

# Μη παρεμβατικές / φαρμακευτικές θεραπείες που χρησιμοποιούμε χωρίς αποδείξεις



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# Conflict of interest

Astellas,  
GSK,  
Lilly,  
Pierre Fabre Medicament,  
Vianex

# Περίγραμμα παρουσίασης

- Placebo effect

*Ορισμοί*

*Μελέτες*

- Θεραπείες χωρίς αποδείξεις

*Off-label χρήση*

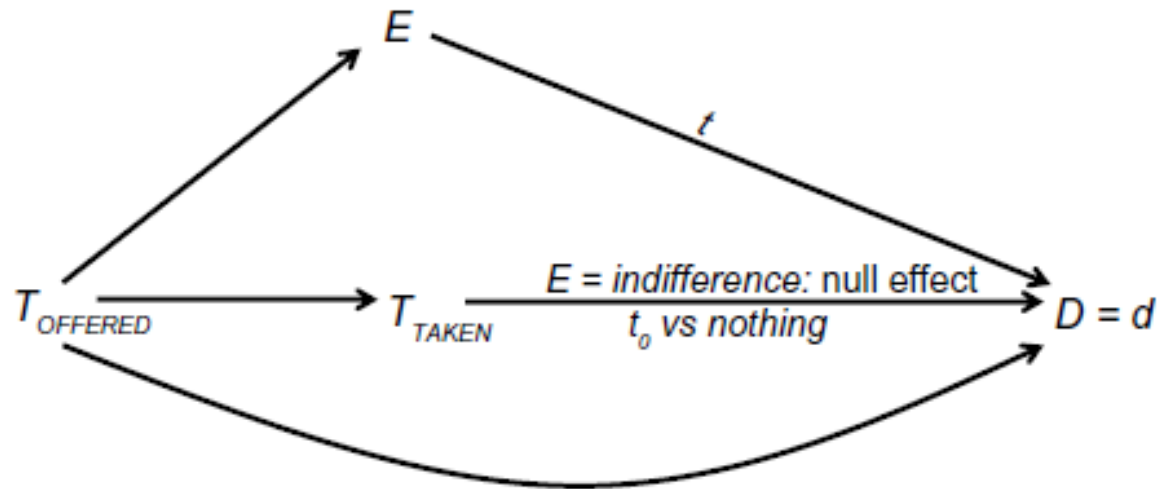
*Λάθη?*

*Παραδείγματα*

# Placebo και Placebo effect

The word “**placebo**” originated from Latin and meant “to please”. **Placebo** was used in medicine to denote “any medication prescribed more to please the patient than to treat the disease”

A **placebo** is a treatment that has no direct physical effect, but may have a psychological effect.



**Notes:**  $T_{OFFERED}$  denotes the treatment offered;  $T_{TAKEN}$  denotes the treatment taken;  $E$  denotes the patient's expectation of the outcome  $D=d$ ;  $t$  denotes a value of  $T_{TAKEN}$

# Placebo effect

Οποιαδήποτε μετρήσιμη, παρατηρούμενη ή αισθανόμενη (felt) αλλαγή ή βελτίωση μετά από χορήγηση μιας ουσίας ή πραγματοποίηση επεμβατικής θεραπείας, η οποία δεν έχει θεραπευτικό αποτέλεσμα για την κατάσταση-νόσο που αντιμετωπίζεται

Off label???

Control group?

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# Biological, clinical, and ethical advances of placebo effects

Damien G Finniss, Ted J Kaptchuk, Franklin Miller, Fabrizio Benedetti

Lancet 2010; 375: 686–95

- Ψυχολογικοί μηχανισμοί  
*Προσδοκία (expectancy)*  
*Μάθηση – τροποποίηση συμπεριφοράς (Conditioning)*
- Νευροβιολογικοί μηχανισμοί  
*Οπιοειδή*  
*Έκλυση νευρομεταβιβαστών – νευρομετατροποιητών (MRI, PET)*

