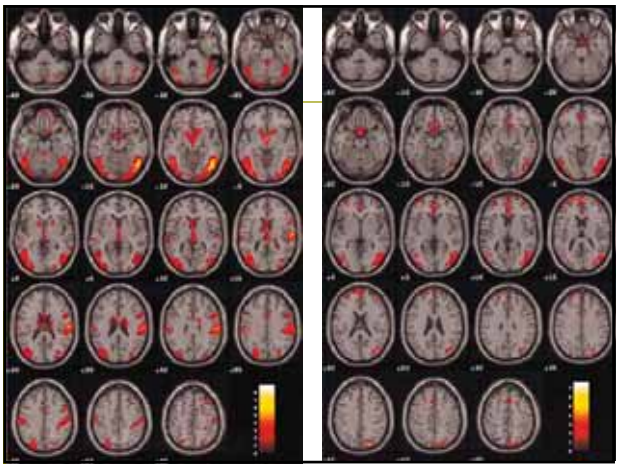
VSS in normal vs depressed

A 42-year-old healthy volunteer on VSS. Prominent activation areas involve the occipital, temporal, cerebellar gyri, and the limbic systems associated with the regulation of sexual behaviors

Note that the level of activation is significantly stronger in a healthy volunteer than in a depressed patient, especially in the visual and cerebellar cortices.

J-C Yang, Kor J Radiol; 2004





HSDD due to infertility

- **HSD**
- **PE / DE**
- **ED**
- **Reduced sexual activity**

Benazon N., *et al.*: J. Sex Marital Ther., 18, 1992.

there is a strong link between a man's perceptions of his own masculinity and **virility** and his ability to **impregnate** women.

The infertility stress is higher when the man is infertile.

The diagnosis of infertility is more stressful when the male is infertile

Slade P., *et al.*, J Reprod Inf Psychol, 10, 1992.
Mikulincer M., *et al.*, Br J Med Psychol, 71, 1998.

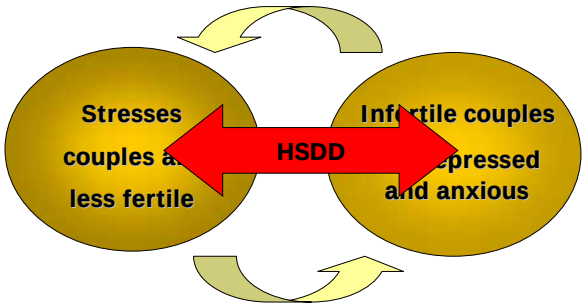
Psychological reaction of male to infertility may be the cause of sexual dusfunction(s)
Irvine S.C.E., Sexual Marital Ther, 11, 1996.

The “breeding bull” syndrome

the *Guidelines* of the European Society for Human Reproduction and Embryology on counseling in infertility suggested that great attention should be paid to the **psychological aspects** of infertile couples and especially of **infertile men**

Boivin J., *et al.*, ESHRE Monographs, 2002.

A vicious circle



FERTILITY AND STERILITY®
VOL. 81, NO. 3, MARCH 2004

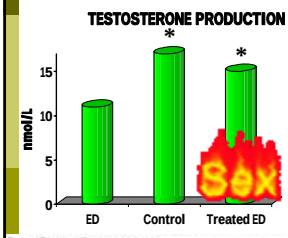
Treatment of sexual dysfunctions secondary to male infertility with sildenafil citrate

Emmanuele A. Jannini, M.D.[a]
Francesco Lombardo, M.D., Ph.D.[b]
Pietro Salacone, M.D.[b]
Loredana Gandini, B.Sc.[b]
Andrea Lenzi, M.D.[b]
Department of Experimental Medicine,[a] University of L'Aquila, L'Aquila; and Department of Medical Physiopathology,[b] 1st University of Rome "La Sapienza," Rome, Italy

Park K, Seo JJ, Kang HK, Ryu SB, Kim HJ, Jeong GW.
A new potential of blood oxygenation level dependent (BOLD) functional MRI for evaluating cerebral centers of penile erection. Int J Impot Res. 2001 Apr;13(2):73-81.

