DE e APPROCCI FARMACOLOGICI COMBINATI

DISFUNZIONI SESSUALI COMPLESSE:
APPROCCIO DIAGNOSTICO E TERAPEUTICO

Incontro congiunto Sezioni SIAMS Lombardia e Piemonte

RESPONSABILI SCIENTIFICI:
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11 NOVEMBRE 2017
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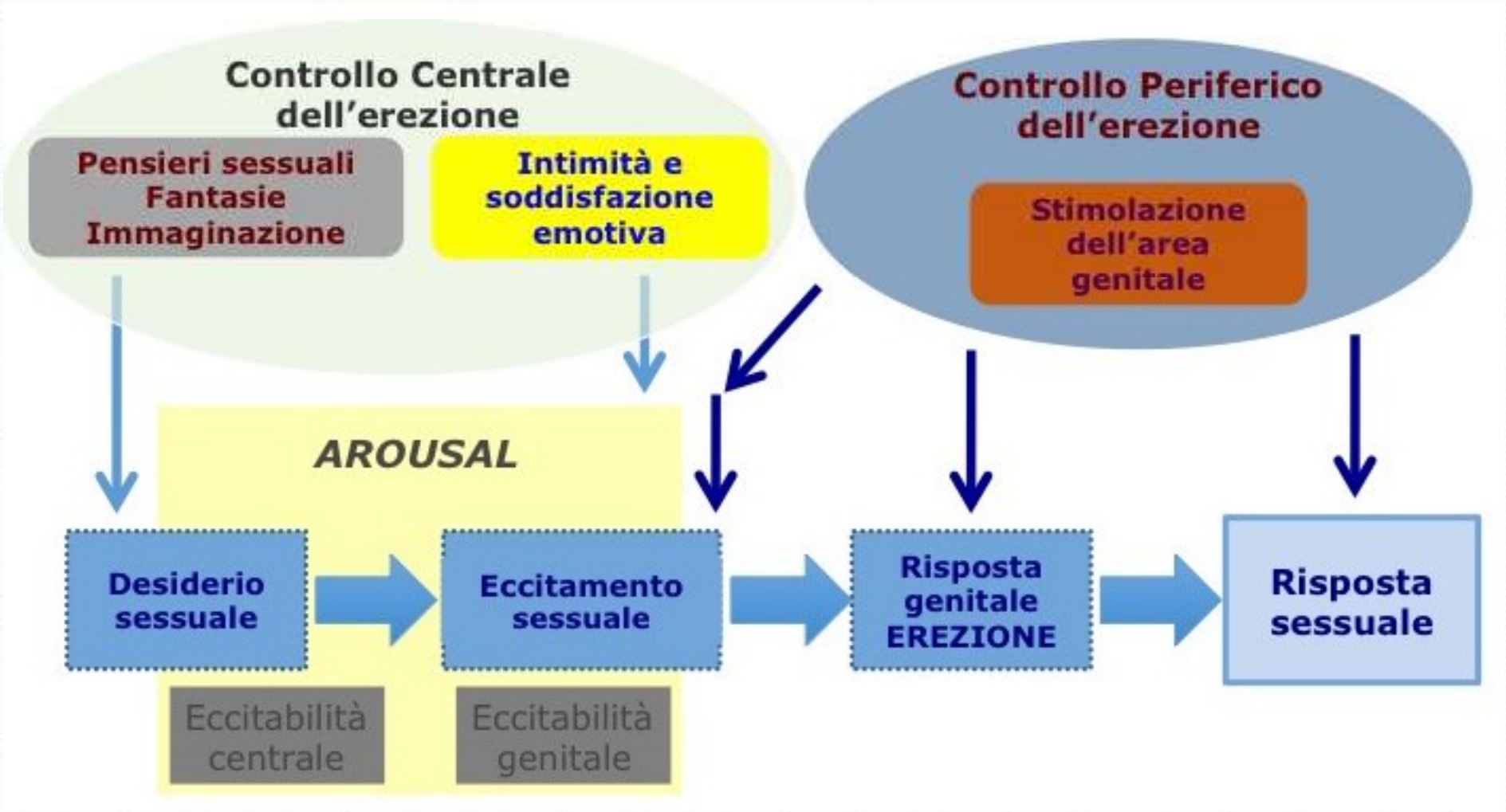
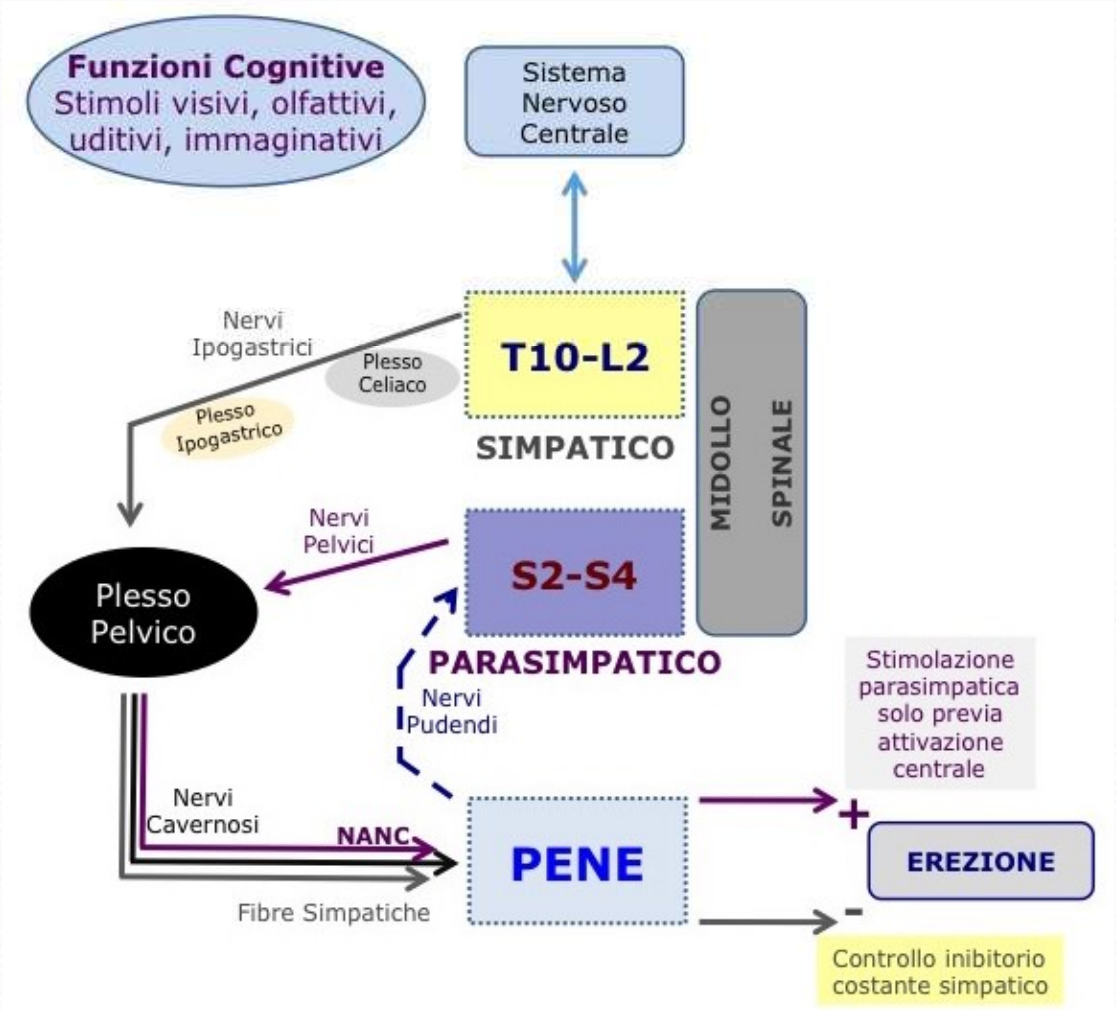
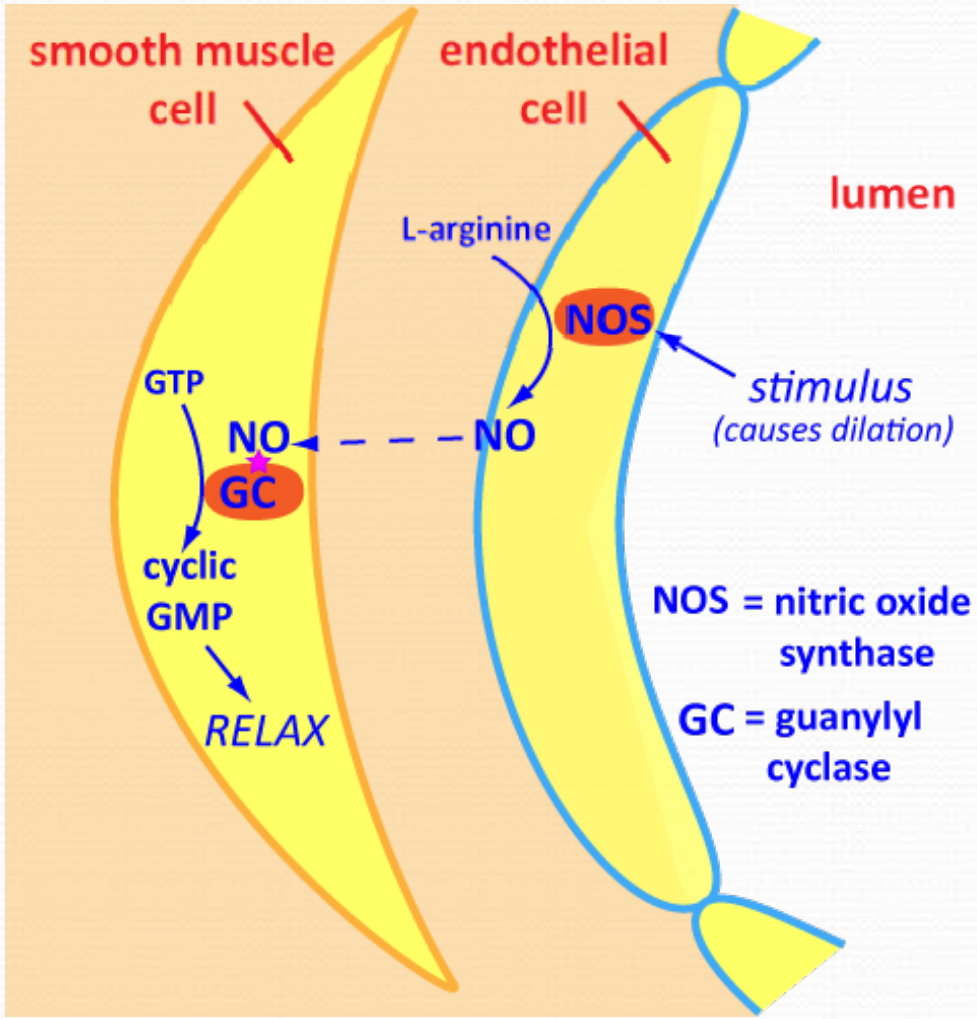
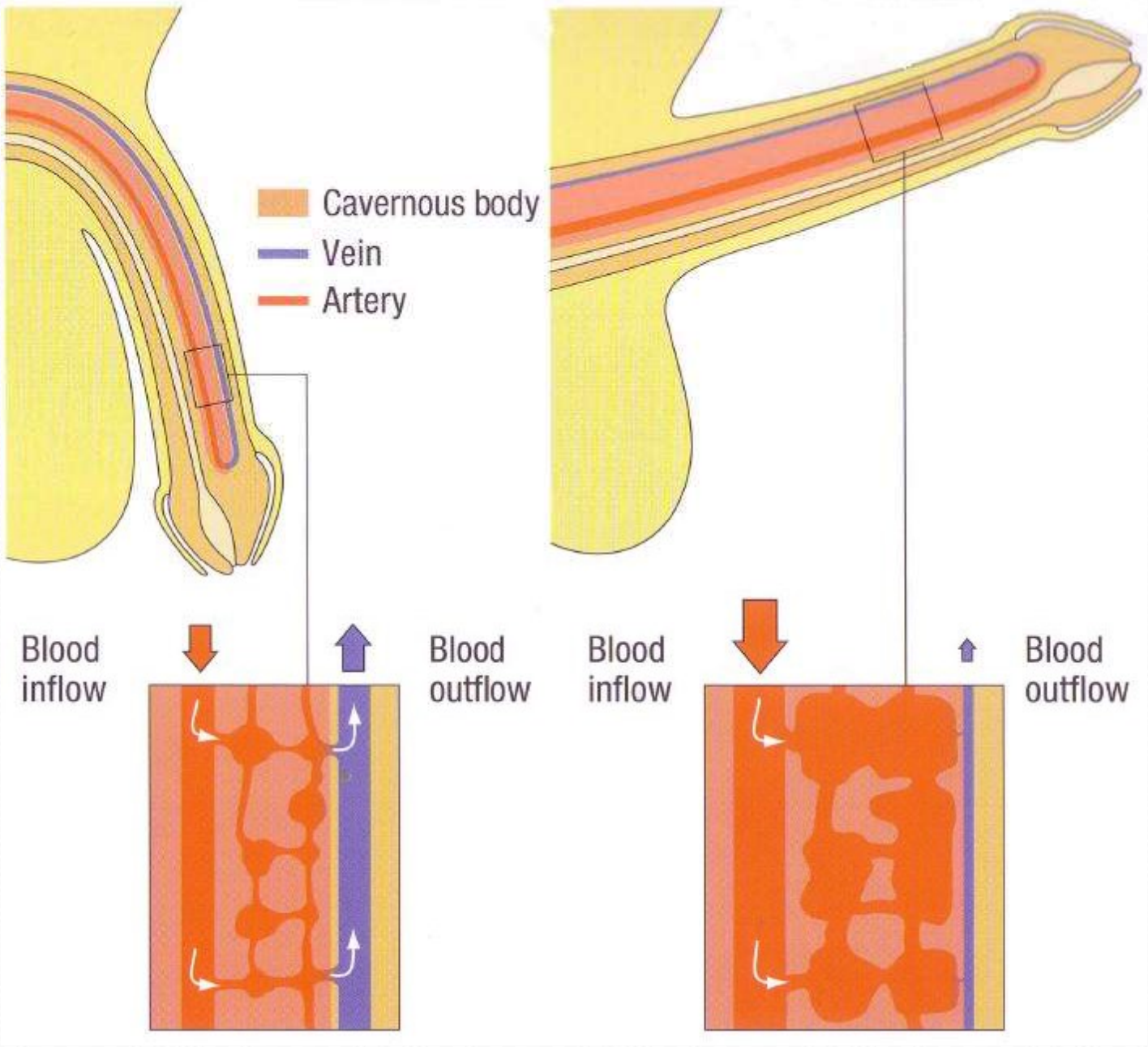

