



ASSOCIAZIONE ITALIANA MEDICI DI FAMIGLIA
ITALIAN ACADEMY OF FAMILY PHYSICIANS

XXIII CONGRESSO NAZIONALE AIMEF

Nuovi orizzonti della Medicina di Famiglia nella gestione integrata delle cronicità

Emmanuele A. Jannini

Accademia Italiana per la Salute della Coppia

Presidente del Congresso
Dott. **Walter Ingarozza**


Caserta 19-21 Maggio 2017
Centro Congressi Grand Hotel Vanvitelli



- STORIE DI ESPERIENZA CLINICA: Speaker, consulente, ricercatore per:





A close-up photograph of a hand holding a lit cigarette. The hand appears to be from an older person, with wrinkled skin. The cigarette is lit, with a small amount of ash at the tip.

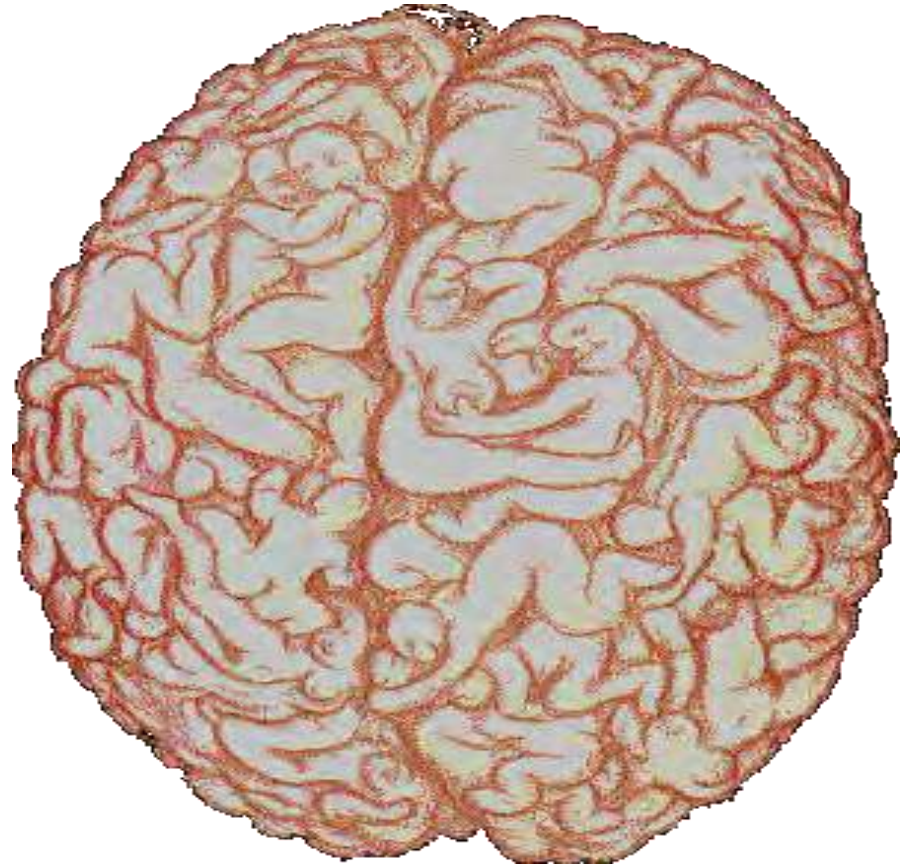
Smoking damages the tissues in your penis

There are over 4,000 chemicals in cigarette smoke. Some of them damage your arteries, including the parts that keep you hard. If they go floppy, so do you.

Still want to inhale? ▶



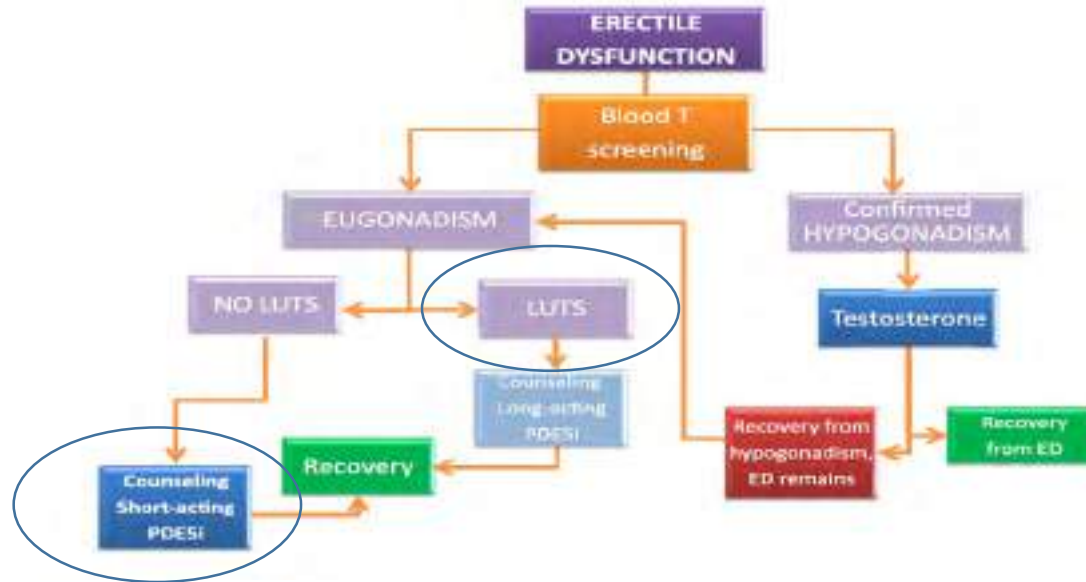
Psicossuologia dell'impotenza



Controversies in Sexual Medicine

Which Is First? The Controversial Issue of Precedence in the Treatment of Male Sexual Dysfunctions