- inferior frontal
- gyrus cingulate
- insula
- corpus callosum
- thalamus
- globus pallidus
- inferior temporal

Sex is good news for sex



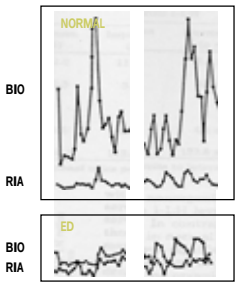
- ED patients of <u>various etiologies</u> without sexual activity have lower testosterone production with respect to an age-matched control group of healthy men.
- <u>Non-hormonal</u> therapies (Talking therapy, Surgical, and Pharmacological Therapies without PDE5-I) restore to normal testosterone production.

Low Serum E... Lack of sexual ... Sexual ina...
Nonorganic ... is associated ... bioavailal...
Altered Gona... testosterone

Type V phosphodiesterase inhibitor treatments for erectile dysfunction increase testosterone levels

E Carosa¹, S Benv... Eleonora Carosa*, Paolo Martini*, Fulvia Brandetti*
... Savino M. Di Stasi†, Francesco Lombardo‡, ... Clinical Endocrinology (2004) 61, 382–386
... *Andrea Lenzi† and Emmanuele A. Jannini*

The hypothalamic site of action



Low Serum Bioactive Luteinizing Hormone In Nonorganic Male Impotence: Possible Relationship with Altered Gonadotropin-Releasing Hormone Pulsatility

ANDREA FABBRI*, EMMANUELE A. JANNINI, SALVATORE ULISSE, LUCIO GNESSI, COSTANZO MORETTI, GAETANO FRAJESE, and ALDO ISIDORI

Journal of Clinical Endocrinology and Metabolism
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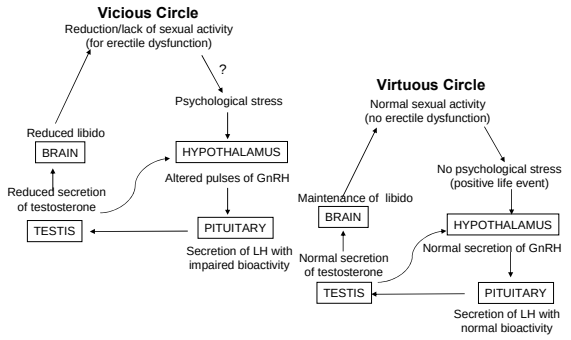
A sexual positive feedback acting on hypothalamus?



Subclinical hypogonadism

Sexual Symptoms in Endocrine Diseases: Psychosomatic Perspectives

Giancarlo Balercia[a] Marco Boscaro[a] Francesco Lombardo[b] Eleonora Carosa[c] Andrea Lenzi[b] Emmanuele A. Jannini[c]

Psychotherapy and Psychosomatics

We propose the name of **subclinical hypogonadism** to describe the condition of impotent patients with psychosomatically **reduced** – with respect to normal controls - T and increased LH.
In fact, this cannot be considered as true hypogonadism, as total and free T and LH serum levels are **within the normal range**.
Furthermore, this particular endocrine condition is characterized by the absence of **overt** signs of androgen deficiency. It is thus subclinical.

Causes of Hyperprolactinaemia

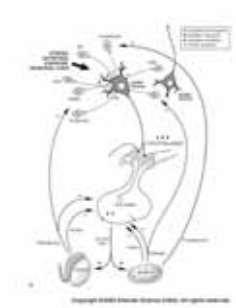
- Drug – induced
- Spurious
  - Stress-induced
  - Macroprolactinaemia
- Pituitary adenoma
  - Non - secreting
  - Prolactin - secreting
- Hypothyroidism
- Systemic diseases e.g. renal

Macroprolactinaemia

- Spurious elevation of PRL (10 – 20% of apparent hyperprolactinaemia)
- Big (60 KDa) or Big big (>150 KDa) IgG-PRL complex cross-reacting in immunoassays
  - Low biologically activity
- Common pitfall in diagnosis of hyperprolactinaemia → unnecessary investigations and treatment
  - Consider macroprolactinaemia when PRL levels and clinical findings discrepant
  - Does not completely exclude pituitary tumour

