Anti Ageing Conference London 2011

Testosterone and PDE5 inhibitors in the aging male

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REVIEW ARTICLE

Andrologia 38 (2006) 115–121

Epidemiology of sexual dysfunction in the male population

M. E. Beutel[1], W. Weidner[2] & E. Brähler[3]

Table 1 Prevalence of erectile dysfunction according to age group

30–39 years: 2.3%[a]
40–49 years: 0%[b] to 9.5%[a]
50–59 years: 2%[b] to 15.7%[a] and 30.8%[c]
60–69 years: 11%[b] to 23%[d], 34.4[a] and 55.1%[c]
>70 years: 15% (70–75 years[e]) to 40%[b]
70–79 years: 47%[d] to 53.4%[a]
80 years and above: 64%[d] to 76% (70–80 years[c])

[a]Braun *et al.* (2000).
[b]Holden *et al.* (2005).
[c]Rosen *et al.* (2003).
[d]Bacon *et al.* (2003).
[e]Feldman *et al.* (1994).

A Study of Sexuality and Health among Older Adults in the United States

N Engl J Med 2007;357:762-74

Stacy Tessler Lindau

3005 U.S. adults (1550 women and 1455 men) 57 to 85 years old

The prevalence of sexual activity declined with age (73% among respondents 57-64 years old, 53% among respondents 65-74 years old, and 26% among respondents 75-85 years old)

The most prevalent sexual problems were erectile difficulties (37%).

14% of all men reported using medication or supplements to improve sexual function.

38% of men reported having discussed sex with a physician since the age of 50 years.

Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing

BMJ 2010;340:c810

Stacy Tessler Lindau, associate professor,[1,2] Natalia Gavrilova, senior research associate[1]

WHAT THIS STUDY ADDS

Frequency of sexual activity, a good quality sex life, and interest in sex are positively associated with health in middle age and later life

Interest in sex among middle aged and older men in the United States has increased since 2000

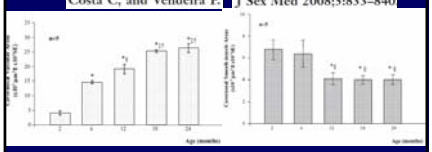
About half of sexually active older women report a poor quality sex life

At age 55, sexually active life expectancy is 15 years for men and 10.6 years for women; although the period is longer for men, they lose more years of sexually active life as a result of poor health than women

"...given the manner in which "second adulthood" has been redefined in recent years, the availability of sexual performance enhancers, the widespread use of the internet for social support, as well as improvements in overall health and better access to care, the news that adults in the US can enjoy many years of sexual activity beyond age 55 is promising" P.Goodson BMJ 340:c850

Does Erectile Tissue Angioarchitecture Modify with Aging? An Immunohistological and Morphometric Approach

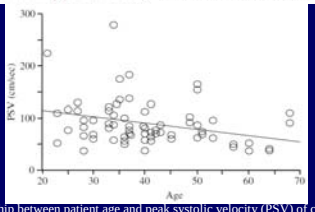
Costa C, and Vendeira P. J Sex Med 2008;5:833–840



Cavernosal angioarchitecture was modified with aging. The decrease in smooth muscle cells and the considerable enlargement of vascular lumens may limit the basic function of penile vascular tree in the elderly.

Impact of aging on penile hemodynamics in men responding normally to prostaglandin injection: A power Doppler study

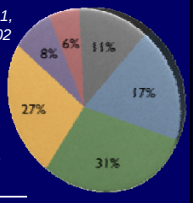
H Sakamoto *et al.* International Journal of Urology (2005) **12**, 745–750



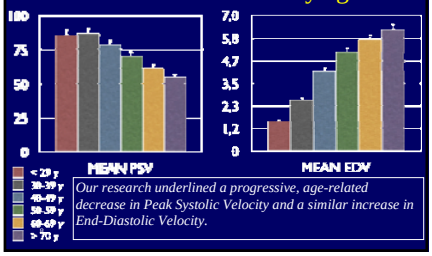
Relationship between patient age and peak systolic velocity (PSV) of cavernous arteries in 36 patients with erectile dysfunction and no definite vascular risk factors, 72 corpora were examined using power Doppler imaging.

Patients

*Our study focused on **1180** consecutive patients aged 18 to 91, recruited in 7 years, between 2002 and 2008; all exams have been performed by the same operator, with the same instrument and following the same procedures. All subjects underwent penile ultrasound evaluation, in basal conditions and 5', 15', 25' and 35' after the injection of Alprostadil.*

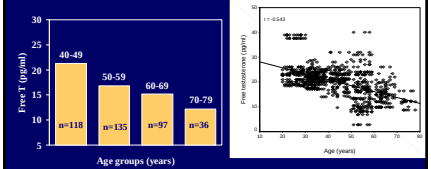


Mean PSV and EDV by age



Our research underlined a progressive, age-related decrease in Peak Systolic Velocity and a similar increase in End-Diastolic Velocity.

MEAN FREE TESTOSTERONE LEVELS IN 386 SUBJECTS DIVIDED INTO FOUR AGE GROUPS REFERRED TO OUR ANDROLOGY OUTPATIENT DIVISION



Latini M, Conte D, Isidori A and Romanelli F.
J Endocrinol Invest 2002; 25:89-90

Testosterone and phosphodiesterase type-5 inhibitors: new strategy for preventing endothelial damage in internal and sexual medicine?

