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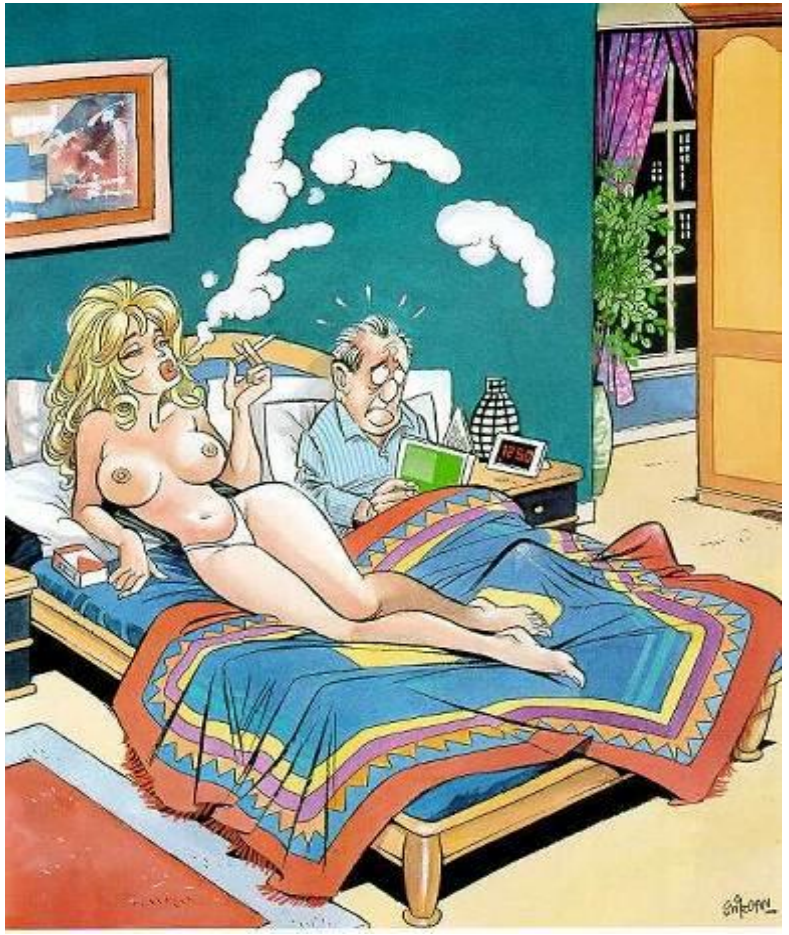
Disturbi e disfunzioni andrologiche nell'adolescente e nell'adulto.

L'Adulto. Prevenzione, diagnosi e terapia.

DOTT. MICHELE MANICA, UROLOGO

DEFICIT ERETTILE: DEFINIZIONE

Persistente incapacità ad ottenere o mantenere un'erezione sufficiente a permettere un rapporto sessuale soddisfacente.



Consensus Conference, Impotence JAMA 1993

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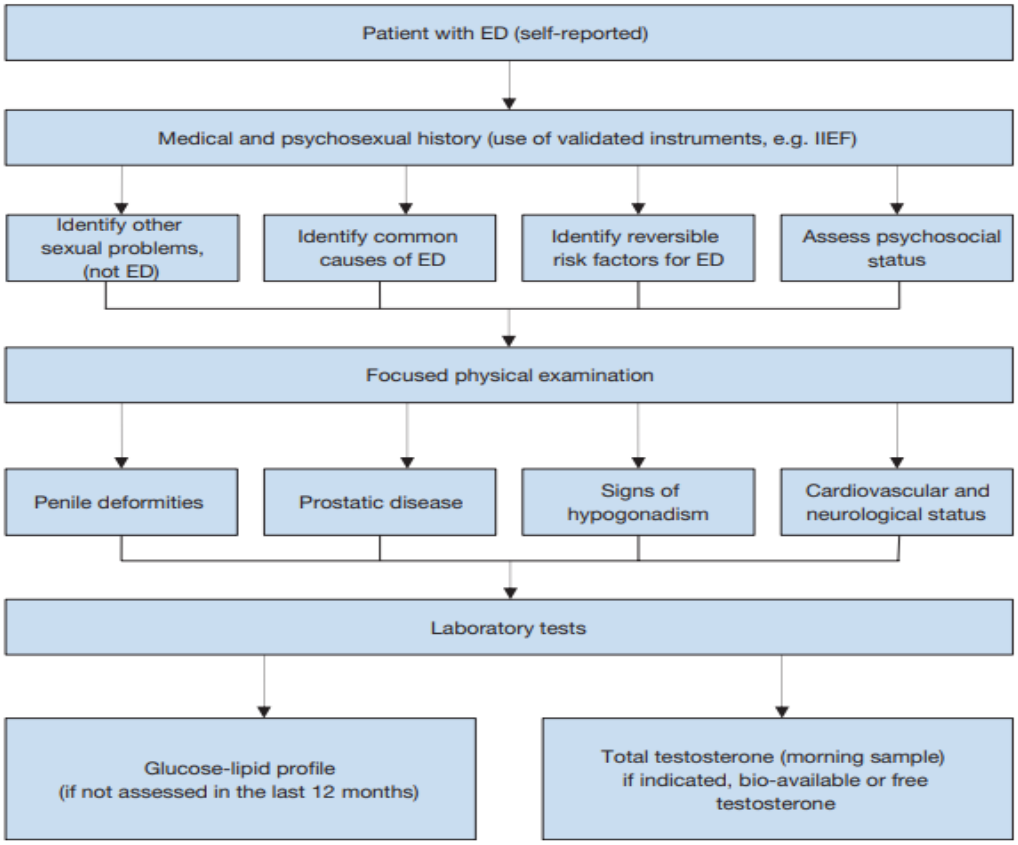
DIAGNOSI

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

DIAGNOSI

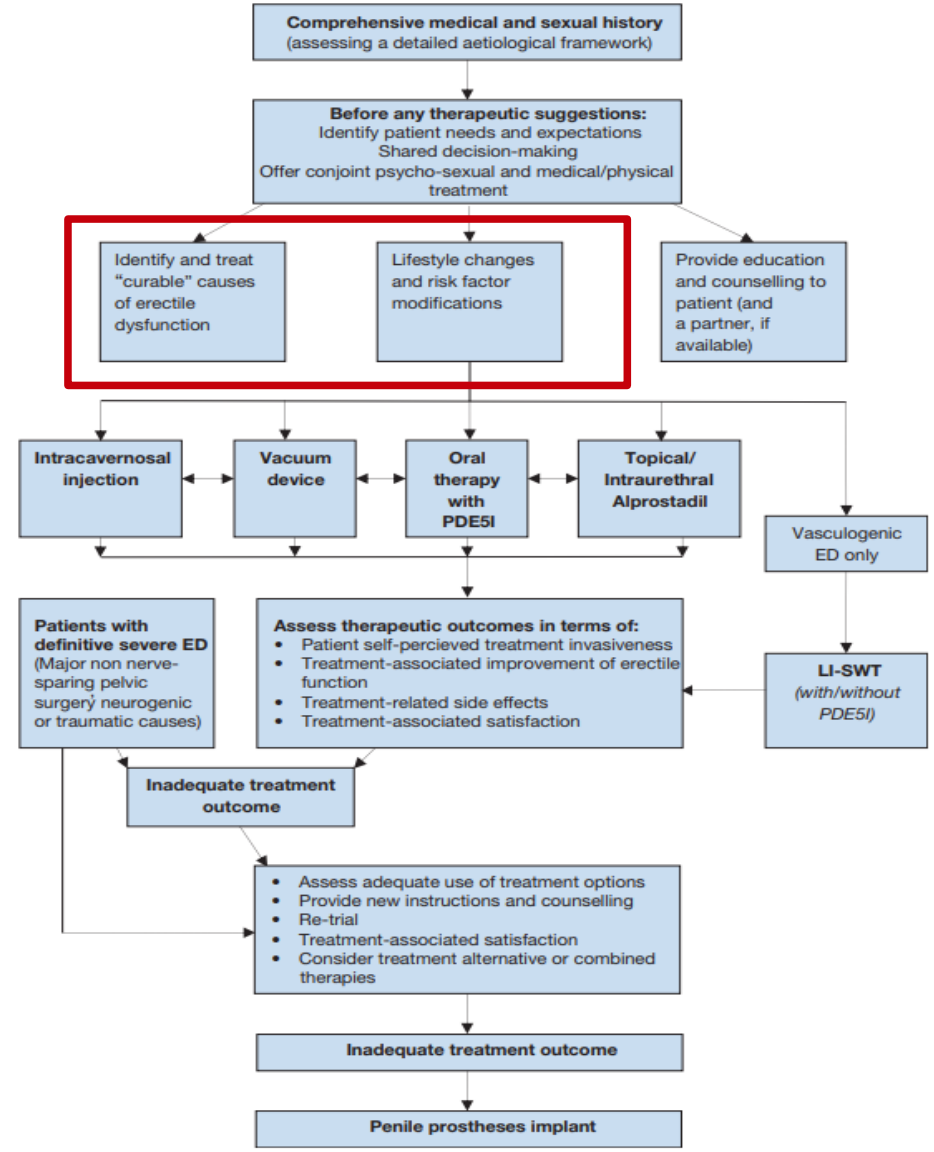
5.5.6 ***Recommendations for diagnostic evaluation of ED***

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 11.	Strong

Nella gestione della DE il primo passo è:

- determinare l'eziologia
- quando possibile, trattare le cause di DE e non solo il sintomo

Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave therapy.

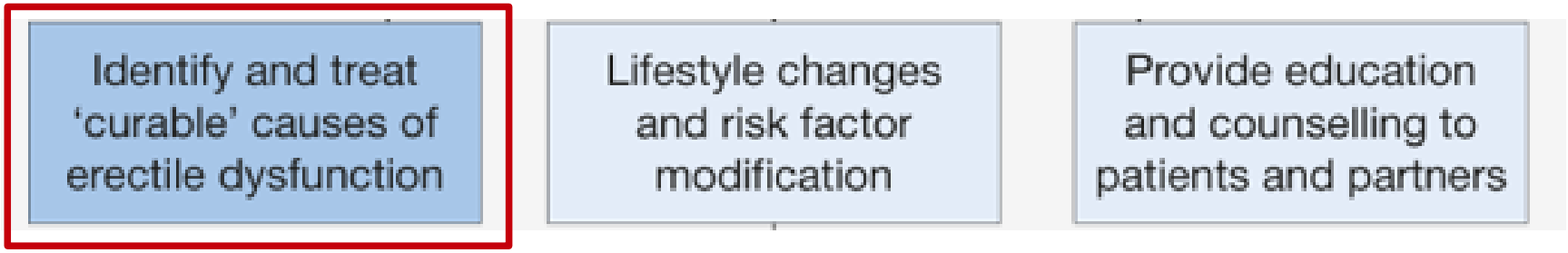
Fisiopatologia

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g., hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure, chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, open urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)

Hormonal
Diabetes mellitus; Metabolic Syndrome;
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiological pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic kidney disease, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, chronic obstructive pulmonary disease, rheumatic disease)
Psoriasis, gouty arthritis, ankylosing spondylitis, non-alcoholic fatty liver disease, chronic periodontitis, open-angle glaucoma, inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5α-reductase inhibitors.
**A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as anti-erectogenic drug. The analysis only assessed the short-term risk [356].*

Cause curabili di DE:



- Cause ormonali
  - Testosterone replacement therapy
  - Terapia dell'iperprolattinemia
- DE arteriogenica post-traumatica in pazienti giovani
  - Rivascolarizzazione chirurgica
- Counselling e terapia psicosessuologica

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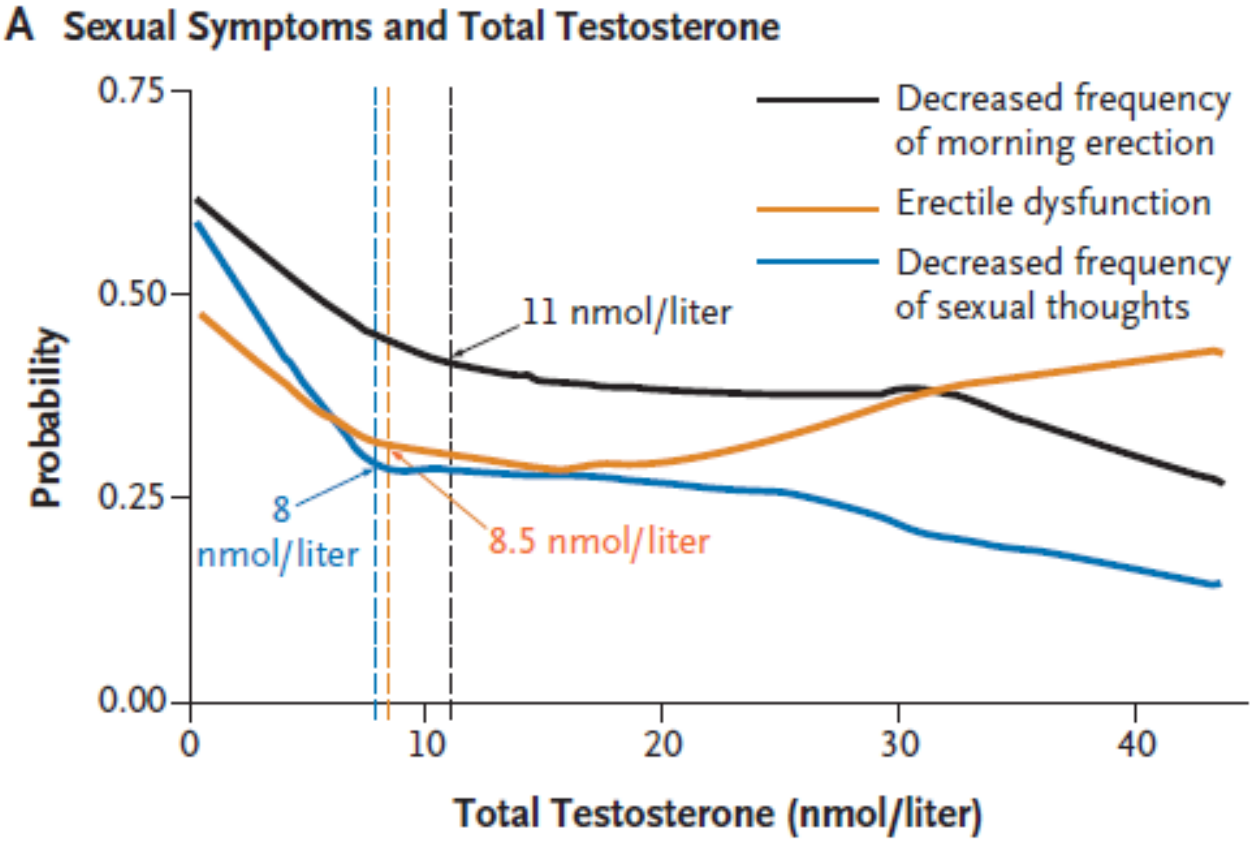
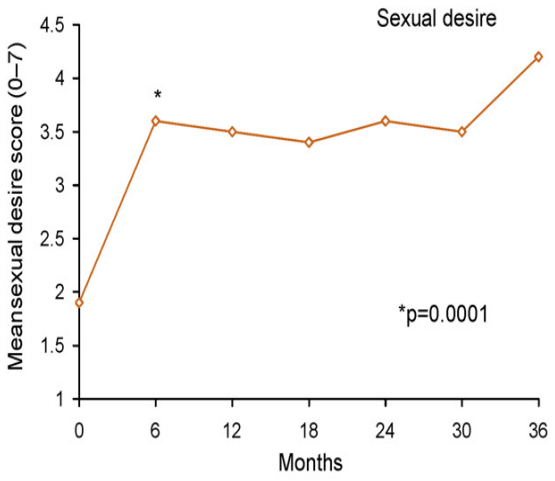
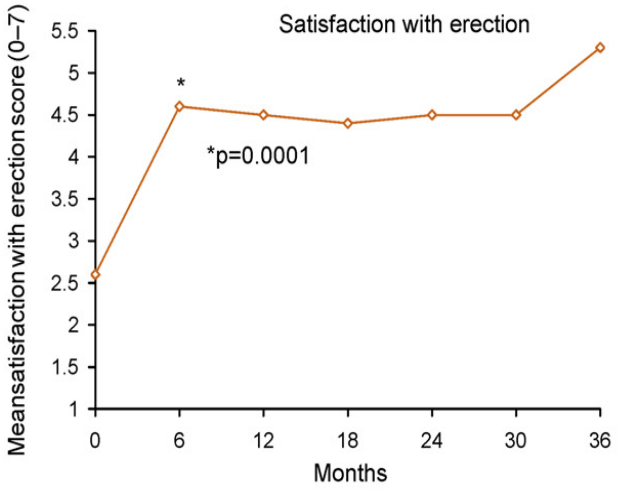
Testosterone totale & funzione sessuale:livelli soglia

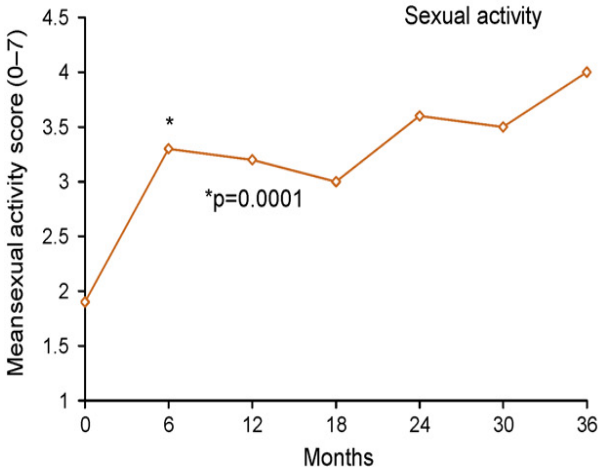


Frederick C.W. Wu et al., NEJM, 2010

Trattamento a lungo termine con testosterone gel







Christian Stief Eur Urol 2007

Fattori di rischio

- *Obesity*
- *Smoking*
- *Physical activity*
- *Alcohol intake*
- *Glycemic control*
- *Lipid profile*