**#Nocebo effect**

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*Lancet* 2010; 375: 686–95

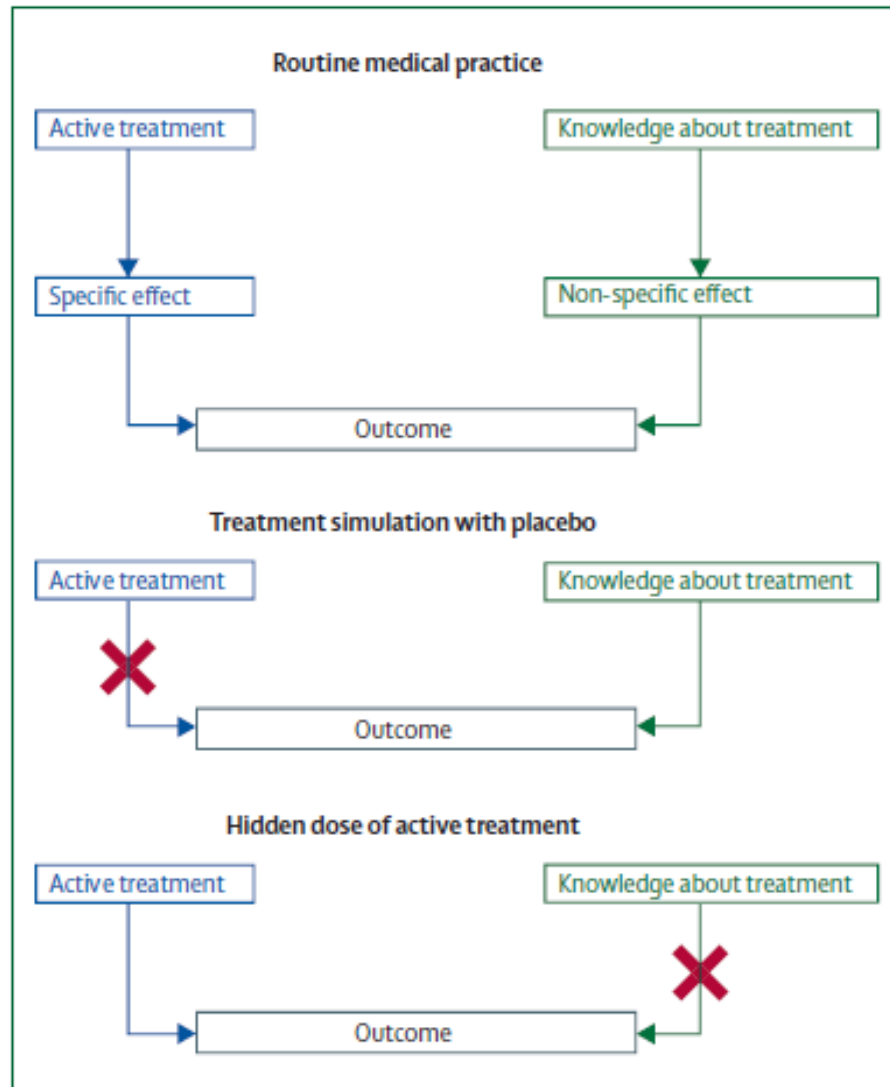
	Mechanisms
Pain	Activation of endogenous opioids and dopamine (placebo); activation of cholecystikinin and deactivation of dopamine (nocebo) <sup>17–22</sup>
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus <sup>23–25</sup>
Depression	Changes of electrical and metabolic activity in different brain regions (eg, ventral striatum) <sup>26,27</sup>
Anxiety	Changes in activity of the anterior cingulate and orbitofrontal cortices; genetic variants of serotonin transporter and tryptophan hydroxylase 2 <sup>28,29</sup>
Addiction	Changes of metabolic activity in different brain regions <sup>30</sup>
Autonomic responses to deep brain stimulation	Change of neuronal excitability in limbic regions <sup>31</sup>
Cardiovascular system	Reduction of $\beta$ -adrenergic activity of heart <sup>32</sup>
Respiratory system	Conditioning of opioid receptors in the respiratory centres <sup>33</sup>
Immune system	Conditioning of some immune mediators (eg, interleukin 2, interferon $\gamma$ , lymphocytes) <sup>34,35</sup>
Endocrine system	Conditioning of some hormones (eg, growth hormone, cortisol) <sup>36</sup>
Physical performance	Activation of endogenous opioids and increased muscle work <sup>37,38</sup>
Alzheimer's disease	Prefrontal executive control and functional connectivity of prefrontal areas <sup>21</sup>

**Table: Mechanisms for placebo effects in medical conditions and physiological systems**

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**Μ/Χ Πόνος:**

NaCl ως placebo

Παυσίπνοο κατ' επίκληση

- Placebo

- 33% λιγότερο:

ισχυρό παυσίπνοο

- 20% λιγότερο: ίσως placebo

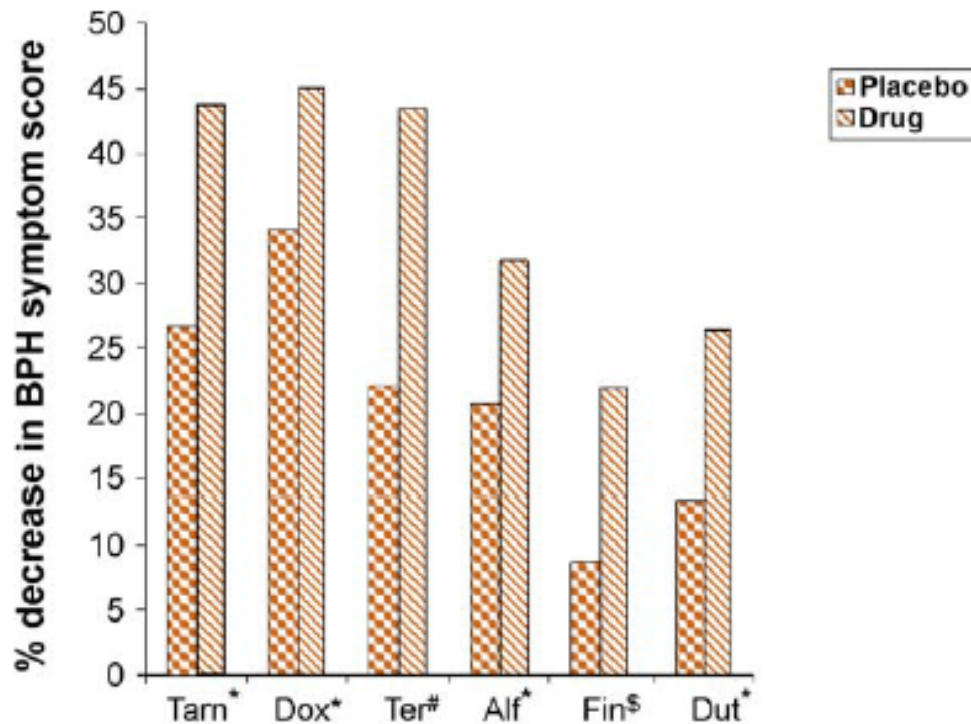
*Pollo A, et al Pain 2001; 93: 77–84.*



# The Placebo Effect in the Pharmacologic Treatment of Patients with Lower Urinary Tract Symptoms

Eur Urol 2006 440–453

Jules H. Schagen van Leeuwen<sup>a,\*</sup>, Ramiro Castro<sup>b</sup>, Michael Busse<sup>b</sup>, Bart L.H. Bemelmans<sup>c</sup>



Placebo  
9–34%

Φάρμακα  
22–45%.

