

Medications for Overactive Bladder

Quantifying Harms and Benefits



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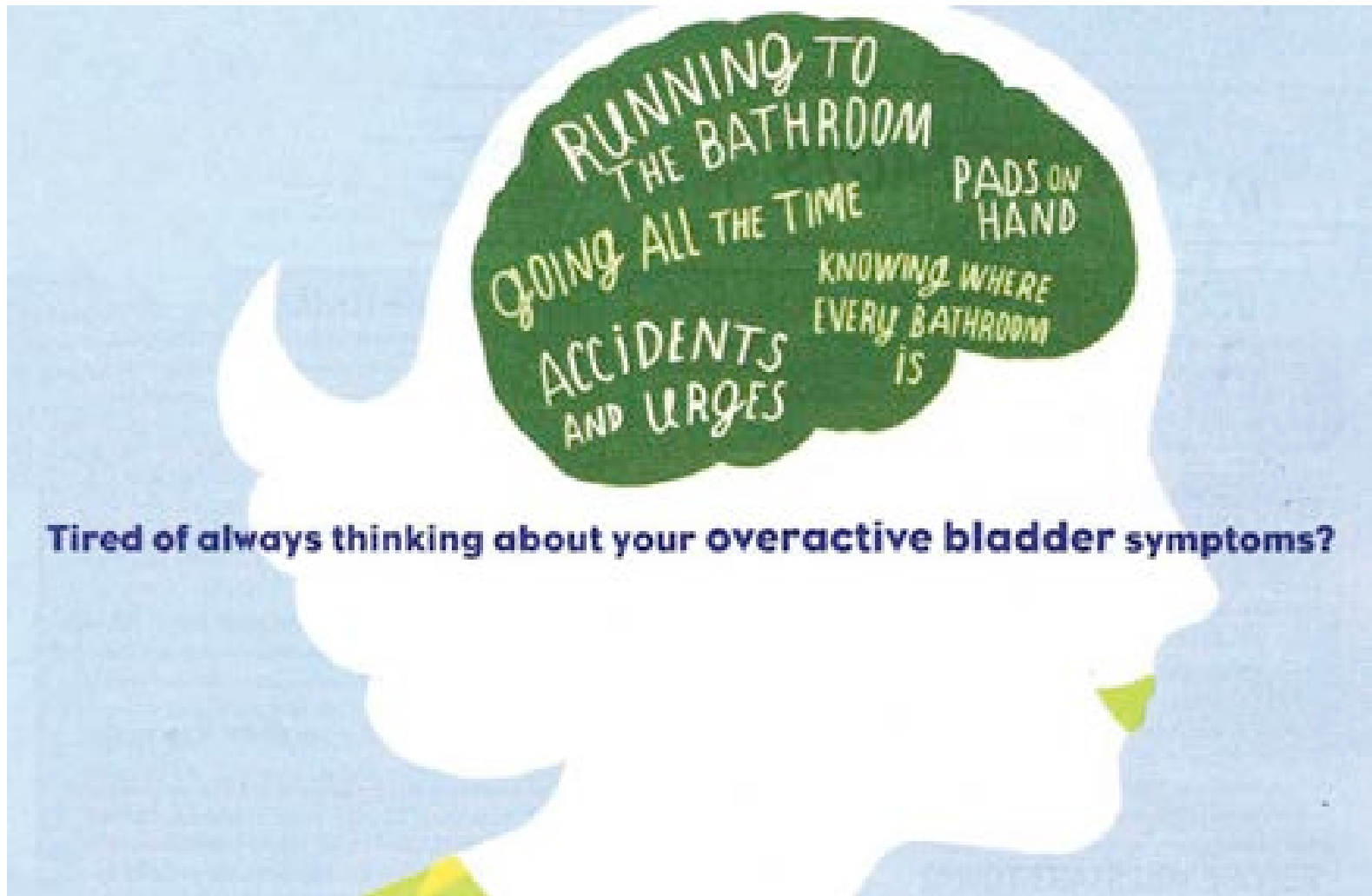
Framing of a drug class systematic review

- Who might benefit from treatment?
- What are the most important outcomes?
- Are comparisons fair (dose equivalent)?
- Do benefits outweigh harm?

What are the equity concerns?