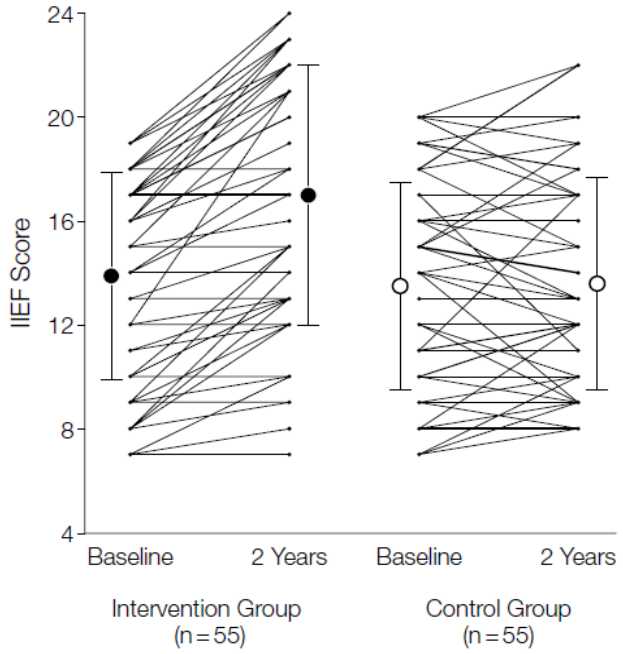
La presenza concomitante di 2 più fattori di rischio aumenta enormemente il rischio di DE

Effect of Lifestyle Changes on Erectile Dysfunction in Obese Men

A Randomized Controlled Trial

Table 4. Clinical and Metabolic Characteristics of the Study Participants after 2 Years*

Characteristic	Intervention Group (n = 55) 2 Years	Intervention Group (n = 55) Mean Change	Intervention Group (n = 55) *P* Value	Control Group (n = 55) 2 Years	Control Group (n = 55) Mean Change	Control Group (n = 55) *P* Value	Corrected Difference in Mean Change at 2 Years (95% CI)	*P* Value at 2 Years

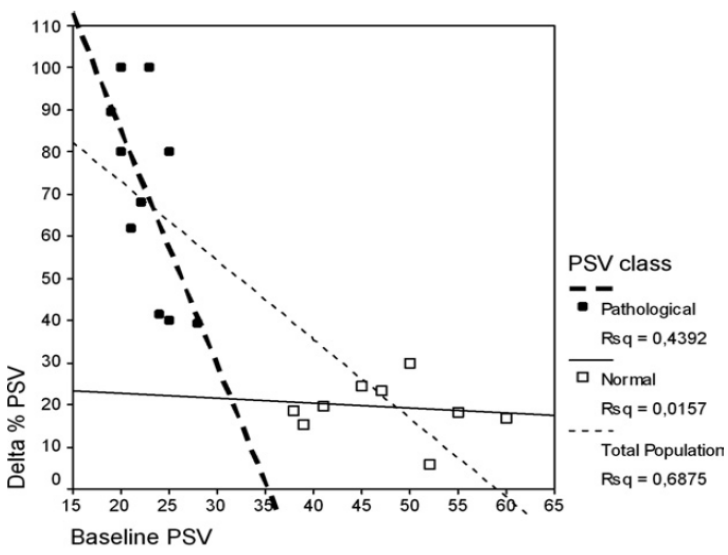


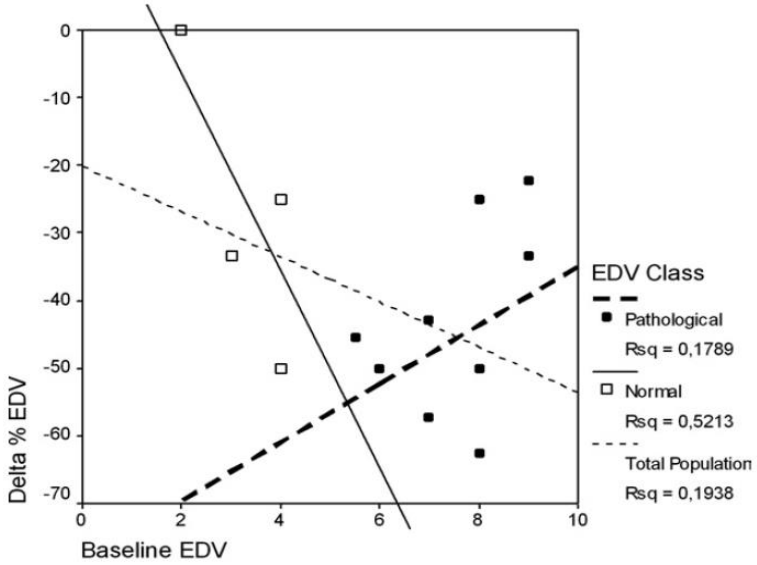
In soggetti obesi il calo ponderale, ottenuto con dieta ed attività fisica, è associato ad un significativo miglioramento della funzione erettile

Figure 2. Individual Changes in Erectile Function Score of Obese Men

Immediate Improvement in Penile Hemodynamics after Cessation of Smoking: Previous Results

M. C. Sighinolfi, A. Mofferdin, S. De Stefani, S. Micali, A. F. G. Cicero, and G. Bianchi





Within 24 to 36 hours of the cessation of cigarette smoking, the color Doppler parameters demonstrated a significant improvement in EDV and a trend toward an increase in PSV.

Urology, 2007

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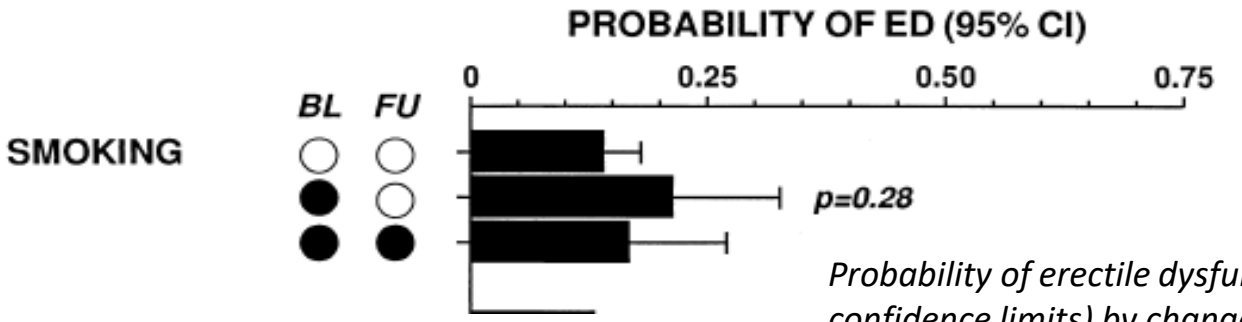
Risk of developing ED among men in Health Professionals Followup Study

	All Subjects RR (95% CI)	Prostate Ca Developed RR (95% CI)	No Known Prostate Ca* RR (95% CI)
No. ED/Total No.	3,905/22,086	726/1,225	3,179/20,861
Smoking status:			
Never smoked	1.0 —	1.0 —	1.0 —
Past smoker	1.1† (1.1–1.2)	1.1 (0.9–1.2)	1.2† (1.1–1.3)
Current smoker	1.4† (1.3–1.6)	1.4† (1.0–1.9)	1.5† (1.3–1.7)

Mantel-Haenszel relative risks adjusted for age and marital status in addition to behaviors listed, "healthy" defined as no known heart disease, hypertension, diabetes, stroke or cancer before 1986.
* Defined as before 1986 or at any time before 2000 questionnaire.
† Statistically significant difference at $p < 0.05$.

MODIFIABLE RISK FACTORS AND ERECTILE DYSFUNCTION: CAN LIFESTYLE CHANGES MODIFY RISK?



Probability of erectile dysfunction (95% confidence limits) by change in smoking

BL=baseline; FU= follow-up; solid circle = risk factor present, open circle = risk factor absent

Smettere di fumare durante la mezza età non riduce significativamente il rischio di DE.

Per ridurre il rischio di DE in soggetti fumatori probabilmente la cessazione del fumo deve essere molto più precoce e prolungata, similmente a quanto necessario per ridurre il rischio di coronaropatia o di infarto del miocardio

Derby CA., et al., Urology, 2000

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The Natural Progression and Remission of Erectile Dysfunction: Results From the Massachusetts Male Aging Study

Thomas G. Travison,*,† Ridwan Shabsigh,‡ Andre B. Araujo,† Varant Kupelian,†
Amy B. O'Donnell† and John B. McKinlay†

TABLE 3. *Multiple logistic regression of ED progression and remission on subject characteristics*

	ED Progression				ED Remission			
Covariates	Age Adjusted OR (95% CI)*	p Value	Multivariate Model OR (95% CI)†	p Value	Age Adjusted OR (95% CI)*	p Value	Multivariate Model OR (95% CI)†	p Value
Age	2.4* (1.7, 3.3)‡	<0.001	2.3 (1.6, 3.3)	<0.001	0.58* (0.45, 0.75)‡	<0.001	0.59 (0.44, 0.79)	<0.001
BMI (kg/m^2)	1.06 (1.00, 1.13)	0.05	1.05 (0.98, 1.12)	0.17	0.95 (0.90, 1.00)	0.05	0.94 (0.89, 0.99)	0.04
Smoking	2.0 (1.1, 3.5)	0.04	2.1 (1.16, 3.68)	0.01	0.95 (0.59, 1.54)	0.85	0.91 (0.56, 1.48)	0.68
General health:								
Excellent	Reference	—	Reference	—	Reference	—	Reference	—
Very good	1.7 (0.9, 3.1)	0.08	1.6 (0.87, 3.1)	0.13	0.54 (0.33, 0.90)	0.02	0.55 (0.32, 0.92)	0.02
Good	1.9 (0.9, 3.7)	0.08	1.6 (0.76, 3.2)	0.23	0.87 (0.49, 1.55)	0.64	0.97 (0.54, 1.78)	0.94
Fair/poor	3.8 (1.3, 11.3)	0.02	3.1 (0.99, 9.6)	0.05	0.72 (0.29, 1.79)	0.48	0.86 (0.34, 2.20)	0.76
Frequency of sexual desire:								
Once/wk or less	Reference	—	Reference	—	Reference	—	Reference	—
Several times/wk	0.55 (0.32, 0.94)	0.03	0.64 (0.36, 1.13)	0.12	1.35 (0.84, 2.18)	0.22	1.31 (0.78, 2.15)	0.29
Daily	0.40 (0.17, 0.96)	0.04	0.58 (0.23, 1.42)	0.23	1.31 (0.66, 2.61)	0.43	1.16 (0.57, 2.38)	0.68

Shaded regions indicate covariates that are statistically nonsignificant in multivariate models.
* Odds ratios summarizing association between covariates and ED progression/remission, controlling only for age.
† Odds ratios summarizing association between covariates and ED progression/remission, controlling for all covariates listed.
‡ Univariate model, multiplicative change in odds of progression/remission per 10-year increase in age.

In fumatori affetti da DE, astenersi dal fumo serve almeno a prevenire l'ulteriore progressione di malattia!

The Journal of Urology, 2007

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All types of exercise provided significant benefit for erectile function in age adjusted and multivariate adjusted analyses

Correre per almeno 2,5 ore a settimana è associato ad un rischio relativo di DE di 0.7 rispetto a non praticare attività fisica

1986 Physical Activity Tertile (hrs/wk)	Age Adjusted RR (95% CI)	Multivariate* RR (95% CI)	Multivariate + Total Activity† RR (95% CI)
Walking:			
0	1.0 —	1.0 —	1.0 —
0.04–0.9	0.9 (0.8–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.2)
1.0–2.4	0.9* (0.8–1.0)	0.9* (0.8–1.0)	0.9 (0.7–1.1)
2.5 or greater	0.8* (0.7–0.9)	0.8* (0.7–0.9)	1.0 (0.8–1.3)
Jogging:			
0	1.0 —	1.0 —	1.0 —
0.04–0.4	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
0.5–1.4	0.7* (0.6–0.9)	0.8* (0.7–1.0)	0.8* (0.6–1.0)
1.5 or greater	0.7* (0.6–0.9)	0.8* (0.6–0.9)	0.9 (0.7–1.1)
Running:			
0	1.0 —	1.0 —	1.0 —
0.04–0.9	0.7* (0.6–0.8)	0.8* (0.6–0.9)	0.8 (0.7–1.0)
1.0–2.4	0.6* (0.5–0.8)	0.7* (0.6–0.9)	0.8 (0.6–1.0)
2.5 or greater	0.8* (0.5–0.7)	0.7* (0.5–0.8)	0.7* (0.6–1.0)
Biking:			
0	1.0 —	1.0 —	1.0 —
0.04–0.4	0.9 (0.8–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
0.5–0.9	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
1 or greater	0.9* (0.8–1.0)	0.9 (0.8–1.0)	1.0 (0.8–1.1)
Swimming:			
0	1.0 —	1.0 —	1.0 —
0.04–0.1	0.9 (0.7–1.1)	0.9 (0.8–1.2)	1.0 (0.8–1.3)
0.2–0.9	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.7–1.1)
1 or greater	0.8* (0.7–0.9)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
Tennis:			
0	1.0 —	1.0 —	1.0 —
0.04–0.9	0.8* (0.7–1.0)	0.8 (0.7–1.0)	0.9 (0.7–1.1)
1–2.4	0.9 (0.8–1.0)	0.9 (0.8–1.1)	1.0 (0.8–1.2)
2.5 or greater	0.7* (0.6–0.8)	0.8* (0.7–0.9)	0.9 (0.7–1.0)
Squash/raquetball:			
0	1.0 —	1.0 —	1.0 —
0.04–0.9	0.9 (0.6–1.2)	0.9 (0.7–1.3)	1.0 (0.7–1.4)
1.0–2.4	0.9 (0.7–1.1)	0.9 (0.7–1.1)	1.1 (0.7–1.4)
2.5 or greater	0.7* (0.5–0.9)	0.7* (0.5–0.9)	0.8 (0.6–1.2)
Rowing/calisthenics/ exercise machine:			
0	1.0 —	1.0 —	1.0 —
0.04–0.4	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.9 (0.8–1.1)
0.5–1.4	0.8* (0.7–0.9)	0.9* (0.8–1.0)	0.9 (0.8–1.0)
1.5 or greater	0.7* (0.6–0.8)	0.8* (0.7–0.9)	0.8 (0.7–1.0)

Bacon CG., The Journal of Urology, 2006

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Assunzione di alcol

- Contradictory results from epidemiological studies are not sufficient to make a conclusion regarding the role of alcohol consumption and ED.

- Further basic science and clinical research is needed by evaluating the amount, the duration, and the type of alcohol consumed in order to delineate if alcohol is a contributor or protector for ED.

Se per un <u>moderato</u> consumo di alcol l'effetto è dubbio, in caso di <u>elevato</u> consumo di alcol non vi sono dubbi sulla nocività !!!

Horasanly K., et al., Asian J Androl., 2008

Does cardiovascular risk reduction alleviate erectile dysfunction in men with type II diabetes mellitus?

- *In pazienti con diabete tipo II l'intervento farmacologico e su stili di vita riportarono miglioramenti significativi di*
  - emoglobina A1c (HbA1c)
  - *pressione arteriosa diastolica*
  - *colesterolo totale*
- ***Miglioramento significativo dello IIEF-5*** (p=*0.01, p=0.01, p=0.04, rispettivamente).

The effect of diabetes mellitus treatment and good glycemic control on the erectile function in men with diabetes mellitus-induced erectile dysfunction: a pilot study.