Ther Adv Urol (2009) 1(4) 179–197

Antonio Aversa, Roberto Bruzziches, Davide Francomano, Marco Natali and Andrea Lenzi

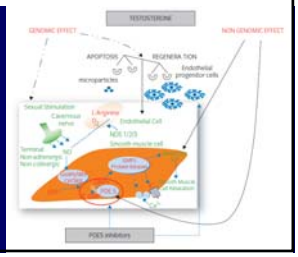
The aim of this review is to show evidence on the role of T and PDE5 inhibitors, alone or in combination, as potential boosters of endothelial function in internal medicine diseases associated with reduced T or NO bioavailability, i.e. metabolic syndrome, obesity, diabetes, coronary artery disease, hyperhomocysteinemia, that share common risk factors with ED.

Endothelial dysfunction and erectile dysfunction in the aging man

International Journal of Urology (2010) 17, 38–47

Antonio Aversa,[1] Roberto Bruzziches,[1] Davide Francomano,[1] Marco Natali,[1] Pietro Gareri[2] and Giovanni Spera[1]

Schematic representation of the molecular mechanisms underlying the control of endothelial function by testosterone and phosphodiesterase type 5 (PDE5) inhibitors.



Regular Intercourse Protects Against Erectile Dysfunction: Tampere Aging Male Urologic Study

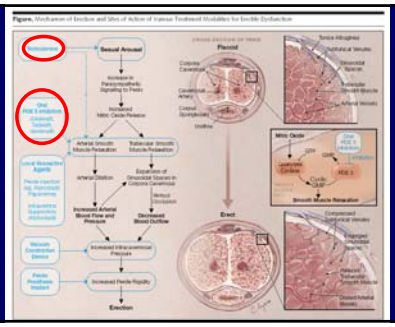
Juha Koskimäki | *The American Journal of Medicine (2008) 121, 592-596*

-Intercourse at least once per week protects against the development of erectile dysfunction (ED).

- We found a dose-response with coital frequency.

- ED incidence was twice among men reporting intercourse less than once a week compared with those having intercourse once a week and more than 4 times higher than those having intercourse 3 times or more a week.

- Regular sexual activity preserves potency in a similar fashion as physical exercise maintains functional capacity



Management of Erectile Dysfunction

JOEL I. HEIDELBAUGH, MD, *University of Michigan, Ann Arbor, Michigan*

American Family Physician www.aafp.org/afp Volume 81, Number 3 • February 1, 20

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Diagnostic testing for erectile dysfunction should usually be limited to obtaining a fasting serum glucose level and lipid panel, thyroid-stimulating hormone test, and morning total testosterone level.	C	8
First-line therapy for erectile dysfunction should consist of oral phosphodiesterase type 5 inhibitors.	A	8, 14, 17
Phosphodiesterase type 5 inhibitors are most effective in the treatment of erectile dysfunction associated with diabetes mellitus and spinal cord injury, and of sexual dysfunction associated with antidepressants.	A	9, 12, 17, 19-21
Additional therapy for erectile dysfunction may consist of psychosocial therapy and testosterone supplementation in men with hypogonadism.	B	8, 13, 36
Testosterone supplementation in men with hypogonadism improves erectile dysfunction and libido.	B	13, 29
Screening for cardiovascular risk factors should be considered in men with erectile dysfunction.	C	39

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

First-line therapy for ED consists of lifestyle changes, modifying drug therapy that may cause ED, and pharmacotherapy with phosphodiesterase type 5 inhibitors.

Guidelines on Male Sexual Dysfunction: Erectile Dysfunction

Konstantinos Hatzimouratidis[#,], Edouard Amar[†], Ian Eardley[‡], Francois Giuliano[§], Dimitrios Hatzichristou[¶], Francesco Montorsi[#], Yoram Vardi[||], Eric Wespes[**]*

EUROPEAN UROLOGY 57 (2010) 804–814

Table 4 - Recommendations for the treatment of erectile dysfunction (ED):

Recommendations	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1b	A
Pro-erectile treatments must be given at the earliest opportunity after radical prostatectomy.	1b	A
If a curable cause of ED is found, treat the cause first.	1b	A
PDE5-Is are first-line therapy.	1a	A
Daily administration of PDE5-Is may improve results and restore erectile function.	1b	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5-Is.	3	B
Testosterone replacement restores efficacy in hypogonadic nonresponders to PDE5-Is.	1b	A
Apomorphine can be used in mild to moderate ED, psychogenic ED, or in patients with contraindications to PDE5-Is.	1b	B
A vacuum constriction device can be used in patients with stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	A
Penile implant is third-line therapy.	4	C

LE = level of evidence; GR = grade of recommendation; PDE5-I = phosphodiesterase type 5 inhibitor.

Treatment is based on phosphodiesterase type 5 inhibitors (PDE5-Is), including sildenafil, tadalafil, and vardenafil. PDE5-Is have high efficacy and safety rates, even in difficult-to-treat populations such as patients with diabetes mellitus.

Erectile dysfunction in aging male

ACTA BIOMED 2010; 81; Suppl 1: 89-94

Francesco Romanelli, Andrea Sansone, Andrea Lenzi

Oral therapy with PDE-5 inhibitors for ED is viable even in aging men: sildenafil, vardenafil and tadalafil are effective in all age groups, with no increase in adverse events with aging. Furthermore, therapy with PDE-5 inhibitors might prevent lower urinary tract symptoms, thus preserving quality of life in the elderly.

Hypogonadism should be treated in all men, regardless of age: combination with PDE-5 inhibitors should be considered in hypogonadal patients not responding to single treatment.