Emmanuele A. Jannini, MD,* Andrea M. Isidori, MD, PhD,[†] Antonio Aversa, MD, PhD,[‡] Andrea Lenzi, MD,[§] and Stanley E. Althof, PhD[‡]

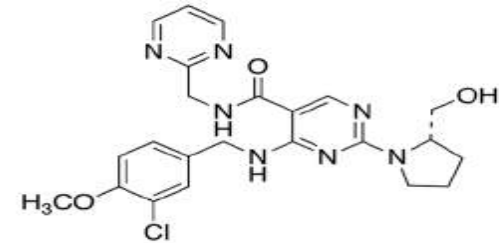




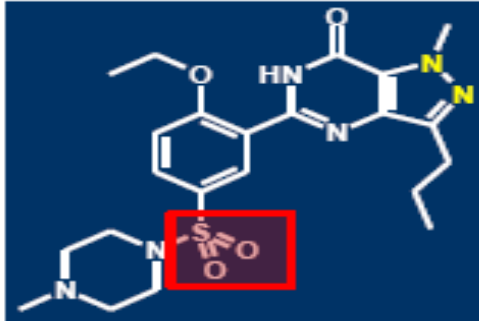
Characteristic	PDE5 inhibitor			
	Avanafil	Sildenafil	Vardenafil	Tadalafil
T_{max} (range)	30–45 min	30–120 min	30–120 min	Not reported
T_{max} (median)	0.5-0.75 h	1 h	1 h	2 h
Effect of food on T_{max}	Delayed by 1.25 h	Delayed by 1 h	Delayed by 1 h	None
Plasma protein binding	99%	96%	95 %	94%
Half-life	6–17 h	3–5 h	4–5 h	17.5 h (mean)
Accumulation in plasma	None	Not reported	None	Not reported
Effect on exposure/clearance, of:				
Age	None	Reduced clearance	Reduced clearance	Reduced clearance
Mild renal impairment	None	None	None	Increased exposure
Moderate renal impairment	None	None	None	Increased exposure
Severe renal impairment	No data	Increased exposure	Increased exposure	Increased exposure
Mild hepatic impairment	None	Increased exposure	Increased exposure	None
Moderate hepatic impairment	Reduced exposure	Increased exposure	Increased exposure	None
Severe hepatic impairment	Not studied	Not studied	Not studied	Limited data

Avanafil: Chemical structure and mechanism of action

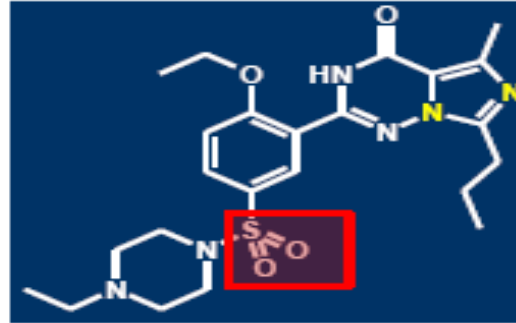
- Highly selective and reversible inhibitor of PDE5
- Unique chemical structure compared with other PDE5 inhibitors
 - Central structure formed by a nitrogen derivative of a pyrimidine carboxamide
 - Sugar component is a cyclic chloromethoxybenzylamino structure
 - Exists as a single enantiomer
 - **Binds to catalytic site of PDE5 regardless of spatial orientation, which may increase affinity for PDE5**