- *No statistically significant difference was observed in both IIEF scores and nocturnal penile tumescence and rigidity (nptr) parameters after the dm regulation (p > 0.05).*

- ***CONCLUSION: there are probably other factors than aggressive treatment and DM regulation for treating DM-induced ED*** *, and probably we must consider preventive strategies with pharmacological agents to prevent progressive decrease in erectile function in diabetic patients.*

Il controllo della glicemia non è sufficiente, da solo, a ripristinare una normale erezione peniena

Yaman O., et al., J Sex Med., 2006

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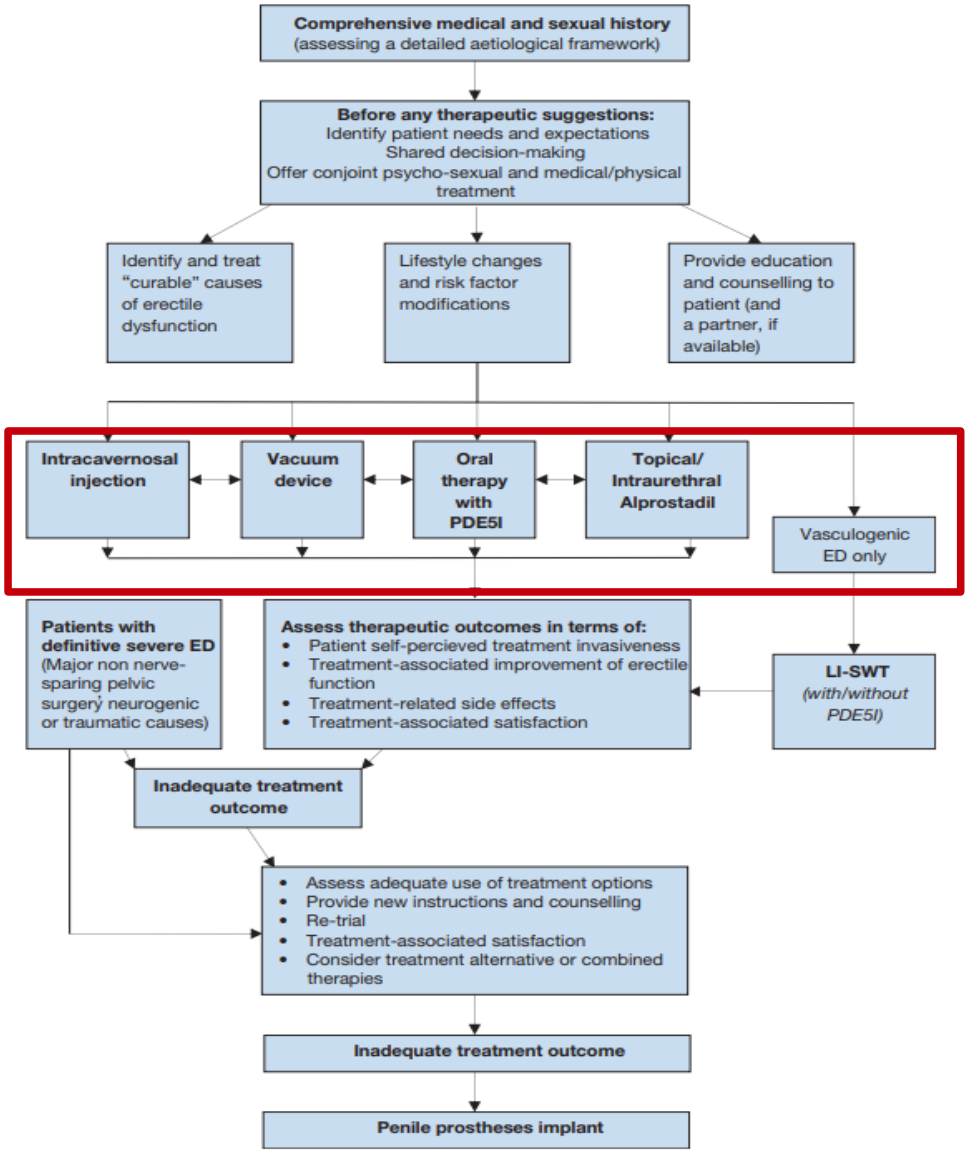
Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave therapy.

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PDE5

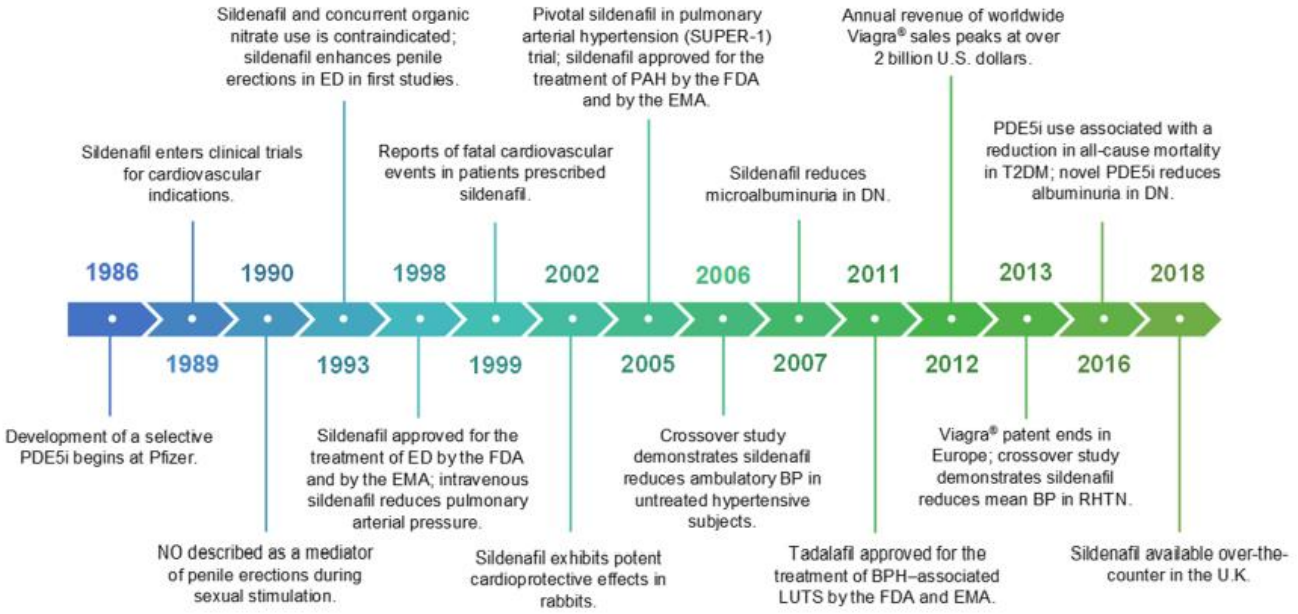

FIGURE 1 Milestones in the development of PDE type 5 inhibitors (PDE5Is). The figure depicts the key milestones in the development of PDE5Is for clinical indications, from their inception and early clinical trials, to their success in the amelioration of several cardiovascular conditions and finally their availability as an over-the-counter medication. BP, blood pressure; BPH, benign prostatic hyperplasia; DN, diabetic nephropathy; ED, erectile dysfunction; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; LUTS, lower urinary tract symptoms; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE5I, PDE type 5 inhibitor; RHTN, treatment-resistant hypertension; T2DM, type 2 diabetes mellitus

Tzoumas et al, Br J Pharmacol. 2020

PDE5: The choice

La selta del farmaco dipende dalla frequenza dei rapporti (uso occasionale o regolare, 3-4 volte a settimana) e dall'esperienza personale del paziente.

Il paziente deve sapere se un farmaco è a breve o lunga durata d'azione, conoscerne i possibili svantaggi e le istruzioni d'uso.

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Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

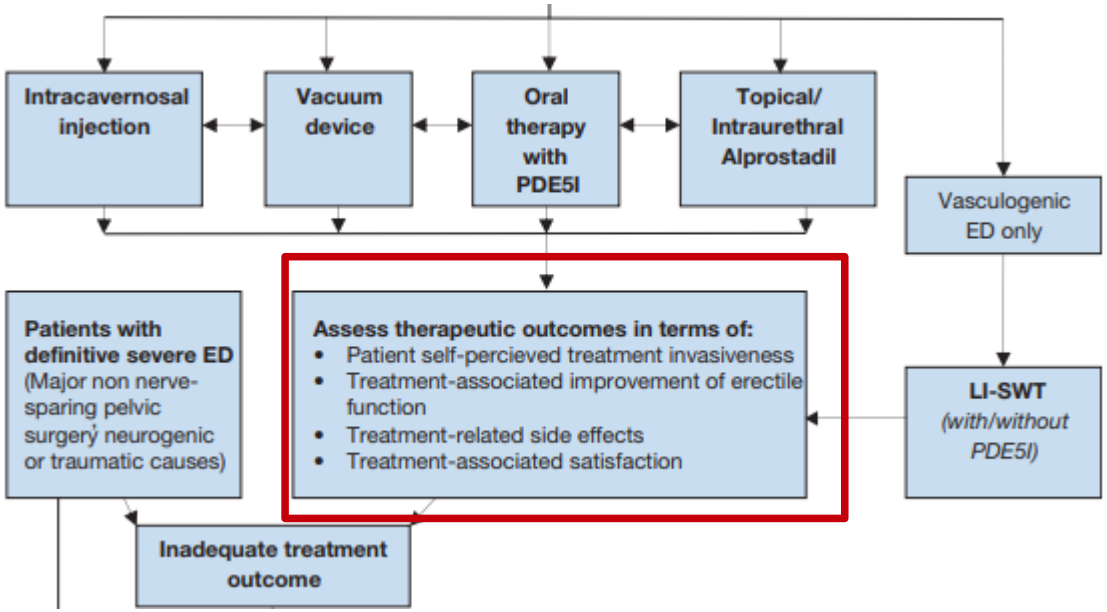
Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T_{max} (median)	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
T1/2	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
AUC	96%	94%	94%	99%
Protein binding	41%	NA	15%	8-10%
Bioavailability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics. C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration time curve.*

Table 15: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*



La valutazione dei risultati del trattamento deve comprendere efficacia, sicurezza, soddisfazione di paziente e partner ed altri fattori di QoL

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Therapeutic Effectiveness and Patient Satisfaction after 6 Months of Treatment with Tadalafil, Sildenafil, and Vardenafil: Results from the Erectile Dysfunction Observational Study (EDOS)

Table 2 – Therapeutic effectiveness

Outcome measure	V2			V3		
	V	S	T	V	S	T
SIQ1: Patient response*						
No, *n* (%)	**183 (47.8)**	**246 (47.0)**	**1710 (57.2)**	**223 (57.5)**	**301 (57.1)**	**1993 (66.8)**
Adjusted OR for T vs. (99%CI)	1.43 (1.05, 1.94)‡	1.41 (1.08, 1.84)‡	–	1.40 (1.02, 1.92)‡	1.39(1.06, 1.83)‡	–
Adjusted OR for S vs. (99%CI)	1.01 (0.69, 1.48)‡	–	–	1.01 (0.69, 1.48)‡	–	–
SIQ2: Patient response†						
Yes, *n* (%)	**277 (72.5)**	**385 (73.5)**	**2372 (79.6)**	**302 (79.1)**	**418 (81.0)**	**2593 (87.3)**
Adjusted OR for T vs. (99%CI)	1.65 (1.17, 2.33)‡	1.39 (1.02, 2.33)‡	–	1.82 (1.24, 2.67)‡	1.60 (1.13, 2.26)‡	–
Adjusted OR for S vs. (99%CI)	1.19 (0.78, 1.81)‡	–	–	1.14 (0.71, 1.81)	–	–

SIQ1: ‘‘Has your erection during the past 6 months been insufficient to initiate or complete intercourse?’’

SIQ2: ‘‘Has the treatment you have been taking in the last 4 weeks solved your problem?’’

Morales AM., et al., Eur Urol, 2007

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Therapeutic Effectiveness and Patient Satisfaction after 6 Months of Treatment with Tadalafil, Sildenafil, and Vardenafil: Results from the Erectile Dysfunction Observational Study (EDOS)

Table 3 – Patient satisfaction

Outcome measure	V2			V3		
	V	S	T	V	S	T
IIEF Q7 (intercourse satisfaction)						
Patients satisfied, *n* (%)	264 (68.2)	368 (70.0)	2182 (72.9)	288 (74.2)	397 (75.3)	2438 (81.5)
Adjusted OR for T vs. (99%CI)	1.41 (1.01, 1.96)*	1.17 (0.87, 1.57)	–	1.50 (1.06, 2.13)*	1.45 (1.06, 1.97)*	–
Adjusted OR for S vs. (99%CI)	1.20 (0.80, 1.81)	–	–	1.04 (0.68, 1.59)	–	–
IIEF Q14 (relationship satisfaction)						
Patients satisfied, *n* (%)	294 (76.2)	407 (77.7)	2439 (81.5)	312 (81.0)	422 (80.4)	2603 (87.2)
Adjusted OR for T vs. (99%CI)	1.47 (1.03, 2.08)*	1.25 (0.91, 1.71)	–	1.58 (1.07, 2.34)*	1.62 (1.16, 2.28)*	–
Adjusted OR for S vs. (99%CI)	1.18 (0.76, 1.81)	–	–	0.98 (0.61, 1.56)	–	–
EDITS Q1 (treatment satisfaction)						
Patients satisfied, *n* (%)	319 (83.1)	449 (85.5)	2605 (87.5)	339 (88.3)	455 (87.8)	2722 (91.8)
Adjusted OR for T vs. (99%CI)	1.45 (0.97, 2.15)	1.17 (0.81, 1.69)	–	1.39 (0.87, 2.21)	1.48 (0.99, 2.22)	–
Adjusted OR for S vs. (99%CI)	1.24 (0.76, 2.03)	–	–	0.94 (0.54, 1.64)	–	–

Morales AM., et al., Eur Urol, 2007

The impact of oral ED medication on female partners' relationship satisfaction

- **METHODS:** In total, 96 men were treated for ED using tadalafil and then sildenafil (or vice versa) each for 3 months. Their female partners were interviewed 3 months after the commencement of treatment.
- **RESULTS:** The findings demonstrated an overall positive effect of the treatment. Female partners perceived improvements in emotional closeness, and communication, and reported that their relationship was more loving, less stressful, and more stable.
- **CONCLUSIONS:** This study demonstrates the positive effects of treatment for ED on the female partner; in particular, on her perception of the quality of her relationship.

McCabe MP, J Sex Med. 2011

In 2007, the European Commission approved low-dose tadalafil to be used as single-daily ED therapy

Tadalafil, 5 mg once daily provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked.

Safety, Efficacy, and Pharmacokinetic Overview of Low-Dose Daily Administration of Tadalafil

Rebecca Wrishko, PhD, Sebastian Sorsaburu, MD, David Wong, MD, Andrew Strawbridge, PhD, and James McGill, MD

Eli Lilly and Company, Indianapolis, IN, USA

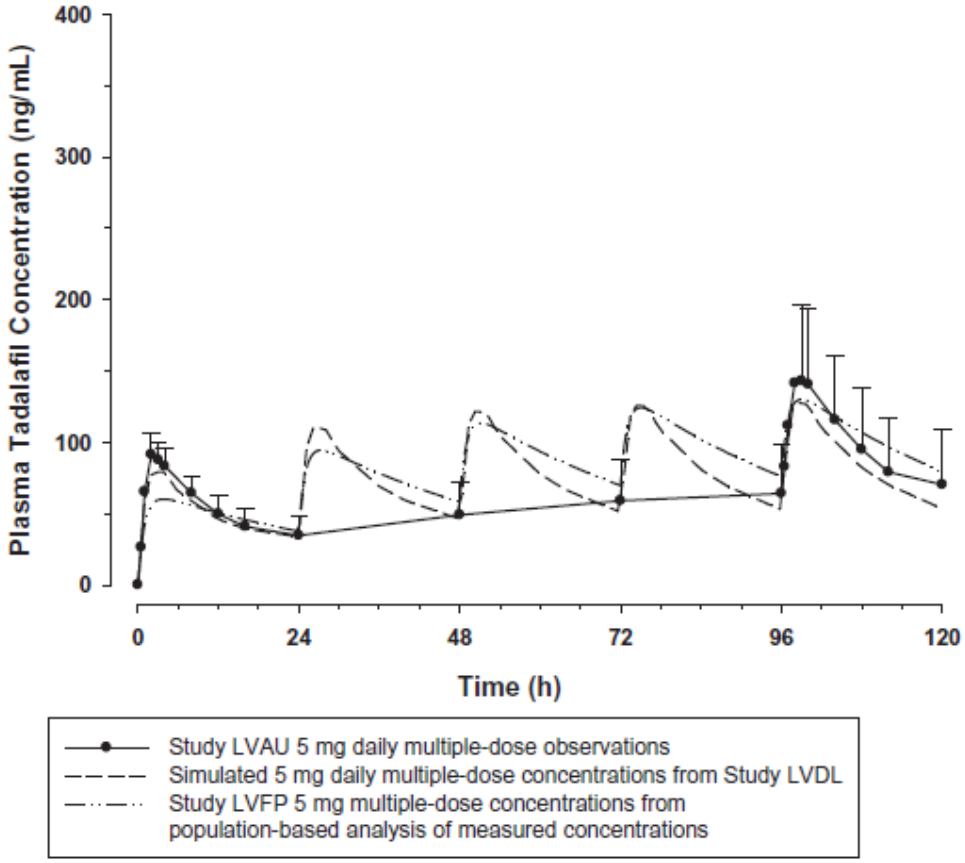

Figure 2 Predicted plasma tadalafil concentration vs. time profile from separate studies (dashed line [Study LVDL—healthy subjects] and dashed-dotted line [pharmacokinetic analyses of Study LVFP—men with erectile dysfunction, data on file]), and those observed for a multiple dose study of 5 mg tadalafil (solid line [Study LVAU—healthy subjects], points are arithmetic means, error bars are standard deviation).

Long term safety of tadalafil 5 mg dosed once daily-2 years-

Nessun grave evento avversofarmaco-correlato in due anni di studio.

Eventi avversi osservati in > o = 5% dei pazienti : dispepsia, cefalea, mal di schiena

Nessuna significativa alterazione all'ECG ed agli esami di laboratorio

Porst H., et al., J Sex Med. 2008

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Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality

Simon G Anderson,[1,2] David C Hutchings,[1] Mark Woodward,[2,3] Kazem Rahimi,[2] Martin K Rutter,[4,5] Mike Kirby,[6] Geoff Hackett,[7] Andrew W Trafford,[1] Adrian H Heald[8,9]

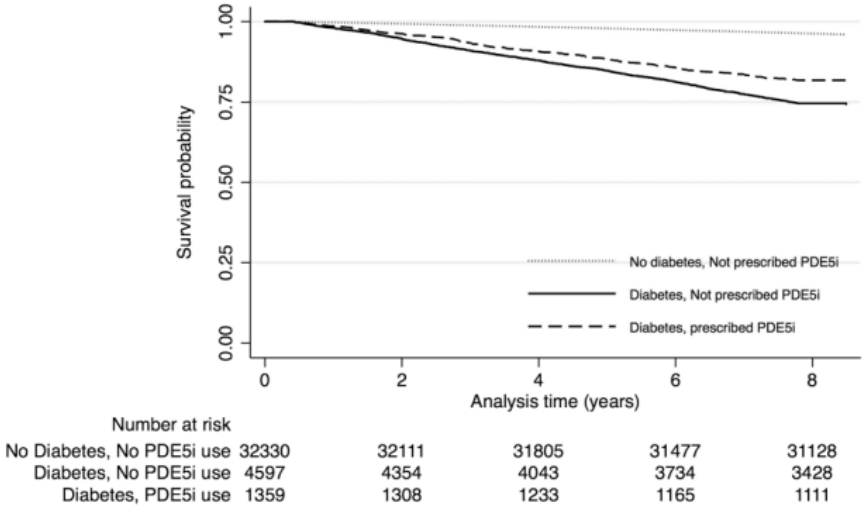

Figure 1 Time to all-cause mortality Kaplan-Meier curves by treatment (PDE5i vs no PDE5i) groups with history of diabetes and including non-users with no history of diabetes (reference population). PDE5i, phosphodiesterase type-5 inhibitor.

