Fesoterodine
A Novel Anti-Muscarinic:
Predictably Dogmatic

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Fesoterodine

Brand Name	Toviaz [fesoterodine fumurate extended-release]
Manufacturer	Pfizer
Indication	Overactive bladder Approved Feb 9th, 2012
Drug-Class	Anti-muscarinic M3 selective receptor inhibitor

Overactive Bladder

- Prevalence increases with age
- Lifetime risk
  - Males 15% & Females 30%
- Detrusor muscle contracts inappropriately
- Detrusor muscle over-activity
  - involuntary bladder contractions
  - *urgency to urge urinary incontinence* (UUI)
  - symptom not a disease

Overactive Bladder

- Symptoms include:
  - urgency, frequency and nocturia
  - incontinence
- Non-pharmalogical therapy (1st-line)
  - Pelvic floor strengthening
  - Behavioural therapy
- Pharmacotherapy (2nd-line)
  - Anti-muscarinic most studied

Treatment of OAB

Anti-Musc vs.	PBO (n=4500)	lidocaine (n=15)	doxasozin (n=59)	flavoxate (n=240)
Improvement*	1.39 [1.28,1.51] 40% improved on PBO	1.50 [0.71,3.16] 50% improved on lidocaine	X-over study Pts that responded to initial therapy did not X-over 40% improved on doxaosin 55% improved on oxybutynin	0.97 [0.90, 1.05] 60% improved on flavoxate
Nocturia	NR	NR		0.96 [0.66, 1.39]
Dry mouth	1.11 [0.91, 1.36]	NR		2.28 [1.45, 3.56]

*individual trial authors definition of cure (objective or subjective criteria)

Cochrane Database of Systematic Reviews 2007, Issue 4

Questionnaires

- Employed for:
  - Clinical assessment
  - Screening
  - HRQOL
- HRQOL scales measure urgency
  - King's Health Questionnaire (35 pt)
  - Urogenital Distress inventory (22 pt)
  - ICSmaleSF (14 pt)
  - OAB-q (13 pt)
- Urgency incontinence greater negative effect on QOL than other components of OAB

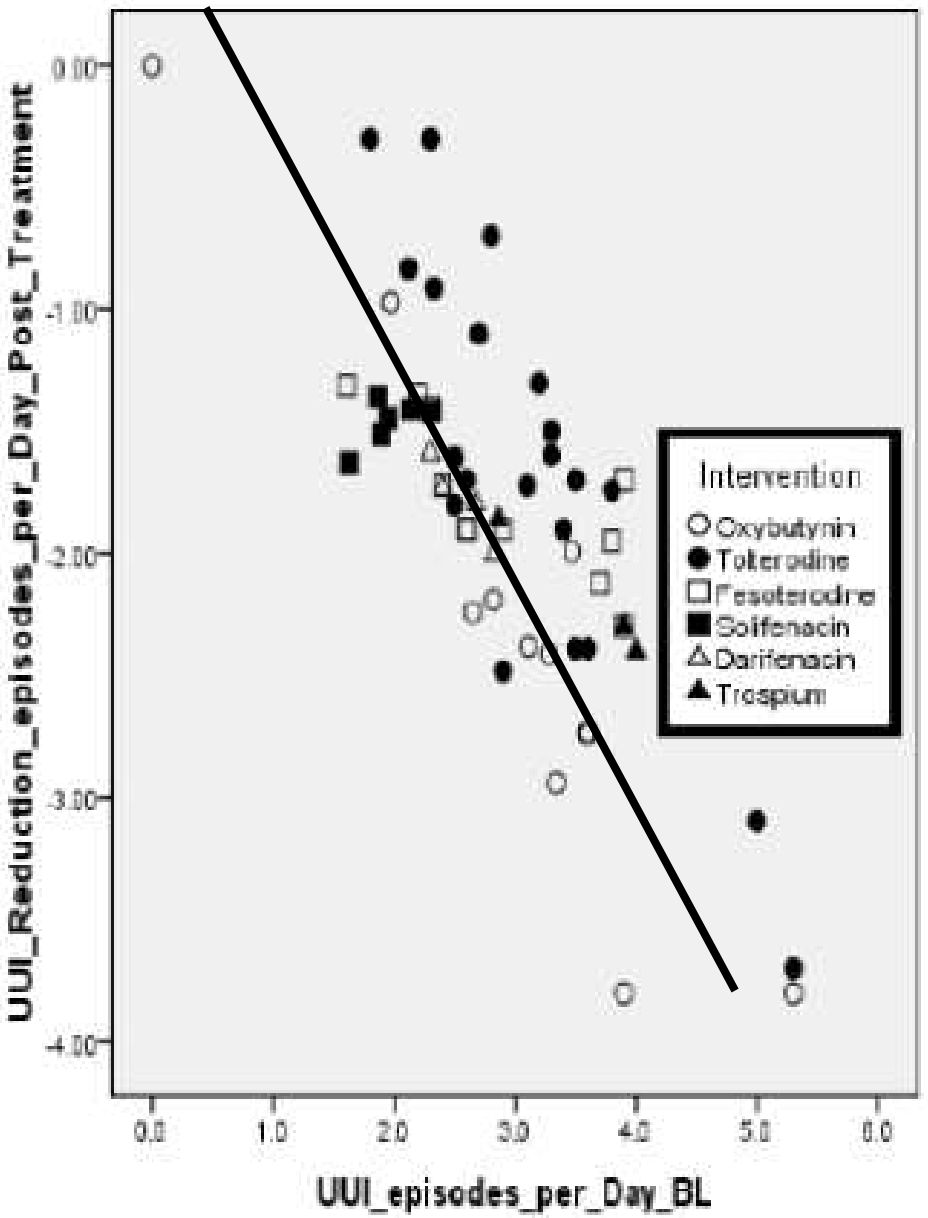
AUA/SUFU GUIDELINE. American Urological Association Education and Research, 2012