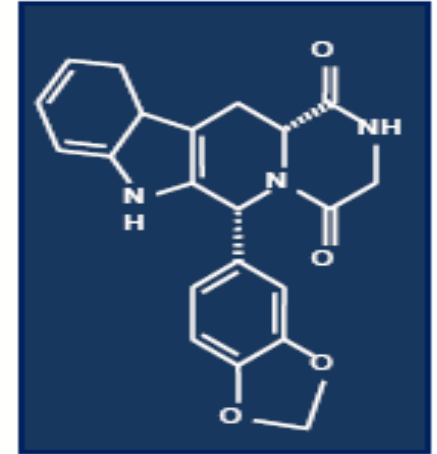
Chemical structures of PDE5 inhibitors



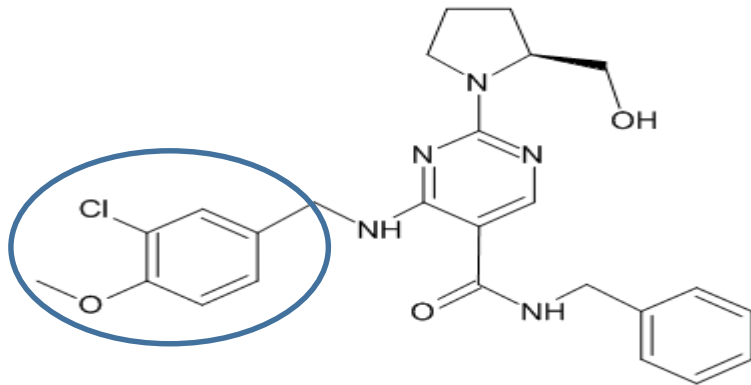
Sildenafil



Vardenafil



Tadalafil

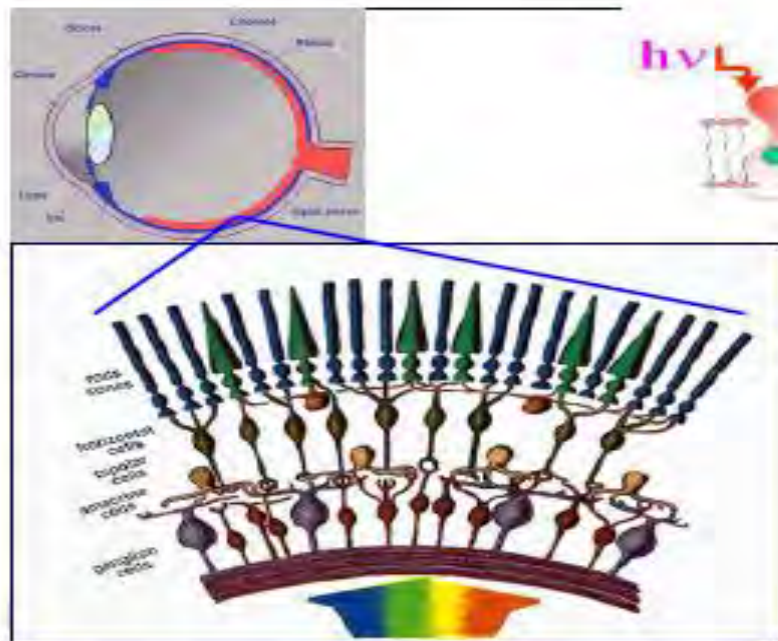


Avanfil: a different molecular structure

Selectivity profiles of PDE5 inhibitors

PDE Isozyme	Selectivity vs PDE5 (fold difference)			
	Avanafil	Sildenafil	Vardenafil	Tadalafil
PDE1	10,192	375	1012	10,500
PDE2	9808	39,375	273,810	>25,000
PDE3	>19,231	16,250	26,190	>25,000
PDE4	1096	3125	14,286	14,750
PDE5	1	1	1	1
PDE6	121	16	21	550
PDE7	5192	13,750	17,857	>25,000
PDE8	2308	>62,500	1,000,000	>25,000
PDE9	>19,231	2250	16,667	>25,000
PDE10	1192	3375	17,857	8750
PDE11	>19,231	4875	5952	25

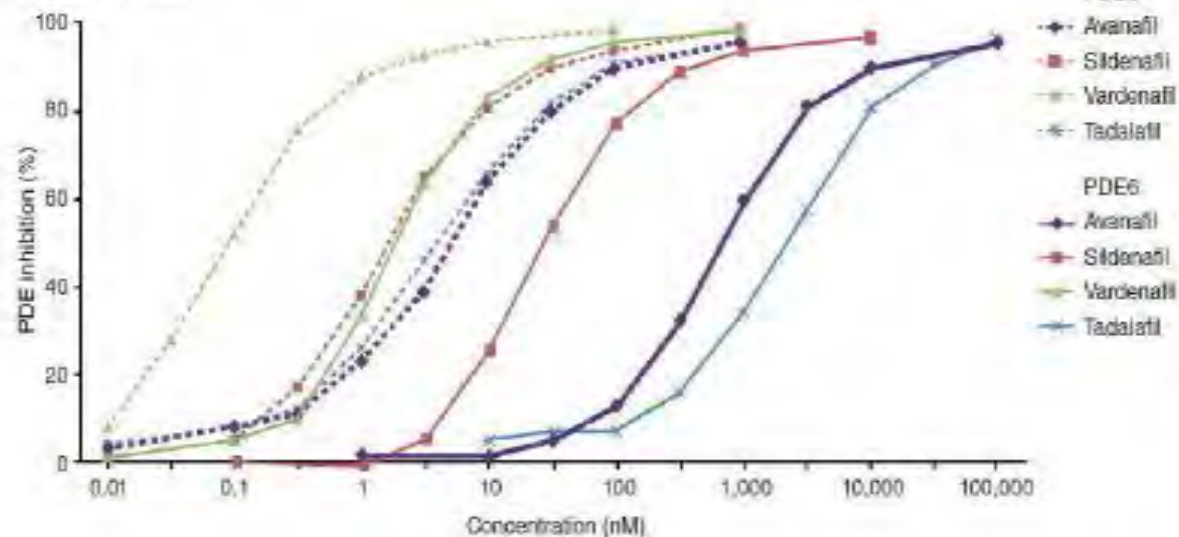
PDE6 and visual signal transduction



- Activation of rhodopsin by light stimulates PDE activity
- c-GMP is a second messenger in signal transduction in the initiation of visual phototransduction