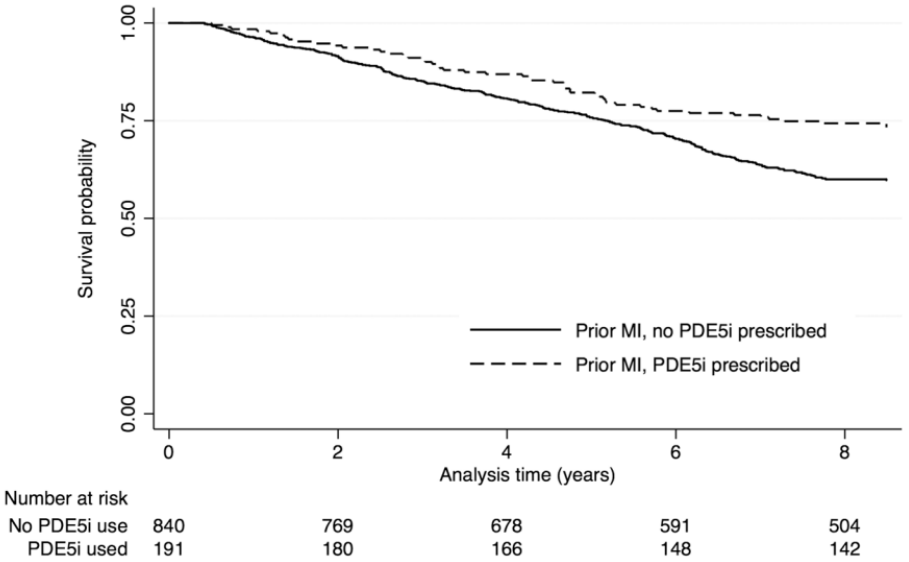

Figure 3 Time to all-cause mortality Kaplan-Meier curves for all men with a prior history of myocardial infarction (n=1031) by the treatment groups (PDE5i vs no PDE5i). PDE5i, phosphodiesterase type-5 inhibitor.

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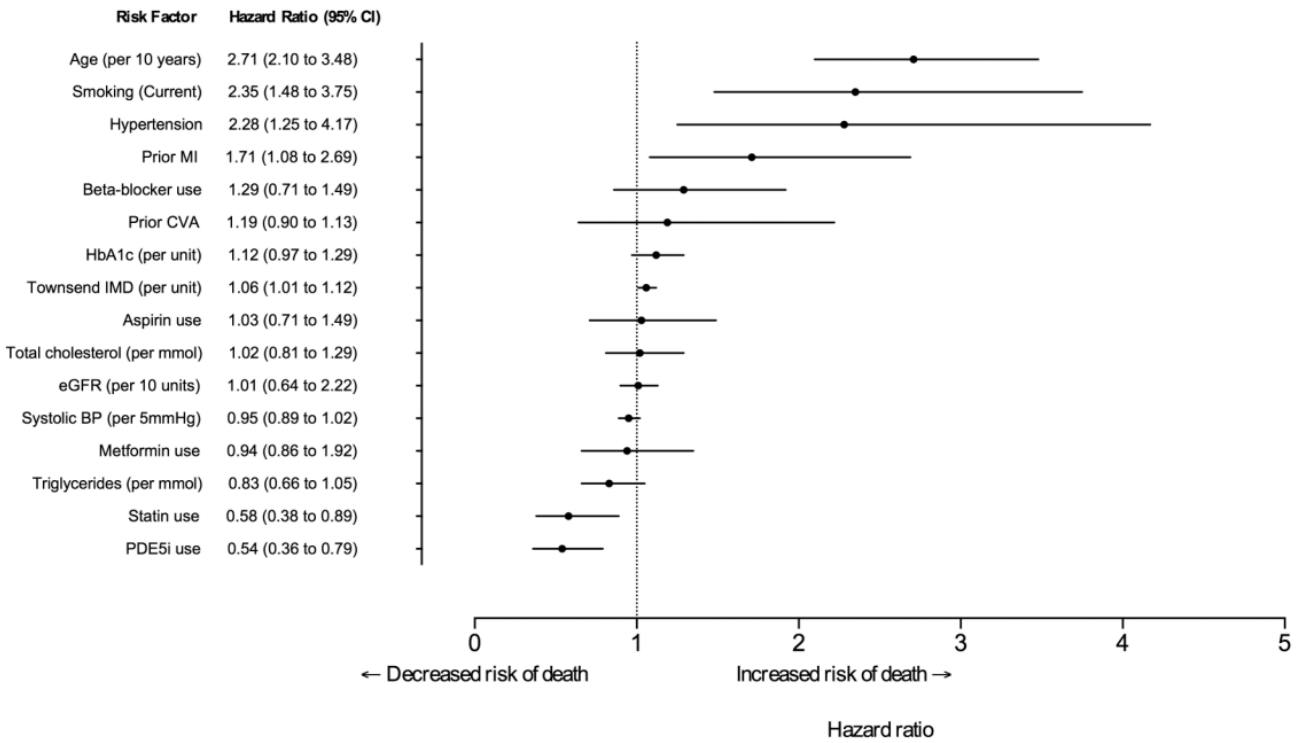

Figure 2 Forest plot of multivariable adjusted HRs of death associated with PDE5i use. PDE5i use adjusted for age, smoking, hypertension, prior MI, β-blocker use, prior CVA, HbA1c level, Townsend index of multiple deprivation (IMD) score, aspirin use, total cholesterol, estimated glomerular filtration rate, systolic BP, metformin use, triglyceride levels and statin use. BP, blood pressure; MI, myocardial infarction; PDE5i, phosphodiesterase type-5 inhibitor.

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...e in pazienti cardiopatici?

Accertarsi innanzitutto che il paziente possa riprendere l'attività sessuale!

Cardiovascular safety of PDE5 inhibitors

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Table 2: Cardiac risk stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

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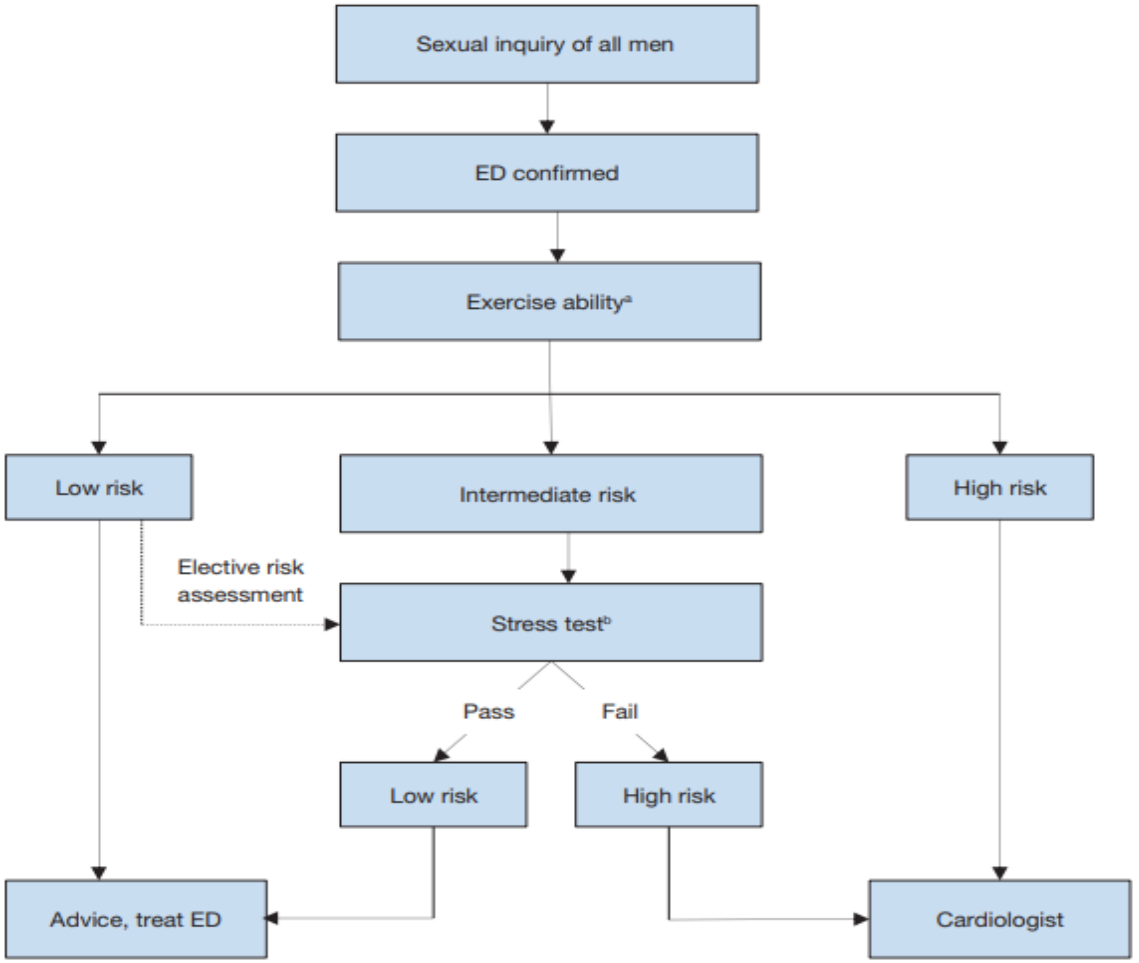
Figure 4: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [413]



[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.*

[b] *Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.*

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...e nei pazienti che assumo farmaci cardiovascolari?

Cardiovascular safety of PDE5 inhibitors

Nitrati

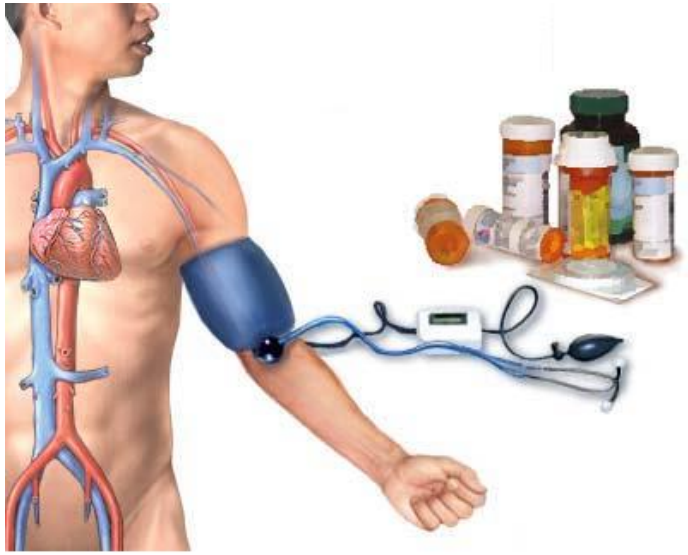
Nitroderivati: controindicazione assoluta all'uso di PDE5i!

In caso un paziente abbia assunto degli inibitori della PDE5 e l'insorgenza di angina renda necessario l'uso di nitrati, bisogna ettendere:

- 24 ore dall'assunzione di sildenafil/vardenafil
- 48 ore dall'assunzione di tadalafil

Nella pratica: i nitroderivati non potranno essere somministrati in pronto soccorso e bisognerà optare per altre soluzioni

Anti-ipertensivi



"Co-administration of PDE5 inhibitors with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, beta-blockers, diuretics) may result in small additive drops in blood pressure, which are usually minor.

In general, the adverse event profile of a PDE5 inhibitor is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents."

Nella pratica: nessuna interazione clinicamente significativa

Alfa-bloccanti

All PDE5 inhibitors show some interaction with alpha-blockers, which under some conditions may result in orthostatic hypotension.

- *Sildenafil labelling currently advises that 50 or 100 mg of sildenafil should not be taken within 4 h following treatment with an alpha-blocker. This restriction does not apply to 25 mg dose of sildenafil.*
- *In the USA, vardenafil is absolutely contraindicated with alpha-blockers. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension.*
- *Tadalafil is contraindicated in patients taking alpha-blockers, except for tamsulosin, 0.4 mg*

Nella pratica: l'interazione con gli alfa-bloccanti richiede attenzione

Management of non-responders to PDE5 inhibitors

- **Check that the patient has been using a licensed medication**
- **Check that the medication has been properly prescribed and correctly used**
  - The main ways in which a drug may be incorrectly used are:
    - **Failure to use adequate sexual stimulation**
    - **Failure to use an adequate dose**
    - **Failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.**

Onset & duration of action

Even though all three drugs have an onset of action in some patients within 30 min of oral ingestion, most patients require a longer delay between taking the medication, with at least 60 min being required for men using sildenafil and vardenafil and up to 2 h being required for men using tadalafil.

It is also possible to wait too long after taking medication before attempting sexual intercourse:

- *The half-life of sildenafil and vardenafil is about 4 h, suggesting that the normal window of efficacy is about 6-8 h following ingestion* of the medication, though responses following this time period are well recognized.
- *Tadalafil had a longer half-life of about 17.5 h, so the window of efficacy is much longer at about 36 h.*

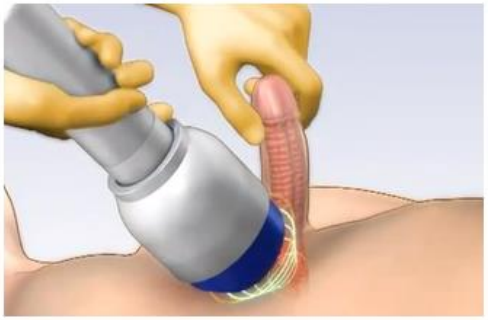
Food may affect drug absorption

Food may affect drug absorption: sildenafil's absorption can be delayed by a meal, while varenafil's absorption can be delayed by a fatty meal.

Tadalafil's absorption is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse.

Possible maneuvers in patients correctly using a PDE5 inhibitor

- Modification of associated risk factors:
  - Limited evidence suggests that, ***in a hypogonadal patient, normalization of the serum testosterone might improve the patient's response to a PDE5 inhibitor .***
- Change the PDE5 inhibitor
- Regular dosing of PDE5 inhibitor



Shockwave therapy

- The use of LI-SWT has been increasingly proposed as a treatment for vasculogenic ED over the last decade.
- Several single-arm trials have shown a beneficial effect of LI-SWT on patient-reported erectile function, but data are conflicting because of the heterogeneity among shockwave generators (i.e., electrohydraulic, electromagnetic, piezoelectric and electropneumatic); type of shockwaves delivered (i.e., focused, linear, semi-focused and unfocused); set-up parameters (e.g., energy flux density and number of pulses per session) and treatment protocols (i.e.,duration of treatment, number of sessions per week, total number of shockwave pulses delivered and penile sites of application)
- Most of the studies have suggested that LI-SWT can significantly increase the IIEF and EHS in patients with mild vasculogenic ED].
- Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are either PDE5Is non-responders or inadequate responders

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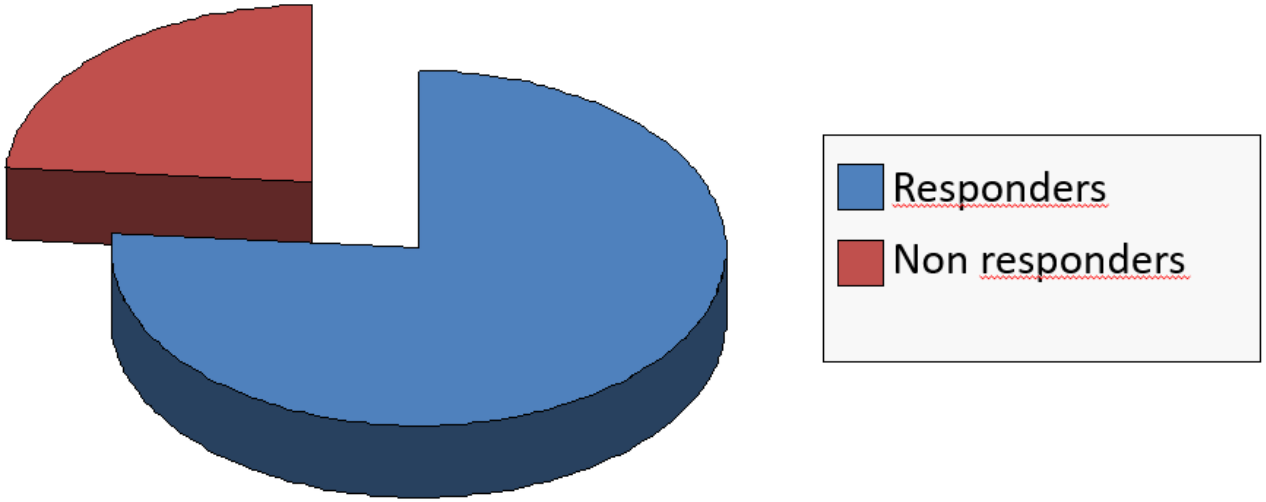
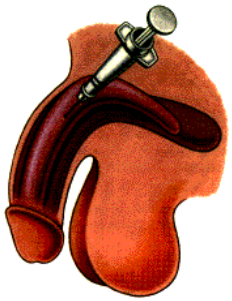
21-32% of pts are non responders to PDE5 inhibitors[1-3]



1. Katz SD et al: efficacy and safety of sildenafil citrate in men with erectile dysfunction. Am J Cardiol (2005)95:36-42
2. Raina R et al: Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. Urology (2003)62:110.115
3. Montorsi F et al.:North America and European Vadenafil groups: vardenafil provides reliable efficacy over time in men with erectile dysfunction. Urology (2004) 64. 1187-95
4. Shabsigh R. et a.: Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology. 2000 Apr, 55(4).477-80