Controllo Centrale dell'erezione
Pensieri sessuali Fantasie Immaginazione
Intimità e soddisfazione emotiva
Controllo Periferico dell'erezione
Stimolazione dell'area genitale
AROUSAL
Desiderio sessuale
Eccitamento sessuale
Risposta genitale EREZIONE
Risposta sessuale
Eccitabilità centrale
Eccitabilità genitale


Funzioni Cognitive
Stimoli visivi, olfattivi, uditivi, immaginativi
Sistema Nervoso Centrale
Nervi Ipogastrici
Plesso Celiaco
Plesso Ipogastrico
T10-L2
SIMPATICO
MIDOLLO SPINALE
Nervi Pelvici
S2-S4
Plesso Pelvico
PARASIMPATICO
Nervi Pudendi
Stimolazione parasimpatica solo previa attivazione centrale
Nervi Cavernosi
NANC
PENE
+
ERezione
Fibre Simpatiche
-
Controllo inibitorio costante simpatico


smooth muscle cell
endothelial cell
lumen
L-arginine
NOS
stimulus
(causes dilation)
GTP
NO
NO
GC
cyclic GMP
RELAX
NOS = nitric oxide synthase
GC = guanylyl cyclase


Cavernous body
Vein
Artery
Blood inflow
Blood outflow
Blood inflow
Blood outflow

Il primo obiettivo di un approccio alla DE è quello di curare: quindi è necessario capire la "causa" della DE, e trattare la malattia e non il sintomo