Hyperprolactinaemia and Male Sexual Dysfunction - Mechanisms

- Anatomical disruption of HP axis
- Interfere with GnRH action
- Inhibit gonadotropin secretion
- Decrease central dopamine action



Hyperprolactinaemia and Male Sexual Dysfunction

- Marked decline in sexual interest + ED
- T low or normal
- Systematic determination of PRL in 3200 patients with ED (Buvat 2003)
  - Elevated >7000 mU/L – 0.7%
  - Pituitary adenoma – 0.4%
  - Macroprolactinaemia – 10%
- Persistent & genuine ↑PRL - search for pituitary adenoma mandatory

Six Months of Treatment with Cabergoline Restores Sexual Potency in Hyperprolactinemic Males: An Open Longitudinal Study Monitoring Nocturnal Penile Tumescence

MICHELE DE ROSA, STEFANO ZARRILLI, GIOVANNI VITALE, CAROLINA DI SOMMA, FRANCESCO ORIO, LIBUSE TAUCHMANOVA', GAETANO LOMBARDI, AND ANNAMARIA COLAO

	Macro prolactinoma	Micro prolactinoma	Controls	*P*
Number	41	10	51	
Age (yr)	33	34	37	
PRL ng/mL	2019	182	4.4	<0.001
FSH U/L	3.8	4.1	4.4	<0.001
LH U/L	3.1	3.5	5.6	<0.001
T ng/ml (↓<normal)	2.5±0.8 (73%)	2.8±0.6 (50%)	4.7±0.6	<0.001
↓ Libido/erection	54%	50%	0	<0.001
NPT <3 episodes	100%	80%	14%	<0.001
RAU	13	14	86	<0.001

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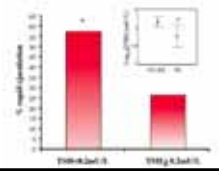
Thyroid Hormone and Male Gonadal Function*

EMMANUELE A. JANNINI, SALVATORE ULISSE, AND MASSIMINO D'ARMIENTO

Psycho-Biological Correlates of Rapid Ejaculation in Patients Attending an Andrologic Unit for Sexual Dysfunctions

G. Corona[a,1], L. Petrone[a,1], E. Mannucci[b], E.A. Jannini[c], R. Mansani[a], A. Magini[a], R. Giommi[d], G. Forti[a], M. Maggi[a,*]

European Urology 46 (2004) 615-622

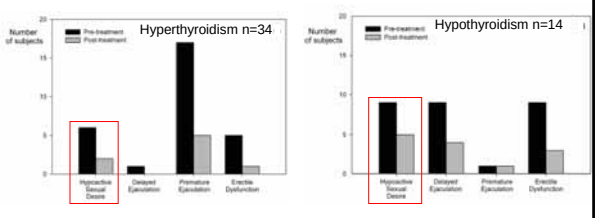


Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients

Cesare Carani, Andrea M. Isidori, Antonio Granata, Eleonora Carosa, Mario Maggi, Andrea Lenzi, and Emmanuele A. Jannini

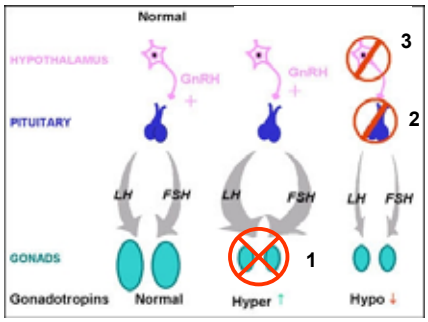
The Journal of Clinical Endocrinology & Metabolism 90(12):0000–0000