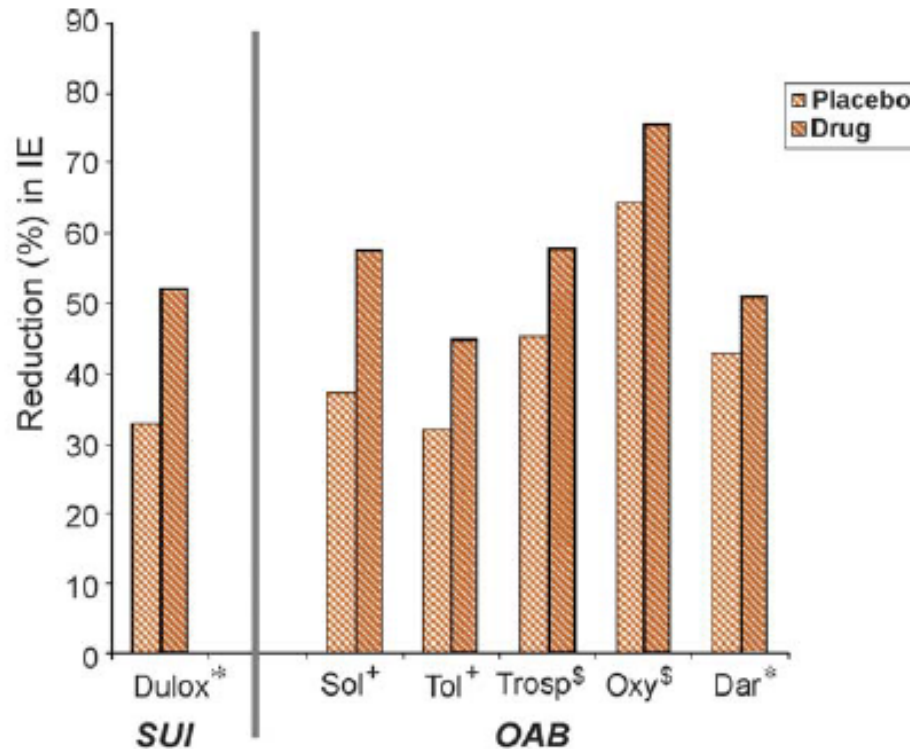
\*IPSS symptom score; # Boyarski symptom score; \$ adapted AUA score; Doxazosin: extended release; Tamsulosin: 0.4 mg/d (recommended dose)

% μείωση συμπτωμάτων

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\*Median reduction in IE per week; \$ mean reduction in IE/week; \*mean reduction in IE per 24h