EAU Guidelines on Erectile Dysfunction, 2014

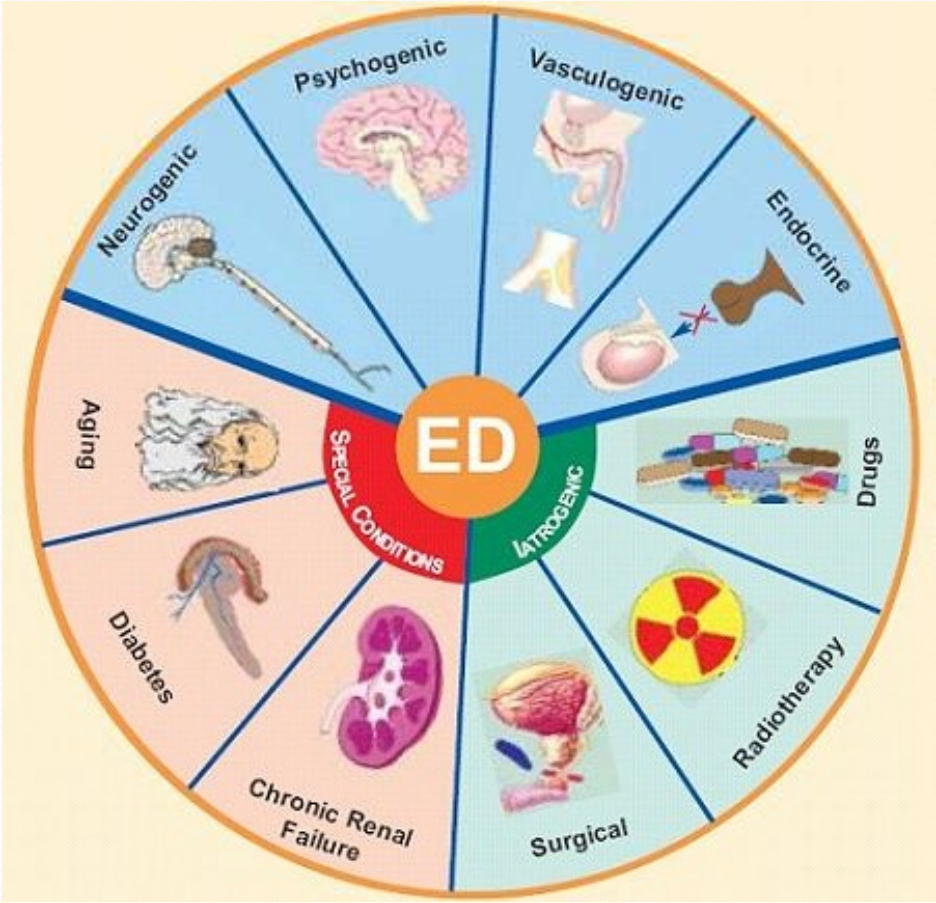
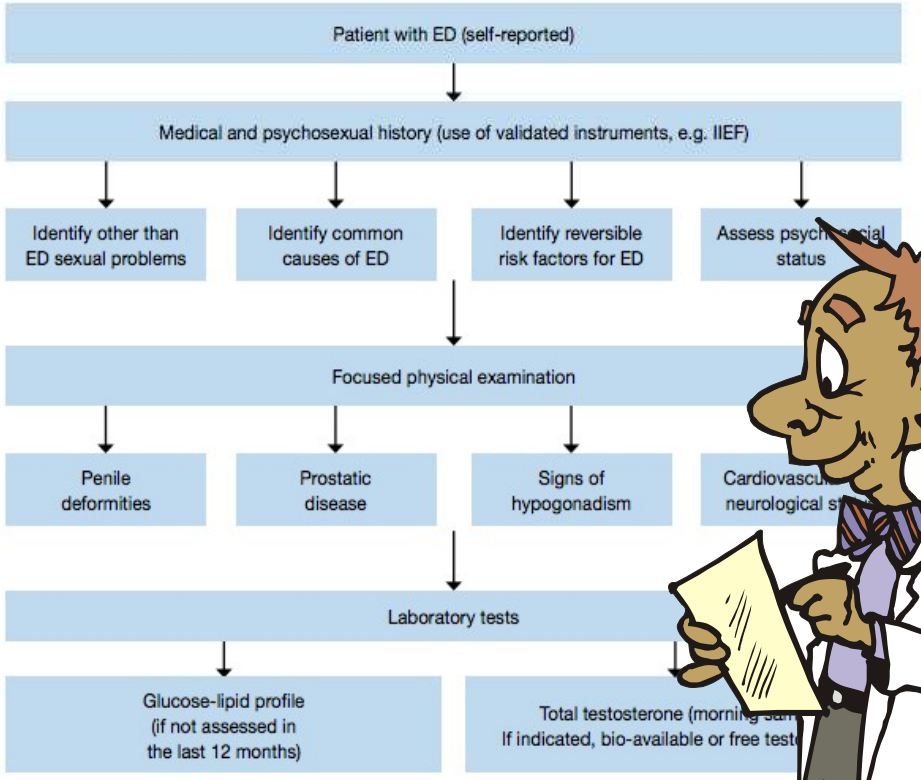


Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



CASO CLINICO: L.A. 67 anni

Anamnesi generale:

- familiarità diabetica
- Fuma 12 sig/die dall'età di 19 anni. Non alcolici. Mai sostanze stupefacenti.
- Pensionato da 4 a (ex dirigente di banca)
- Iperteso in trattamento con cardioASA e ACE-inibitore.
-Chirurgia: ernioplastica inguinale sin a 44 a
-Ecg ed EE 2 a fa, nella norma (con PSA)

Anamnesi sessuologica:

-Vedovo da 3 a, 1 figlia (partner deceduta per k.uterino dopo 8a da chirurgia – chemio e radioterapia) → Non rapporti possibili negli ultimi 3a di vita

-Incontri sessuali saltuari con altra partner fissa 5aa fa con buona gratificazione sessuale →relazione interrotta bruscamente per volontà di lui (riferisce "senso di colpa")

-Da 4 mesi relazione con **F 54 a**, impiegata, separata (nullipara)

-costante DE di mantenimento con ridotta rigidità (penetrazione possibile 8/10) –

-Freq. Coitale 1-2/w – erezioni mattutine saltuarie meno rigide

Questionario IIEF5

L'International Index of Erectile Function - 5 (IIEF-5) è stato creato allo scopo di fornire un questionario sensibile e specifico per valutare la funzione erettiva.

PUNTEGGIO IIEF-5= 15 (DE LIEVE-MODERATA)

provato piacere?

POCO	0	1	2	3	4	5	MOLTO

22-25 punti → **attività sessuale normale.**

17-21 punti → **ED lieve.**

12-16 punti → **ED lieve-moderata.**

8-11 punti → **ED moderata.**

5-7 punti → **ED grave.**

Questionario IPSS

L'International Prostate Symptom Score (IPSS) è un test utilizzato a livello internazionale per classificare i numerosi e differenti sintomi che accompagnano un IPB.

Nell'ultimo mese

PUNTEGGIO IPSS= 7 (lieve)

6. …quante volte nell'ultimo mese ha dovuto sforzarsi per iniziare ad urinare?
7. …quante volte si è alzato per andare ad urinare la notte?

NESSUNA VOLTA	0	1	2	3	4	5	QUASI SEMPRE

0-7 punti → **sintomatologia da assente a lieve**

8-19 punti → **sintomatologia moderata**

20-35 punti → **sintomatologia severa**

QoL

Se dovesse trascorrere il resto della Sua vita con la Sua attuale condizione urinaria, come si sentirebbe?

BENE		COSÌ COSÌ			MOLTO MALE
0	1	2	3	4	5

Esame obiettivo: L.A. 67 anni

Generale: nella norma

Andrologico:	
- Testicoli	dx 14 ml – sn 12 ml
- Pene	Nella norma
- Adipe/mammelle	Adipomastia (non ginecomastia)
- Riflesso cremasterico	Elicitabile
- Riflesso bulbo-cavernoso	Elicitabile
- Tono perineale	Inversione del comando
- Prostata	Vol x 1,2

INDAGINI: L.A. 67 anni

Ematochimici (glicemia, emoglobina glicata, colesterolemia, trigliceridi, emocromo, AST/ALT, azotemia, creatininemia, PSA)	Nella norma (PSA 1,9 ng/ml)
ICI test	PGE_1 10µg → erez>80% x 40' A.cav dx 33/0 ; A. cav sn 34/0 Ecogenicità a strie del tessuto cavernoso
ECD penieno dinamico	
Potenziali Evocati Sacr.	Nella norma
Ormoni (testosterone totale e libero,PRL, E2, TSH, FSH, LH)	Nella norma (testosterone 380 ng/dl)
Uroflussimetria	320/12 t allungato

Terapia: L.A. 67 anni

Sospensione del fumo

Fisiochinesiterapia del Piano Perineale

Inibitore PDE5 long-acting x os cronico per 3 mesi

Ad 1 mese, riprende buona risposta sessuale, con erezioni mantenute.

Dopo 1 settimana sospende la terapia orale (e riprende il fumo) – continua (non costantemente) la ginnastica perineale → buona sessualità spontanea.

Chiede per "sicurezza": Inibitore PDE5 rapido on demand

Prescritto: Vardenafil orodispersibile

L.A. 73 anni

Stessa partner

Fuma ancora 8-10 sigarette al dì

Comparsa di LUTS ostruttivi – IPSS 24

0-7 punti → sintomatologia da assente a lieve

8-19 punti → sintomatologia moderata

20-35 punti → sintomatologia severa

Peggioramento della DE

– IEEF (5) 10

22-25 punti → attività sessuale normale.

17-21 punti → ED lieve.

12-16 punti → ED lieve-moderata.

8-11 punti → ED moderata.

5-7 punti → ED grave.

- non responder a Vardenafil 20 mg
- non responder a Sildenafil 100 mg

INDAGINI: L.A. 73 anni

Ematochimici (glicemia, emoglobina glicata, colesterolemia, trigliceridi, emocromo, AST/ALT, azotemia, creatininemia, PSA)	PSA 2,4 ng/ml (6 anni prima era 1.9)Nella norma gli altri
ICI test	PGE_1 10µg → erez>70% x 20'
ECD penieno dinamico	A.cav dx 32/6 ; A. cav sn 30/6 cm/sec Ecogenicità a strie del tessuto cavernoso
Potenziali Evocati Sacr.	Non effettuati
Ormoni (testosterone totale)	(testosterone 310 ng/dl)
Uroflussimetria	360/8 t allungato

A questo punto: .....