Selectivity for PDE5 vs PDE6

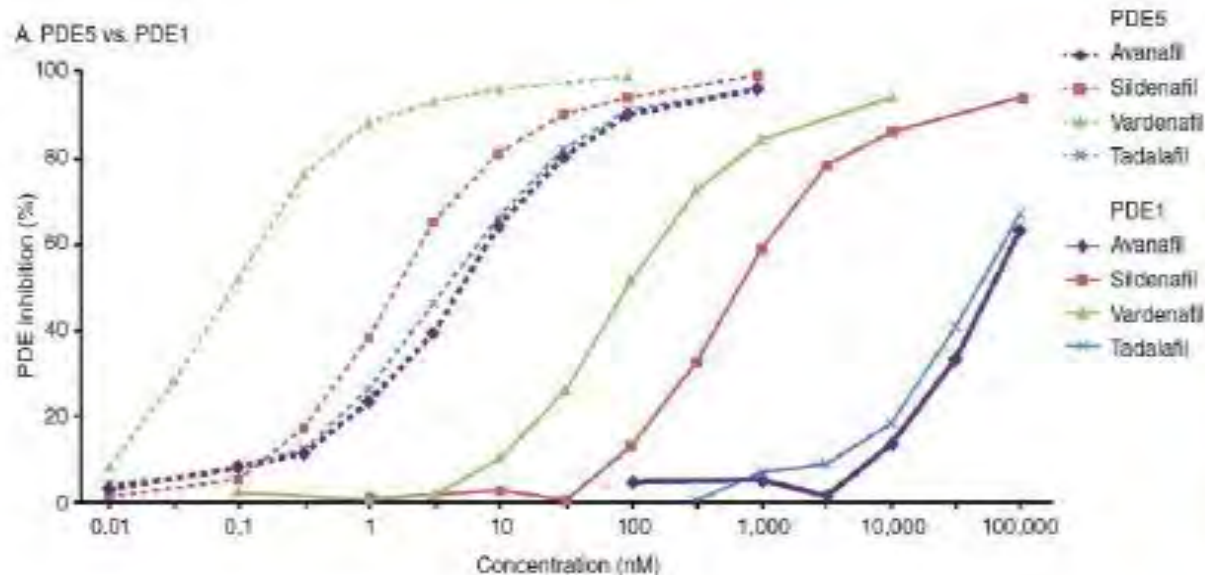
B. PDE5 vs. PDE6



Compound	PDE6
Target tissues	Retina
Avanafil	121
Sildenafil	16
Vardenafil	21
Tadalafil	550

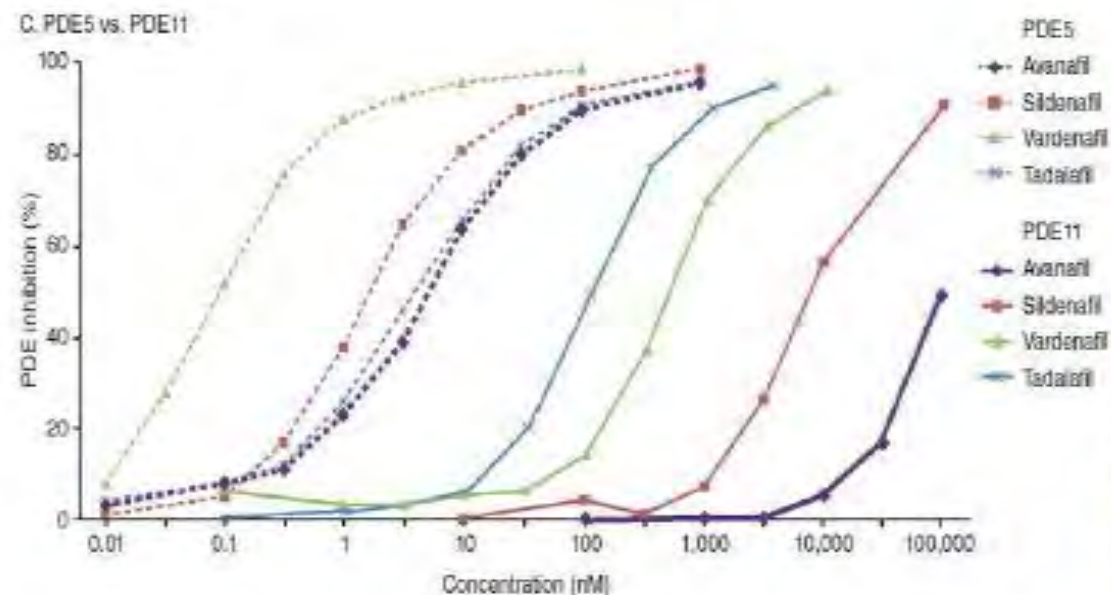
• Avanafil has 121 higher selectivity for PDE5 against PDE6 compared to 16-fold for sildenafil