Urgency Severity Score

- 5-point scale to assess urinary urgency

- Rate bladder urgency on a 5-point scale:
  - 1 point (pt) Continue activity eventually go to bathroom
  - 2 pts Mild urgency: Finish activity quickly go right to bathroom
  - 3 pts Moderate urgency: Stop activity go right to bathroom
  - 4 pts Severe urgency: Stop activity run to bathroom
  - 5 pts Urge incontinence: Didn't make it to bathroom

Neurourology and Urodynamics 30:360–365 (2011)



AUA/SUFU GUIDELINE. American Urological Association Education and Research, 2012

Clinical Question

Patient	Symptoms of OAB Experiencing UUI
Intervention	fesoterodine
Control	Placebo Anti-muscarinic agent
Outcome	Mortality Urge Incontinence episodes Adverse effects □ Dry mouth □ Decline in cognition □ Falls □ Cardiac arrhythmias

Literature Search

Databases	Pubmed, Medline, Embase, Cochrane, Google Scholar, IPA
Search Terms	fesoterodine, anti-muscarinic, over active bladder, urge incontinence
Limits	English, Human
Results	5 randomized controlled trial 1 dose-response model analysis

	Nitti 2005 (n=173)	Cole 2004 (n = 727)	Chapple 2007 (n = 1132)	Nitti 2007 (n=836)
Design	R DB PC UUI* 1.5/d	R DB PC UUI 2.3/d	R DB PC UUI 3.7/d	R DB PC UUI 3.8/d
Comparison	FST** 4, 8, 12mg	FST 4, 8, 12 mg	FST 4, 8mg, Tolt 4mg	FST 4, 8 mg
Δ UUI / d	FST 4 [-0.80] FST 8 [-1.34] FST 12 [-1.30]	FST 4 [-1.3] FST 8 [-1.8] FST 12 [-2.1]	PBO [-1.14] Tolt [-1.72] FST 4 [-1.74] FST 8 [-2.22]	PBO [-0.96] FST 4 [-1.65] FST 8 [-2.28]
Comparison	FST > PBO	FST > PBO	FST > PBO FST = Tolt	FST > PBO
Dry Mouth (%)	PBO (8) FST 4 (30) FST 8 (30) FST 12 (38)	NR	PBO (7.1) Tolt (16.9) FST 4 (21.7) FST 8 (33.8)	PBO (7) FST 4 (16) FST 8 (36)

*Baseline mean UUI / d ; FST = fesoterodine

Modeling dose-response relationships of the effects of fesoterodine in patients with overactive bladder

Linda Cardozo[1*], Vik Khullar[2], Ahmed El-Tahtawy[3], Zhonghong Guan[3], Bimal Malhotra[3], David Staskin[4]

Design	Data from 2 phase II and 2 phase III trials Population-based longitudinal dose-response model of fesoterodine from clinical trials Sponsored by Pfizer

Patients	n = 2514 F 80% Age ~ 65 <u>Excluded</u>: PVR >100ml Tolterodine treatment group

Intervention & Control	Fesoterodine 4 mg (n= 759) Fesoterodine 8 mg (n= 762) Fesoterodine 12 mg (n= 225) PBO (n= 768)

BMC Urology 2010, 10:14

Outcome	Dose-response model for:
	Δ UUI episodes / 24 hrs
	# Micturation / 24 hrs
	Mean volume voided (MVV) / micturation