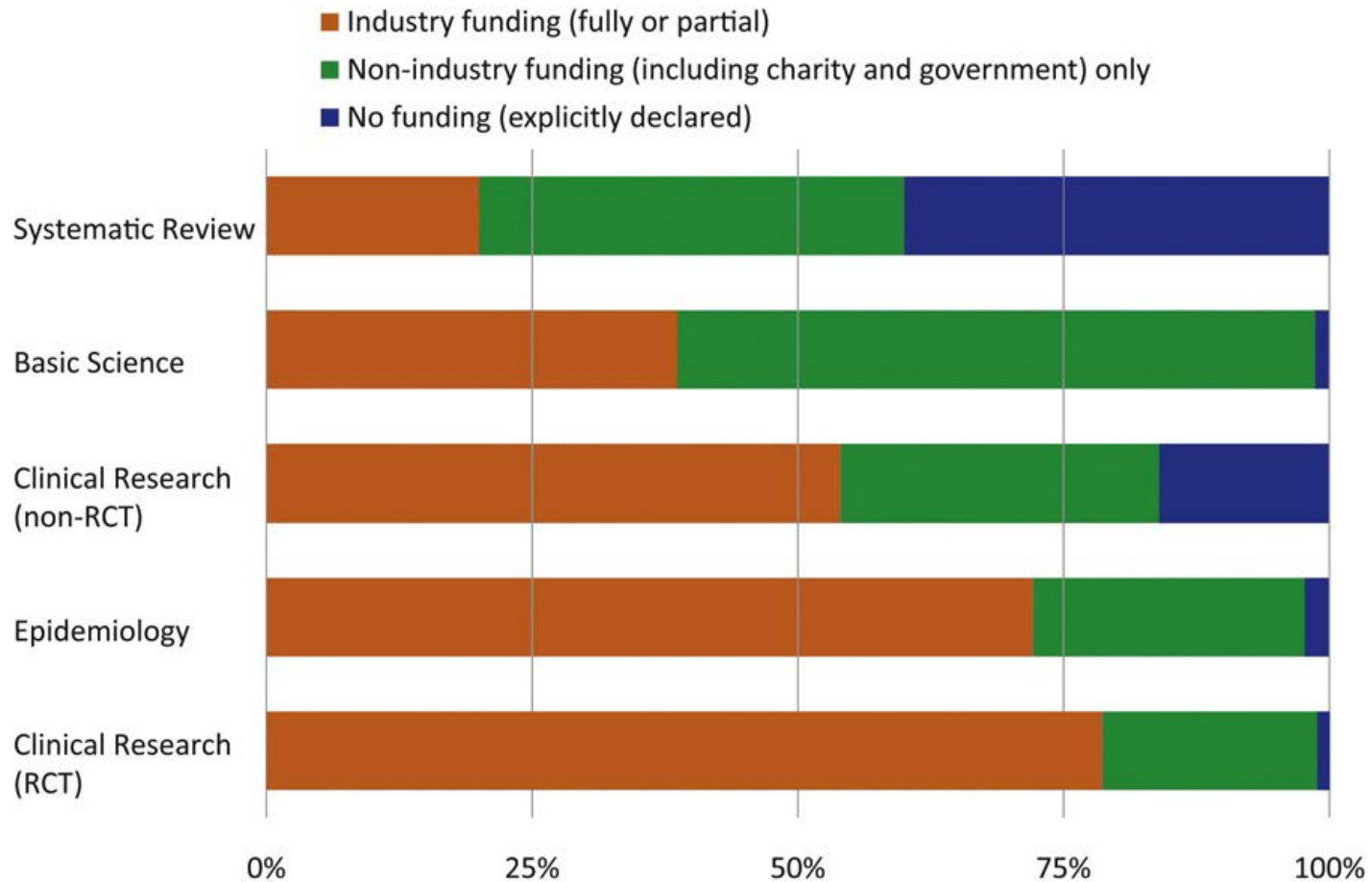
Sex and gender issues?



Sex and gender issues

- Women affected more than men
- Who is “normal” (< 8 times a day)?
- Older women a vulnerable target group
- Contributes to polypharmacy
- Older men also increasingly targeted
 - Symptoms similar to prostate problems
 - Drugs not effective for BPH

Additional equity concern information asymmetry of evidence base




Do benefits outweigh harm?

- RCTs short-term ≤ 12 weeks
- Selected populations, not frail elderly
- Observational studies often highly flawed
- Rare, serious harms under-investigated



Who might benefit?



Does running to the bathroom count for a good portion of your cardio?

Time Out. It could be Overactive Bladder.