Φάρμακο:  
45-77%

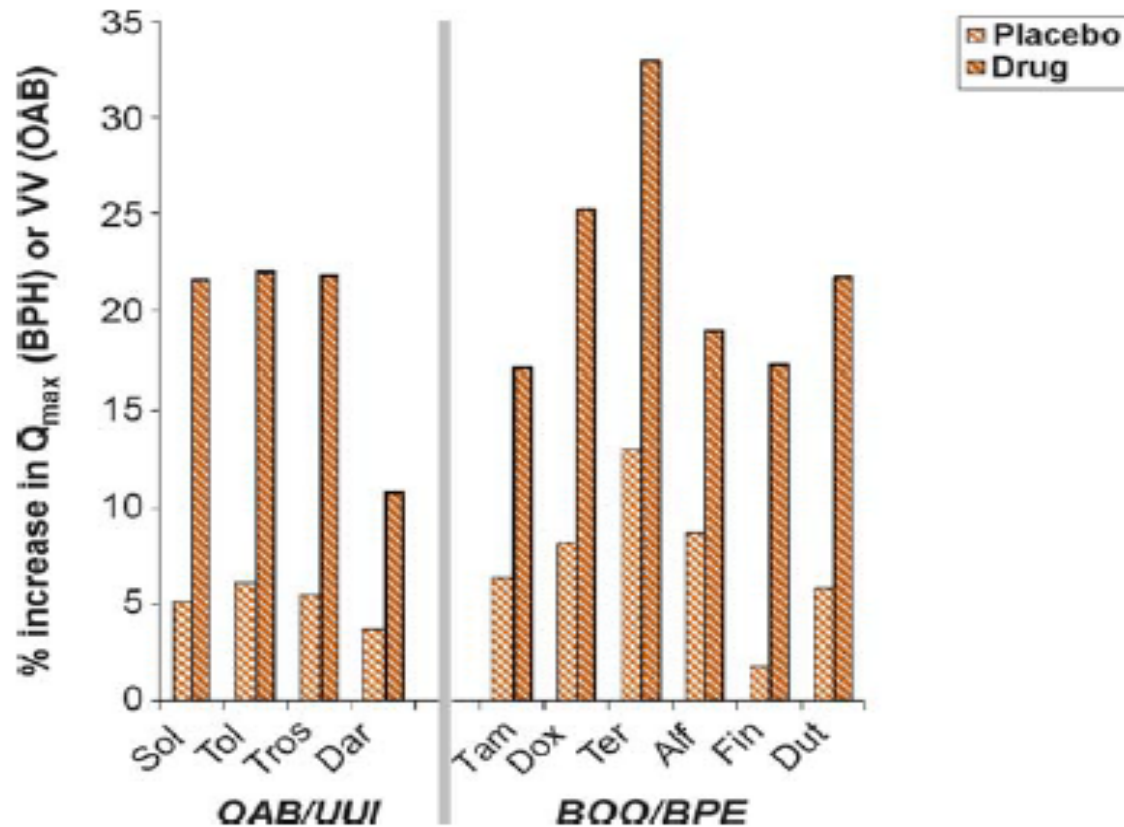
Placebo:  
32-65%

% μείωση επεισοδίων ακράτειας

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Φάρμακο:  
10-22%

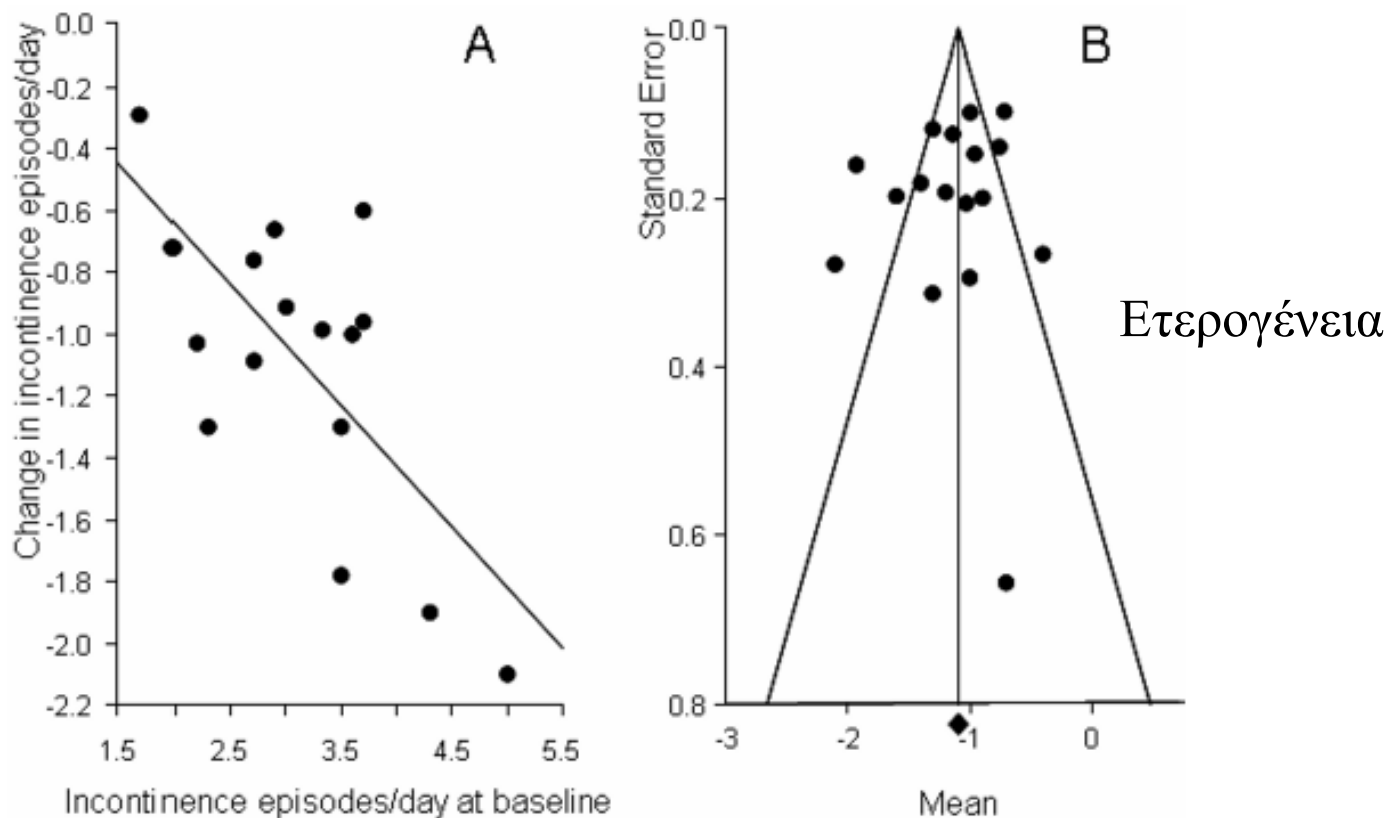
Placebo:  
4-6%

% αύξηση όγκου ούρησης ή Qmax

# A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder

Soyon Lee<sup>1</sup>, Bimal Malhotra<sup>2</sup>, Dana Creanga<sup>3</sup>, Martin Carlsson<sup>3</sup> and Paul Glue<sup>\*4</sup>