BMC Urology 2010, 10:14

Population-based modeling

- FDA & EMA provide guidelines for application of population PK/PD modeling:
  - Used to identify the ideal dose
  - Sparse amount of patient data but large number of patients
  - Allows for identification and control of covariates
  - Provides accurate estimate of covariance (interpatient variability)
- Results can are applied to guide dosing in clinical setting

Model Development

- Pooled data from 4 RCTs at each follow-up time
  - From bi-weekly diary entries
  - Nonlinear mixed-effects modeling (NONMEM)
- Age, gender, and baseline OAB symptoms analyzed as covariates
- Validation of model with Positive Predictive Check
  - $\alpha = 0.01$ for comparisons between the models

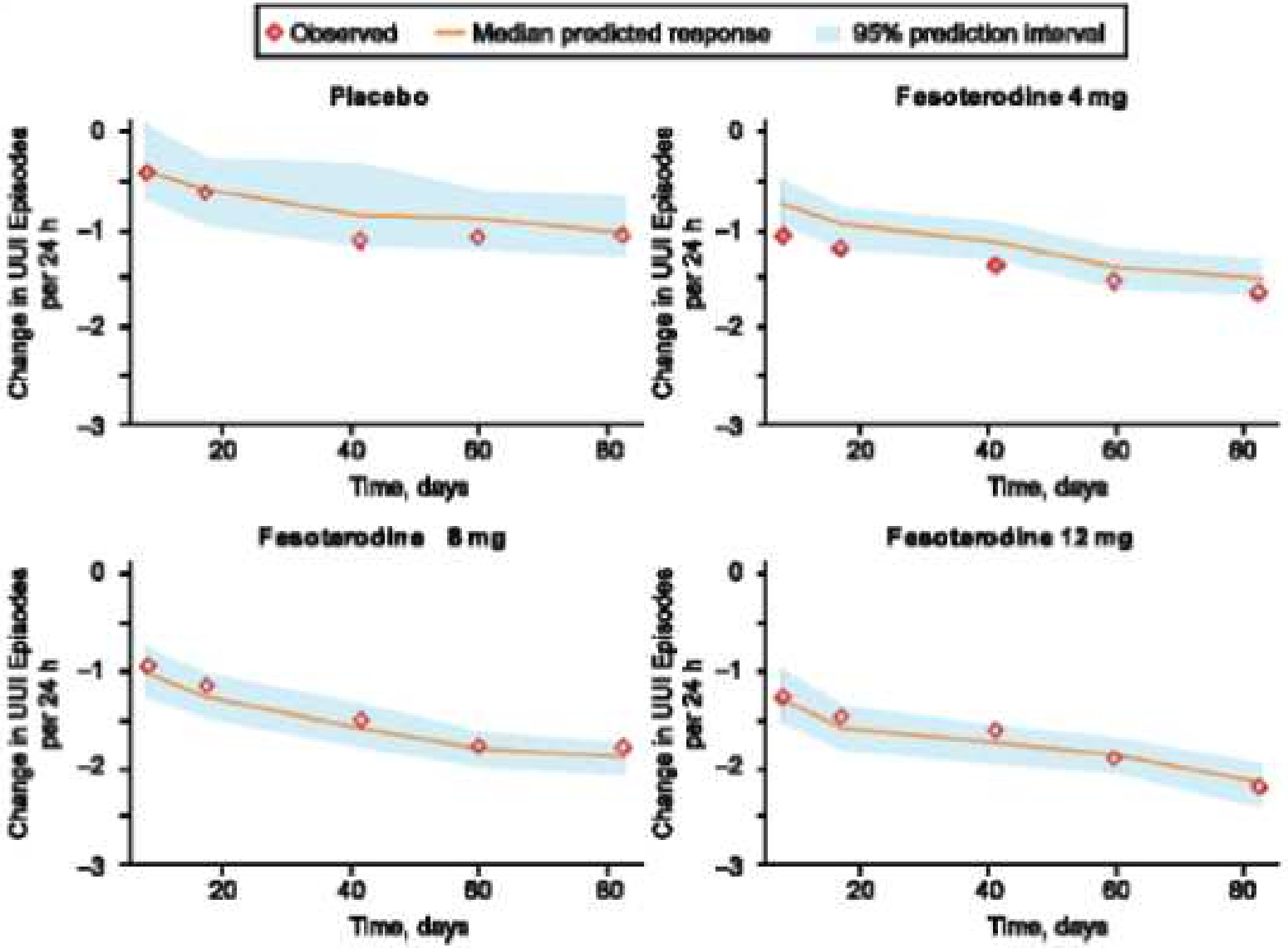


Figure 2 Posterior predictive check for change from baseline in number of urgency urinary incontinence (UUI) episodes after taking placebo or fesoterodine 4 mg, 8 mg, or 12 mg.