However, treatment with these medications should only be started after the assessment of other conditions: all comorbidities, including metabolic syndrome, diabetes, hypertension, drugs, psychiatric fac-

Pharmacotherapy for Erectile Dysfunction

Ian Eardley | J Sex Med 2010;7:524–540.

Table 2 Pharmacokinetics of the phosphodiesterase type 5 inhibitors

Parameter	Tadalafil 20 mg [11]	Sildenafil 100 mg [11]	Vardenafil 20 mg [11]	Udenafil 100 mg [13,14]	SLx-2101 [15]	Avanafil 100 mg [16]	Mirodenafil 100 mg [17]	Lodenafil 160 mg [18]
Cmax (ng/ml)	378	440	20.8	416.2	No data	No data	No data	157
Tmax (hour)	2	0.8	0.7–0.9	1.1.5	1	0.5–1.5	1.25	1.2
T1/2 (hour)	17.5	3–5	4–5	11–13	9–14	<1.5	2.5	2.4
Bioavailability		40%	15.4%					

Table 1 Pharmacodynamics of the phosphodiesterase type 5 (PDE5) inhibitors

Inhibitor	IC_{50} for PDE5	PDE selectivity	Source
Udenafil	6.2 nM	Low activity against PDE3, PDE6	Doh H et al. [6]
SLx-2101	0.24 nM	—	Sweetnam et al. [7]
Avanafil	1 nM	"Highly" selective	Kotera J et al. [8]
Mirodenafil	0.33 nM	Similar to sildenafil	Lee et al. [9]
Sildenafil	3.5–10 nM		Francis SH et al. [10]
Sildenafil*	3.7 nM	Low activity against PDE6	Francis SH and Corbin JD [11]
		Very low activity against PDE1	
Vardenafil	0.14–1 nM		Francis SH et al. [10]
Vardenafil*	0.091 nM	Low activity against PDE6	Francis SH and Corbin JD [11]
		Very low activity against PDE1	
Tadalafil	1.8–10 nM	—	Francis SH et al. [10]
Tadalafil*	1.8 nM	Low against PDE11	Francis SH and Corbin JD [11]
Tadalafil	—	Slight against PDE11	Weeks JL et al. [12]

*Time head to head
IC_{50} = half maximal inhibitory concentration.

British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction

J Sex Med 2008;5:1841–1865

Table 8 Adverse events reported with PDE5 inhibitor use

	Incidence (%)		
Adverse event	Sildenafil (N = 5,918) [84]	Vardenafil (N = 2,203) [85]	Tadalafil (N = 804) [10]
Headache	14.6	14.5	14
Flushing	14.1	11.1	4
Dyspepsia	6.2	3.7	10
Rhinitis	2.6	9.2	5
Back pain	0	0	6
Visual disturbance	5.2	0	0

Analysis of the efficacy and safety of sildenafil citrate in the geriatric population

Alexander Müller

2007 BJU INTERNATIONAL | 100, 117–121

TABLE 1 Patient demographics, EF outcome after sildenafil, the distribution of the sildenafil dose in responders

Variable	Total	Group 1 60–69	2 70–79	3 ≥80
Number of patients	167	103	42	22
Mean (SD):				
Age, years	72 (9)	66 (4)	75 (2)	82 (3)
Duration of ED, years	5 (3)	3 (2)	5 (2)	6 (3)
Follow-up, months	8 (4)	7 (2)	8 (4)	7 (4)
Hypertension, %	37	35	38	39
Diabetes, %	26	29	27	22
Dyslipidaemia, %	28	25	30	24
CVD, %	18	22	19	16
LUTS, %	46	44	48	51*

167 patients with no significant differences in ED duration and comorbidities

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Number of patients	167	103	42	22
Mean (SD):				
Age, years	72 (9)	66 (4)	75 (2)	82 (3)
EF outcome after sildenafil				
Responders, n/N (%)†	90/167 (54)	59/103 (57)	23/42 (55)	11/22 (50)†
Δ EF domain score	5.7	8.0	6.4	4.5†
EF domain score ≥26, %	42	46	42	36†
Distribution of sildenafil dose (% or n/N) in responders				
Number of patients	90	59	23	11
25 mg	8	11	7	9%
50 mg	20	18	21	23%
100 mg	72	67	71	74%

Sildenafil is an effective agent in elderly men, but had a lower efficacy rate with increasing age, especially in men aged > 80 years.

Analysis of the efficacy and safety of sildenafil citrate in the geriatric population

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Number of patients	167	103	42	22
Mean (SD):				
Age, years	72 (9)	66 (4)	75 (2)	82 (3)
AEs, %				
Number of patients	167	103	42	22
Headache	18	17	14	19
Flushing	8	7	12	9
Heartburn	8	4	5	5
Nasal congestion	5	4	5	5

The incidence of side-effects was similar to that in the general population taking sildenafil with no difference in adverse events among the different age groups

Tadalafil Is Efficacious and Well Tolerated in the Treatment of Erectile Dysfunction (ED) in Men over 65 Years of Age: Results from Multiple Observations in Men with ED in National Tadalafil Study in the United States

Ira D. Sharlip J Sex Med 2008;5:716–725

Table 2 International Index of Erectile Function (IIEF) domains: changes from baseline to end point

	Patients aged >65 years without diabetes mellitus or clinical depression		
Domain	Baseline	End point	Change
EF	12.8	21.6	8.8*
IS	6.5	10.3	3.8*
OS	4.7	7.3	2.6*
OF	4.7	6.9	2.2*
SD†	6.7	7.3	0.7*

*P < 0.001 end point vs. baseline.
†Baseline value + change does not equal end-point value because of rounding.
EF = erectile function: IIEF questions 1–5 and 15; total possible score = 30 (range: 1–30); IS = intercourse satisfaction: IIEF questions 6–8; total possible score = 15 (range: 0–15); OS = overall satisfaction: IIEF questions 13–14; total possible score = 10 (range: 2–10); OF = orgasmic function: IIEF questions 9–10; total possible score = 10 (range: 0–10); SD = sexual desire: IIEF questions 11–12; total possible score = 10 (range: 2–10).