One in six people has Overactive Bladder. Find out how you can do more than just cope. See your doctor and go to www.overactivebladder.com

International Continence Society standardized definition, 2002

“urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.”

- “suggestive of detrusor overactivity”
- symptom-based; diagnosis of exclusion

Abrams et al. *Neurourology and Urodynamics* 2002; 21: 167-178



“momentum toward a very broad definition in marketing was a factor in the updated consensus definition...”

Hartmann et al. U.S. AHRQ 2009



Age-standardized prevalence

- 6.5% (95% CI 5.5% - 7.6%) in men
- 9.3% (95% CI 7.9% to 10.6%) in women

If urge incontinence required:

- 0.7% of men
- 2.4% of women

Medication use a balancing act



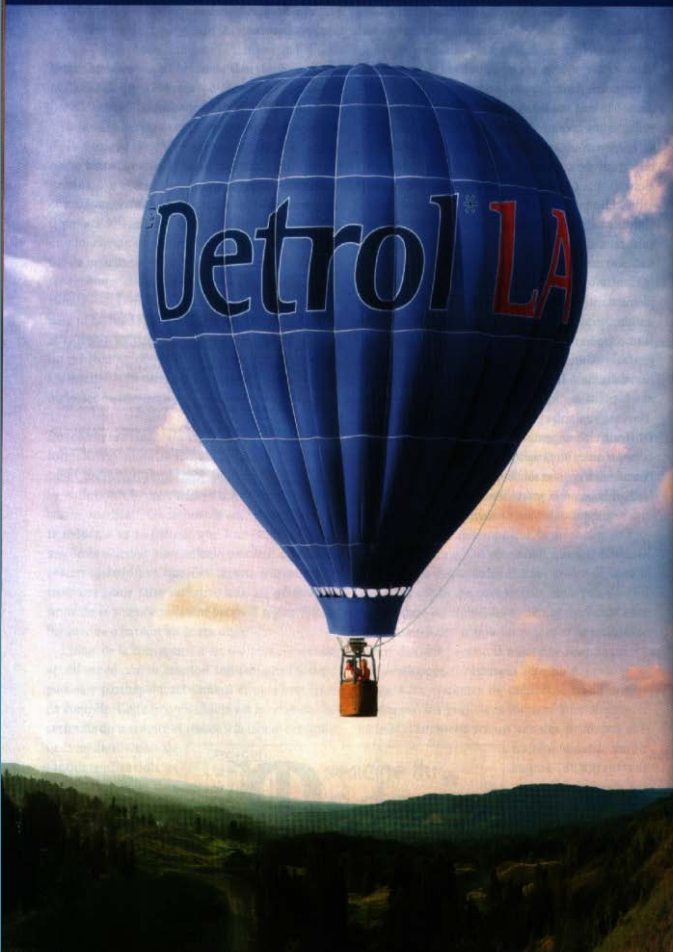
Harm

- Medication
- Disease severity
- Patient
- Conditions of use

Benefit

- Medication
- Disease severity
- Patient
- Conditions of use

How effective is drug treatment?



There are no bathrooms at 800 feet

NAME CHANGE!
UnitDet* is now called
Detrol LA

DETROL LA can help free your patients from Overactive Bladder (OAB) symptoms.¹

High efficacy

- DETROL LA was 18% more effective than DETROL* in reducing median urge incontinence episodes ($p < 0.05$).^{2†}
- DETROL LA produced a 6-fold increase in the number of patients able to complete tasks before voiding vs. baseline in response to urgency [33% vs. 5% baseline for extended-release tolterodine 4 mg; 18% vs. 6% baseline for placebo ($p < 0.001$ vs. placebo)].^{2†}

Reduction of incontinence episodes after 12 weeks: Median: DETROL LA 71%, DETROL 60%, placebo 33%. DETROL LA vs. DETROL, $p < 0.05$ for median percent reduction.^{2†} Mean: DETROL LA 53%, DETROL 46%, placebo 30%.^{2†}

*Significance was not calculated between DETROL and DETROL LA, significance was shown vs. placebo ($p = 0.0001$ and $p = 0.0008$ respectively). Baseline incontinence episodes per week: DETROL LA 22.1, DETROL 23.2, placebo 23.3.