Selectivity for PDE5 vs PDE1



	PDE1
Target tissues	Heart, brain, vascular smooth muscle
Avanafil	10,192
Sildenafil	375

Selectivity for PDE5 vs PDE11



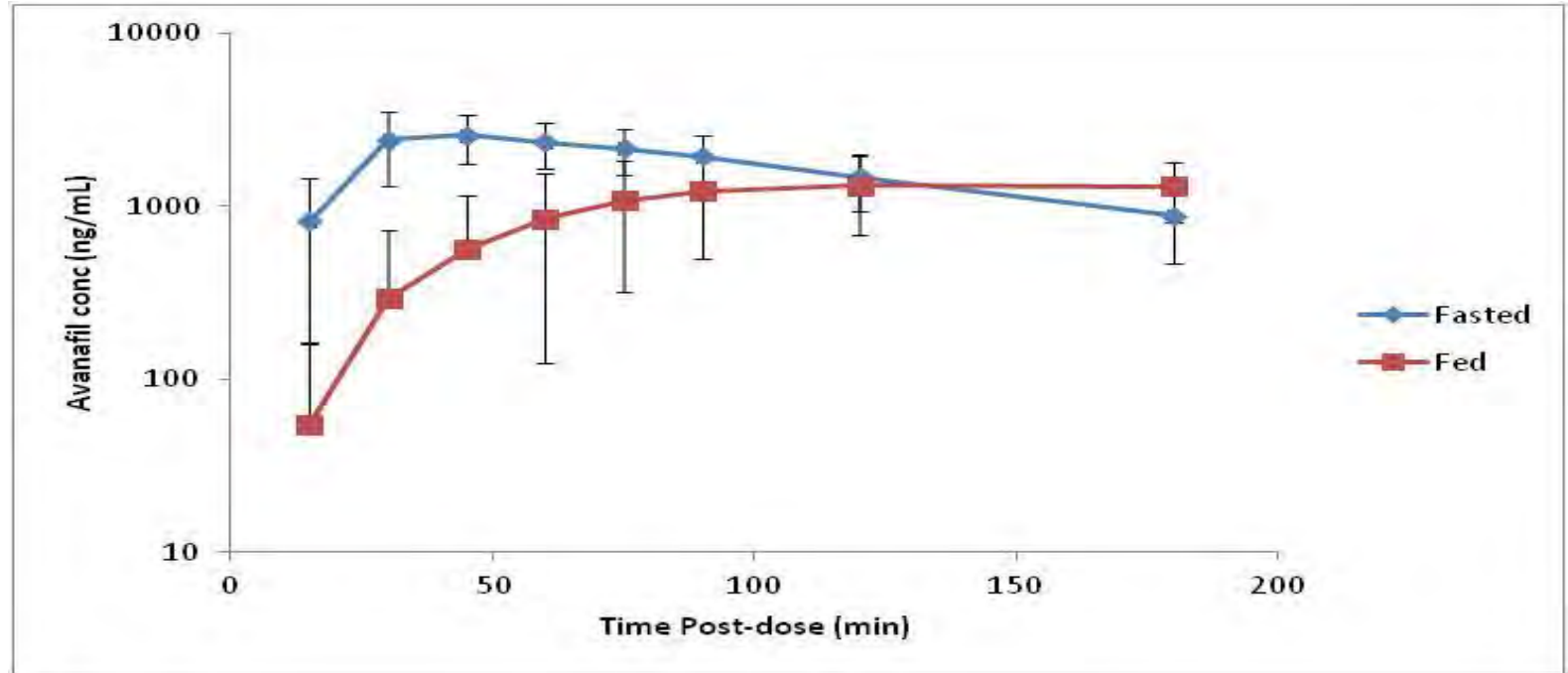
Compound	PDE11
Target tissues	Skeletal muscle, prostate, liver, kidney, pituitary, testis
Avanafil	>19,231
Sildenafil	4,875
Vardenafil	5,952
Tadalafil	25

Comparative PK profile

Characteristic	PDE5 inhibitor			
	Avanafil	Sildenafil	Vardenafil	Tadalafil
T_{max} (range)	30–45 min	30–120 min	30–120 min	Not reported
T_{max} (median)	30-45 min	1 h	1 h	2 h
Half-life $T_{1/2}$	6 - 8 h	3–5 h	4–5 h	17.5h

- **Avanafil has the shortest median time to maximal plasma concentrations (T_{max}), ranging from 0.5 to 0.75 hours**

Plasma Avanafil Concentrations in Fasted and Fed Subjects

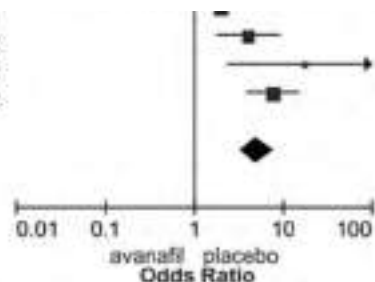


Avanafil for male erectile dysfunction: a systematic review and meta-analysis

Yuan-Shan Cui, Nan Li, Huan-Tao Zong, Hui-Lei Yan, Yong Zhang

Zhao C 2011	18	68	10	66	34.7%	2.02 [0.85, 4.77]	2011
Goldstein Ir 2012	27	126	8	127	29.1%	4.06 [1.76, 9.33]	2012
Mulhail JP 2012	15	94	1	96	3.9%	18.04 [2.33, 139.57]	2012
Goldstein I 2012	58	157	11	155	32.4%	7.67 [3.83, 15.34]	2012