Nei pazienti che continuano a non rispondere ai PDE5i…



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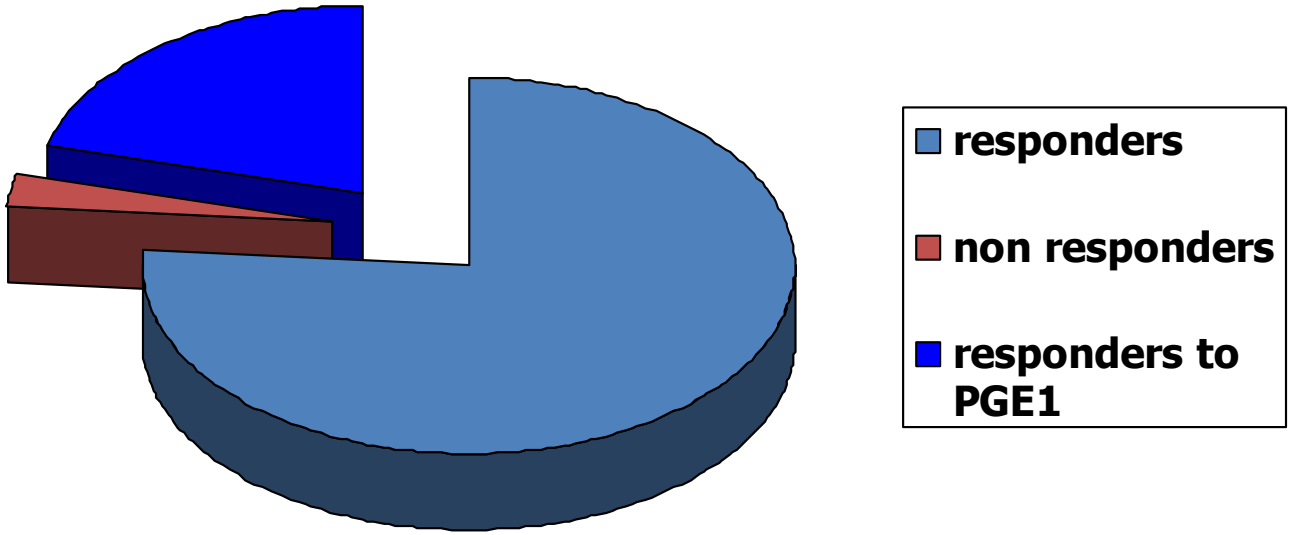
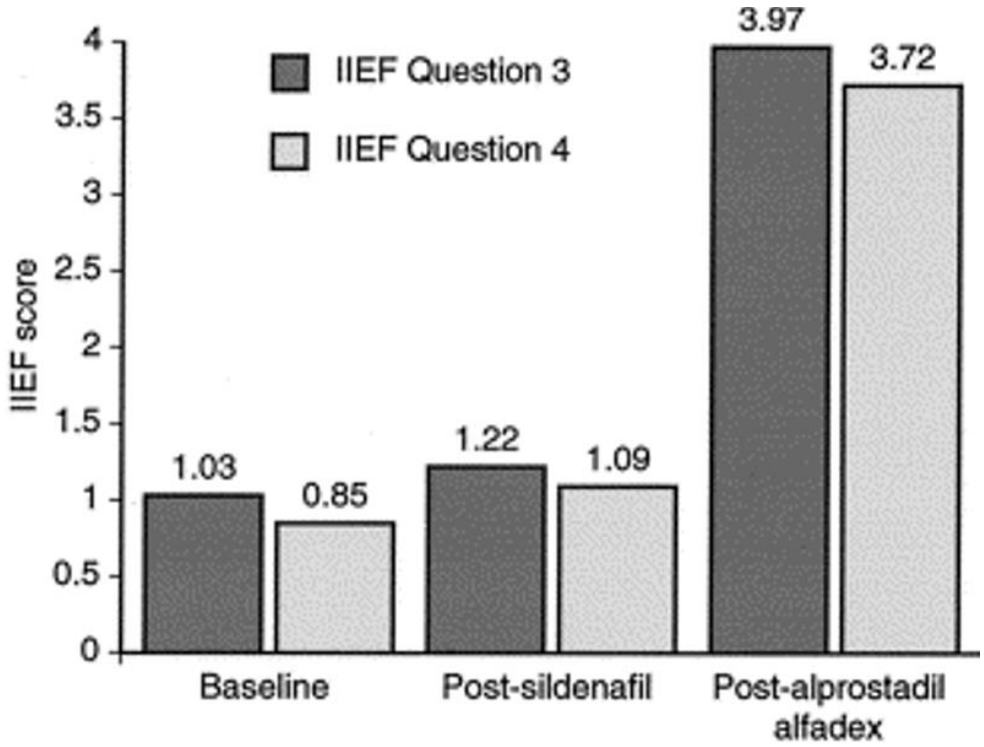


85-90% of non responders t oPDE5i respond to PGE1[4]

Improvement after sildenafil and Alprostadil Alfadex in 67 pts. non responders to sildenafil



Shabsigh R. et a.: Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology. 2000 Apr, 55(4).477-80

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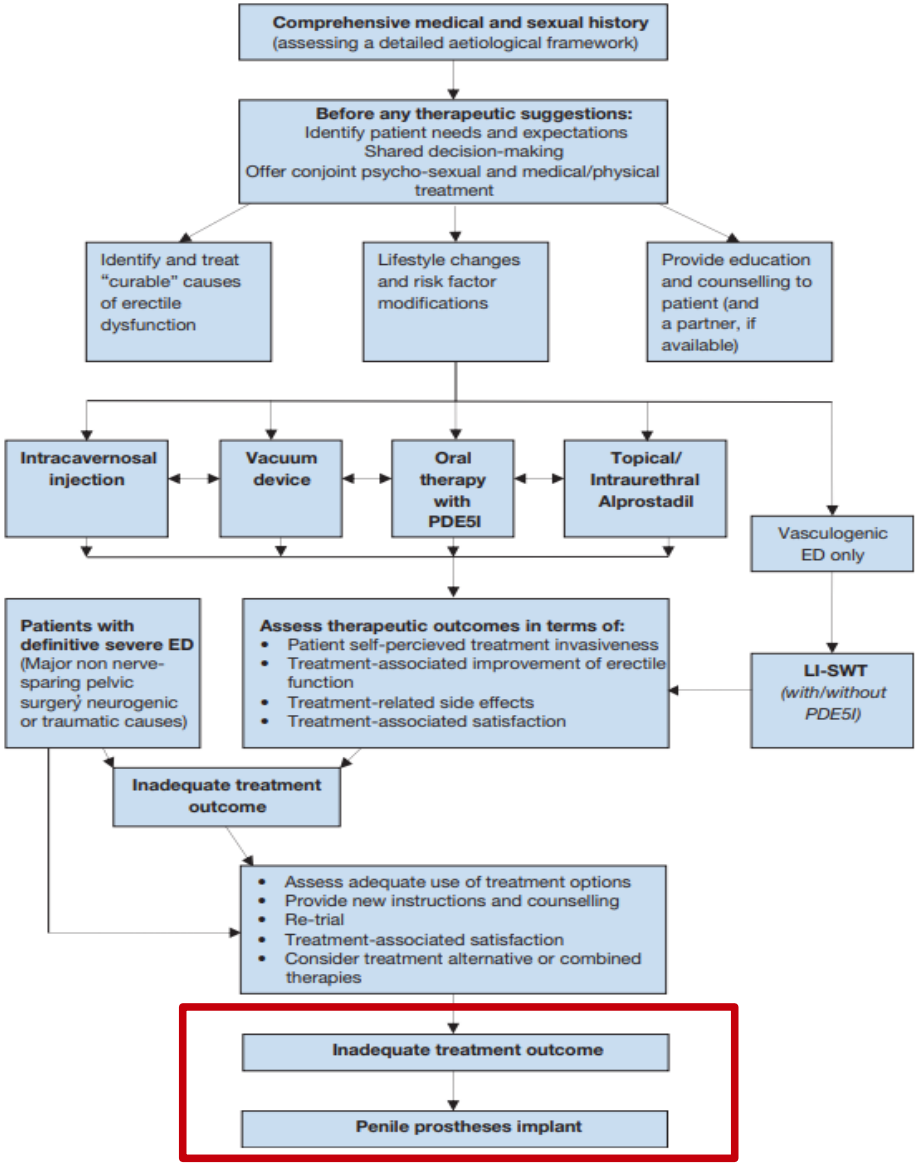
Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave therapy.

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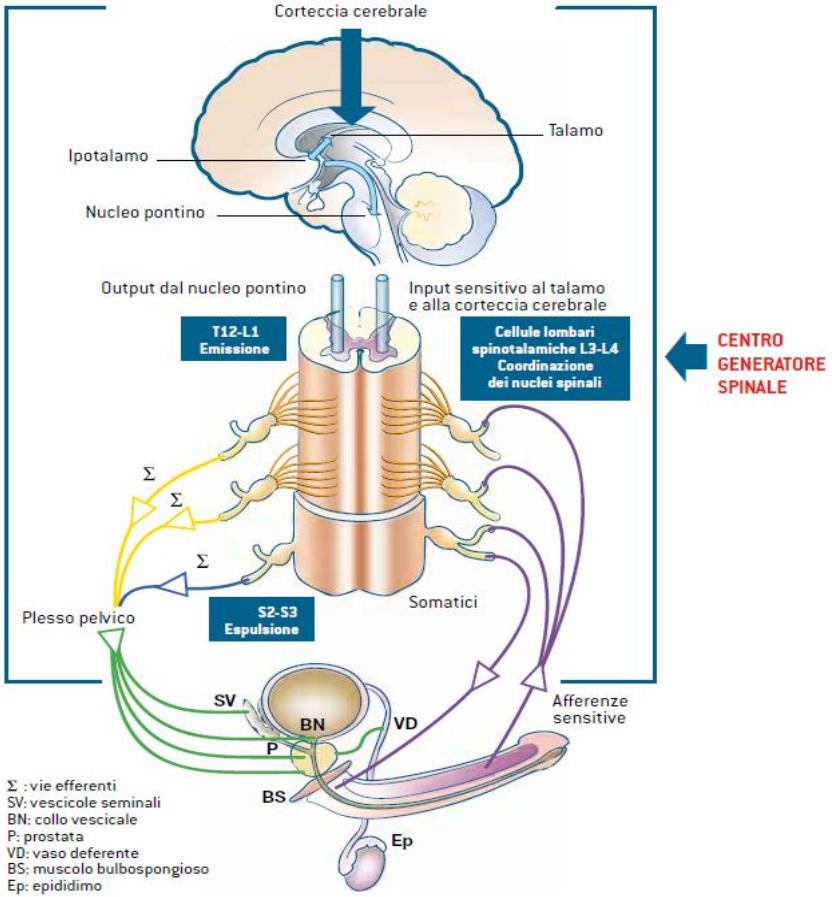
European Association of Urology

5.6.3 *Recommendations for treatment of ED*

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is).	Weak
Use Cognitive Behaviour Therapy as a psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time, as initiating ED treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use PDE5Is as first-line therapeutic option.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak
Use topical/intraurethral alprostadil as an alternative first-line therapy, in well-informed patients, who do not wish to have intracavernous injections or in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices (VEDs) as first-line therapy in well-informed patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/ pelvic surgery and other curative treatments for prostate cancer.	Weak

IL PROCESSO EIACULATORIO



I centri nervosi che controllano l'eiaculazione si trovano in varie aree, prevalentemente nell'area preottica mediana, nel sistema limbico, nel talamo. La serotonina è uno dei neurotrasmettitori centrali più importanti con un effetto di inibizione dell'eiaculazione.

Il sistema simpatico, nel tratto T12-L1 del midollo spinale, attiva l'eiaculazione (fase di emissione) tramite rilascio di noradrenalina e stimolazione dei recettori alfa α1 (contrazione della prostata, veschicole, dotti deferenti e eiaculatori, chiusura del collo vescicale). Il nervo pudendo rilascia lo sfintere esterno e contrae il muscolo bulbocavernoso.

Il sistema parasimpatico sacrale (S2-S3-S4) inibisce l'eiaculazione.

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LA RISPOSTA SESSUALE NELL'UOMO

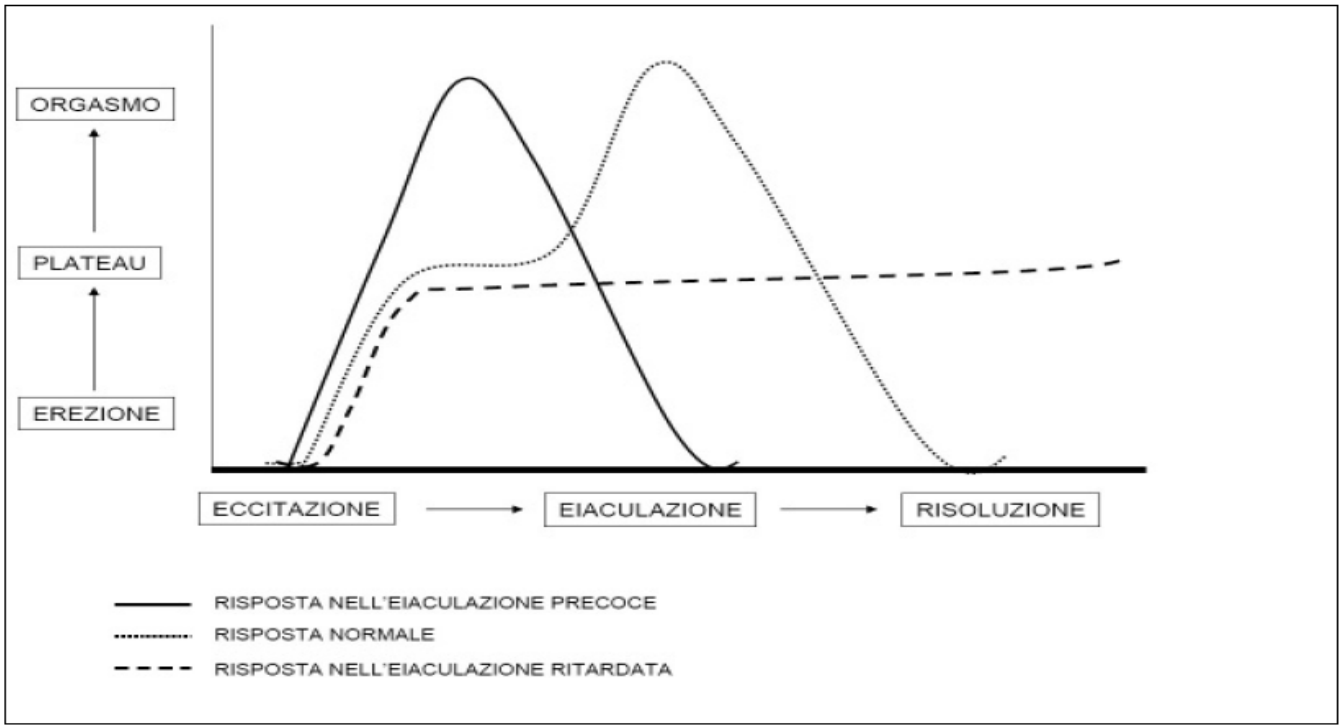

Figura 1. La risposta sessuale nell'uomo. Sotto l'effetto dell'eccitazione, l'uomo raggiunge la fase di "plateau", e quindi l'orgasmo; gli uomini con eiaculazione precoce hanno una fase di rapido eccitamento, che procede direttamente verso l'orgasmo con una scarsa o nulla fase di plateau. Il ciclo si conclude quasi subito dopo aver avuto inizio. Nell'eiaculazione ritardata il soggetto reagirà agli stimoli sessuali con buone erezioni ma con la difficoltà ad eiaculare, pur provando l'urgente desiderio della scarica orgasmica.