Proven tolerability profile

- DETROL LA was generally well tolerated, with a 23% lower incidence of dry mouth than DETROL [23% vs. 30% ($p < 0.02$)].^{2†}

DETROL LA is indicated for the symptomatic management of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.¹


DETROL LA is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or known hypersensitivity to the drug or its ingredients.¹

The initial dose of 4 mg once daily may be reduced to 2 mg once daily based on individual response and tolerability.¹

Patients with impaired hepatic function, patients with renal impairment or patients treated with potent CYP3A4 inhibitors should not receive doses of DETROL LA greater than 2 mg once daily.¹

No overall differences in safety were observed between older and younger patients.¹

The most commonly reported adverse events were dry mouth (23.4%), headache (6.3%), constipation (5.9%) and abdominal pain (3.8%).¹



It's all about effective control



*Based on a 12-week, double-blind, multicenter, randomized, placebo-controlled trial in patients with urinary frequency and urge incontinence. Dosing: DETROL LA 4 mg once daily (n = 507), DETROL 2 mg twice daily (n = 514), or placebo (n = 508).^{2†}

†Based on a 12-week, double-blind, multicenter, randomized, placebo-controlled trial in patients with urinary frequency, urgency, and urge incontinence. Dosing: DETROL LA 4 mg once daily (n = 398) or placebo (n = 394).^{2†}

References: 1. DETROL LA Product Monograph, Pfizer Canada Inc. July 2004. 2. Van Kesterenck P, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology* 2003;61(4):481-487. 3. Fenwick K, et al. Reduced perception of urgency in treatment of overactive bladder with extended-release tolterodine. *Urology* 2003;61(2):261-263.

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For prescribing information see page 1417

Anti-muscarinic drugs for overactive bladder syndrome (OAB)

Drug	Brand	Date approved
Oxybutynin IR	Ditropan	> 30 years ago
Oxybutynin ER	Ditropan XL	2001
Oxybutynin TDS	Oxytrol	2004
Oxybutynin CR	Uromax	2006
Oxybutynin gel	Gelnique	2011
Tolterodine IR	Detrol	1998
Tolterodine ER	Detrol LA	2002
Trospium	Trosec	2006
Darifenacin	Enablex	2006
Solifenacin	Vesicare	2006
Fesoterodine	Toviaz	2012

CR=controlled release; ER=extended release;
IR=immediate release; TDS=transdermal

How do these drugs work?

- Block activation of muscarinic receptors on smooth muscle, inhibit acetylcholine
- Affect bladder contractions
- Adverse effects due to anti-muscarinic effects:
 - Dry mouth
 - Constipation
 - Blurred vision
 - Heart rhythm (QT prolongation)
 - Cognition

Effectiveness: drug vs. placebo

Outcome	# trials	n	Absolute difference
Patient feels better or cured	8	2742	56% vs. 41% ARR 15% (95% CI 11%-13%)
Incontinence episodes/ 24hr	12	1482	Mean reduction: - 0.5 (95% CI -0.7 to -0.4)
Nocturia	NR	NR	NR
Frequency/24hr	12	5977	Mean reduction: -0.7 (95% CI -0.8 to -0.5)
Dry mouth	27	9372	31% vs. 10% ARR 21%(95% CI 19%-23%)*

ARR= absolute risk reduction; RR = relative risk; CI=confidence interval;
NR = not reported; *87% heterogeneity; differences by drug

Effectiveness of placebo

Outcome	# trials*	Baseline mean \pm SD	Mean difference (95% CI)
Incontinence episodes/ 24 hr	18	3.2 \pm 1.0	- 1.2 (-1.0 to -1.3)
Frequency *placebo arms in RCTs	17	11.1 \pm 0.9	- 1.3 (-1.5 to - 1.0)

Lee et al. BMC Medical Research Methodology 2009; 9: 55

Competition within drug class



Do benefits outweigh harm? oldest drug - oxybutynin

Oxybutynin
(Ditropan®)

Benefits

About 1 out of 10 women became continent using this medicine.



About 2 out of 10 women improved their symptoms using this medicine.



Side Effects

About 3 to 4 out of 10 women had dry mouth using this medicine.