doi: 10.1210/jc.2005-1135



How to pick-up the problem –
diagnosis of HSDD

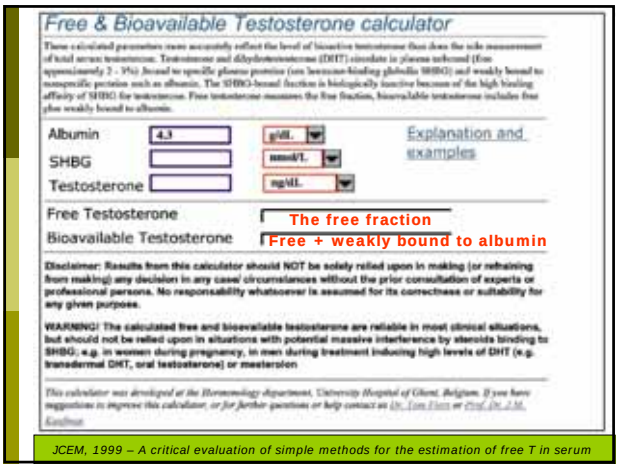
Hypogonadism



IN THE ELDERLY
Decrease in GnRH pulsatility
Decrease in LH bioactivity
Decrease in Leydig cell activity

Different methods

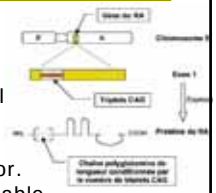
- Free testosterone by the equilibrium dialysis method.
  - Difficult to perform, not automated and largely inaccessible to most clinicians.
- Free Testosterone by radioimmunoassay method
  - Widely available but should be discouraged due to its unreliability.
- Bioavailable testosterone calculation
  - Attainable in some parts of the world but it is expensive and not readily accessible.
- Total testosterone
  - Readily available but the results need to be interpreted with caution, particularly in the elderly and the obese in whom elevations of SHBG may result in a factual hypogonadism that is not disclosed by the results of a total testosterone determination.
- Calculated free testosterone
  - An adequate compromise when only determinations of total testosterone and SHBG are available.



JCEM, 1999 – A critical evaluation of simple methods for the estimation of free T in serum

Relative hypogonadism: A role for CAG-triplets polymorphism?

- Testosterone exerts its effects on gene expression via the androgen receptor (AR).
- Modulations of the transcriptional activity induced by the AR is due to a polyglutamine stretch of variable length within the receptor.
- This stretch is encoded by a variable number of CAG-triplets in the AR gene.
- Longer triplet residues mitigate binding of androgen receptor co-activators and, hence, facilitate decreased androgenicity.
- This aspect could gain clinical significance especially in older men.



Prof. Eberhard Nieschlag

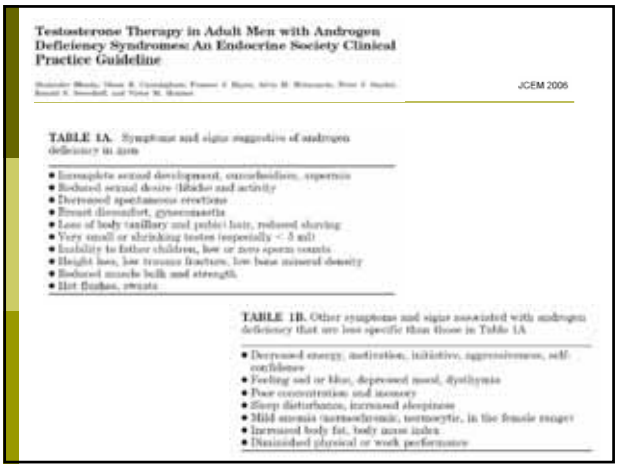
Normal values

- TOTAL TESTOSTERONE:
  - <230 ng/dl (< 8 namol/l) = OVERT HYPOGONADISM
  - 230-346 ng/dl (8-12 nmol/l) = GREY ZONE
  - > 346 ng/dl (> 12 nmol/l) = EUGONADISM

TOTAL TESTOSTERONE

8 nmol/L 12 nmol/L
230 ng/dL 350 ng/dL

Vermeulen, JCEM, 1999



Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

JCEM 2006

TABLE 1A. Symptoms and signs suggestive of androgen deficiency in men

- Incomplete sexual development, eunuchoidism, aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small or shrinking testes (especially < 5 ml)
- Inability to father children, low or zero sperm counts
- Height loss, low trauma fracture, low bone mineral density
- Reduced muscle bulk and strength
- Hot flushes, sweats

TABLE 1B. Other symptoms and signs associated with androgen deficiency that are less specific than those in Table 1A