Model Predicted Change from Baseline

	PBO	FST 4mg	FST 8mg
Δ UUI episodes / 24h*	**- 1.1**	**- 1.3**	**- 1.4**
Micturations / 24h	- 1.2	- 1.7	- 2.2
MVV (ml)	9.7	23.9	38.1

*For a patient with 2 UUI / d

- Onset of clinical effect at 4 weeks
- For UUI / d:
  - FST 4 mg vs. PBO SS
  - FST 4 mg vs. 8 mg NSS
- Did not report prediction for FST 12 mg; stated NSS vs. 8mg

Results

- Reduction in UUI episodes predicted by model less than effect observed in phase III trials

- p-values & confidence intervals not reported for comparing models

- Predicted linear dose response relation for:
  - # of micturations / day
  - Δ UUI episodes / day

- Internal validity:
  - No mention of heterogeneity
  - LOCF for missing data in RCTs
- Generalizability:
  - Fixed dose regimens
  - Coefficient of variation within 15% to 20% for each endpoint
- Covariates not well described
  - Random effect variable in model equation

Bottom-Line

- Placebo group reduction in UUI / day by 1 episode
- Fesoterodine 4mg reduces UUI / day by 1.3 episodes
  - Prevent one episode for every 3 days of therapy
  - When baseline UUI 2x / day
- Onset ~ 4 weeks

Anti-Muscarinics

	Symptom Improvement	Dry Mouth
oxybutynin v. tropsium (n=136)	1.41 [1.04, 1.89] 40% on tropsium	0.66 [0.48, 0.91] 50% on tropsium
tolterodine v. oxybutynin (n=1381)	1.01 [0.93, 1.11] 55% on oxybutynin	0.52 [0.40, 0.66] 30% on oxybutynin
solifenacin v. tolterodine (n=2200)	1.25 [1.13, 1.39] 56% on tolterodine	1.37 [0.84, 2.23] 18% on tolterodine
tolterodine 1mg, 2mg, 4mg / day -> = efficacy; ↑ dry mouth		
solifenacin 5mg or 10mg -> ↓ frequency / urgency; ↑ dry mouth		

Cochrane Database of Systematic Reviews 2012, Issue 1.

Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial

Sender Herschorn, Steven Swift*, Zhonghong Guan†, Martin Carlsson†, Jon D. Morrow†, Marina Brodsky† and Jason Gong†

Design	12 week trial with 2 week run-in phase R DB PCT DD with AC Sponsored by Pfizer

Patient	N=1712 Excluded: lower GU pathology, neurological condition (e.g. CVA, MS, spinal cord injury, PD), anti-muscarinic for OAB w/in 2 wks
Intervention	2-week run-in period on placebo Placebo **Fesoterodine 4mg (1/52) with option to titrate to 8mg (11/52)** **Tolterodine ER 4mg** x 12/52
Control	*all medications taken once daily in the morning

BJUI 2009; 105,58–66

Outcome	3 day bladder diaries baseline, bi-weekly x 12 wks Efficacy: UUI / day (primary), MVV, Total # voids Used USS rating scale [other questionnaires PPBC, UPS and OAB-Q]

Baseline Characteristics:

Age (mean) = 58

Female 80%

Duration of OAB 7 yrs

Baseline UUI / d ~ 2.5

	PBO	FST	Tolt
Mean Δ UUI / day	- 1.46	- 1.72	- 1.61
Comparison	FST > PBO (p <0.001) FST > Tolt (p = 0.017)		
Dry Mouth	6 %	27.8 %	16.4 %

- Internal validity:
  - Overall well designed phase trial
  - LOCF (167 pts ~ 9.5%)

- Generalizability:
  - Fixed dose titration as part of protocol
  - Duration of trial 12 weeks

	Δ UUI*	Dry mouth	Cost
No treatment	- 1.0	7%	$ 0
Fesoterodine 4mg	- 1.5	+ 13%	$ 1.5 / day
Fesoterodine 8mg	- 1.75	+ 10%	$ 1.5 / day
Tolterodine 4mg	- 1.5	16%	$ 1.91 / day

*Pre-treatment UUI 2 / d

Fesoterodine	Tolterodine
Toviaz (Pfizer)	Detrol LA (Pfizer)
4mg, 8mg (SR)	1, 2, 4mg (SR)
■ 5-HMT (serum esterases) ■ Can't actually measure serum fesoterodine	■ 5-HMT (CYP2D6) ■ Tolterodine undetectable ~2 hrs after dose

Bottom-Line

- Fesoterodine 4mg:
  - Appropriate starting dose
  - Re-assess in 4 weeks
  - ↑ dose on average does not result in clinical significant benefit
- Fesoterodine is less expensive than tolterodine, until it is off-patent in Febuary 2013
- No trial comparing fesoterodine to solifenacin or darifenacin