*BMC Medical Research Methodology* 2009, **9**:55



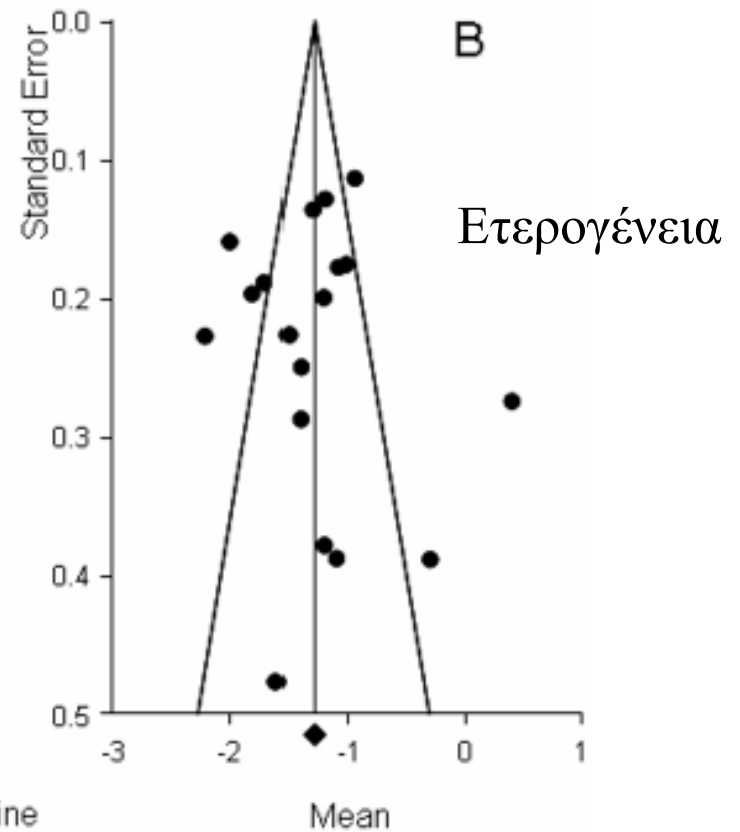
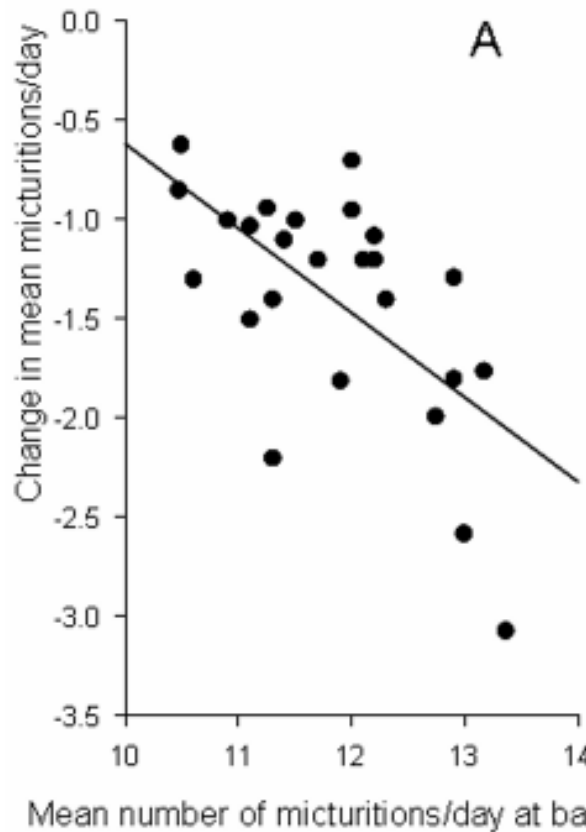
Η μεταβολή στα incontinence episodes/day  
σχετίζεται με τις baseline τιμές

# A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder

Soyon Lee<sup>1</sup>, Bimal Malhotra<sup>2</sup>, Dana Creanga<sup>3</sup>, Martin Carlsson<sup>3</sup> and Paul Glue<sup>\*4</sup>

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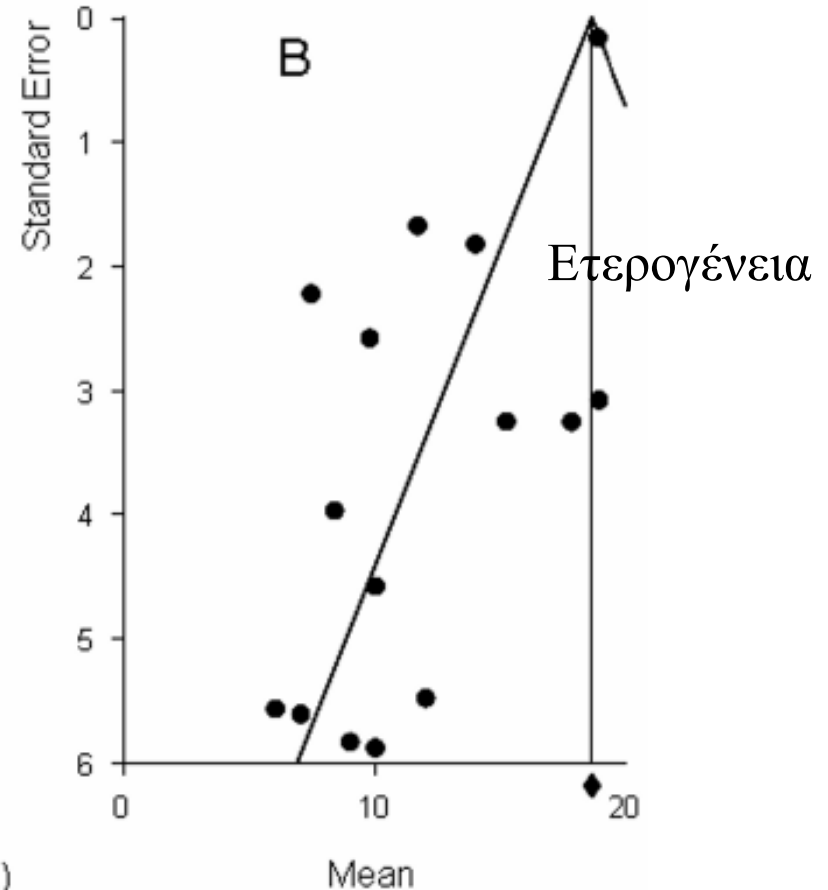
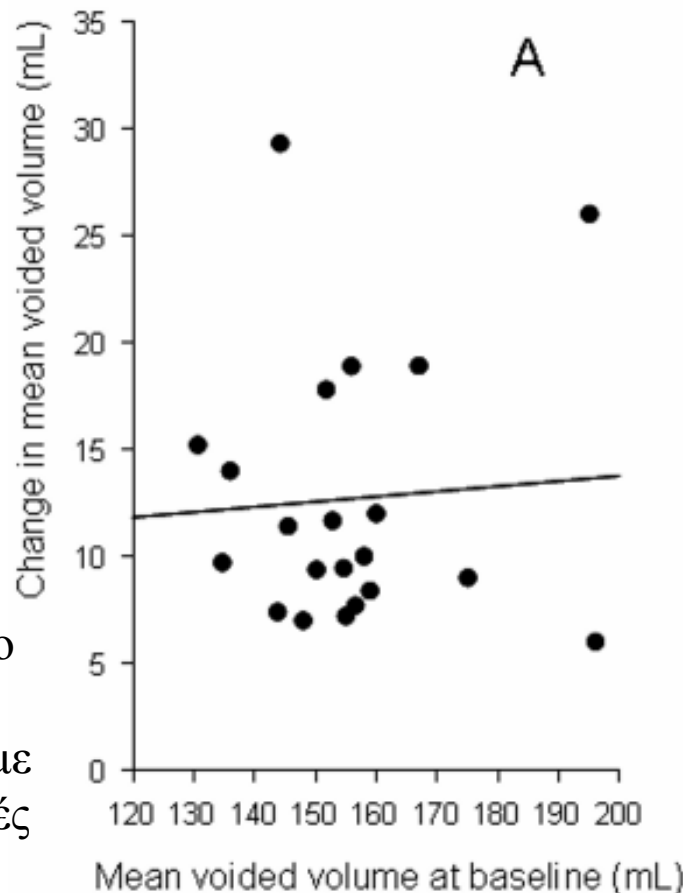
Η μεταβολή στις micturations/day σχετίζεται με τις baseline τιμές