EAU guidelines 2016

3.1.4.5. Recommendations for the treatment of ED

Recommendations	LE	GR
Enact lifestyle changes and risk factor modification prior to or accompanying erectile dysfunction (ED) treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapy.	1a	A
Assess all patients for inadequate/incorrect prescriptions and poor patient education, since they are the main causes of a lack of response to PDE5Is.	3	B
Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	4	C
Use intracavernous injections as second-line therapy.	1b	B
Use implantation of a penile prosthesis as third-line therapy.	4	C

Cause di fallimento terapeutico

- Severità della patologia sottostante
- Uso inappropriato del farmaco
- Difficili dinamiche relazionali
- Severa ansia da prestazione
- Altri conflitti intrapsichici

- Il 50%-80% dei pazienti messi in terapia riceve informazioni inappropriate ed ha un follow-up inadeguato.
- Dopo informazioni adeguate il 30%-50% dei "non-responder" iniziali diventa "responder"

Hatzichristou et al, 2005

Prescrizione

- Meccanismo d'azione (comune)
- Farmacocinetica (differente)
- Interazioni farmacologiche
- Efficacia (variabile)

Tab. 1 Übersicht über die verfügbaren Phosphodiesterase-5-Inhibitoren und deren pharmakokinetischen Eigenschaften

Wirkstoff	Sildenafil	Tadalafil	Vardenafil	Avanafil
Präparat	Viagra®	Cialis®	Levitra®	Spedra®
Dosierung (mg)	25/50/100	5/10/20	5/10[a]/20	50/100/200
Einnahme vor Geschlechtsverkehr	1 h	Mindestens 30 min	25–60 min	15–30 min
t_{max}[b]	1 h (0,5–2 h)	2 h	T: 30–120 min ST: 45–90 min	30–45 min
Beeinflussung durch Nahrung	Ja	–	T: ja (fettreich) ST: Flüssigkeiten	Ja (fettreich)
Terminale Halbwertszeit	4 h (3–5 h)	17,5 h	4–6 h	6–17 h

Valutazione della coppia

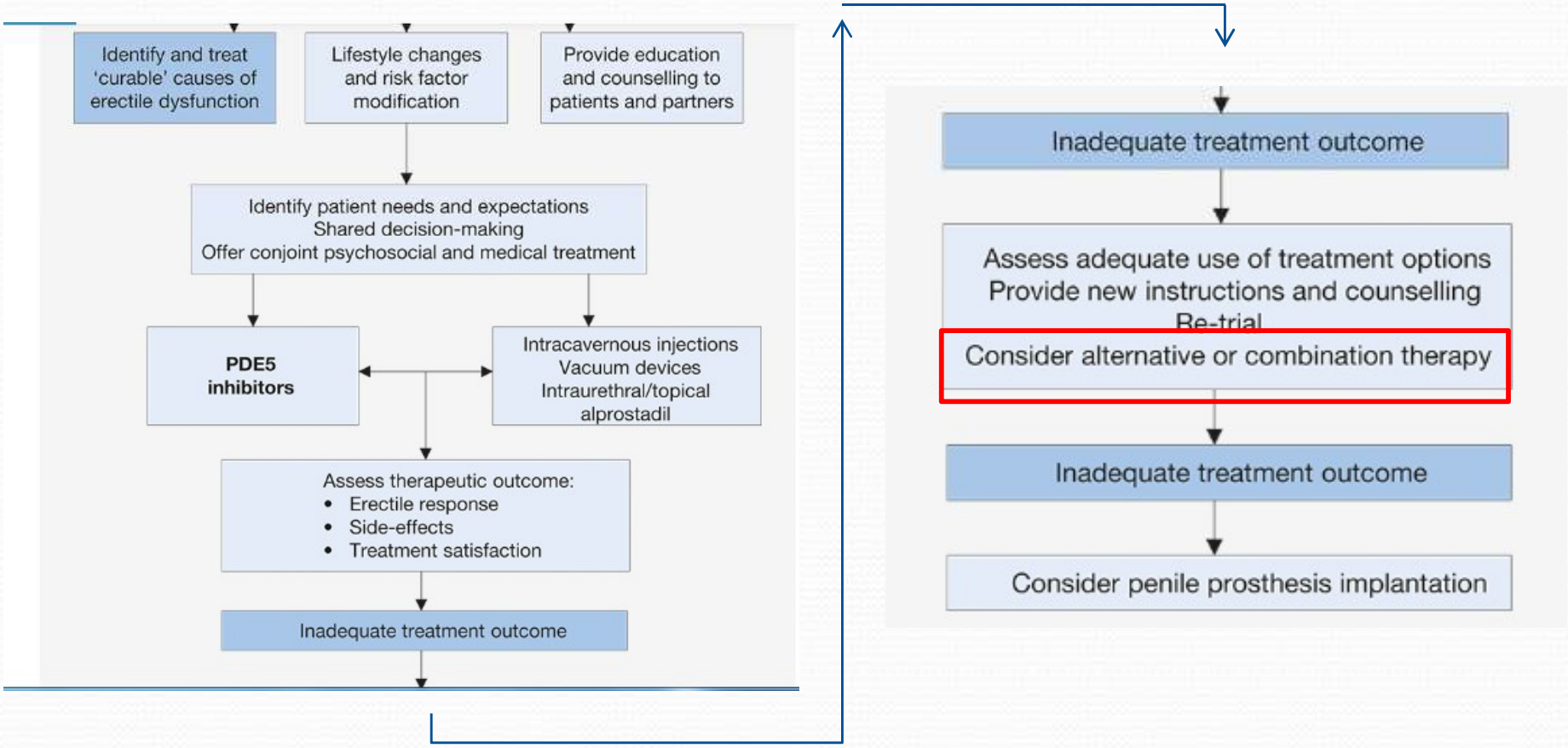
L'assenza di benessere fisico, sessuale ed emotivo della partner possono esacerbare la disfunzione sessuale di un uomo affetto da DE.

- Ostacoli psicobiologici:
  - Lunghi periodi di astinenza sessuale
  - Relazione "travagliata" e/o partner poco predisposta ad attività sessuale
  - Avversione sessuale
  - Dolore sessuale (vaginismo, dispareunia)
  - Desiderio sessuale ipoattivo

Controllo

- Le valutazioni successive sono essenziali per la massimalizzazione della risposta terapeutica.

EAU guidelines 2016



TERAPIE ATTUALI DELLA DE

TABLE 1
Drugs used in the treatment of male erectile dysfunction

Agent	Target	Effect	Route of Administration
PGE_1	EP receptor	Increase cAMP	IC, IU, oral, topical
Forskolin	Adenylate cyclase	Increase cAMP	IC (exp)
PGE_1/prazosin	EP receptor/α-AR	Increase cAMP, block α-AR	IU
VIP/phentolamine	VIP receptor/α-AR	Increase cAMP, block α-AR	IC
Forskolin	Adenylate cyclase	Increase cAMP	IC (exp)
Nitroglycerine	Guanylate cyclase	Increase cGMP	Topical
Minoxidil	K_{ATP} Channel	K_{ATP} opener	Topical
Papaverine	PDE	Increase cAMP/cGMP	IC, topical
Milrinone	PDE3	Increase cAMP	IC (exp)
Sildenafil	PDE5	Increase cGMP	Oral
IC351	PDE5	Increase cGMP	Oral
Vardenafil	PDE5	Increase cGMP	Oral
Phentolamine	α-AR	Block α-AR	Oral, IC
Prazosin	α-AR	Block α-AR	IC
Chlorpromazine	α-AR	Block α-AR	IC
Yohimbine	α_2-AR	Block α_2-AR	Oral
Trazodone	5-HT_{2c}/α-AR	Activate 5-HT_{2c}, block α-AR	Oral
Apomorphine	D_2-like DA receptor	Activate DA CNS pathways	SL

α-AR, α-adrenoceptor; exp, experimental; IC, intracavernosal; IU, intraurethral; SL, sublingual.

These appropriate treatment options should be applied in a stepwise fashion with increasing invasiveness and risk balanced against the likelihood of efficacy. (AUA Guidelines 2014)

FATTORI CORRELABILI CON LA SCELTA DI UN FARMACO PER LA DE

FARMACO	PAZIENTE	MEDICO
EFFICACIA	STATO CIVILE	ESPERIENZA
SICUREZZA	CULTURA	FAMILIARITA'
TOLLERABILITA'	STATO FINANZIARIO	COMPETENZA
DURATA D'AZIONE	COMORBIDITA'	
INTERAZIONE CON IL CIBO	ASPETTATIVE	
REPUTAZIONE		
NOVITA'		
COSTO		