- Decreased energy, motivation, initiative, aggressiveness, self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat, body mass index
- Diminished physical or work performance

The A.D.A.M. Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Note: Positive questionnaire result is defined as a “yes”answer to questions 1 or 7 or any 3 other questions

ISSAM Recommendation (Nieschlag E et al. Eur Urology, 2005)

- Clinical diagnosis + biochemical tests confirming the presence of hypogonadism.
- Blood sample for testosterone determination between 8 and 11 a.m.
  - Total testosterone
  - Calculated free testosterone (SHBG)
  - Bio-available testosterone
  - Free testosterone(by equilibrium dialysis)

Endocrine Society Clinical Practice Guidelines 2006

- STRONG RECOMMENDATION. Diagnosis of androgen deficiency only in men with consistent **symptoms and signs** and unequivocally low serum testosterone levels.
- WEAK RECOMMENDATION Screening by the measurement of morning **total testosterone.**
- STRONG RECOMMENDATION Confirmation of the diagnosis by **repeating** the measurement of morning total testosterone and in **some** patients by measuring of free or bioavailable testosterone level using an appropriate assays
  - No screening in the general population No use of case finding instruments • Case detection in men with certain clinical disorders

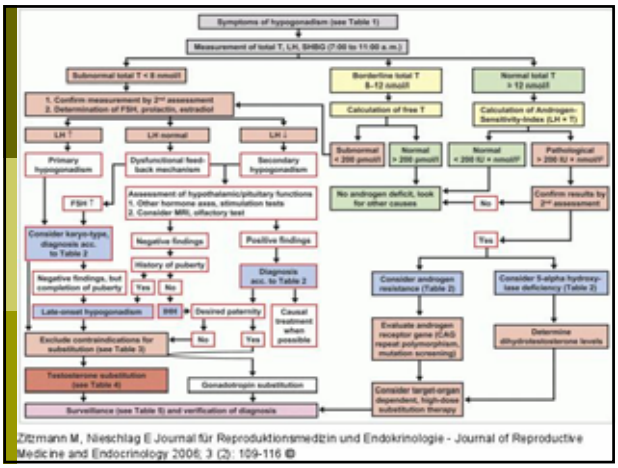
Practical aspects of general examination

A. Blood pressure
B. Breasts for gynecomastia
C. Secondary sex characteristics
D. Peripheral circulation
E. Genital examination (especially for penile fibrosis, testicular atrophy, bulbocavernosal reflex)
F. Rectal examination (especially assess prostate)

Action: Follow-up on abnormal findings—that is, cardiovascular findings, suspected endocrine diseases, or abnormal prostate

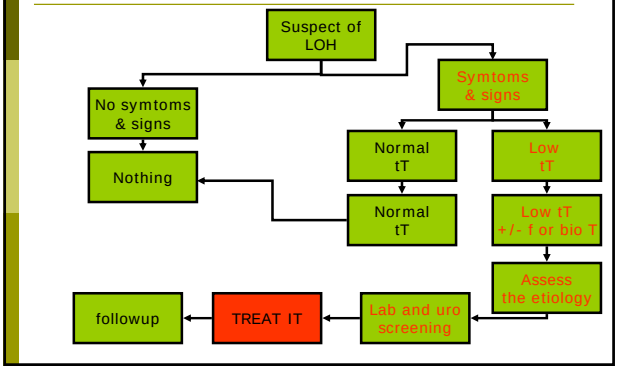
Practical aspects of laboratory tests in HSDD

A. Testosterone
B. Prolactin
C. SHBG
D. Thyroid-stimulating hormone and/or free thyroxine if hypothyroidism suspected
E. Other tests, depending on history and physical examination

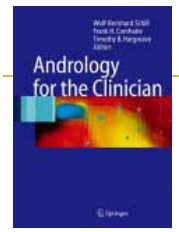


Zitzmann M, Nieschlag E Journal für Reproduktionsmedizin und Endokrinologie - Journal of Reproductive Medicine and Endocrinology 2006; 3 (2): 109-116 ©