# A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder

Soyon Lee<sup>1</sup>, Bimal Malhotra<sup>2</sup>, Dana Creanga<sup>3</sup>, Martin Carlsson<sup>3</sup> and Paul Glue<sup>\*4</sup>

*BMC Medical Research Methodology 2009, 9:55*

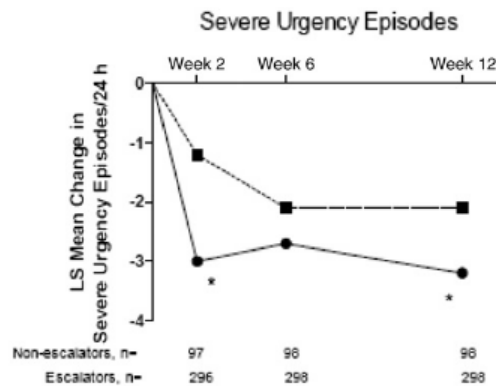
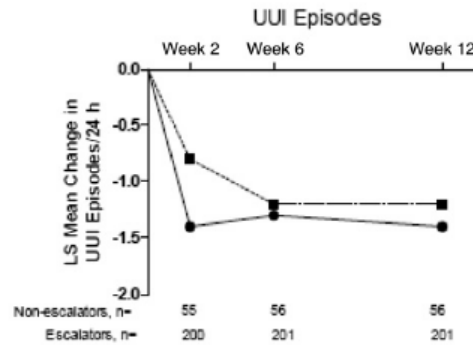
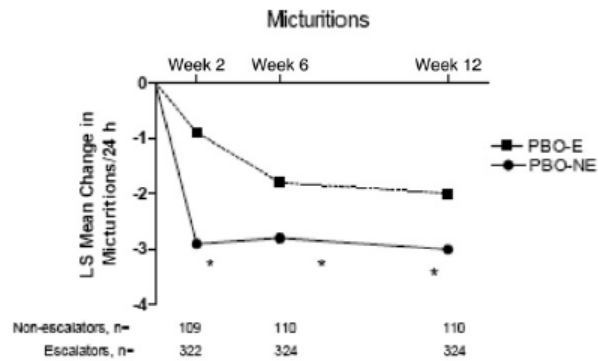


Η μεταβολή στο voided volume δεν σχετίζεται με τις baseline τιμές

# The Effect of Elective Sham Dose Escalation on the Placebo Response During an Antimuscarinic Trial for Overactive Bladder Symptoms

THE JOURNAL OF UROLOGY 2012

David R. Staskin,<sup>\*,†</sup> Martin C. Michel,<sup>‡</sup> Franklin Sun,<sup>§</sup> Zhonghong Guan<sup>§</sup> and Jon D. Morrow<sup>||</sup>



Μέση βελτίωση ουρήσεις/24h, επεισόδια επιτακτικότητας/24h στατιστικά σημαντική για PBO-NE σε σχέση με PBO-E, @ wks 6, 12

Βελτίωση στα σοβαρά επεισόδια επιτακτικότητας μόνο @ wk 12

Βελτίωση στα επεισόδια UUI μεγαλύτερη στους PBO-NE αλλά μη στατιστικά σημαντική @wks 2,4, 6.

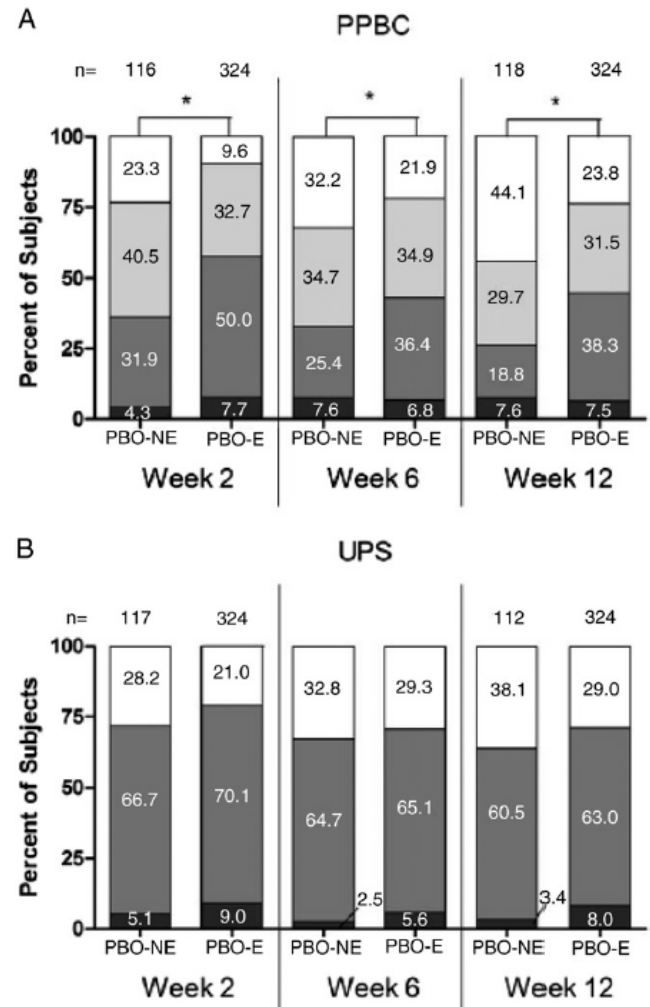
# The Effect of Elective Sham Dose Escalation on the Placebo Response During an Antimuscarinic Trial for Overactive Bladder Symptoms