Raheem & Kell, 2009

Tailoring

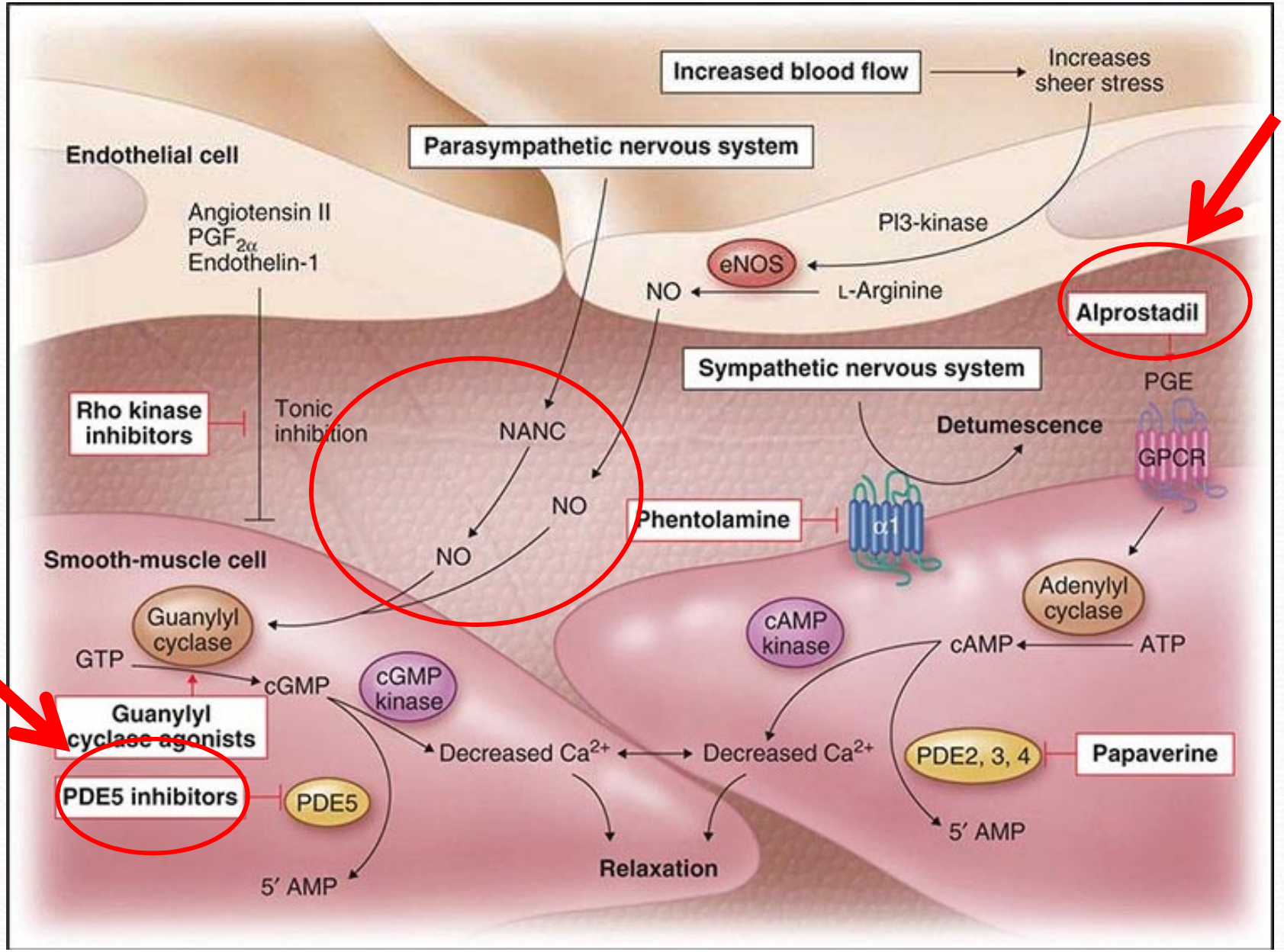
La prescrizione di una terapia per la DE richiede la stessa accuratezza del confezionamento di un abito su misura. A volte sono necessarie molte prove.

(Ljuggren et al, 2008)

Outcome

- A differenza di altri campi della medicina dove l'efficacia di una terapia è misurabile (es. esami di laboratorio, radiologia) nel campo della DE l'outcome si basa esclusivamente sul giudizio del paziente e del partner.

PDE5i + Alprostadil



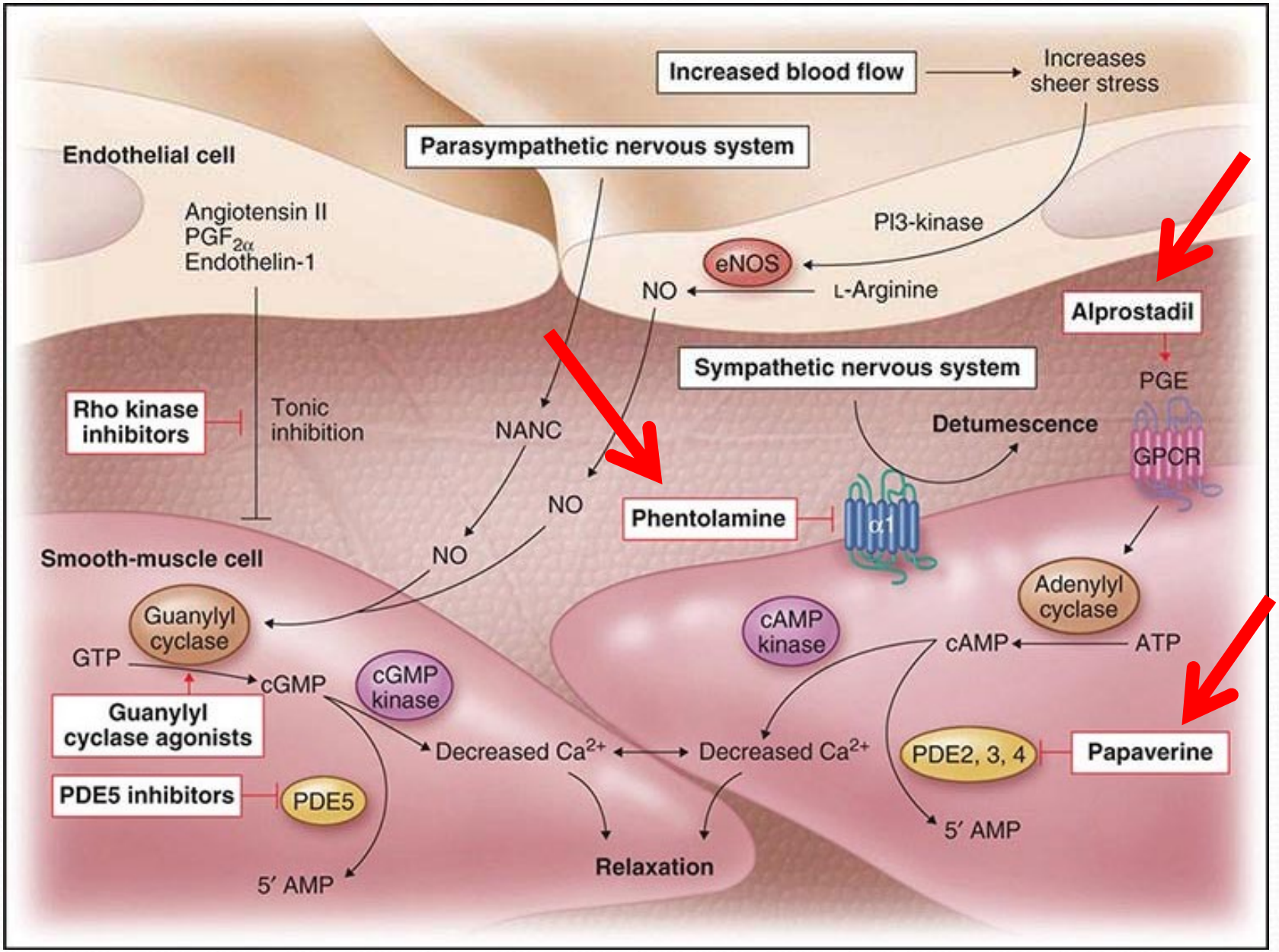
PDE5i + MUSE

Table 2 Phosphodiesterase-5 inhibitors (PDE5Is) plus intraurethral alprostadil

Author (year)	*Study design*	*No. of patients*	*Follow-up*	*Evaluation questionnaire*	*Results*			*Evidence level*
					Sildenafil	*Alprostadil*	*Combination*	
Mydlo *et al.* (2000)[12]	Case series	120	18 months	IIEF-EF	19.8±1.8	15.2±1.6	24.1±2.0*	IV
					Comments: 1. All 120 patients failed both monotherapies. 2. High discontinuation rate (7.6%–27.0%) depending on the clinical setting of the patient.			
Nehra *et al.* (2002)[13]	Case series	28	30 months	GAQ	**Comments:** 1. All 28 patients failed either sildenafil and/or alprostadil monotherapy. 2. 100% improvement on GAQ in combination arm from 0% in monotherapy. 3. 100% compliance rate to combination therapy at 30 months.			IV
Raina *et al.* (2005)[14]	Case series	23	at least four attempts	IIEF VAS	13.2±5.8		18.6±5.2	IV
					Comments: 1. All patients had NSRP. 2. 83% (19/23) report improvement of erectile function. 3. 38% increase on VAS with combination.			

Abbreviations: GAQ, global assessment question; IIEF, international index of erectile function; NSRP, nerve-sparing radical prostatectomy; VAS, visual analog scale to gauge rigidity.
*$P<0.001$, compared with each monotherapy.

TRIMIX-ICI


Increased blood flow
Increases sheer stress
Endothelial cell
Parasympathetic nervous system
Angiotensin II
$PGF_{2\alpha}$
Endothelin-1
PI3-kinase
eNOS
NO
L-Arginine
Alprostadil
Sympathetic nervous system
PGE
Rho kinase inhibitors
Tonic inhibition
NANC
Detumescence
GPCR
NO
Phentolamine
α1
Smooth-muscle cell
NO
Adenylyl cyclase
Guanylyl cyclase
cAMP kinase
cAMP
ATP
GTP
cGMP
cGMP kinase
Guanylyl cyclase agonists
Decreased Ca^{2+}
Decreased Ca^{2+}
PDE2, 3, 4
Papaverine
PDE5 inhibitors
PDE5
5′ AMP
5′ AMP
Relaxation

PDE5i + ICI

Table 3 Phosphodiesterase-5 inhibitors (PDE5Is) plus intracavernous injection (ICI)

Author (year)	*Study design*	*No. of patients*	*Follow-up*	*Evaluation questionnaire*	*Results*			*Evidence level*
					PDE5I	*ICI*	*Combination*	
McMahon *et al.* (1999)[16]	Case series	93	Every 4 weeks for 3.5 months	IIEF Q3 score	3.1	2.3	3.3	IV
				IIEF Q4 score	2.4	1.9	3.1	
					Comments: 1. All 93 patients were ICI failure. 2. 34% (32/93) patients achieved erections sufficient for intercourse with salvage sildenafil. 3. 48% (29/61) responded to combined therapy (sildenafil and ICI) with erections sufficient for intercourse. 4. Overall, 66% (61/93) ICI failures responded to salvage sildenafil monotherapy or combined therapy. 5. Side effects: 31% for ICI, 37% for salvage Sildenafil and 49% with combination therapy.			
Nandipati *et al.* (2006)[17]	Case series	22	6 months	IIEF CDU	10.5±1.8	19.4±2.4*	22.1±0.3**	IV
					Comments: 1. 42.9% (9/21) require combination therapy after RP. 2. Early combination therapy with sildenafil allowed a lower dose of ICI.			