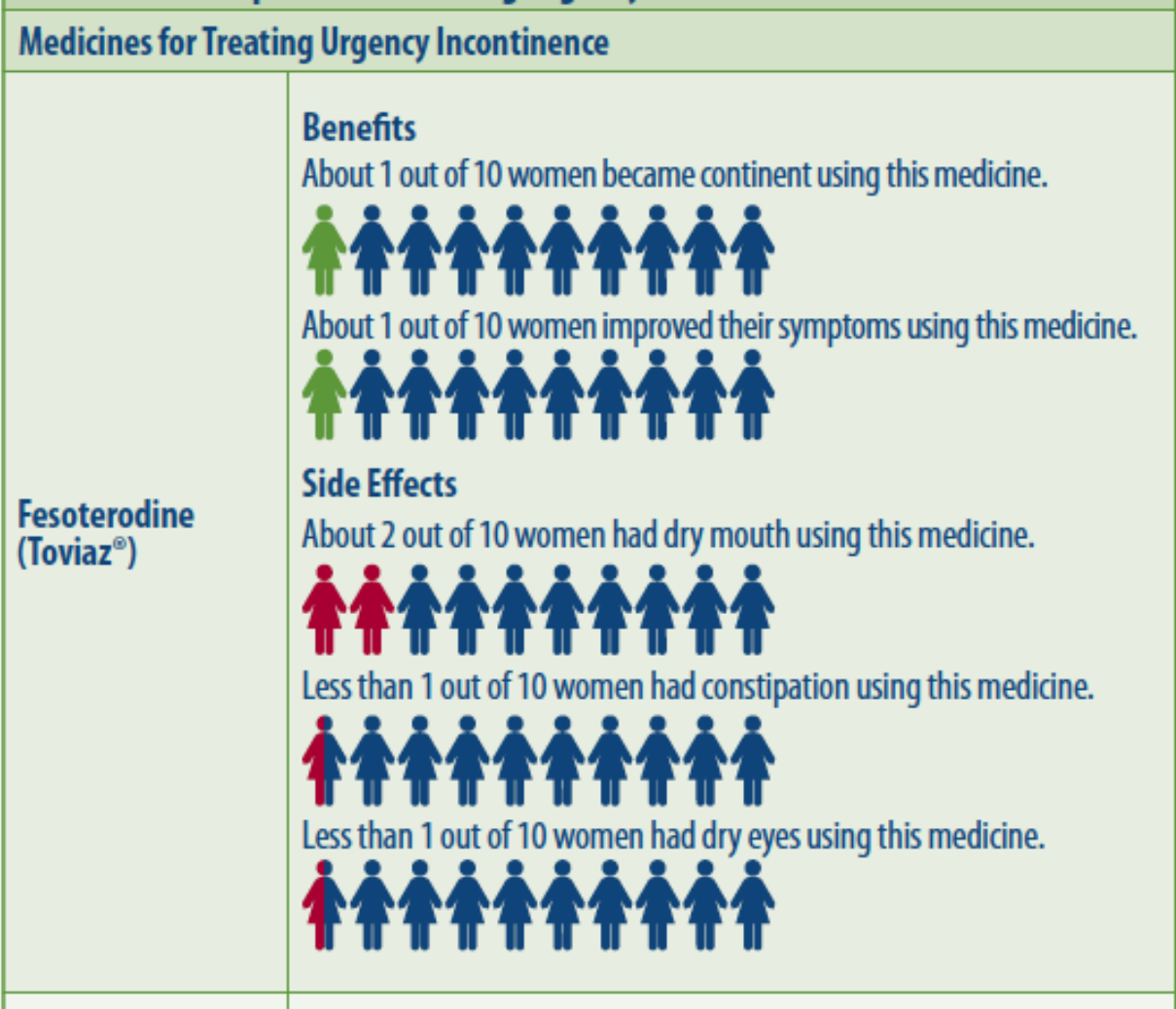


About 1 out of 10 women had an upset stomach using this medicine.



Constipation: No difference from women taking a placebo (sugar pill).

Do benefits outweigh harm? newest drug - fesoterodine



AHRQ consumer summary 2012; <http://www.ahrq.gov/>

Do benefits outweigh harm?

Warning: Doctors and patients have also reported some serious side effects that can occur with these medicines. Although they do not happen very often, they are more dangerous than the common side effects listed above. These side effects include rapid irregular heart rate, hallucinations, problems with thinking, and rarely death. The chance of having a serious side effect is greater for elderly patients, for patients who take many different medicines at the same time, and for patients who take some antihistamines (allergy medicines) and antibiotics along with these UI medicines. Ask your doctor about these more serious side effects.

Comparisons of harm

- High risk of bias due to market pressure:
 - Non-equivalent doses
 - Selective reporting
 - Incomplete follow up



What can be done?

Three key problems to address

- Information asymmetries
- Regulatory standards for drug approval
- Effects of marketing and conflicts of interest on disease definitions