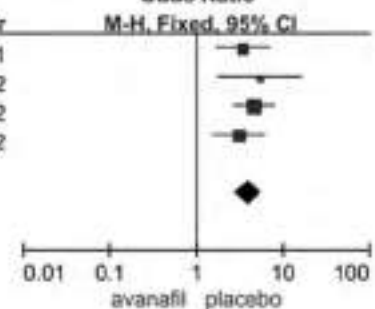
Total (95% CI) 445 444 100.0% 5.06 [3.29, 7.78]
 Total events 118 30
 Heterogeneity: $\chi^2 = 7.51$, $df = 3$ ($P = 0.06$); $I^2 = 60\%$
 Test for overall effect: $Z = 7.39$ ($P < 0.00001$)



Successful vaginal penetration

Study or Subgroup	avanafil		placebo		Weight	Odds Ratio	M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total				
Zhao C 2011	37	68	17	66	23.7%	3.44 [1.66, 7.13]	2011	
Mulhail JP 2012	18	94	4	96	9.6%	5.45 [1.77, 16.78]	2012	
Goldstein I 2012	68	157	22	155	37.8%	4.62 [2.66, 8.01]	2012	
Goldstein Ir 2012	33	126	13	127	28.8%	3.11 [1.55, 6.25]	2012	

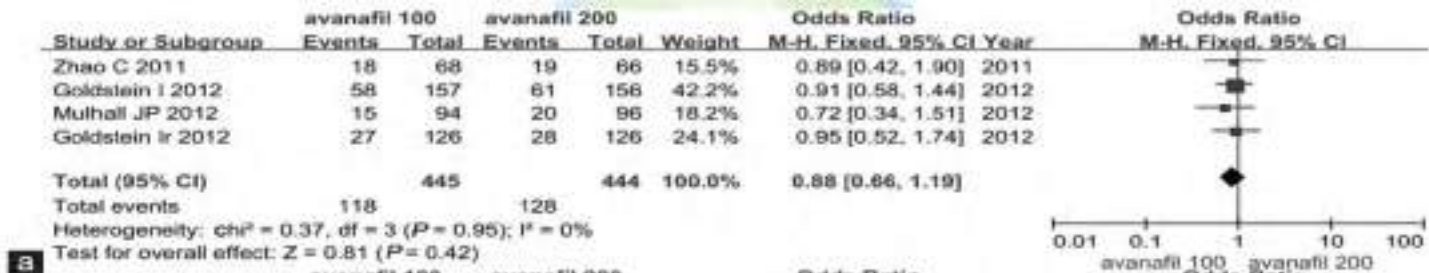
Total (95% CI) 445 444 100.0% 3.99 [2.80, 5.67]
 Total events 156 56
 Heterogeneity: $\chi^2 = 1.21$, $df = 3$ ($P = 0.75$); $I^2 = 0\%$
 Test for overall effect: $Z = 7.69$ ($P < 0.00001$)



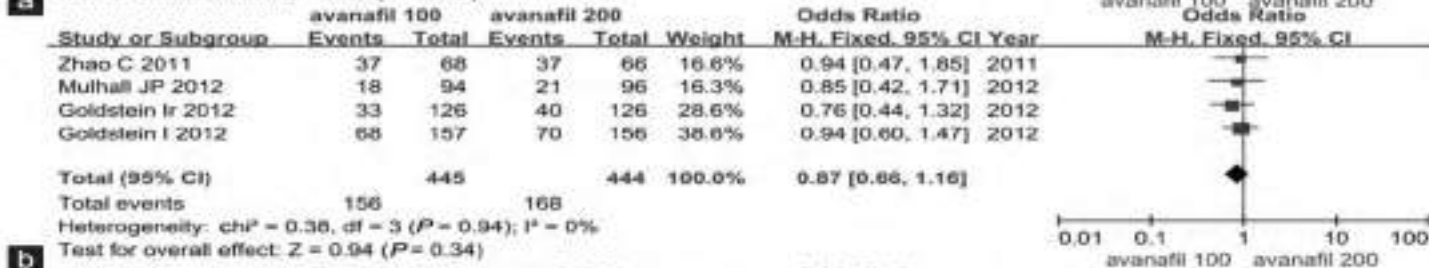
Successful intercourse

Four publications, involving a total of 1381 patients, randomized controlled trials (RCTs) that compared avanafil with a placebo.