Abbreviations: CDU, color doppler ultrasonography; IIEF, international index of erectile function; RP, radical prostatectomy.
*$P<0.05$, compared with PDE5I monotherapy. **$P<0.05$, compared with two monotherapies.

PDE5i + supplementazione androgenica

Table 4 Phosphodiesterase-5 inhibitors (PDE5Is) and androgen supplementation

Author (year)	*Study design*	*No. of patients*	*Follow-up*	*Evaluation questionnaire*	*Results*	*Evidence level*
Aversa *et al.* (2003)[20]	RCT	20	1 month	IIEF	1. All patients were sildenafil failure (100 mg six consecutive attempts) with low-normal T (12.8±2.1 nmol) and free T (260±18 pmol). 2. Transdermal (5 mg) or placebo patches (daily) and 100 mg Viagra on demand for 1 month with sexual activity at least twice weekly. 3. Significant improvements of IIEF (21.8±2.1 versus 14.4±1.4, $P<0.05$) and arterial flow by penile Doppler study were seen in combination groups.	II
Shabsigh *et al.* (2004)[21]	RCT	75	12 weeks	IIEF	1. All patients were sildenafil failure (IIEF Q3 and Q4 ⩽2 and 3) with T ⩽ 400 mg dl^{-1}. 2. 1% T-Gel or 5 mg placebo gel as adjunctive therapy to 100 mg Sildenafil for 12 weeks. 3. Combination arm had statistically significant erectile function domain increase at 4 weeks but lost statistical significance thereafter.	I
Greenstein *et al.* (2005)[22]	Case series	49	6 months	IIEF; GAQ	1. All patients had total T<400 mg dl^{-1} and were treated with T-Gel for 6 months. 2. 31/49 had improved EF scores (from 13.6±1.9 to 27.0±0.8) and GAQ improvement. 3. 17/49 had EF scores <26 who were treated with combination of T-Gel and sildenafil and the EF scores became normal and GAQ improved.	IV
Rosenthal *et al.* (2006)[23]	Case series	24	16 weeks	Custom-made erectile scale (1–5)	1. All 24 patients were sildenafil failure (100 mg at least three attempts in 3 months) with T<400 mg dl^{-1}. 2. 1% T-Gel for 4 weeks, then sildenafil was added on demand and evaluated at week 16. 3. 92% (22/24) of patients reported improved potency capable of penetration with erection quality score of 4 or greater.	IV
Yassin *et al.* (2006)[24]	RCT	69	10 weeks	IIEF	1. All patients were tadalafil failure (poor EF score and persistent dissatisfaction) with T ⩽ 3.4 ng ml^{-1}. 2. Testogel started for 10 weeks with tadalafil restart at 4 weeks (20 mg twice/week) in one group. 3. IIEF was improved in both T monotherapy and combination groups, but greater improvement in combination.	II

PDE5i + altri farmaci

Table 6 Phosphodiesterase-5 inhibitors (PDE5Is) and other medications

Author (year)	*Study design*	*No. of patients*	*Follow-up*	*Evaluation questionnaire*	*Combination modality*	*Results*	*Evidence level*
Gentile *et al.* (2004)[37]	RCT	40	24 weeks	IIEF	Sildenafil/PLG	Statistically significant increase of IIEF in combination group	II
Cavallini *et al.* (2005)[38]	RCT	96	4 months	IIEF	Sildenafil/PLG+ALC	Statistically significant increase in IIEF scores in combination arm	II
Herrmann *et al.* (2005)[39]	RCT	12	12 weeks	IIEF	Sildenafil/atorvastatin	Statistically significant increase in mean IIEF in combination arm	II
Diamond *et al.* (2005)[41]	RCT	19	6 hours post-dose	RigiScan	Sildenafil/PT-141	Statistically significant increase in erectile response in combination arm	II
Taneja *et al.* (2007)[42]	Case series	18	2 weeks	EDIS	Sildenafil/trazodone	66.7% of patients had considerable EDIS increase with addition of trazodone	IV
Osdal *et al.* (2008)[43]	Case series	68	8 weeks	IIEF	Sildenafil/pentoxifylline	Statistically significant increase in mean IIEF score in combination compared with sildenafil monotherapy	IV
Kondoh *et al.* (2008)[44]	Case series	9	<1 month	IIEF	PDE5Is/vitamin E	Increased IIEF score with combination arm	IV

Abbreviations: ALC, acetyl-L-carnitine; EDIS, erectile dysfunction intensity scale; IIEF, international index of erectile function; PLG, propionyl-L-carnitine; PT-141, melanotan-II metabolite.

I PDE5i migliorano la funzione endoteliale

International Journal of Impotence Research (2007) 19, 200–207

0955-9930/07 $30.00
www.nature.com/ijir

ORIGINAL ARTICLE

Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study

A Aversa, E Greco, R Bruzziches, M Pili, G Rosano and G Spera

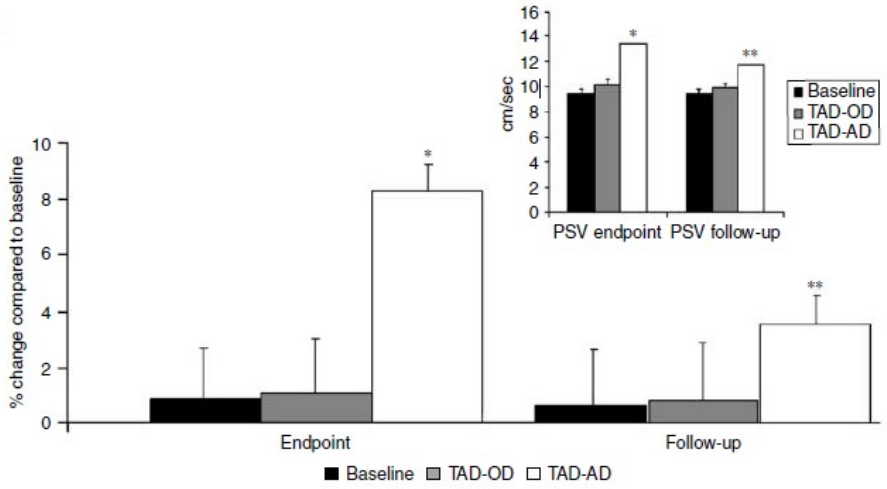


Figure 2 Percent change compared with baseline in endothelial function of cavernous arteries (FMD) in patients treated with TAD-AD and TAD-OD after 4 weeks of therapy and after 2 weeks of discontinuation of therapy. Inset indicates variations in cavernous arteries inflow as recorded by color-duplex ultrasound in the flaccid state. The *P*-values refer to comparison between end point vs baseline. $^{*}P<0.0001$; $^{**}P<0.005$.

Effetto antiossidante della terapia combinata

EUROPEAN UROLOGY 52 (2007) 1768–1776

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Andrology

Antioxidant Treatment Associated with Sildenafil Reduces Monocyte Activation and Markers of Endothelial Damage in Patients with Diabetic Erectile Dysfunction: A Double-Blind, Placebo-Controlled Study

Susanna Morano [a,], Elisabetta Mandosi [a], Mara Fallarino [a], Alessandra Gatti [a], Claudio Tiberti [a], Maurizio Sensi [a], Loredana Gandini [b], Barbara Buchetti [c], Luisa Lenti [c], Emmanuele Angelo Jannini [d], Andrea Lenzi [b]*

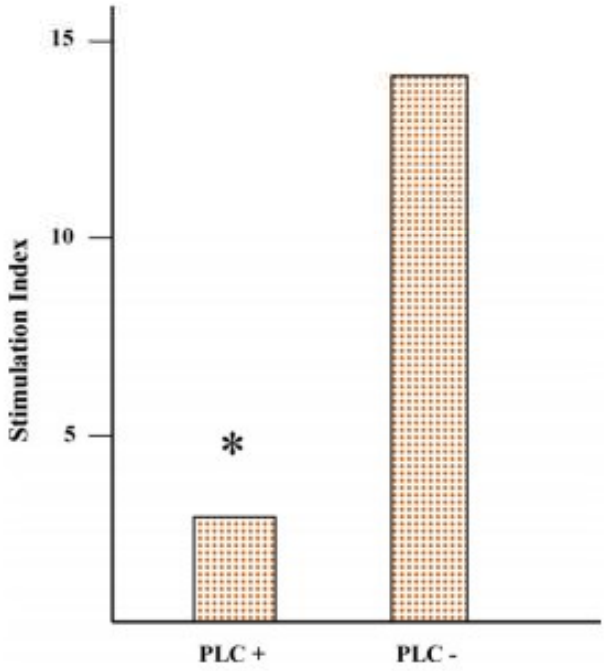


Fig. 1 – Stimulation index in patients treated (PLC+) and untreated (PLC–) with propionyl L-carnitine (PLC); * $p < 0.05$.