A personal flow-chart in LOH



How to solve - **therapy**



Prof. Wolf Schill Giessen Germany
Prof. Frank Comhaire Gent Belgium
Dr. Tim Hargreave Edinburgh UK

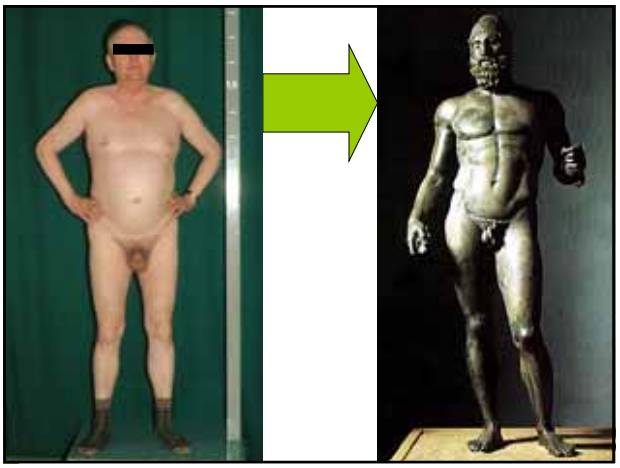
II.4.19 Behavioural Therapy and Counselling
E.A. Jannini, A. Lenzi, G. Wagner

Giving time

- Recent sexual anamnesis can be obtained using a simple **questionnaire** (Rosen et al. 1997) or a **semi-structured interview** (Petrone et al. 2003). Alternatively, it can be explored asking questions on:
  - the frequency of sex and on libido,
  - erection (morning, masturbation, sexual),
  - ejaculation, and orgasm.
  - The patient should also give his opinion of the couple's general life.
- Information (never sufficient for diagnosis) must be obtained on the timing and modalities of the sexual dysfunction.
- The simplest way to obtain critical information is to ask: "tell me about your last sexual experience" (Perelman 2003).

Threshold of Androgen Action on Sexual Desire

- **Level of T required for sexual activation is lower than the normal adult circulating T range**
- **Above this threshold, T increases would not have any behavioural consequences**
- **Below this threshold, sexual function is impaired and increases in T will stimulate libido**
- **Threshold T level is not well defined - wide individual variability**

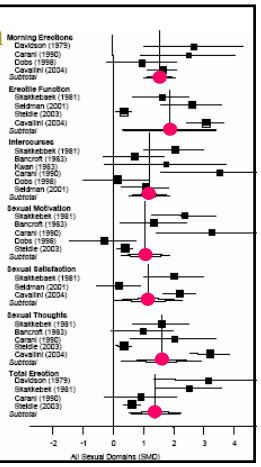


Effect of T therapy in men with T < 10 nmol/L

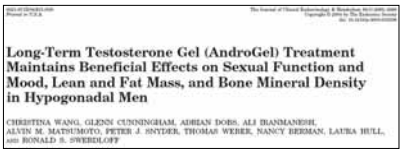
Clinical Endocrinology 2005,

EFFECTS OF TESTOSTERONE ON SEXUAL FUNCTION IN MEN: RESULTS OF A META-ANALYSIS

Andrea M. Isidori, Elisa Giannetta, Daniele Gianfrilli, Emanuela A. Greco, Vincenzo Bonifacio, Antonio Aversa, Aldo Isidori, Andrea Fabbri^ and Andrea Lenzi*

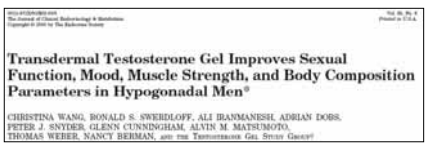


Testosterone



Long-Term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men

CHRISTINA WANG, GLENN CUNNINGHAM, ADRIAN DOBS, ALI IRANMANESH, ALVIN M. MATSUMOTO, PETER J. SNYDER, THOMAS WEBER, NANCY BERMAN, LAURA HULL, AND RONALD S. SWERDLOFF