THE JOURNAL OF UROLOGY 2012

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Μεταβολές PPBC score σημαντικά καλύτερες για PBO-NE σε σχέση με PBO-E (p 0.001) @wk 6

Μεταβολές UPS scores μεγαλύτερες στους PBO-NE αλλά μη στατιστικά σημαντικές (p 0.148, 0.630 and 0.304) @wks 2,4, 6.





# Παράγοντες που επηρεάζουν την απάντηση στο placebo σε ασθενείς με LUTS

- Condition-specific factors

*Symptom severity, treatment naivety, neurotransmitters*

- Patient-specific factors

*Personality, age*

- Trial-related factors

*Study design, duration, run-in period, visits, frequency of dosages, subjective vs objective outcome*

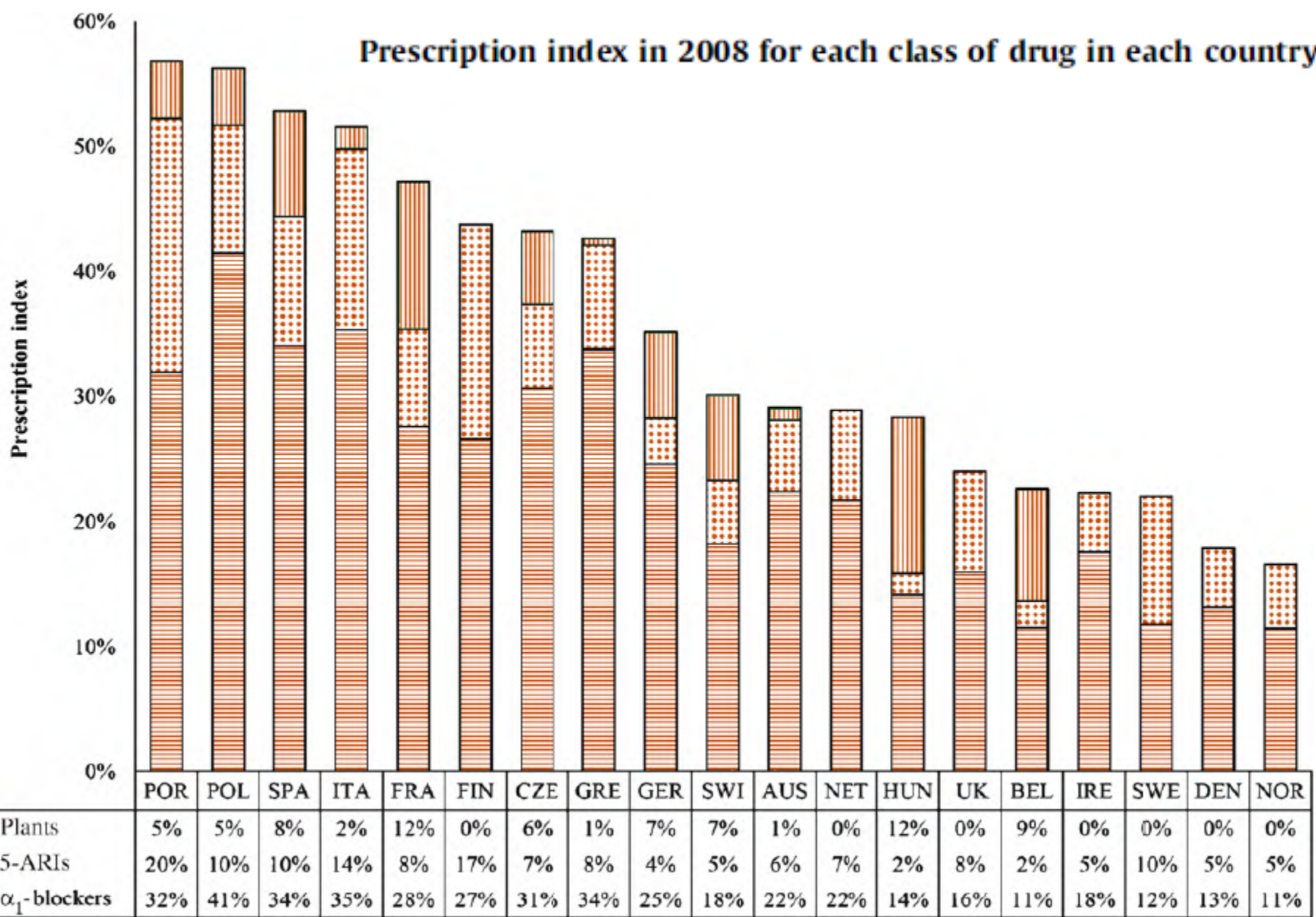
*Eur Urol 2006 440–453*

# Θεραπείες χωρίς αποδείξεις

## 3B.3.4.5 Recommendations for non-operative treatment of Peyronie's disease

	LE	GR
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of the disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b	C
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridium collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	1b	B
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	C
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	C
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	C
Extracorporeal shock-wave treatment fails to improve penile curvature and plaque size, and should not be used with this intent, but may be beneficial for penile pain.	1b	C
Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.	2b	C
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain. Therefore, intralesional treatment with steroids cannot be recommended.	1b	B
Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature or plaque size and should not be used with this intent.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine) are not recommended.	3	C

Prescription index in 2008 for each class of drug in each country.