Ridotta produzione di monociti

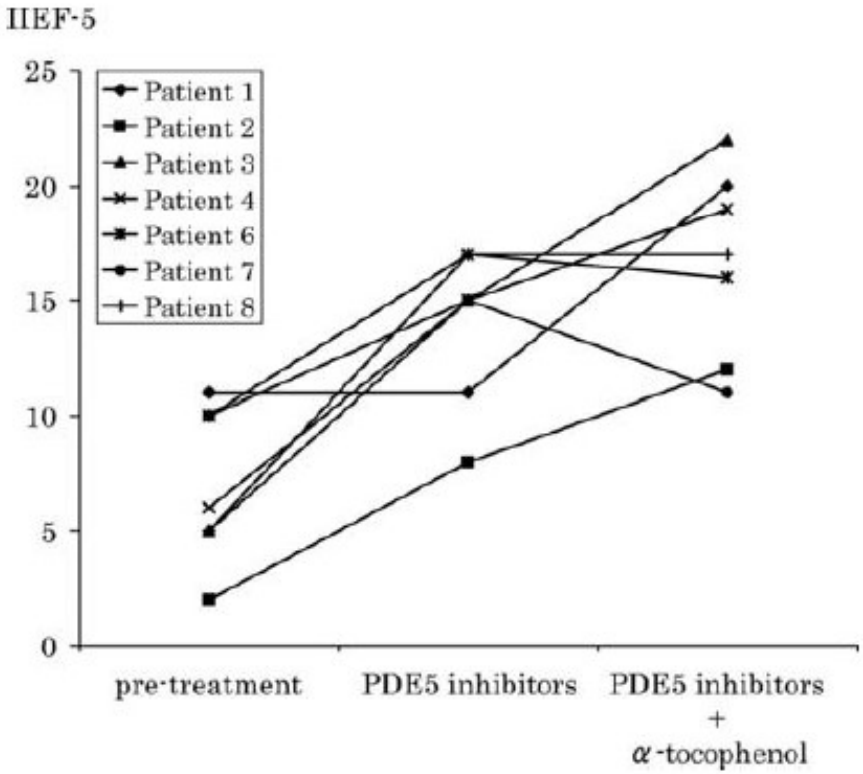
PDE5i + VitE

The Aging Male, December 2008; 11(4): 167–170

informa
healthcare

Salvage therapy trial for erectile dysfunction using phosphodiesterase type 5 inhibitors and vitamin E: Preliminary report

NOBUYUKI KONDOH, YOSHIHIDE HIGUCHI, TAKUO MARUYAMA, MICHIO NOJIMA, SHINGO YAMAMOTO, & HIROKI SHIMA



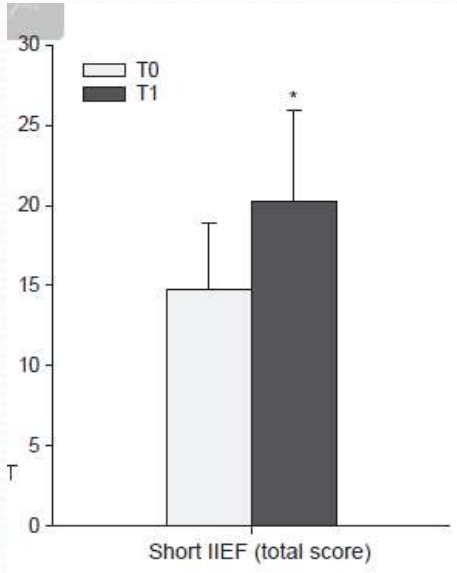
First International Journal of Andrology
ANDROLOGIA

ORIGINAL ARTICLE

Propionyl-L-carnitine, L-arginine and niacin in sexual medicine: a nutraceutical approach to erectile dysfunction

D. Gianfrilli[1], R. Lauretta[1], C. Di Dato[1], C. Graziadio[1], C. Pozza[1], J. De Larichaudy[2], E. Giannetta[1], A. M. Isidori[1] & A. Lenzi[1]

Andrologia 2012, **44**, 600–604



Brief report

Effect of propionyl-L-carnitine, L-arginine and nicotinic acid on the efficacy of vardenafil in the treatment of erectile dysfunction in diabetes ›

Vincenzo Gentile, Gabriele Antonini, Maria Antonella Bertozzi, Nicola Dinelli, Cosimo Rizzo, Mohamed Ashraf Virmani & Aleardo Koverech

Current Medical Research and Opinion **Published Online:** 23 Jul 2009

Safety and efficacy of L-carnitine and tadalafil for late-onset hypogonadism with ED: A randomized controlled multicenter clinical trial

ZHANG Wei[1,2], LI Peng[1], CAI Zhi-kang[2], ZHENG Jun-hua[3], DAI Ji-can[1], WANG Yi-xin[1], WANG Zhong[2], LI Zheng[1]

NJA
中华男科学杂志
National Journal of Andrology
Zhonghua Nan Ke Xue Za Zhi
2014, 20(2): 133 – 137
http://www.androl.cn

Terapia combinata e apoptosi

La terapia con antiossidanti endoteliali nei pazienti con DE vasculogenica migliora il tasso di successo del Sildenafil suggerendo l'utilità del trattamento combinato in questa categoria di pazienti allo scopo di aumentare l'NO biodisponibile e di neutralizzare i ROS che a loro volta inattivano l'NO. (Vicari et al, 2010).

- Diversi studi hanno dimostrato gli effetti del Tadalafil e di altri PDE5i sull'apoptosi endoteliale. (Lysiak et al 2008)

Journal of Andrology, Vol. 33, No. 2, March/April 2012

Endothelial Antioxidant Compound Prolonged the Endothelial Antiapoptotic Effects Registered After Tadalafil Treatment in Patients With Arterial Erectile Dysfunction

SANDRO LA VIGNERA, ROSITA CONDORELLI, ENZO VICARI, ROSARIO D'AGATA, AND ALDO E. CALOGERO

Tadalafil + Atorvastatina

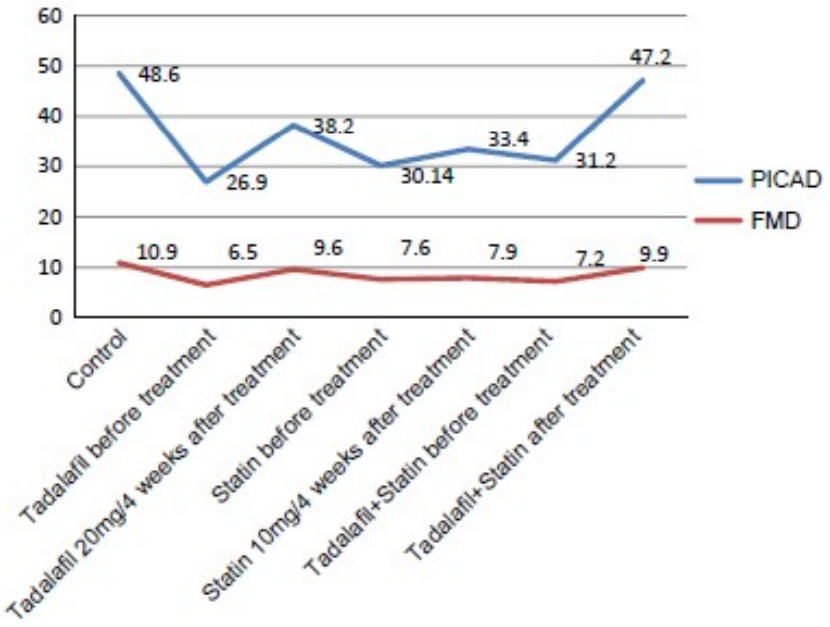
First International Journal of Andrology
ANDROLOGIA

ORIGINAL ARTICLE

Effect of tadalafil and 3-hydroxy-3-methylglutaryl coenzyme A inhibitor statin on the haemodynamics of cavernous and brachial arteries

A. Simsek[1], E. Ozbek[2] & M. Oncu[3]

- Noninvasive evaluation of brachial artery flow-mediated dilatation (FMD) and percentage of increase in cavernosal arteries diameter (PICAD)



Andrologia 2014, **46**, 808–813

Sartanico + Tadalafil

International Journal of Impotence Research (2012) 24, 217–220

www.nature.com/ijir

ORIGINAL ARTICLE

Losartan improves erectile dysfunction in diabetic patients: a clinical trial

Y Chen[1], S Cui[1], H Lin[1], Z Xu[1], W Zhu[1], L Shi[1], R Yang[1], R Wang[2] and Y Dai[1]

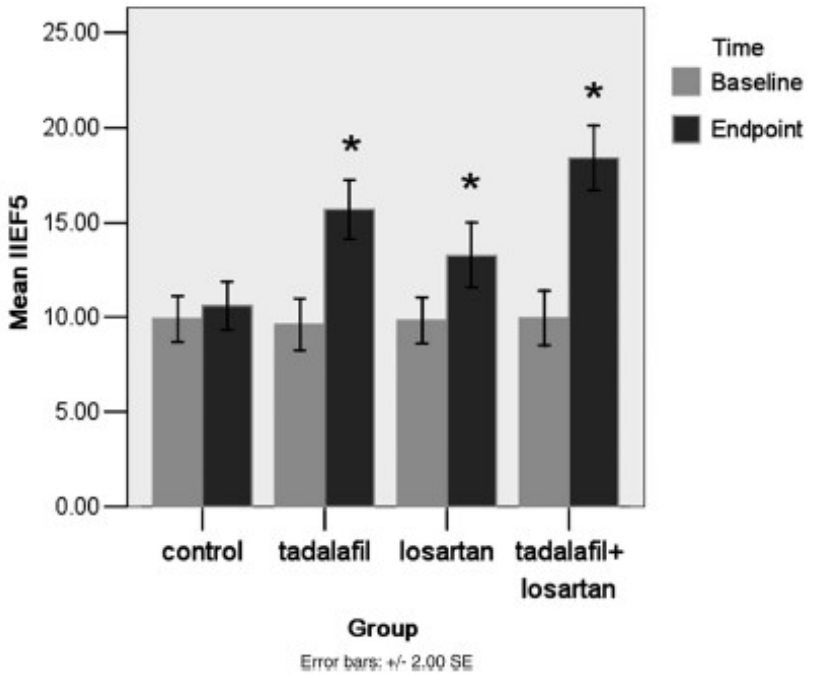


Figure 1. Mean IIEF-5 (International Index of Erectile Function) scores at baseline and endpoint of each group. $^{*}P<0.05$ for end point vs baseline of each group. The treatment of tadalafil, losartan or losartan plus tadalafil were effective on increasing the mean IIEF-5 scores. $^{\#}P<0.05$ for tadalafil or losartan vs losartan plus tadalafil at end point. The treatment of the combination of losartan and tadalafil were more effective than single-use.