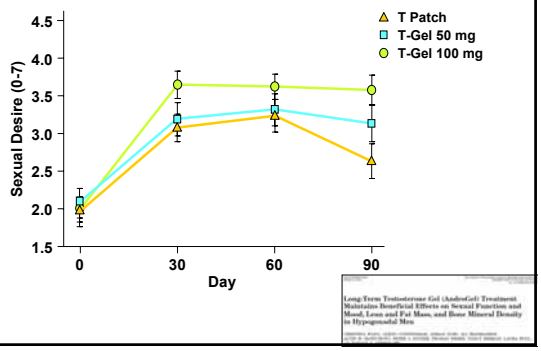
Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men*

CHRISTINA WANG, RONALD S. SWERDLOFF, ALI IRANMANESH, ADRIAN DOBS, PETER J. SNYDER, GLENN CUNNINGHAM, ALVIN M. MATSUMOTO, THOMAS WEBER, NANCY BERMAN, AND THE TESTOSTERONE GEL STUDY GROUP†

Testosterone

- ORAL:
  - T undecanoate: 120-240 mg/die (80 X3)
- PARENTERAL:
  - T enanthate: 200 mg 2 times/month
  - T enanthate + T propionate (depot)
- TRANSDERMAL:
  - Androderm: 1-2 patch/die

Sexual Desire After Daily Application of Transdermal Testosterone



Long-Term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men

Testosterone long acting

1000 mg testosterone undecanoate in a novel formulation. Testosterone levels remain within the physiological range for approximately 12 weeks.

Table 4. Recommendations for Monitoring Testosterone-Replacement Therapy.

Time	Recommended Steps*
Base line	Determine base-line voiding history or use standardized questionnaire.
	Determine history of sleep apnea.
	Perform digital rectal examination.
	Perform blood tests for base-line testosterone levels, PSA, and hematocrit or hemoglobin.
	Perform prostate biopsy if PSA level is above 4.0 ng/ml or digital rectal examination is abnormal.
Follow-up	Perform efficacy evaluation with dosage adjustment for suboptimal response at 1 to 2 mo.
	Perform monitoring evaluation with repeated testing every 3 to 6 mo for the first year and annually thereafter.
	Assess urinary symptoms and presence or exacerbation of sleep apnea or gynecomastia.
	Perform digital rectal examination.
	Perform blood tests for testosterone, hematocrit or hemoglobin, and PSA.
	Perform prostate biopsy if the digital rectal examination shows change or there is a substantial increase in PSA.

J. Endocrinol. Invest. 28 (Suppl. to no. 3): 117-121, 2005

Psychosocial issues of ART in aging male

E. Carosa[1], R. Volpe[1], P. Martini[1], F. Brandetti[1], S.M. Di Stasi[2], F. Lombardo[3], P. Salacone[3], P. Sgrò[3], L. Gandini[3], A. Lenzi[3], and E. A. Jannini[1]

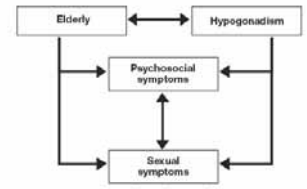


Fig. 1 - *The vicious circle of amplification of sexual and psychosocial symptom rising from both elderly and hypogonadism.*

Practical aspects of treatments

A. Related to risk factors
- Action: Diagnose diabetes
- Stop any substance abuse
- Change medications
- Treat abnormal hormones (testosterone, prolactin, thyroid)

B. Nonspecific treatments (PDE5-Is +/- testosterone)

C. Psychological referral

D. Surgical referrals (urologist) (Severe Peyronie's disease, LUTS, Selected cases of arterial damage or venous ligation, Penile injections, Vacuum pump, Penile implants [as last resort])

Always assess erectile function and treat it

- …Testosterone given to an eugonadal man with ED increases desire but not erectile activity.
- …Testosterone given to a hypogonadal man with a multifactorial ED (*i.e.* diabetes) is risky and frequently not useful if risk factors have not been assessed and symptomatic therapy not administered.

Testosterone administration not considering ED could be as to lash a lame horse

The approach of the sexual medicine expert

HSDD classification and diagnosis, as well as etiological and symptomatic therapies should be performed in an '**holistic'** and **eclectic** way, tacking into account the potency of **drugs**, the **couple**'s dynamics and providing specific sexual **counseling**.