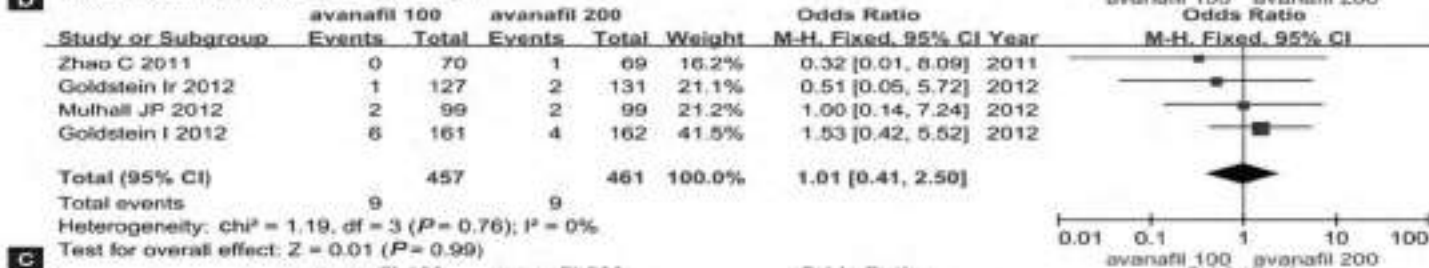
Successful vaginal penetration



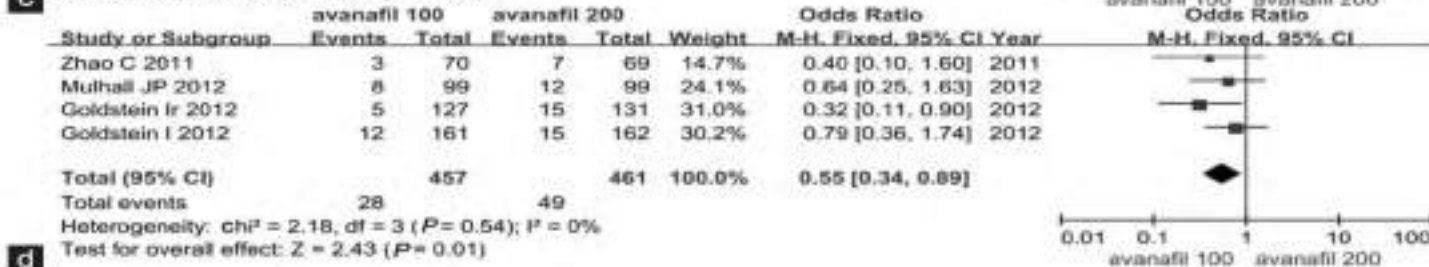
Successful intercourse



Discontinued do due to Adverse Events



Headaches



Avanafil: from Pharmacokinetics to Clinical Implications

Erections sufficient for intercourse as soon as 15 min after intake

Fast on-demand dosing without any need to plan sexual activity

Avoids accumulation
Minimizes adverse events from concomitant use of other drugs

Erections sufficient for intercourse even after 6 hours from intake –
No compromise in the 'window' of opportunity

Practical Tips for using Avanafil

- In difficult patients (most of patients): start 200 mg
- In those discontinuing other PDE5i for headaches: start with 100 mg.
- Rapidity of onset: flexibility and discretionary !
- Cost is an issue: as much as generic sildenafil (but high quality control drug)
- Safety (cardiac, nitrates, visual) a significant advantage.

Quale dosaggio prescrivere? 50-100-200???

Prescriviamo la massima dose

- Per evitare la risposta incompleta nel paziente complesso
- Per aumentare la confidenza del pz in se stesso
- Per massimizzare l'effetto
- Perchè è più facile titolare verso il basso che verso l'alto

*Staab A et al. Pharm Res 2004;21:1463-70.
Cohen JS. Drug Saf 2000;23:1-9*

Come prescriviamo un antibiotico?

- Di scarsa efficacia?
- Inducente resistenza batterica?
- A basse dosi?
- Di lenta azione?
- Tossico?



EVITIAMO DI
INDURRE
FENOMENI DI
'FARMACORESISTENZA'
AI PDE5I QUANDO
ABBIAMO UN
PROFILO DI
TOLLERABILITA'
CHE LO PERMETTE

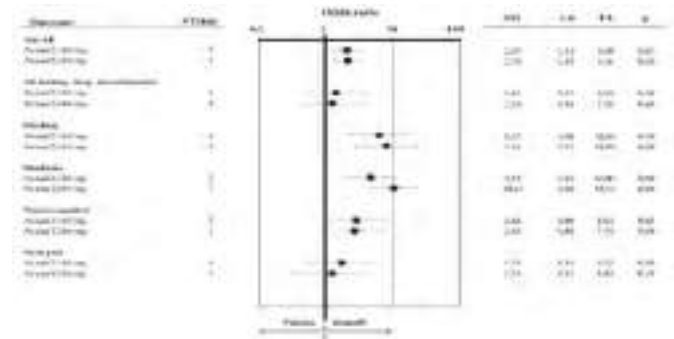
Selectivity profiles of PDE5 inhibitors

An unique diaminopyrimidine chemical structure

	PDE1	PDE6	PDE11	
Target tissues	<ul style="list-style-type: none"> • Heart • Brain • Vascular smooth muscle 	<ul style="list-style-type: none"> • Retina 	<ul style="list-style-type: none"> • Skeletal muscle • Prostate • Liver • Kidney • Pituitary • Testes 	
	Selectivity vs PDE5 (fold-difference activity) ¹			Reported off-target AEs
Avanafil	>10,192	121	>19,231	One case of cyanopsia in clinical trial program ²
Sildenafil	375	16	4875	Cyanopsia (0.8% with 50 mg and 1.4% for 100 mg vs 0.03% placebo ^{3,4}
Vardenafil	1012	21	5952	Cyanopsia (uncommon) ⁵
Tadalafil	10,500	550	25	Common back pain and myalgia (2–3%) ⁶