DEFINIZIONE

PE is defined *a "male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about* ***one minute*** *of vaginal penetration, and the* ***inability to delay*** *ejaculation on all or nearly all vaginal penetrations, and* ***negative personal consequences****, such as distress, bother, frustration and/or the avoidance of sexual intimacy"*

International Society of Sexual Medicine
2008

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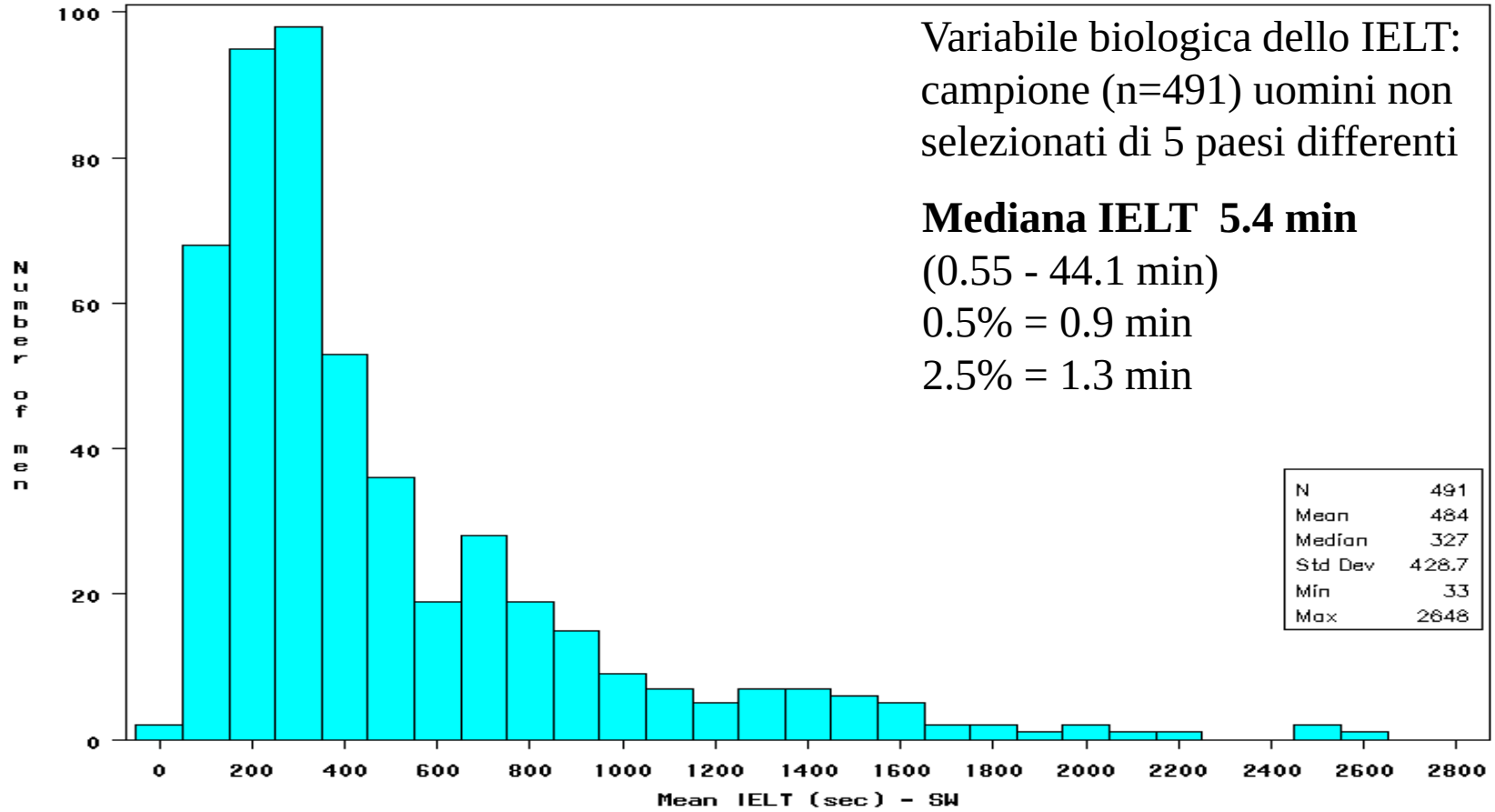
DISTRIBUZIONE DELLA LATENZA EIACULATORIA (IELT)



Variabile biologica dello IELT: campione (n=491) uomini non selezionati di 5 paesi differenti

Mediana IELT 5.4 min
(0.55 - 44.1 min)
0.5% = 0.9 min
2.5% = 1.3 min

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The Use of Old and Recent DSM Definitions of Premature Ejaculation in Observational Studies: A Contribution to the Present Debate for a New Classification of PE in the DSM-V

	Lifelong PE	Acquired PE	Natural Variable PE	Premature-Like Ejaculatory Dysfunction
1	Very short IELT	(Very) short IELT	Normal IELT	Normal / long IELT
2	Neurobiological genetic	Medical psychological	Normal variation	Psychological
3	Medication	Medication psychotherapy	Reassurance	Psychotherapy
4	Low prevalence	Low prevalence	High prevalence	High prevalence

→

Figure 1 Proposal for a new classification of PE for the DSM-V.
The arrow shows different continuums of PE subtypes; from very short to normal and long IELT durations, from more neurobiologically to more psychologically determined subtypes and from rather small prevalence to possibly high prevalence in the general population.
PE = premature ejaculation; IELT = intravaginal ejaculatory latency time.

J Sex Med 2008;5:1079–1087

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REGIONE LOMBARDIA

Disorders of Orgasm and Ejaculation in Men

Chris G. McMahon, MB, BS, FACSHP,* Carmita Abdo, MD,† Luca Incrocci, MD,‡ Michael Perelman, PhD,§ David Rowland, PhD,¶ Marcel Waldinger, MD,# and Zhong Cheng Xin, MD**

Table 1 Proposed etiologies of premature ejaculation

Psychogenic	Anxiety
	Early sexual experience
	Frequency of sexual intercourse
	Ejaculatory control techniques
	Evolutionary
	Psychodynamic theories
Biological	Penile hypersensitivity
	Hyper-excitable ejaculatory reflex
	Arousability
	Endocrinopathy
	Genetic predisposition
	5-HT receptor dysfunction

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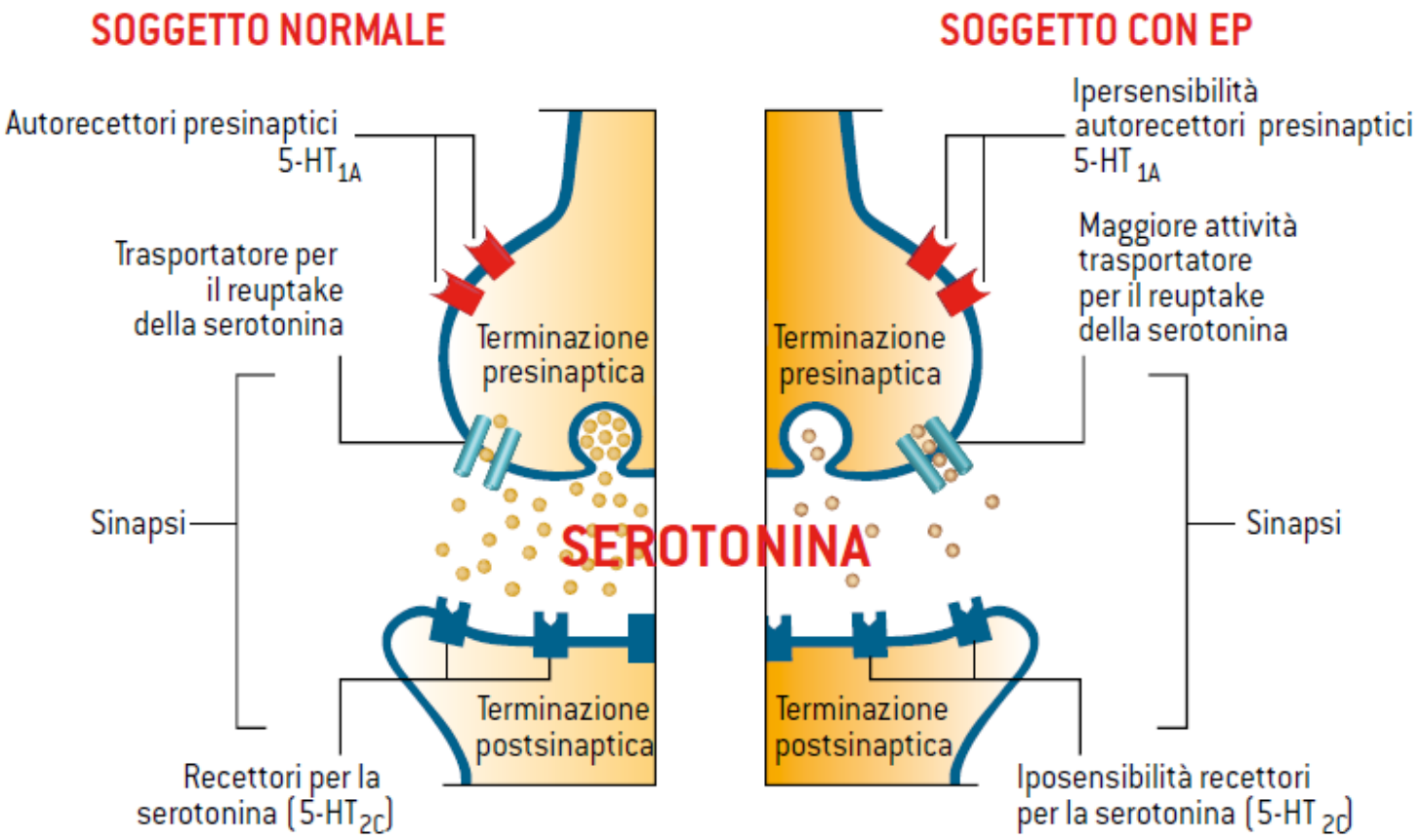
IL RUOLO DELLA SEROTONINA



FATTORI GENETICI

Genetics of PE

In his classic article, Bernhard Schapiro noted that some family members of men with PE also have PE [59]. Many years later Waldinger et al. hypothesized that both the IELT and lifelong PE for some men are genetically determined [43]. Supporting this hypothesis was the report of a high prevalence of lifelong PE (defined in terms of and IELT of less than 1 minute) among first degree male relatives of Dutch men with lifelong PE [60].

Models to explain premature and delayed ejaculation were developed based on examination of 1,196 Finish male twins between the ages of 33 to 43 years [56]. The PE model suggested a moderate additive genetic variance of 28%, with no shared environmental variance (0%) and 72% nonshared environmental variance. One possible interpretation of these findings is that genetic influences may create a diathesis or predisposition in some men to ejaculate prematurely.

The first DNA study on PE was performed in 89 Dutch men with lifelong PE, in whom IELT was measured by a stopwatch [61]. Men with PE were compared with a cohort of mentally and physically healthy Dutch Caucasian men. The data demonstrated an association of the 5-HTLPR gene polymorphism and the duration of the IELT. Men with lifelong PE, defined as IELTs of less than 1 minute, and with the LL genotype ejaculated in a 100% shorter time than PE men with the SL and SS genotype. Additionally, the study showed that there was no difference in the prevalence of the LL, SL, and SS genotypes in men with lifelong PE compared with their prevalence in the general male Dutch population. Given that the distribution of the polymorphism is similar in lifelong premature ejaculators and mentally and physically healthy Dutch men, this study also lends support to a predisposition/diathesis model rather than the conclusion that genetic influences underlie all men with lifelong PE.

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Frenulo breve ed eiaculazione precoce (PE)

- Nello studio di Gallo et al, circa 43% di pazienti con eiaculazione precoce permanente soffriva di frenulo breve.
- Alla valutazione di base, l'IELT medio era 1.65 minuti (+/-1.15), e lo score del questionario PE era 15.8 (+/-2.85).
- Dopo frenuloplastica, l'IELT era 4.11 minutes (+/-1.77), e lo score del questionario PE era 9.85 (+/-3.2), un' aumento statisticamente significativo rispetto alla valutazione alla baseline.

"**Conclusion.** We suggest always ruling out at physical examination the presence of a short frenulum in all patients complaining of PE and to propose frenulectomy as first-line treatment in these cases."

Gallo L et al. The role of short frenulum and the effects of frenulectomy on premature ejaculation. Volume 7, Issue 3, pages 1269–1276, March 2010

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Fimosi e PE

- Obiettivo di questo studio era di valutare l'effetto della circoncisione sulla percezione di soddisfazione sessuale in maschi con partner sessuali fissi.
- Circa 82% dei pazienti hanno riportato miglioramento della qualità dei loro rapporti sessuali dopo l'intervento di circoncisione.
- Il tasso di eiaculazione precoce è diminuito da 31.8% al 13.6% dopo la procedura chirurgica, suggerendo un possibile ruolo della fimosi sulla patogenesi della PE (ipersensibilità peniena??)

[Does circumcision affect male's perception of sexual satisfaction?].
Arch Esp Urol. 2009 Nov;62(9):733-6.

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Ipersensibilità peniena e PE

- Molti autori hanno suggerito che gli uomini con PE presentanto ipersensibilità peniena e come conseguenza raggiungono il limite eiaculatorio più rapidamente o presentano un limite eiaculatorio inferiore rispetto ai controlli normali.

(Rowland et al, 1989 ; Strassberg et al, 1990)

FATTORI ENDOCRINOLOGICI

International Society for Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation

Stanley E. Althof, PhD,[1] Carmita H.N. Abdo, MD, PhD,[2] John Dean, MD,[3] Geoff Hackett, MD,[4] Marita McCabe, PhD,[5] Chris G. McMahon, MD,[6] Raymond C. Rosen, PhD,[7] Richard Sadovsky, MD,[8] Marcel Waldinger, MD, PhD,[9] Edgardo Becher, MD,[10] Gregory A. Broderick, MD,[11] Jacques Buvat, MD,[12] Irwin Goldstein, MD,[13] Amr I. El-Meliegy, MD,[14] Francois Giuliano, MD, PhD,[15] Wayne J.G. Hellstrom, MD,[16] Luca Incrocci, MD, PhD,[17] Emmanuele A. Jannini, MD,[18] Kwangsung Park, MD, PhD,[19] Sharon Parish, MD,[20] Hartmut Porst, MD,[21] David Rowland, PhD,[22] Robert Segraves, MD, PhD,[23] Ira Sharlip, MD,[24] Chiara Simonelli, PhD,[25] and Hui Meng Tan, MD[26]

Thyroid Hormones

Endocrine control of the ejaculatory reflex is still not completely clarified [66]. There is evidence to indicate a link between depression, serotonin, and thyroid hormones [67,68]. Carani reported that 50% of hyperthyroid men had PE and when successfully treated the prevalence of PE fell to 15% [53,54,66].

PROSTATITI ED EP

PREVALENCE OF CHRONIC PROSTATITIS IN MEN WITH PREMATURE EJACULATION

EMILIANO SCREPONI, ELEONORA CAROSA, SAVINO M. DI STASI, MARIO PEPE, GIUSEPPE CARRUBA, AND EMMANUELE A. JANNINI

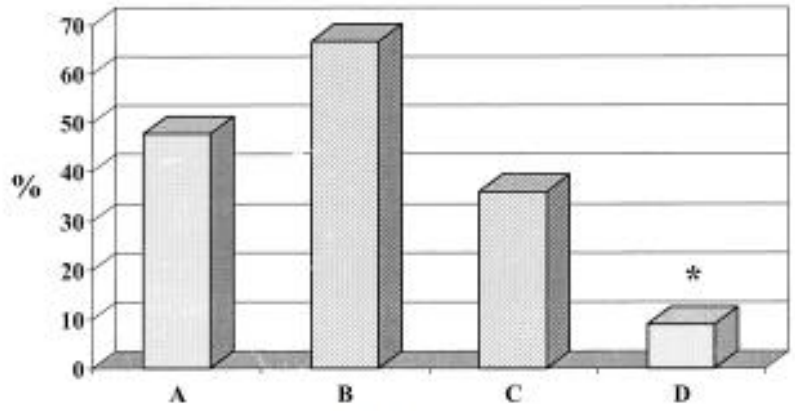

FIGURE 1. *Prevalence of chronic bacterial prostatitis in 46 men with premature ejaculation (total group [A], PPE [B], and SPE [C]) and in 30 healthy controls (D). Asterisk indicates P <0.05 versus group with premature ejaculation.*

CONCLUSIONS

If larger studies confirm our findings, a routine examination of the prostate in the clinical evaluation of patients with premature ejaculation should be performed. The bacteriologic localization test, as described by Meares and Stamey,[23] even in the absence of symptoms, should be performed before considering psychosexual or pharmacologic therapies for this sexual disorder.

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IPOTESI PATOGENETICHE di EP da DE

§ Risposta comportamentale conscia o inconscia alla D.E.
§ Associazione con ansia da prestazione (ipertono adrenergico)

H.S. Kaplan, 1989 – B. Zilbergeld, 1992

L'ipertono adrenergico attiva l'emissione seminale destabilizzando il controllo del riflesso eiaculatorio

J. Volpe, 1982 – W. William, 1984

L'ipertono adrenergico riduce la percezione dei segnali prodromici dell'orgasmo

HS. Kaplan, 1989 – B. Zilbergeld, 1992

Può non essere una vera E.P., ma un'eiaculazione da iperstimolazione in caso di reiterati e protratti tentativi di indurre l'erezione

FATTORI PSICO-SESSUOLOGICI

Fattori Intrapsichici (psicanalitici)

L'EP esprime l'incapacità del soggetto di gestire emotivamente il conflitto tra sentimenti inconsci di ostilità nei confronti delle donne e desiderio cosciente di vivere un rapporto di relazione

C. Simonetti, R . Rossi., *2000*

Fattori Immediati

- Insufficienti informazioni sull'anatomo-fisiologia e sulle dinamiche del rapporto sessuale

W. Hawton, 1987

- Fenomeno dello "Spectatoring"
  Tentativo di instaurare difese percettive ed intellettuali contro le proprie sensazioni erotiche, fino a perdere il contatto con le sensazioni di piacere e di eccitazione

W.H. Master, V.E. Johnson, 1970

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FATTORI PSICO-SESSUOLOGICI

Da un punto di vista psicologico, l'Eiaculazione Precoce può nascere da fattori psicologici :

In particolare:

un'ambivalenza nei confronti dell'universo femminile e della relazione di coppia;
un vissuto di ansia verso la sessualità e forme di ansia relazionale;
conflitti di coppia;
paura del rifiuto e del confronto;
aspettative non realistiche sulla sessualità;
presenza di una compagna con disfunzione sessuale
eccessivo desiderio di soddisfare la partner;
inesperienza sessuale (soprattutto nei giovanissimi) tale da non consentire una buona gestione dell'eiaculazione

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IL RUOLO DELL'ANSIA

A) L'effetto iper-adrenergico correlato all'ansia attiva l'emissione seminale, destabilizzando il controllo del riflesso eiaculatorio

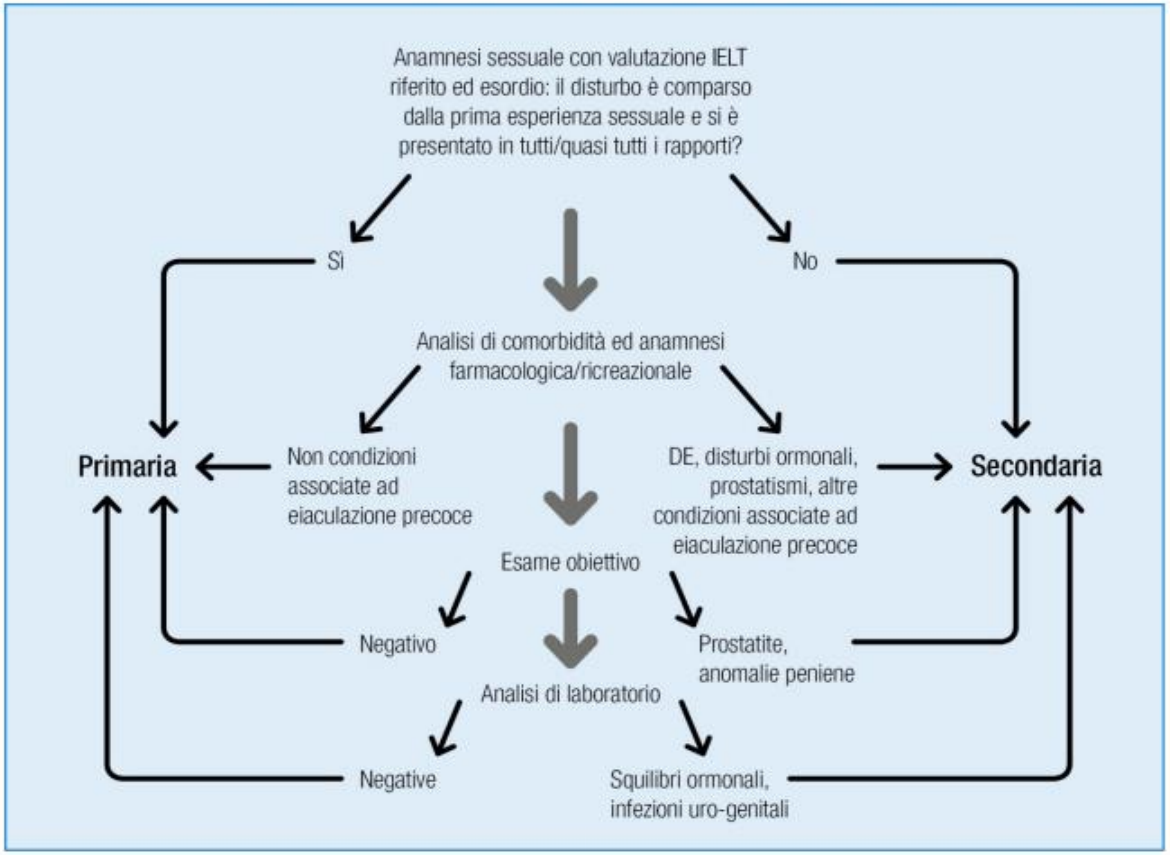
J. Wolpe, 1982 - W.William, 1984

B) I soggetti ansiosi, sono condizionati dalla costante autovalutazione critica della loro prestazione sessuale.