PDE5i + Pentossifillina

La Pentossifillina è una metilxantina, PDEi che a cascata inibisce diverse citokine coinvolte nei processi di degenerazione nervosa, apoptosi e fibrosi.

Int Urol Nephrol (2008) 40:133–136
DOI 10.1007/s11255-007-9255-1

ORIGINAL ARTICLE

The effect of sildenafil citrate and pentoxifylline combined treatment in the management of erectile dysfunction

Ozdem Levent Ozdal · Cuneyt Ozden · Serkan Gokkaya · Guvenc Urgancioglu · Binhan Kagan Aktas · Ali Memis

Table 3 Mean IIEF scores before and after sildenafil treatment according to vasculogenic ED degree

	Before treatment	After treatment	*P* value[a]
Mild–moderate	13.4 ± 2.5	18.5 ± 2.7	0.0001
Severe	6.3 ± 2.6	12.2 ± 3.3	0.0001

[a] Wilcoxon Sign Rank test

Table 4 Mean IIEF scores before and after combination treatment according to vasculogenic ED degree

	Before treatment	After treatment	*P* value[a]
Mild–moderate	12.9 ± 2.3	22.1 ± 2.8	0.0001
Severe	6.5 ± 2.4	16.2 ± 5.0	0.0001

[a] Wilcoxon Sign Rank test

COMBINATION THERAPY OF TADALAFIL AND PENTOXIFYLLINE IN SEVERE ERECTILE DYSFUNCTION; A PROSPECTIVE RANDOMIZED TRIAL

SANTOSH KUMAR[1], RAJESH ROAT[2], SWATI AGRAWAL[1], KUMAR JAYANT[3], RAVIMOHAN S. MAVUDURU[3], SHRAWAN KUMAR[3]

POLSKI
PRZEGLĄD CHIRURGICZNY
2015, 87, 8, 377–383

Table 4. Intergroup comparison based on various categories of ED subgroups

IIEF5 pre therapy	Group	Patients	Mean IIEF (% change) ±SD	p value
Overall	A	117	90,70 ± 15,20	0,014
	B	120	95,6 ± 13,40	
Mild to moderate	A	29	54,08 ± 11,52	0,027
	B	27	63,38 ± 24	
Moderate	A	58	101,80 ± 36,80	0,012
	B	58	119,50 ± 38,50	
Severe	A	30	72,70 ± 47,20	0
	B	35	132,30±54,30	

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by unpaired Student's t-test

Table 5. Treatment related side effects between the two groups

Adverse effect	Group A	Group B	p value
Headache	9	11	0,34
Back-Pain	4	3	0,89
Nasal stuffiness	2	1	0,78

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by unpaired Student's t-test

Combination of **Tadalafil + Pentoxifylline** showed :
significant improvement in IIEF scores in patients of ED.
This improvement was more seen in patients with severe ED who received combination of Tadalafil 10 mg OD + Pentoxifylline 1200 mg in three divided doses.

PDE5i + alfalitici

Author (year)	*Study design*	*No. of Patients*	*Follow-up*	*Evaluation Questionnaire*	*Results*			*Evidence level*
						Sildenafil	Combination	
de Rose *et al.* (2002)[30]	RCT	28	60 days	IIEF		13.5±4.1	20.86±3.2*	II
					Comments: 1. All 28 patients were sildenafil failure. 2. 78.6% (11/14) patients with doxazosin daily and sildenafil on demand showed a significant IIEF increase compared to sildenafil on demand only group.			
					Alfuzosin	PDE5I	Combination	
Kaplan *et al.* (2007)[31]	RCT	62	12 weeks	IIEF-EF,	20.3±5.2	21.4±5.7	25.7±4.9	II
				IPSS	14.6±3.7	14.9±4.2	13.5±4.2	
Liguori *et al.* (2009)[34]	RCT	66	12 weeks	IIEF-EF,	16.0±4.6	18.8±4.8	19.9±4.8	II
				IPSS	10.5±3.6	12.5±5.6	9.0±4.0	
					Comments: The greatest improvements of IIEF-EF and IPSS are observed with the combination therapy compared to the baseline.			

Abbreviations: IIEF-EF, international index of erectile function-erectile function; IPSS, international prostate symptom score.

*$P<0.001$, compared with sildenafil monotherapy.

Hemodynamic Effects of Once-daily Tadalafil in Men With Signs and Symptoms of Benign Prostatic Hyperplasia on Concomitant α_1-Adrenergic Antagonist Therapy: Results of a Multicenter Randomized, Double-Blind, Placebo-controlled Trial

Evan Goldfischer, John J. Kowalczyk, William R. Clark, Erin Brady, Michael Anne Shane, Nancy Dgetluck, and Suzanne R. Klise

UROLOGY 79 (4), 2012

Table 2. Primary endpoint: treatment-emergent dizziness

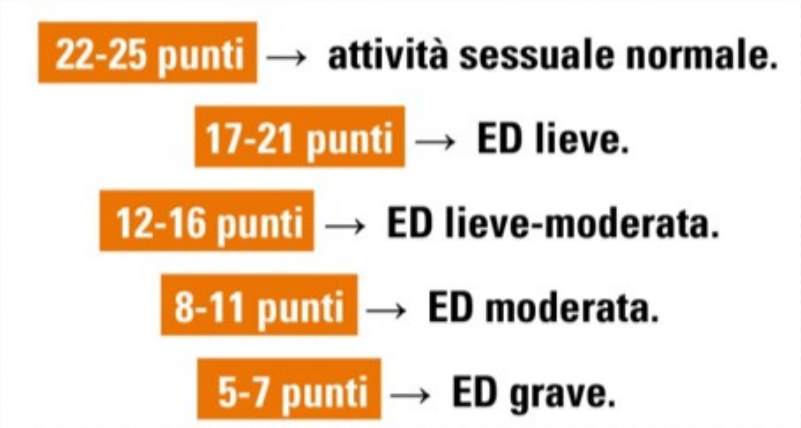
Medical Dictionary for Regulatory Activities Preferred Term	Placebo (n = 159*)	Tadalafil 5 mg (n = 158)	*P* Value (1-Sided)
Patients with ≥1 TEAE	9 (5.7)	11 (7.0)	.403
Dizziness	8 (5.0)	10 (6.3)	
Dizziness postural	1 (0.6)	1 (0.6)	

The proportion of participants reporting treatment-emergent dizziness or with a positive orthostatic test was similar between the tadalafil/α-blocker combination therapy group and the placebo/α-blocker combination therapy group.

- The changes in hemodynamic signs and symptoms were similar for tadalafil and placebo groups with concomitant α-blocker therapy.
  - However, consistent with previous clinical pharmacology studies of healthy subjects, the present study showed a trend toward increased hemodynamic signs and symptoms in men taking concomitant tadalafil and nonuroselective α-blockers, most notably those taking doxazosin.

L.A. 72 anni

Dopo 3 mesi di trattamento con Tamsulosina 0.4 mg dopo pranzo + Vardenafil 20 mg 2 volte la settimana a distanza di 2 ore dalla cena.
Miglioramento dei LUTS ostruttivi – IPSS 9 (era 24)
Ripresa di rapporti soddisfacenti (a volte anche il giorno dopo assunzione di Vardenafil)– IEEF (5) 18 (era 10)



Conclusioni

- I PDE5 inibitori, per le loro caratteristiche di efficacia, maneggevolezza e tollerabilità sono la prima scelta terapeutica nella DE.
- In caso di non risposta si deve eseguire un nuovo re-trail su misura (tailoring) con PDE5i
- In caso di ulteriore mancata risposta si possono utilizzare, da sole o in associazione le prostaglandine o altre sostanze vasoattive, sotto diverse forme farmacologiche (ICI, intrauretrale, topica).
- La nutraceutica associata ai PDE5i può avere un ruolo
- In caso di ipogonadismo associato è indicato combinare la terapia sostitutiva con Testosterone
- Il miglioramento dei LUTS può migliorare anche la risposta farmacologica ai PDE5i.
- Contemporaneamente si devono sempre trattare e/o eliminare tutte le cause di DE, inclusi gli stili di vita e le noxe esogene.


grazie!