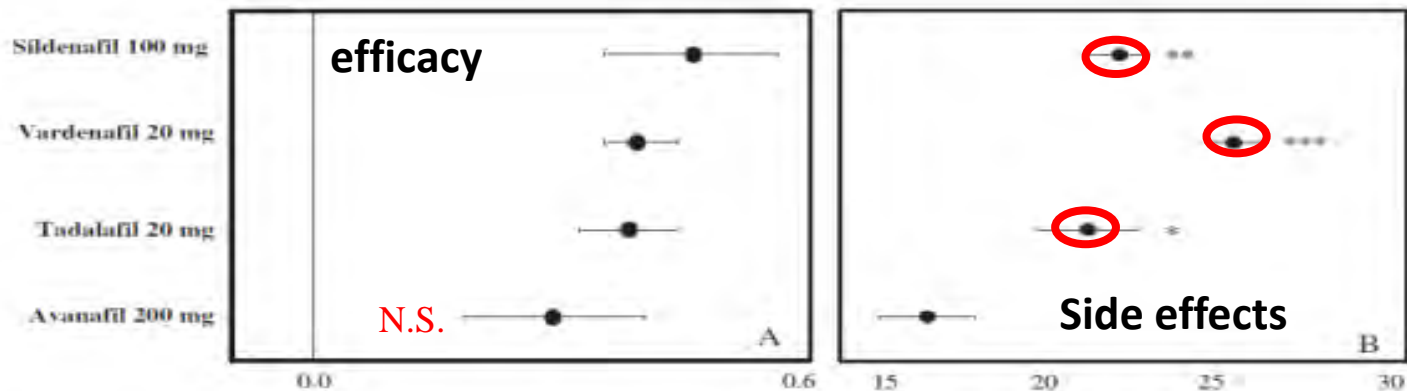
1.Wang et al. J Sex Med 2012; 2.Belkoff et al. BJU Int 2013; 3.Giuliano et al. Int J Clin Pract 2013; 4.Sildenafil SmPC June 2013; 5.Vardenafil SmPC April 2013; 6.Tadalafil SmPC April 2013

No differences between 100 and 200 mg of avanafil and placebo for the incidence severe adverse events is observed:
 OR=1.99 [.67;5.93] and 1.7 [.54;5.31] for 100 and 200 mg over placebo, respectively,

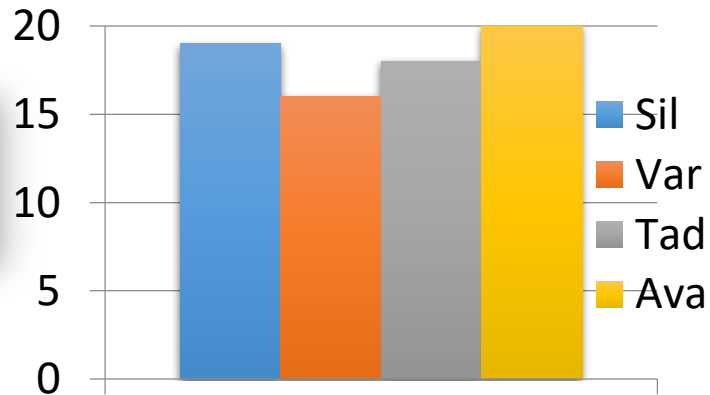


Metanalyzing data on side effects

About **2000** published patients treated with Avanafil or Placebo



EFFICACY/SAFETY RATIO



EXPERT OPINION ON DRUG SAFETY, 2016
<http://dx.doi.org/10.1517/14740338.2016.1130126>

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DRUG SAFETY EVALUATION

The safety and efficacy of Avanafil, a new 2nd generation PDE5i: comprehensive review and meta-analysis

Giovanni Corona^a, Giulia Rastrelli^a, Andrea Burri^a, Emmanuele A. Jannini^a and M Maggi^b

Trucchi e segreti

Come superare alcuni dei limiti dei PDE5i di prima generazione, ottenendo una miglior aderenza alla terapia con PDE5i?

Avanafil ha una comparabile efficacia ma una assai minor presenza di effetti collaterali quando confrontato con i PDE5i di prima generazione



Una nuova equazione clinica:
SENZAPENSIERI = SPONTANEITA'
SPONTANEITA' = VELOCITA' x SICUREZZA

EXPERT OPINION ON DRUG SAFETY, 2016
<http://dx.doi.org/10.1177/1474033820161136126>



DRUG SAFETY EVALUATION

The safety and efficacy of Avanafil, a new 2nd generation PDE5i: comprehensive review and meta-analysis

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Conclusione: il PDE5i
3 volte
senzapensieri