# Φυτοθεραπεία

Trials	Duration (weeks)	Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q <sub>max</sub> [ml/s]	PVR [mL]	LE
Bach (2000) [6]	52	placebo	243	-5.5	n.s.	n.s.	1b
		Cucurbita pepo (Prosta Fink™ forte)	233	-6.7 a	n.s.	n.s.	
Berges et al. (1995) [8]	24	placebo	100	-2.3	+1.1	-16.8	1b
		<i>Hypoxis rooperi</i> (Harzol™)	100	-7.4 a	+5.2 a	-35.4 a	
Klippel et al. (1997) [9]	26	placebo	89	-2.8	+4.3	-4.1	1b
		<i>Hypoxis rooperi</i> (Azuprostat™)	88	-8.2 a	+8.8 a	-37.5 a	
Wilt et al. (2000) [7]	4-26	placebo	475	-4.9 b	+3.9 b	-28.6 b	1a
Wilt et al. (2002) [10]	4-18	placebo	1562	RR 2.07 b	+2.5 b	-13.2 b	1a
		<i>Pygeum africanum</i> (β-sitosterol)					
Wilt et al. (2000) [11]	12-24	placebo	444	RR 2.4 b	-1.6	-14.4	1a
		<i>Secale cereale</i> (Cemilton™)					
Wilt et al. (2002) [18]	4-48	placebo	3139	-1.41 b	+1.86 b	-23 b	1a
		<i>Serenoa repens</i> /Sabal cerrulata					
Bent et al. (2006) [19]	52	placebo	113	-0.7	-0.01	-19	1b
		<i>Serenoa repens</i>	112	-0.7	+0.42	-14	
Carraro et al. (1996) [20]	26	finasteride	545	-6.2	+3.2*	-	1b
		<i>Serenoa repens</i> (Permixon™)	553	-5.8	+2.7	-	
Debruyne et al. (2002) [21]	52	tamsulosin	354	-4.4	+1.9	-	1b
		<i>Serenoa repens</i> (Permixon™)	350	-4.4	+1.8	-	
Schneider & Rübben (2004) [14]	52	placebo	122	-4.7	+2.9	-4	1b
		<i>Urtica dioica</i> (Bazoton uno™)	124	-5.7 a	+3.0	-5	
Safarinejad (2005) [15]	26	placebo	316	-1.5	+3.4	0	1b
		<i>Urtica dioica</i>	305	-8.0 a	+8.2 a	-37	
Lopatkin et al. (2005) [16]	24	placebo	126	-4	+1.9	-	1b
		<i>Sabal cerrulata</i> + <i>Urtica dioica</i> (Prostatgutt™ forte)	127	-6 b	+1.8	-	
Sökelland & Albrecht (1997) [17]	48	finasteride	244	-5.6	+2.8	-17.1	1b
		<i>Sabal cerrulata</i> + <i>Urtica dioica</i> (Prostatgutt™ forte)	245	-4.8	+2.0	-10.2	

## *EAU Guidelines for Male LUTS:*

Αδυνατούν να κάνουν κάποια σύσταση σχετικά με τη χρήση της φυτοθεραπεία σε ασθενείς με LUTS εξαιτίας της μεγάλης ετερογένειας και των μεθολογικών προβλημάτων των μετα-αναλύσεων

*Όμως.....*

# Off-label χρήση

Recommendations for MET	LE	GR
Offer $\alpha$ -blockers as MET as one of the treatment options.	1a	C
Counsel patients regarding the lack of efficacy in a recent large multicentric trial, attendant risks of MET, including associated drug side effects as well as inform the patient that $\alpha$ -blockers are administered off-label <sup>†**</sup> .	1b	A*
Follow up patients in short intervals to monitor stone position and assessed for hydronephrosis.	4	A*

*EAU Guidelines on Urolithiasis 2016*

# Τι κάνουμε: Όρια-μελέτες

- Σύγκριση με ενεργό φάρμακο

*The doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing*

- Όρια

Mean (SE) change in symptom score*	Patient assessment of improvement
- 8.8 (0.34)	Marked
- 5.1 (0.29)	Moderate
- 3.0 (0.27)	Slight
+ 2.7 (0.93)	Worse

# Τι κάνουμε: Όρια-μελέτες

- Σχεδιασμός καλύτερων μελετών

*Placebo effect*

*Run-in period*

*Μέγεθος ομάδων*

*Μεγάλο FU*

*Όρια*

**A**

		Patient told
Treatment	Drug	Drug or placebo
	Placebo	Drug or placebo
	Nothing	Neither drug nor placebo

**B**

		Patient told
Treatment	Drug	Drug
	Drug	Nothing

**C**

		Patient told	
Treatment	Drug	Drug	Placebo
	Placebo	Drug	Placebo

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# Biological, clinical, and ethical advances of placebo effects

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Lancet 2010; 375: 686–95

Ηθικοί προβληματισμοί:

- *Placebo* ως “θεραπεία»
- Ενημέρωση (*deception* – απάτη)

Πως;

*Εξακολουθεί να δουλεύει;*



Ευχαριστώ πολύ