Patients receiving tadalafil 20 mg had a statistically significant ($P < 0.001$) and clinically relevant mean increase of 8.8 in the IIEF-EF domain from 12.8 at baseline to 21.6 at end point.

Tadalafil Is Efficacious and Well Tolerated in the Treatment of Erectile Dysfunction (ED) in Men over 65 Years of Age: Results from Multiple Observations in Men with ED in National Tadalafil Study in the United States

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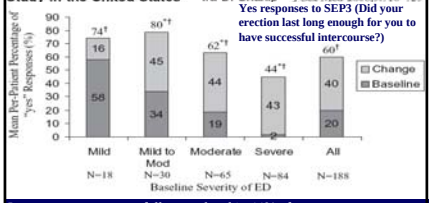


Intercourse was successfully completed in 44% of attempts among men with severe ED at baseline up to 80% of attempts among men with mild-moderate ED after 12 weeks of tadalafil treatment.

Effect of Sildenafil on Middle-Aged Sexually Active Males with No Erectile Complaints: A Randomized Placebo-Controlled Double-Blind Study

EUROPEAN UROLOGY 55 (2009) 969–978

Ian Gruenwald[a,*], Ronit Leiba[b], Yoram Vardi[a]

A prospective, placebo-controlled, double-blind, crossover study included sexually active middle-aged males who were never evaluated/treated for erectile dysfunction (ED) and who had an IIEF Erectile Function (EF) Domain score ≥22.

Significant differences between the sildenafil vs placebo groups in the EDITS (70.8 ±18 vs 60.3±19, p=0.013), SEAR (57.6±1vs 51±1. p< 0.0001), and IIEF–EF Domain score (25.1±4.8 vs 23±5.3, p = 0.013).

This is the first placebo-controlled study performed on a selected group of individuals suggesting that middle-aged subjects without

Is Sildenafil Citrate Associated With an Amelioration of the Symptomatology of Androgen Decline in the Aging Male?

Dmitry Koulikov,* Alon Fridmans, Boris Chertin, Ofer Shenfeld, Amicur Farkas and Irving M. Spitz

THE JOURNAL OF UROLOGY® Vol. 177, 2267-2271, June 2007

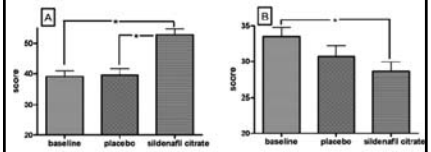


FIG. 4. IIEF (*A*) and AMS (*B*) scores in all patients. Asterisk indicates significance between groups ($p < 0.001$).

In the total group of patients sildenafil citrate was associated with expected improvement in erectile functionand in the Aging Male Symptoms questionnaire without any alteration in hormonal pattern

"COUNSELING"

Partner involvement

Delivery characteristics

Therapeutic window

Drug dosage

Number of attempts

Contraindications and side effects

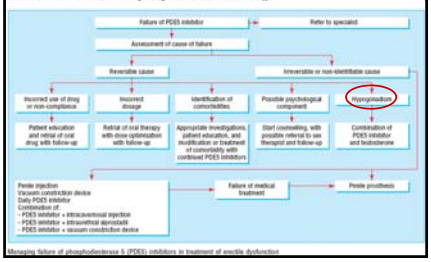
Food and drug interaction

Follow up

Practice pointer BMJ 2006;332:589-592

Treating erectile dysfunction when PDE5 inhibitors fail

Chelsea N McMahon, Christopher J Smith, Ridwan Shabsigh



Managing failure of phosphodiesterase 5 (PDE5) inhibitors in treatment of erectile dysfunction

Prevalence of Androgen Deficiency in Men with Erectile Dysfunction

UROLOGY 71 (4), 2008

Tobias S. Köhler, Johnny Kim, Kendall Fela, Josh Bodie, Nick Johnson, Antoine Makhlouf, and Manoj Monga

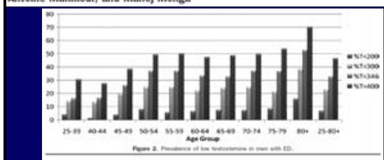


Figure 2. Prevalence of low testosterone in men with ED.