Ciò comporta la ridotta percezione delle sensazioni eccitatorie e dei segnali prodromici dell'orgasmo

H.S. Kaplan, 1989 - B. Zilbergeld, 1992

ALGORITMO DIAGNOSTICO



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PREMATURE EJACULATION DIAGNOSTIC TOOL (PEDT)

1) Quanto è difficile per te ritardare l'eiaculazione?

- per niente	0
- un po' difficile	1
- moderatamente difficile	2
- molto difficile	3
- estremamente difficile	4

2) Ti capita di eiaculare prima che lo desideri?

- quasi mai o mai (0% delle volte)	0
- meno della metà delle volte (circa il 25% delle volte)	1
- circa metà delle volte (il 50% delle volte)	2
- più della metà delle volte (circa il 75% delle volte)	3
- quasi sempre o sempre (100% delle volte)	4

3) Ti capita di eiaculare con una minima stimolazione?

- quasi mai o mai (0% delle volte)	0
- meno della metà delle volte (circa il 25% delle volte)	1
- circa metà delle volte (il 50% delle volte)	2
- più della metà delle volte (circa il 75% delle volte)	3
- quasi sempre o sempre (100% delle volte)	4

4) Ti senti frustrato perché eiaculi prima di quando vuoi?

- per niente	0
- un po'	1
- moderatamente	2
- molto	3
- estremamente	4

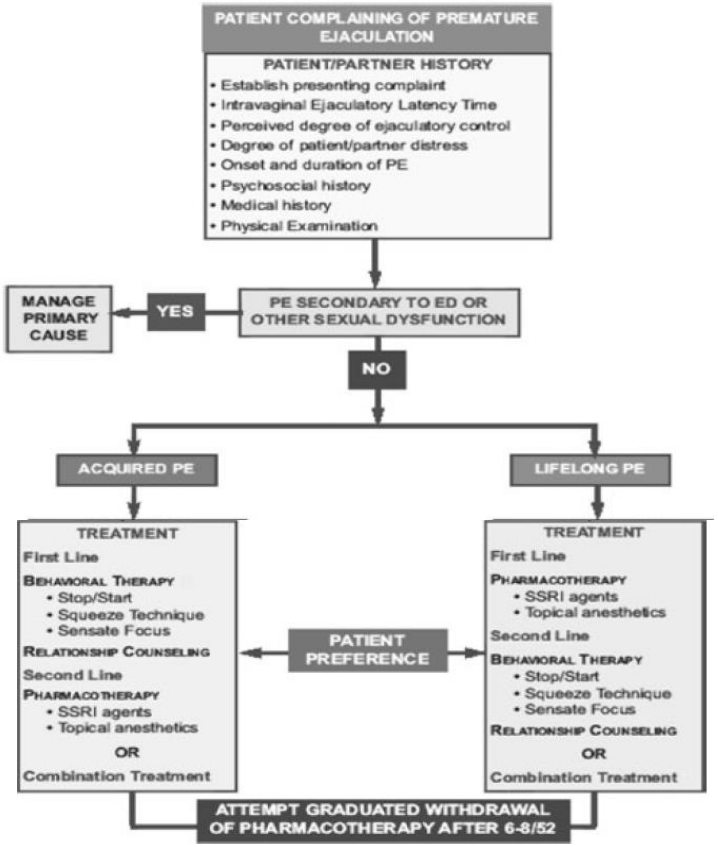
5) Quanto sei preoccupato che la velocità di eiaculazione lasci insoddisfatta la tua partner?

- per niente	0
- un po'	1
- moderatamente	2
- molto	3
- estremamente	4

I risultati dei punteggi suggeriscono le seguenti conclusioni:

- **≤8 non evidenza di *eiaculazione precoce***
- **Da 9 a 10 sospetta *eiaculazione precoce***
- **≥11 *eiaculazione precoce***

ALGORITMO TERAPEUTICO



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© Journal of Sexual Medicine 1743 6095

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La terapia farmacologica della EP con Dapoxetina™, l'unico SSRI short-acting approvato per la terapia sintomatica on demand della EP

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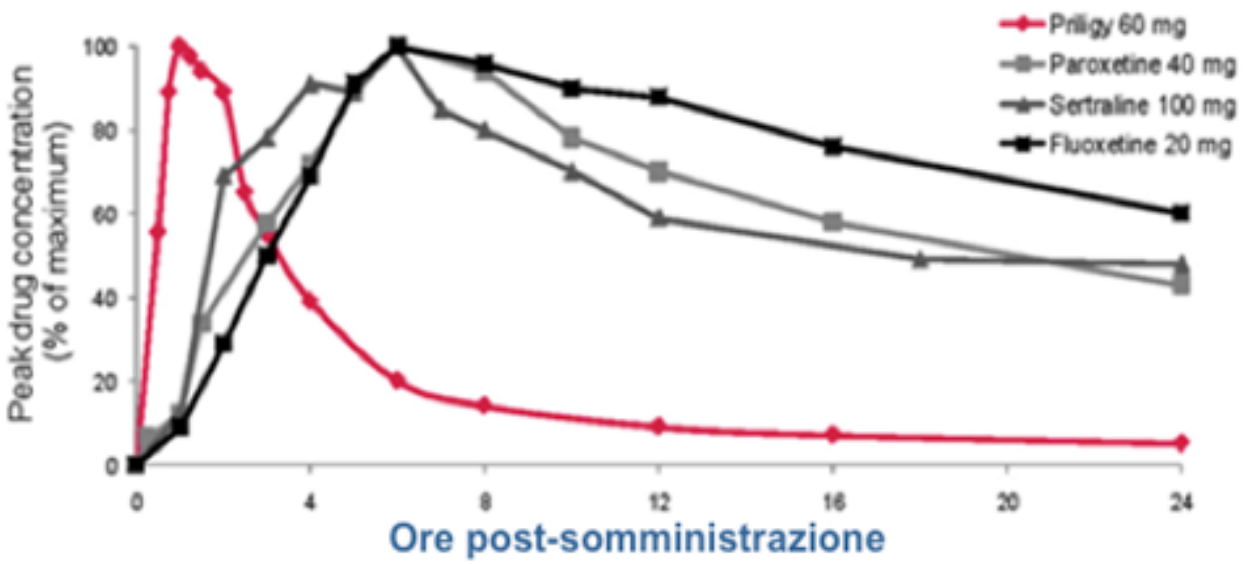
E' assorbita ed eliminata molto più velocemente degli SSRIs tradizionali

Concentrazioni plasmatiche di SSRIs a 24 ore



McMahon CG. Ther Adv Urol. 2012

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Profilo farmacocinetico

	C_{max}	Emivita	Steady state
Dapoxetina [41]	1 ora	Iniziale: 1,4 ore	4 giorni (con minimo accumulo)
Paroxetina [41]	5 ore	16-18 ore	7-14 giorni
Fluoxetina [41]	6-8 ore	1-4 giorni	2-4 settimane
Sertralina [44]	4,5-8,4 ore	26 ore	1 settimana

Gli SSRI convenzionali sono generalmente somministrati cronicamente e possono richiedere giorni o settimane per raggiungere le concentrazioni plasmatiche allo steady state, con emivite che variano da 16 ore a 4 giorni

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Raccomandazioni per l'assunzione

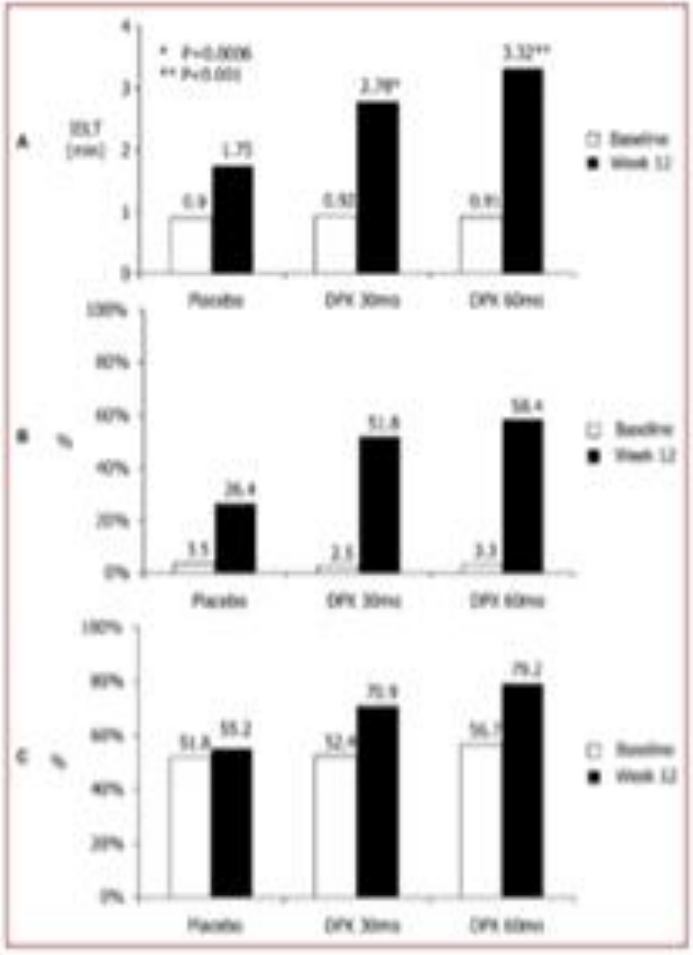
- Cautela nei pazienti con insufficienza renale/ epatica di grado moderato-grave
- Può essere assunta in corrispondenza o lontano dai pasti
- Nessuna variazione in caso di pasto ad alto contenuto lipidico
- Cautela nell'assunzione di alcool

THE LANCET

Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials

Studio in doppio cieco di 12 settimane, placebo-controllato, multicentrico di fase III su 2614 uomini con TLEI basale < 2 m'

§ Assunta 1-2 h. prima del rapporto, Dapoxetina è efficace, ben tollerata ed incrementa il TLEI di 2-3 volte sopra il valore di base ed in maniera dose-dipendente



§ Dapoxetina 30 o 60 mg **è stata più efficace del** placebo per tutti gli *endpoints* dello studio

A. TLEI = da 0.9' a 2.78' e 3.32'

B. Controllo sull'eiaculazione = da 3.5% a 51.8% e 58.4%

C. Livello di soddisfazione = da 55.2% a 70.9% e 79.2%

Pryor, J.L. "Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomized trials" *The Lancet* 2006; 368: 929-937

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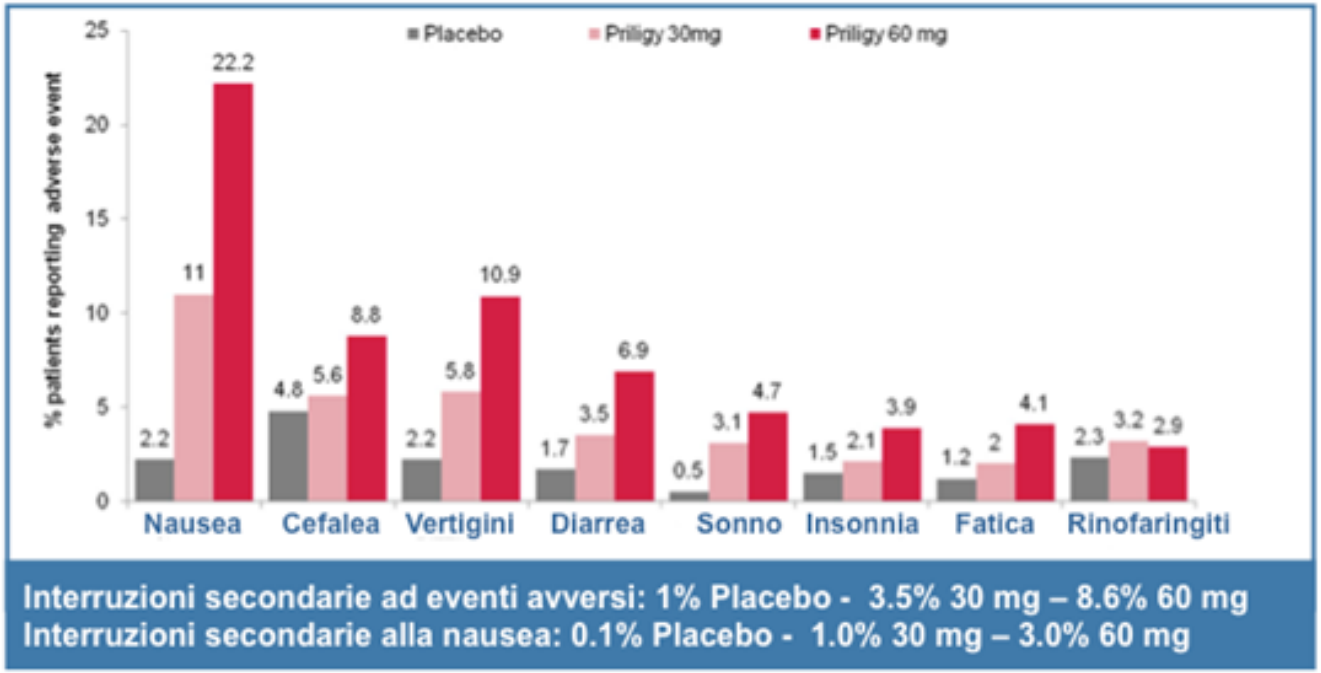
TOLLERABILITA' E SICUREZZA

Più comuni eventi avversi riscontrati nei soggetti con frequenza ≥ 2%



Interruzioni secondarie ad eventi avversi: 1% Placebo - 3.5% 30 mg – 8.6% 60 mg
Interruzioni secondarie alla nausea: 0.1% Placebo - 1.0% 30 mg – 3.0% 60 mg

McCarty E, Dinsmore W. Core Evid. 2012

TOLLERABILITA' E SICUREZZA

Eventi avversi (incidenza ≥2%)	Sospensione a causa di EA (n=1.774) %
Nausea	1,6
Vertigini	1
Diarrea	0,8
Cefalea	0,6
Insonnia	0,5

L'incidenza di effetti collaterali sessuali e' molto bassa (<5%)