Table 1. Factors affecting testosterone levels

Regaining Lost Youth: The Controversial and Colorful Beginnings of Hormone Replacement Therapy in Aging

Arnold Kahn

Journal of Gerontology: BIOLOGICAL SCIENCES 2005, Vol. 60A, No. 2, 142–147

Voronoff's elder brother before and after rejuvenation

FIG. 8.3. Advertisement published in *The Strand Magazine* in 1912, indicating the extravagant

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

C. Wang,* E. Nieschlag,† R. Swerdloff,* H. M. Behre,‡ W. J. Hellstrom,§ L. J. Gooren,¶ J. M. Kaufman,** J.-J. Legros,†† B. Lunenfeld,‡‡ A. Morales,§§ J. E. Morley,¶¶ C. Schulman,*** I. M. Thompson,††† W. Weidner‡‡‡ and F. C. W. Wu§§§

Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations

EUROPEAN UROLOGY 55 (2009) 121–130

Christina Wang[a,], Eberhard Nieschlag[b], Ronald Swerdloff[a], Hermann M. Behre[c], Wayne J. Hellstrom[d], Louis J. Gooren[e], Jean M. Kaufman[f], Jean-Jacques Legros[g], Bruno Lunenfeld[h], Alvaro Morales[i], John E. Morley[j], Claude Schulman[k], Ian M. Thompson[l], Wolfgang Weidner[m], Frederick C.W. Wu[n]*

CONSENSUS STATEMENT European Journal of Endocrinology (2008) 159 507–514

Investigation, treatment and monitoring of late-onset hypogonadism in males

ISA, ISSAM, EAU, EAA and ASA recommendations

C Wang, E Nieschlag[1], R Swerdloff, H M Behre[2], W J Hellstrom[3], L J Gooren[4], J M Kaufman[5], J-J Legros[6], B Lunenfeld[7], A Morales[8], J E Morley[9], C Schulman[10], I M Thompson[11], W Weidner[12] and F C W Wu[13]

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

Recommendation 1

LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels.

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

Recommendation 1

This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

C. Wang,* E. Nieschlag,† R. Swerdloff,* H. M. Behre,‡ W. J. Hellstrom,§ L. J. Gooren,¶ J. M. Kaufman,** J.-J. Legros,†† B. Lunenfeld,‡‡ A. Morales,§§ J. E. Morley,¶¶ C. Schulman,*** I. M. Thompson,††† W. Weidner‡‡‡ and F. C. W. Wu§§§

Recommendation 7

The initial assessment of all men with erectile dysfunction and/or diminished libido should include <u>determination of serum testosterone</u>.

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

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Recommendation 7

Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy.

REVIEW ARTICLE 2008 European Academy of Andrology • International Journal of Andrology 32, 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males

C. Wang,* E. Nieschlag,† R. Swerdloff,* H. M. Behre,‡ W. J. Hellstrom,§ L. J. Gooren,¶ J. M. Kaufman,** J.-J. Legros,†† B. Lunenfeld,‡‡ A. Morales,§§ J. E. Morley,¶¶ C. Schulman,*** I. M. Thompson,††† W. Weidner‡‡‡ and F. C. W. Wu§§§

Recommendation 7

There is evidence suggesting <u>therapeutic synergism with combined use of testosterone and phosphodiesterase-5 inhibitors</u> in hypogonadal or borderline eugonadal men. The combination treatment should be considered in hypogonadal patients with ED failing to respond to either treatment alone.

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

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

Boston University School of Medicine (S.B.), Boston, Massachusetts 02118; Baylor College of Medicine/Veterans Affairs Medical Center (G.R.C.), Houston, Texas 77030; St. Vincent's University Hospital (F.J.H.), Dublin 4, Ireland; University of Washington/Veterans Affairs Puget Sound Health Care System (A.M.M.), Seattle, Washington 98108; University of Pennsylvania School of Medicine (P.J.S.), Philadelphia, Pennsylvania 19104; Harbor University of California, Los Angeles Medical Center (R.S.S.), Torrance, California 90502; and Mayo Clinic (V.M.M.), Rochester, Minnesota 55905

Objective: Our objective was to update the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men published previously in 2006.

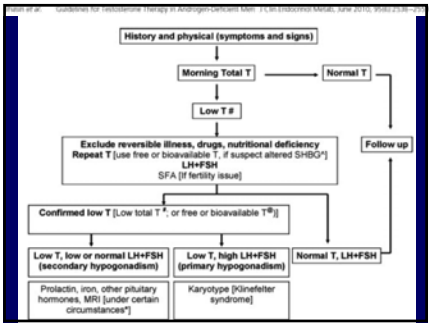
Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. (2⊕◯◯◯)

We recommend confirmation of the diagnosis by repeating measurement of total testosterone. (1⊕⊕◯◯)

We suggest measurement of free or bioavailable testosterone level, using an accurate and reliable assay, in some men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected. (2⊕⊕◯◯)

We suggest that an evaluation of androgen deficiency should not be made during an acute or subacute illness. (2⊕⊕◯◯)



1.2 Screening for androgen deficiency (general population)

We recommend against screening for androgen deficiency in the general population. (1⊕◯◯◯)

1.2.2 Case finding of androgen deficiency

We suggest that clinicians not use the available case-finding instruments for detection of androgen deficiency in men receiving health care for unrelated reasons. (2⊕◯◯◯)

We suggest that clinicians consider case detection by measurement of total testosterone levels in men with certain clinical disorders, listed in Table 3, in which the prevalence of low testosterone levels is high or for whom testosterone therapy is suggested/recommended in Section 2.0. (2⊕◯◯◯)

2.0 Treatment of androgen deficiency with testosterone

We recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density. (1⊕⊕◯◯)

We recommend against testosterone therapy in patients with breast (1⊕◯◯◯) or prostate cancer. (1⊕⊕◯◯)

We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy.

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

J Clin Endocrinol Metab, June 2010, 95(6):2536–2559

We recommend against testosterone therapy in patients with hematocrit above 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms (AUA/IPSS > 19), *or uncontrolled or poorly controlled heart failure, or in those desiring fertility.* (1⊕◯◯◯)

Overall mortality, cardiovascular event rates, prostate cancer, lower urinary tract symptom scores, and systolic and diastolic blood pressure did not differ among testosterone- and placebo-treated men (2).

TABLE 4. Conditions in which testosterone administration is associated with a high risk of adverse outcome and for which we recommend against using testosterone

- Very high risk of serious adverse outcomes
  - Metastatic prostate cancer
  - Breast cancer
- Moderate to high risk of adverse outcomes
  - Unevaluated prostate nodule or induration
  - PSA >4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African-Americans or men with first-degree relatives who have prostate cancer)
  - Hematocrit >50%
  - Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS >19
  - Uncontrolled or poorly controlled congestive heart failure

British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction

Hackett et al. J Sex Med 2008;5:1841–1865

There is no evidence that giving testosterone to men with ED and normal androgen levels restores or improves their erectile function (Grade A—level Ib). Hypogonadal men restored to the eugonadal state with testosterone replacement may experience:

- A general improvement in sexual function.
- Improved erection.
- Restored or enhanced responsiveness to PDE5 inhibitors [15,21] (Grade A—level Ia).

Does Testosterone Have a Role in Erectile Function?

Nasser Mikhail, MD, The American Journal of Medicine, Vol 119, No 5, May 2006

Endocrinology Division, Department of Medicine, Olive View-UCLA Medical Center, Sylmar, Calif.

CLINICAL SIGNIFICANCE

- Although evidence suggests that testosterone plays an important role in erectile function, testosterone levels below the lower limit of normal range may be sufficient to retain normal erection in most men.
- The minimal circulating level of testosterone necessary to maintain erection is unknown.
- Approximately 65% of hypogonadal men may have improvement in erectile function with testosterone replacement therapy.
- Testosterone replacement therapy may improve the response of hypogonadal men to PDE5 inhibitors such as sildenafil citrate.

Table Conclusions Obtained From Studies of Treatment of ED With Testosterone

Comment	References
Most studies are of average quality (lack of placebo, inadequate statistical power, and no clear definition of hypogonadism and patient characteristics at baseline)	17, 60, 61-64, 66
Effectiveness of testosterone is variable, but generally superior to placebo	65, 67
Erectile function is more likely to improve with testosterone therapy in men with severe degrees of hypogonadism	13, 44, 61
Testosterone therapy may improve the response to PDE5 inhibitors	38, 68, 69

Are Androgens Critical for Penile Erections in Humans? Examining the Clinical and Preclinical Evidence

J Sex Med 2006;3:382–407

Abdulmaged M. Traish, PhD,* and André T. Guay, MD†

Possible role of androgens in the corpus cavernosum

1) Regulation of NOS isoform expression and activity;
2) Regulation of PDE5 expression and activity;
3) Regulation of the alpha adrenoceptor expression and function;
4) Regulation of smooth muscle cell growth and response to vasodilators;
5) Regulation of connective tissue metabolism and deposition of ECM;
6) Regulation of differentiation of progenitor vascular-stroma cells into myogenic and adipogenic lineages;
7) Maintaining neural structure and function

The benefits and risks of testosterone replacement therapy: a review

Bassil et al Therapeutics and Clinical Risk Management 2009:5 427–448

Table 2 Potential benefits of testosterone replacement therapy

Improve sexual desire and function
Increase bone mineral density
Improve mood, energy and quality of life
Change body composition and improve muscle mass and strength
Improve cognitive function

Men with erectile dysfunction (ED) and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy. Adequate testosterone treatment can restore venous leakage in the corpus cavernosum which is a frequent etiological factor in ED in elderly men. Overviews of randomized controlled clinical trials indicate some benefit of testosterone therapy on sexual health-related outcomes.

Review Maturitas 66 (2010) 16–22

Testosterone and the aging male: To treat or not to treat?

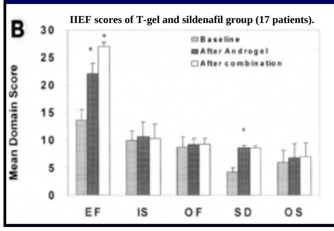
Jerald Bain[a,b,c,*]

"Given all the accumulated information, from the thousands of documented patients with no evidence of prostate cancer, the more appropriate question is, why not treat?
Four to six months of treatment and monitoring will determine whether the patient is responsive.
Why would treatment not be initiated given all the pathophysiological events associated with hypogonadism and the possible benefits of TRT both in terms of metabolic stabilization and improvement in symptoms which may well result?"

DOES SILDENAFIL COMBINED WITH TESTOSTERONE GEL IMPROVE ERECTILE DYSFUNCTION IN HYPOGONADAL MEN IN WHOM TESTOSTERONE SUPPLEMENT THERAPY ALONE FAILED?

ALEXANDER GREENSTEIN,* NICOLA J. MABJEESH, MARIO SOFER, ISSAC KAVER, HAIM MATZKIN AND JUZA CHEN

IIEF scores of T-gel and sildenafil group (17 patients).



The combination of sildenafil and T-gel has a beneficial effect on hypogonadal patients with erectile dysfunction whose condition did not improve satisfactorily with T-gel treatment alone.

RANDOMIZED STUDY OF TESTOSTERONE GEL AS ADJUNCTIVE THERAPY TO SILDENAFIL IN HYPOGONADAL MEN WITH ERECTILE DYSFUNCTION WHO DO NOT RESPOND TO SILDENAFIL ALONE

R. SHABSIGH,* J. M. KAUFMAN, C. STEIDLE AND H. PADMA-NATHAN

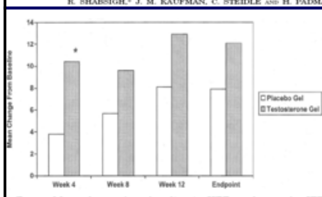


FIG. 4. Mean change from baseline in IIEF total score by ITT population. Asterisk denotes significance between groups at 0.049 level (ANOVA). Positive changes from baseline were indicative of improvement.

T-gel (1%) taken with sildenafil may be beneficial in improving erectile function in hypogonadal men with ED who are unresponsive to sildenafil alone.

Combining Testosterone and PDE5 Inhibitors in Erectile Dysfunction: Basic Rationale and Clinical Evidences

EUROPEAN UROLOGY 50 (2006) 940–947

Emanuela A. Greco, Giovanni Spera, Antonio Aversa*
Department of Medical Pathophysiology, University of Rome "La Sapienza," 00161 Rome, Italy

Table 1 – Randomized controlled trials assessing the effects of combined therapy with testosterone plus sildenafil in men with erectile dysfunction unresponsive to monotherapy

Authors	No. of subjects/hypogonadism	Sildenafil response at baseline	Overall efficacy/adverse events
Aversa et al. [9]	20/no	Failure	60%/none
Kalinchenko et al. [25]	120/yes	Failure	70%/none
Shabsigh et al. [10]	75/yes	Failure	70%/not evaluated
Chatterjee et al. [36]	12/yes	Not evaluated	100%/none
Shamloul et al. [26]	40/no	Failure/present	Improved/none
Greenstein et al. [37]	49/yes	Not evaluated	63%/18% skin irritation
Hwang et al. [27]	32/yes	Failure	57%/none
Rosenthal et al. [28]	24/yes	Failure	92%/1% headache
Tan et al. [38]	23/yes	Not evaluated	34%/none

Screening for hypogonadism in all men with ED is necessary to identify men with severe hypogonadism and some cases of mild to moderate hypogonadism, who may benefit from T treatment.

Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis

M. Mercè Fernández-Balsells, Mohammad Hassan Murad, Melanie Lane, Juliana F. Lampropulos, Felipe Albuquerque, Rebecca J. Mullan, Neera Agrwal, Mohamed B. Elamin, Juan F. Gallegos-Orozco, Amy T. Wang, Patricia J. Erwin, Shalender Bhasin, and Victor M. Montori

J Clin Endocrinol Metab, June 2010, 95(6):2560–2575

Objective: The aim of this study was to conduct a systematic review and meta-analyses of testosterone trials to evaluate the adverse effects of testosterone treatment in men.

Data Synthesis: The methodological quality of the 51 included studies varied from low to medium and follow-up duration ranged from 3 months to 3 yr. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, −0.49 mg/dl; 95% CI, −0.85 to −0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes.

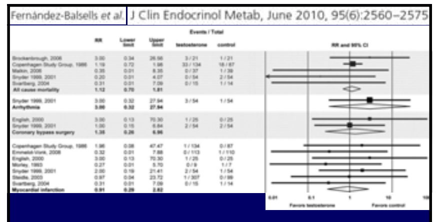
Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis

Prostatic/urological outcomes

There was no significant effect of testosterone therapy on patient-important outcomes such as the incidence of prostatic cancer or the need for prostate biopsy, when compared with the placebo/nonintervention group (Fig. 2). There was no significant difference between the two groups in the risk of other prostatic and urological outcomes such as a significant increase of PSA, changes in IPSS lower urinary tract symptoms, or the composite prostate outcome (Table 4).

J Clin Endocrinol Metab, June 2010, 95(6):2560–2575

Fernández-Balsells *et al.* J Clin Endocrinol Metab, June 2010, 95(6):2560–2575



There were no significant differences in the rates of death, myocardial infarction, revascularization procedures, or cardiac arrhythmias between the testosterone and the placebo/nonintervention groups.

Sex Steroid Hormone Concentrations and Risk of Death in US Men

Andy Menke, Eliseo Guallar, Sabine Rohrmann, William G. Nelson, Nader Rifai, Norma Kanarek, Manning Feinleib, Erin D. Michos, Adrian Dobs, and Elizabeth A. Platz*

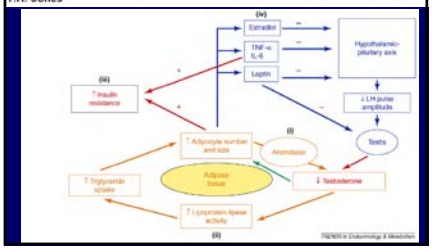
Am J Epidemiol 2010;171:583–592

In summary, adult men from the general US population with no history of cardiovascular disease or cancer but with low free and bioavailable testosterone concentrations may have a higher risk of all-cause and cardiovascular death than men with high levels within 9 years of hormone measurement. In addition, we found that men with low estradiol and free estradiol concentrations had a higher risk of cardiovascular disease mortality than men with higher levels within 9 years of hormone measurement. Screening

Testosterone deficiency: a risk factor for cardiovascular disease?

T.H. Jones[1,2]

Trends in Endocrinology and Metabolism 21 (2010) 496–503



Testosterone deficiency: a risk factor for cardiovascular disease?

T.H. Jones[1,2]

Trends in Endocrinology and Metabolism 21 (2010) 496–503

Concluding remarks

There is now convincing evidence that testosterone deficiency is a marker for early death in men and is closely associated with cardiovascular risk factors and the presence and degree of atherosclerosis. The first important question, therefore, is whether testosterone deficiency is a cause or consequence of atherosclerosis. Current evidence suggests that it can be both, with testosterone deficiency adversely affecting several cardiovascular risk factors and with central adiposity and the inflammatory state of atherosclerosis further suppressing testosterone levels.

Androgens and cardiovascular disease

Bu B. Yeap[a,b]

Current Opinion in Endocrinology, Diabetes & Obesity 2010, 17:269–276

Obervational studies highlights the association of reduced circulating testosterone with insulin resistance, metabolic syndrome and type 2 diabetes.

Lower testosterone levels are associated with carotid and aortic atheroma and lower limb arterial disease in cross-sectional studies, with limited longitudinal data associating reduced androgens with progression of carotid intima–media thickness (CIMT) and incidence of coronary events.

Emerging cardiometabolic complications of androgen deprivation therapy

KAREN CHOONG & SHEHZAD BASARIA *The Aging Male*, March 2010; 13(1): 1–

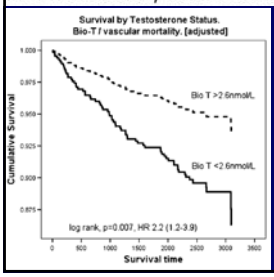
regional PCa, Keating et al. [33] showed that GnRH agonist is associated with incident coronary heart disease, myocardial infarction and sudden cardiac death. Even after adjustment for age, tumor characteristics and co-morbidities, this relationship remained significant [33].

Although these studies suggest that ADT is associated with cardiovascular disease, further confirmation is needed to delineate if there is a direct causal relationship between ADT and cardiovascular disease or if the increase in cardiovascular disease seen with ADT use is a consequence of hypogonadism and the treatment-related metabolic abnormalities.

Low serum testosterone and increased mortality in men with coronary heart disease

Chris J Malkin

Heart online October 19, 201



The prevalence of biochemical testosterone deficiency is common in men with coronary disease and is present in 24% of this sample… Testosterone deficiency is associated with premature death in a cohort of patients with vascular disease.

Testosterone deficiency syndrome (TDS) and the heart

Graham Jackson* European Heart Journal (2010) **31**, 1436–1437

Haring and colleagues add to the growing evidence of the importance of a link in a prospective population-based study (mean follow-up 7.2 years) showing in a sample of men aged 20–79 years that a testosterone level ,8.7 nmol/L (250 ng/dL) doubled the risk of all-cause mortality independently of age, waist circumference, cigarette smoking, excess alcohol, and decreased physical activity.

Whilst there is no evidence that testosterone replacement reduces CVD risk or all-cause mortality (randomized trials are needed), we have good evidence that replacement may be symptomatically beneficial in hypogonadic men with angina or heart failure.[12,13] Importantly, there is no evidence that replacement increases CVD risk.

Testosterone Replacement Therapy in Males With Erectile Dysfunction

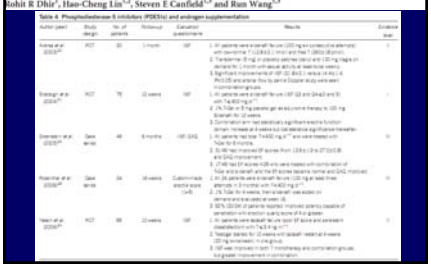
Bobby C. Jacob, PharmD Journal of Pharmacy Practice 2011 24(3) 298-306

"The use of TRT does not represent a benign treatment approach, given the significant adverse events that can result. For the present time, current guidelines recommend the use of TRT in men who are consistently symptomatic and have unequivocally low serum testosterone levels, after consideration of established therapies."

Combination therapy for erectile dysfunction: an update review

Asian Journal of Andrology (2011) 13, 382–390

Rohit R Dhir[1], Hao-Cheng Lin[1,2], Steven E Canfield[1,3] and Run Wang[1,3]



Looking to the Future for Erectile Dysfunction Therapies

Konstantinos Hatzimouratidis and Dimitrios G. Hatzichristou

Drugs 2008; 68 (2): 231-260

Table I. New drugs under clinical development for the treatment of erectile dysfunction

Drug	Target	Drug company	Clinical phase	Comments
Bremelanotide[PT-141]	Melanocortin receptors MC3R and MC4R	Palatin Technologies, Inc.	Phase II	Intranasal administration, fast onset of action
Avanafil[TA-1]	PDE5	Vivus, Inc.	Phase II	Rapid absorption, short half-life
Udenafil[]	PDE5	Dong-A PharmaTech Co., Ltd	Phase III (approved in Korea)	Long lasting (up to 24 hours) with relatively rapid onset
SLx-2101[]	PDE5	Surface Logic, Inc.	Phase II	Long lasting (up to 48 hours) through conversion to an active metabolite
Mirodenafil[]	PDE5	SK Chemicals Co., Ltd	Phase III (approved in Korea)	Similar pharmacokinetic profile to sildenafil and vardenafil
Topical alprostadil[]	$EP_{2/4}$ receptor activation, increased intracellular cAMP levels	Microchem Corporation (Topiglan®); Nexmed, Inc. (Alprox-TD)	Phase III	Lack of new data for the last 3 years
Combination of aviptadil and phentolamine for intracavernosal injection[]	Increased intracellular cAMP levels, α-adrenergic receptors	Ardana Bioscience Ltd (Invicorp®)	Phase III (approved in Denmark and New Zealand)	Similar efficacy to intracavernosal alprostadil, significantly less likely to cause pain

cAMP = cyclic adenosine monophosphate; EP = E prostanoid receptor; PDE = phosphodiesterase.