Placebo	*1,9%*
Dapoxetina 30 mg	*2,9%*
Dapoxetina 60 mg	*3,8%*

Assenza di sindrome da sospensione

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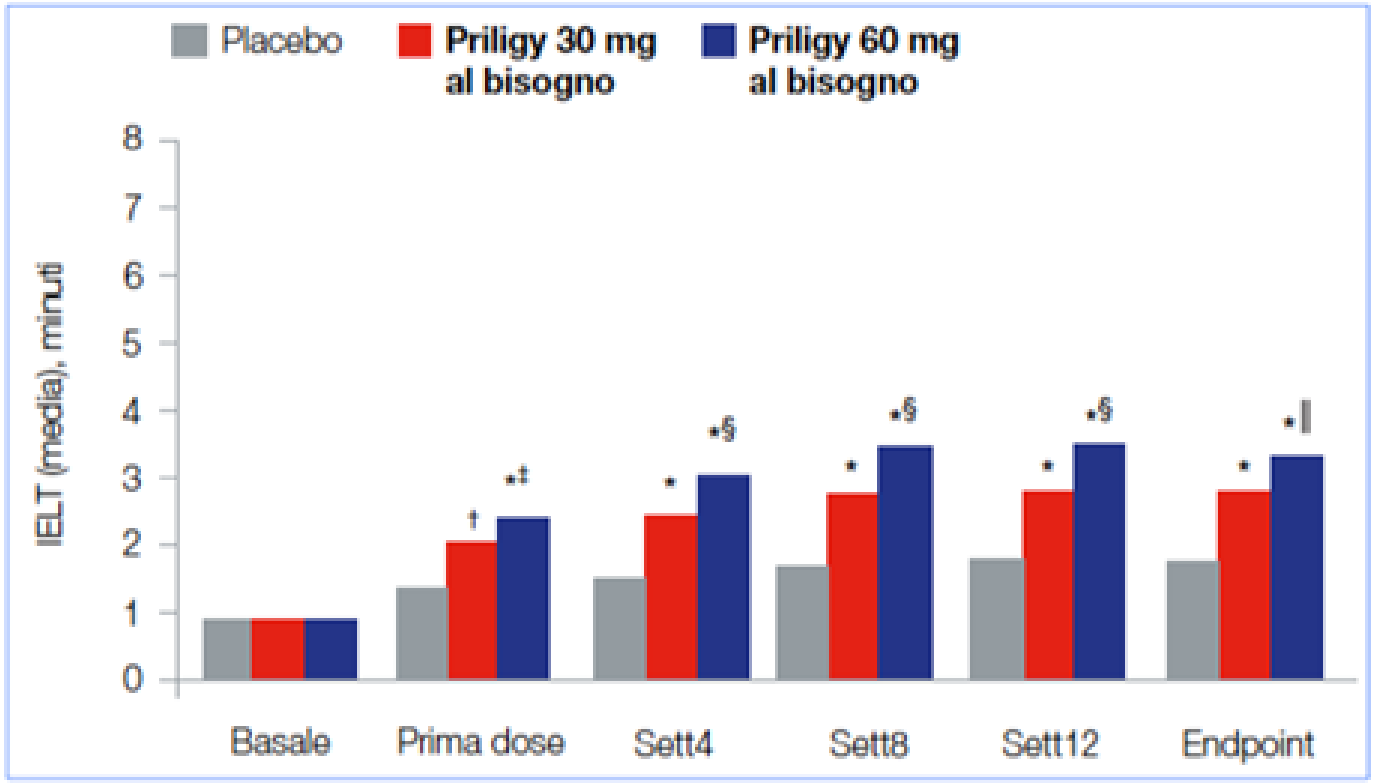
EFFICACIA SULLO IELT



Buvat J et al. Dapoxetine for the Treatment of Premature Ejaculation: Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial in 22 Countries. Eur Urol 2009;55:957-968

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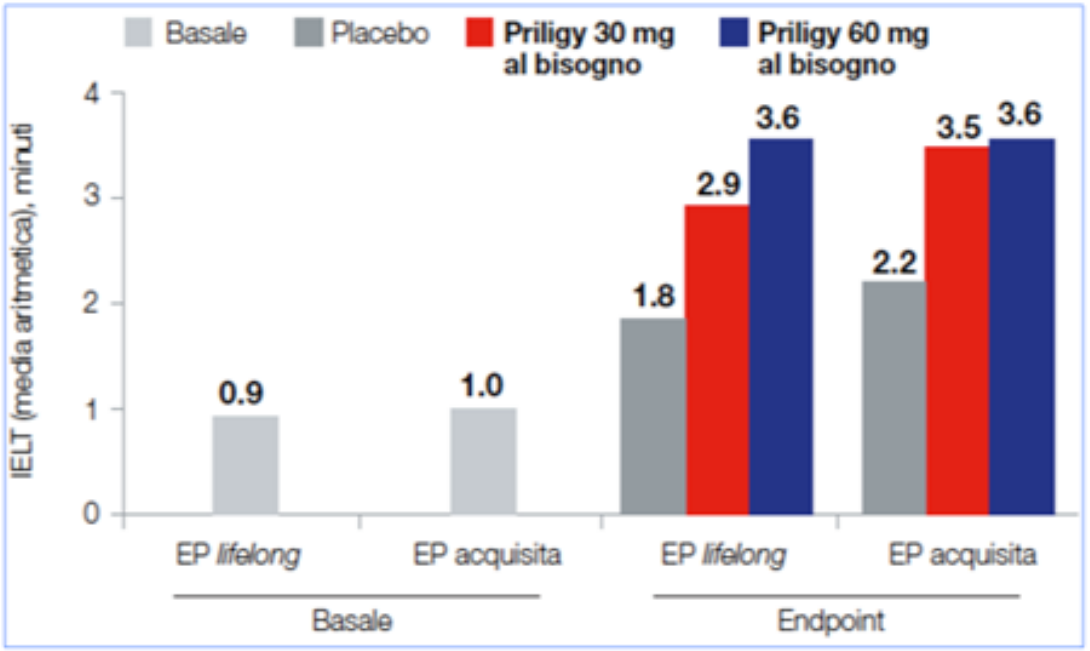
EFFICACIA SULLO IELT



Buvat J et al. Dapoxetine for the Treatment of Premature Ejaculation: Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial in 22 Countries. Eur Urol 2009;55:957-968

DESENSIBILIZZAZIONE DEL GLANDE CON ANESTETICI TOPICI

Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation

Wallace W. Dinsmore[1], Geoffrey Hackett[1], David Goldmeier[2], Marcel Waldinger[3], John Dean[4], Patrick Wright[5], Michael Callander[6], Kevan Wylie[7], Claire Novak[8], Charlotte Keywood[8], Patricia Heath[8], Michael Wyllie[9,*]

Issue

BJU International
Volume 99, Issue 2, pages 369–375, February 2007

E' efficace quando l'EP è secondaria ad ipersensibilità del glande

ANESTETICI TOPICI LOCALI come lidocaina e/o prilocaina in crema, gel o spray (Promescent® G&H Brands e Lovelong® Themis Medicare // 2-5 gr prima del rapporto mantenuti per 10'-20')

SVANTAGGI

§ Possibilità di DE da perdita delle sensazioni somatiche glandulari
§ Rischio di reazioni allergiche
§ Se il farmaco non è **accuratamente rimosso** con lavaggio (o non si usa il *condom*), è possibile il suo assorbimento transvaginale, con DSF da perdita della sensibilità vulvo-vaginale

Wyllie MG, Hellstrom WJ. BJU Int. 2011

Eutectic Lidocaine/Prilocaine Metered Dose Spray (Fortacin)

- Prima terapia topica ufficialmente approvata per eiaculazione precoce
- Spray pre-dosato a base di lidocaina 150 mg/ml e prilocaina 50 mg/ml in assenza di eccipienti eccetto che il propellente spray (norflurano)
- La miscela eutettica dei 2 componenti lidocaina e prilocaina ottimizza il loro assorbimento attraverso un tessuto non cheratinizzato come quello del glande, massimizza l'estensione del blocco neurale e minimizza l'insorgere del torpore.
- Il sistema di erogazione spray a dose controllata consente ai componenti di essere depositati in un film concentrato sul glande e di essere assorbiti dalla mucosa ma non dalla superficie cheratinizzata del pene in modo che possa essere mantenuta una sensazione conservata nell'asta.

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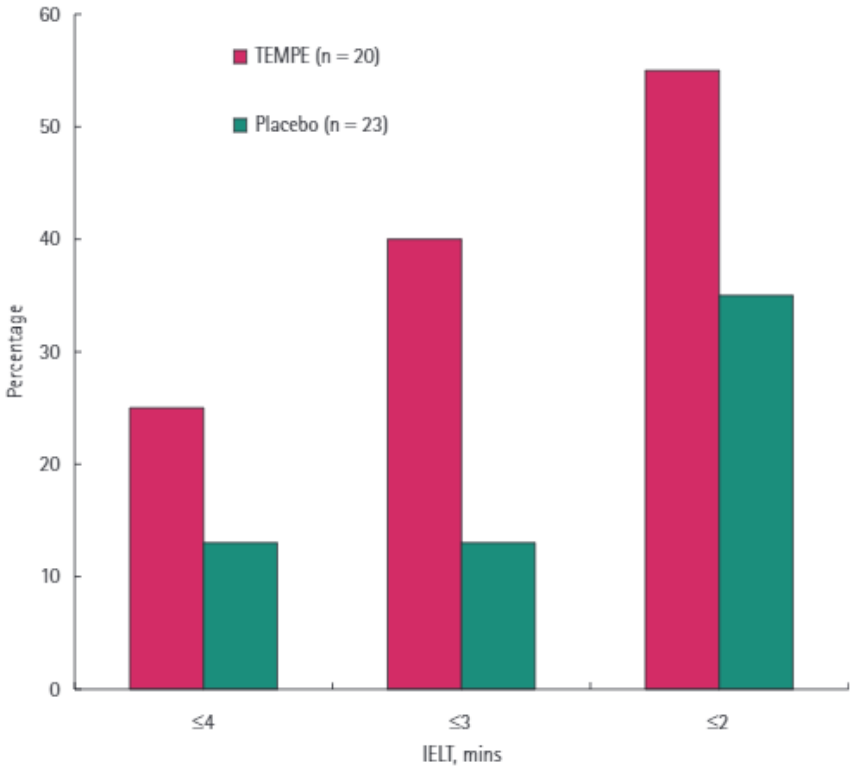
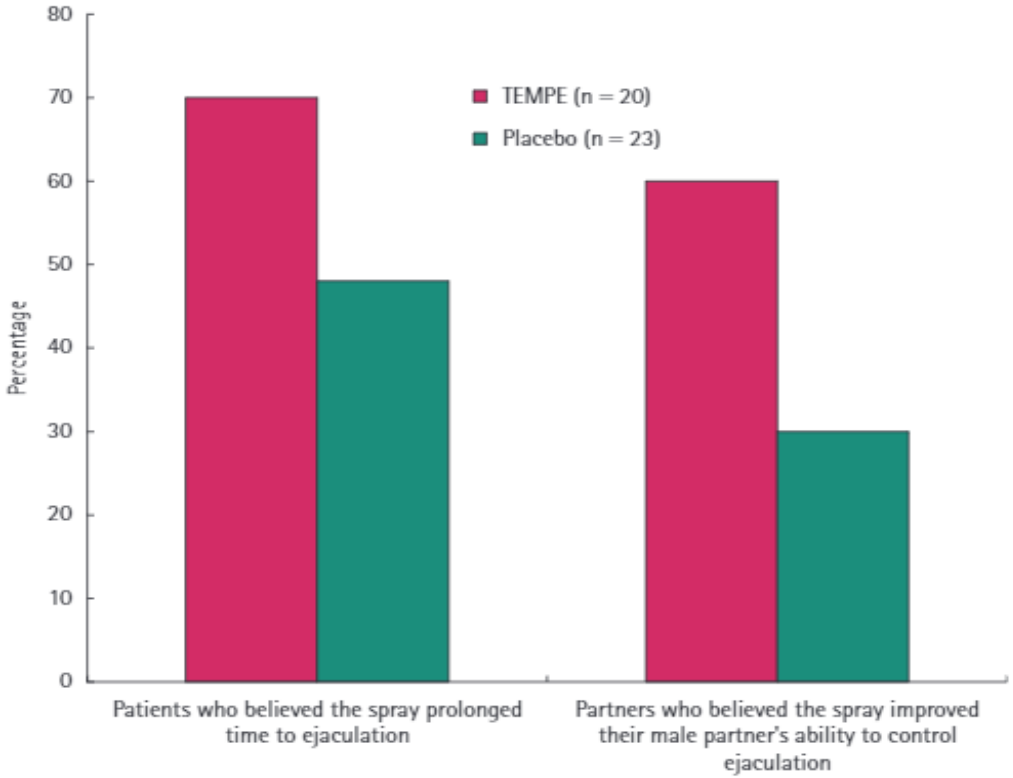
Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation

© 2006 BJU INTERNATIONAL | 99, 369-375 | doi:10.1111/j.1464-410X.2006.06583.x





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Urologia Internationalis

Original Paper

Does Lidocaine Ointment Addition Increase Fluoxetine Efficacy in the Same Group of Patients with Premature Ejaculation?

Metin A.[a] · Kayıgil Ö.[b] · Ahmed[c]

Archivos Espanoles de Urologia
Volume 53, Issue 9, November 2000, Pages 856-858

Comparison of the efficacy of fluoxetine alone vs. fluoxetine plus local lidocaine ointment in the treatment of premature ejaculation (Article)

Atan, A., Murat Basar, M., Aydoğanli, L.

Combination therapy is clearly superior to either monotherapy,especially in the difficult to treat PE patients with IELT<1to2minutes or ante-portal ejaculation

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ASSUNZIONE ON-DEMAND DI PDE5I

Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review

CHRIS G. McMAHON[1], CHELSEA N. McMAHON[1], LIANG JOO LEOW[2], CHRISTOPHER G WINESTOCK[3]

BJU International
Volume 98, Issue 2, pages 259–272, August 2006

In Letteratura esistono "*lavori*" che supporterebbero la capacità dei PDE5i di allungare i tempi di latenza eiaculatoria, in misura più efficace degli SSRi

1 **Mancanza di qualsiasi solida evidenzia a supporto di un ruolo dei PDE5i nel trattamento dell'E.P. (salvo quando essa sia secondaria a DE)**

2 **Di 14 lavori recensiti, solo uno soddisfaceva i criteri della MBE e questo studio non riuscì a dimostrare alcun effetto di Sildenafil su IELT**

- La maggior parte dei benefici sull'EP indotti dai PDE5i potrebbe essere determinata dalla **ridotta ansia da *performance*** conseguente al miglioramento dell'erezione
- Sildenafil non ha effetto sulla EP negli uomini senza coesistente ED, ma spesso **riduce il periodo refrattario** post-eiaculatorio

McMahon CG, et al. J Sex Med 2005; 2:368-75

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ASSUNZIONE CRONICA DI SSRi LONG ACTING

Il sistema centrale 5HT-mediato esercita un effetto inibitorio anche sul controllo neuronale del comportamento sessuale del maschio e, in particolare, sull'eiaculazione.
QUINDI: Agenti che aumentino la trasmissione di 5-HT (es. SSRi) incrementano questo effetto.

LA 5-HT AGISCE PER ATTIVAZIONE DI SPECIFICI RECETTORI
(15 sottotipi di recettori 5-HT raggruppati in 7 classi maggiori)

Attivazione recettori post-sinaptici 5-HT2C → Ritarda l'eiaculazione

Attivazione autorecettori pre-sinaptici 5-HT1A inibendo la secrezione di serotonina → Facilita l'eiaculazione

M.D. Waldinger and B. Olivier. Curr Opin Investig Drugs 2004; 5:743–747

Questi recettori sono presenti nei Centri Superiori del SNC, nel Centro Spinale dell'eiaculazione, nei deferenti e nelle vescicole seminali

F. Giuliano. Trends in Neurosciences 2007; 30(2):79-84

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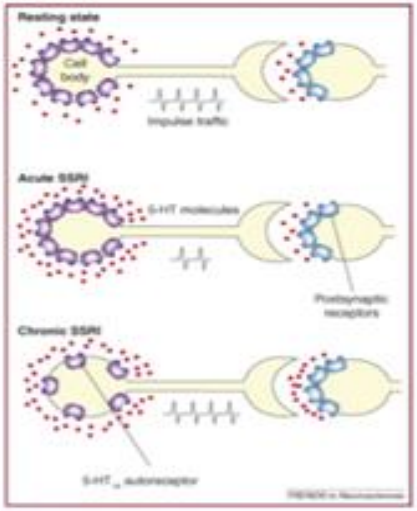
ASSUNZIONE CRONICA DI SSRi LONG ACTING

A Assunzione Acuta di SSRi convenzionali (*L-A*)

§ Il blocco della rimozione dalla fessura sinaptica di 5-HT ottenuto con la somministrazione acuta di SSRIs, aumenta la serotonina nella fessura sinaptica stessa e attiva i recettori post-sinaptici 5-HT2C

§ Ma l'aumento di 5-HT porta anche all'attivazione degli autorecettori presinaptici 5-HT1A che innescano un processo di feedback negativo che riduce l'attivazione cellulare dei neuroni serotoninergici ribilanciando il sistema

B. Olivier et al., Int. Clin. Psychopharmac. 1998 13 (Suppl. 6), S9 -S14



B Assunzione Cronica di SSRi convenzionali (*L-A*)

Determinerebbe un notevole aumento della neuro-trasmissione serotoninergica a causa di alcuni processi di adattamento che possono comprendere la downregulation e la desensibilizzazione degli autorecettori 5-HT1A

De Jong TR, et al. J Sex Med 2007;4:14–28

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LIMITI DELLE TERAPIE OFF-LABEL

I Paz. sono spesso riluttanti ad assumere farmaci *off label* per un lungo periodo di tempo, per trattare l'E.P.

In particolare, la maggior parte dei Pazienti considera il rischio di eventi avversi, legati all'uso di antidepressivi, tollerabile per alleviare la depressione ma meno accettabile per trattare la E.P.

F. Giuliano, Trends in Neurosciences 2007; 30(2):79-84

POSSIAMO CONSIDERARE ETICA LA SOMMINISTRAZIONE QUOTIDIANA CRONICA DI FARMACI NEUROLOGICI NON *"SHORT-ACTING"*, PER IL TRATTAMENTO SOLO SINTOMATICO DELLA E.P.P. ?

Possibili questioni MEDICO-LEGALI circa l'opportunità di una somministrazione *off label* di prima scelta, quando sul mercato sia disponibile DAPOXETINA, ufficialmente approvata per l'EP

6.2.7 *Summary of evidence on the epidemiology/aetiology/pathophysiology of PE*

Summary of evidence	LE
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and eutectic lidocaine/prilocaine spray (a topical desensitising agent) which are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a

6.2.8 *Recommendations for the treatment of PE*

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Stong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak