

The Effectiveness of Anticholinergic Therapy for Overactive Bladders: Systematic Review and Meta-Analysis

Eficácia da terapia anticolinérgica na bexiga hiperativa: revisão sistemática e metanálise

Andrea Moura Rodrigues Maciel da Fonseca¹ Mariana Furtado Meinberg¹ Marilene Vale de Castro Monteiro¹ Matheus Roque¹ Jorge Milhen Haddad² Rodrigo Aquino Castro³

¹ Urogynecology Division, Gynecology Discipline, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

² Urogynecology Division, Gynecology Discipline, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil

³ Urogynecology Division, Gynecology Discipline, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

Rev Bras Ginecol Obstet 2016;38:564-575.

Abstract

The overactive bladder (OAB) has a significant negative impact on the quality of life of patients. Antimuscarinics have become the pharmacological treatment of choice for this condition. The objective of this systematic review and meta-analysis is to examine the evidence from randomized clinical trials about the outcomes of the antimuscarinic drugs available in Brazil on OABs. We searched MEDLINE and the Cochrane Central Register of Controlled Trials from the inception of these databases through to September 2015. The primary outcome measures were the mean decrease in urge urinary incontinence episodes and the mean decrease in the frequency of micturition. The results suggest that there is a moderate to high amount of evidence supporting the benefit of using anticholinergic drugs in alleviating OAB symptoms when compared with placebo. It is still not clear whether any of the specific drugs that are available in Brazil offer advantages over the others. These drugs are associated with adverse effects (dry mouth and constipation), although they are not related to an increase in the number of withdrawals.

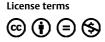
Keywords► overactive bladder

- urge incontinence
- urge meonumence
 uripary froquoncy at
- urinary frequency and antimuscarinics

Resumo

A bexiga hiperativa determina um impacto negativo na qualidade de vida dos nossos pacientes. Os antimuscarínicos tornaram-se o tratamento farmacológico de escolha para essa condição. O objetivo desta revisão sistemática e metanálise é examinar as melhores evidências científicas sobre estas medicações disponíveis no Brasil no tratamento de mulheres com bexiga hiperativa. As bases de dados utilizadas foram MEDLINE e a biblioteca da Cochrane, das quais selecionamos os ensaios clínicos

received November 27, 2015 accepted September 30, 2016 DOI http://dx.doi.org/ 10.1055/s-0036-1594289. ISSN 0100-7203. Copyright © 2016 by Thieme-Revinter Publicações Ltda, Rio de Janeiro, Brazil



Address for correspondence Andrea Moura Rodrigues Maciel da , Fonseca, PhD, Avenida Professor Alfredo Balena 190, 30130-100-Belo Horizonte, Minas Gerais, Brazil (e-mail: andreamrmf@qmail.com).

Palavras chaves

- bexiga hiperativaincontinência de
- urgência
 frequência urinária e antimuscarínicos

randomizados até setembro de 2015. Os principais desfechos analisados foram a diminuição dos episódios de incontinência urinária de urgência e a diminuição da frequência de micção. Os resultados sugerem que as drogas existentes no Brasil sustentam o benefício dos anticolinérgicos no alívio dos sintomas da bexiga hiperativa quando comparadas com o placebo. Em termos de eficácia, as medicações apresentam resultados semelhantes no controle dos sintomas. Essas drogas estão associadas a efeitos adversos importantes, tais como boca seca e constipação, e esses efeitos adversos não influenciaram no uso da medicação.

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence (UUI), in the absence of a urinary tract infection or another obvious pathology.¹ Overactive bladder is a highly prevalent disease in both men and women, affecting 12–17% of the adult population. This condition has a significant negative impact on the quality of life of patients, affecting emotional, physical, social, occupational, and domestic functions.^{2–4}

Overactive bladder symptoms are thought to develop as a result of inappropriate contractions of the bladder detrusor during the filling phase of the micturition cycle. Normal and abnormal bladder contractions occur via cholinergic activation of the muscarinic receptors. As is the case in other chronic conditions, OAB typically requires long-term persistence and adherence to therapy.⁵ Behavior modification, which includes education about the disorder, lifestyle changes (, such as avoiding caffeinated beverages, for example), as well as pelvic floor muscle training and bladder retraining, represent the first-line therapy options for this condition. However, when these approaches are insufficient, second-line therapy involves pharmacological treatment, and antimuscarinic agents are the treatment of choice.^{6–8}

Although anticholinergic medications have been shown to improve patients' symptoms, they create a widespread blockade of cholinergic activity that often results in side effects such as dry mouth, cognitive changes, constipation, urinary retention, blurred vision, and dyspepsia.⁹ These problems can be difficult to manage, and may contribute to poor patient adherence to treatment.¹⁰

The objective of this systematic review and meta-analysis was to examine the currently available evidence from randomized clinical trials (RCTs) about the outcomes of the pharmacological management of OAB, and to summarize the comparative effectiveness of the drugs available in Brazil. Only antimuscarinic agents commercialized in Brazil were included in the analysis, since this meta-analysis is the basis for the development of Brazilian urogynecology guidelines.¹¹

Methods

This study was exempt from institutional review board approval, given that it was a systematic review and metaanalysis; it did not involve the use of any interventions on humans. To report the results of this meta-analysis, we utilized the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement.¹²

Search Strategy

An exhaustive electronic search was performed using the MEDLINE database, as well as the Cochrane Central Register of Controlled Trials, with the dates of the included articles spanning from the inception of these databases through to September 2015. We also searched the references of the identified articles and restricted the search to articles published in English. The search combined relevant terms and descriptors related to OAB, anticholinergic drugs, oxybutynin, darifenacin, tolterodine, solifenacin, and RCTs.

Eligibility Criteria and Data Extraction

The review only included RCTs featuring adult male and female patients diagnosed with OAB or with a diagnosis of detrusor over activity, and who were also submitted to any of the anticholinergic treatments available in Brazil. The selection criteria are described in **-Table 1**. In a first screening, two independent authors (AMRMF and MVCM) assessed all of the abstracts retrieved from the search; they then obtained the full manuscripts of the citations that met the inclusion criteria. These authors evaluated the studies' eligibility and quality, and extracted the data subsequently. Any discrepancies were solved by agreement, and, if needed, the authors reached a consensus with a third author (MR). The meta-analysis included studies that provided accurate data related to those primary outcomes that could be analyzed. Thus, only studies that provided the mean, sample size, and standard deviation (SD) values of the primary outcomes were included in the analysis. Otherwise, when the available data were expressed as the median, it was necessary that the study provided the range values (lowest and highest values) to extrapolate the mean. If only the ranges of continuous variables were reported, we would estimate the SD by dividing the range by four. Dose escalation and crossover studies were excluded, as it was not possible to abstract the data related to our primary outcomes.

Outcome Measures

The primary outcomes of interest for this systematic review and meta-analysis were the mean decrease in the number of UUI episodes per day and the mean decrease in the number

	Included	Excluded
Population	Symptomatic diagnosis of overactive bladder (OAB) or a urodynamic diagnosis of detrusor over activity	OAB as consequence of surgery
Intervention	Anticholinergic drugs available in Brazil (oxybutynin 5 mg and 10 mg; darifenacin 7.5 mg and 15 mg; tolterodine 1 mg, 2 mg, and 4 mg; solifenacin 5 mg and 10 mg)	Anticholinergic drugs not available in Brazil or with different doses or routes of administration that are not available in Brazil
Comparison	Placebo, comparison between different drugs, or comparison between different doses of the same drug	
Outcomes	 Primary outcomes Mean decrease in urge urinary incontinence (UUI) episodes per day Mean decrease in the number of micturitions per day Secondary outcomes Mean decrease in total incontinence episodes (related or not to urgency) Dry mouth Constipation Withdrawals resulting from drug-related adverse effects 	
Study type	Randomized controlled trials (RCTs)	Non RCTs

Table 1 Selection criteria of included studies	(PICOs)	
---	---------	--

Abbreviation: PICOs, population, intervention, comparison and outcomes.

of micturitions per day. The secondary outcomes included the mean decrease in total incontinence episodes (either related or not to urgency), dry mouth, constipation, and withdrawals resulting from drug-related adverse effects. We tried to perform meta-analytic comparisons between each drug (and their different dosages) versus placebo, comparisons between different drugs, and comparisons between different dosages of the same drug.

Risk of Bias Assessment

We followed the guidance suggested by the Cochrane Collaboration¹³ to assess the risk of bias from the included studies. We evaluated sequence generation, allocation concealment, blinding, and incomplete outcome data for each trial included in the review. A low risk of bias was considered when a judgment of "yes" for all domains was obtained, whereas a high risk of bias was considered when a judgment of "no" for one or more domains was obtained. An unclear risk of bias was defined when an "unclear" judgment in any domain was considered. The quality assessment of the included trials is shown in **-Table 2**.

Analysis

We pooled the data of the continuous outcomes from the original studies to obtain the mean difference (MD) for the occurrence of an outcome event, and presented their corresponding 95% confidence intervals (CIs). Data for dichotomous outcomes from the original studies were pooled to obtain the relative ratio (RR), and the corresponding 95% CIs were calculated. Statistical significance was set at a *p*-value of < 0.05. In order to quantify the statistical heterogeneity,

Rev Bras Ginecol Obstet Vol. 38 No. 11/2016

we used the I2 statistic to describe the variations across trials that were due to heterogeneity and not to sampling error. We pooled the outcome data from each study using a Mantel–Haenszel model, and applied the fixed-effects model. When the heterogeneity was greater than 50% (I2 > 50%), we applied the random-effects model.¹⁴ We used the software Review Manager (RevMan, Version 5.3; Copenhagen) to conduct the meta-analysis.

Results

Our electronic search retrieved 468 articles. After screening the titles and abstracts, we ended up with 37 articles that were considered eligible for inclusion in this review by one or both reviewers, and the full texts were subsequently assessed. The complete article selection process is presented in **~ Fig. 1**.

Description of Included Studies

Fifteen RCTs assessing the pharmacological management (drugs and dosages available in Brazil) of OAB met the inclusion criteria and provided data to perform the metaanalysis. With the available data of the included studies,^{15–29} it was only possible to perform comparisons between tolterodine (and its different dosages) versus placebo, solifenacin versus placebo, and oxybutynin versus tolterodine.

Excluded Studies

Twenty-two articles were excluded because they either did not meet the inclusion criteria^{30–35} or they did not provide adequate data to be included in the meta-analysis.^{36–51}

Study	Sequence generation	Allocation concealed	Blinding	Incomplete outcome data
Appell et al. ¹⁵	Unclear	Yes	Yes	Yes
Drutz et al. ¹⁶	Unclear	Yes	Yes	Yes
Lee et al. ¹⁷	Yes	Yes	Yes	Yes
Malone-Lee et al. ¹⁸	Unclear	Unclear	Yes	Yes
Chapple et al. ¹⁹	Unclear	Yes	Unclear	Yes
Jacquetin et al. ²⁰	Unclear	Yes	Unclear	Yes
Khullar et al. ²¹	Yes	Yes	Yes	Yes
Millard et al. ²²	Unclear	Unclear	Unclear	Yes
Swift et al. ²³	Yes	Yes	Yes	Yes
Van Kerrebroeck et al. ²⁴	Unclear	Unclear	Unclear	Yes
Van Kerrebroeck et al. ²⁵	Yes	Yes	Yes	Yes
Zinner et al. ²⁶	Yes	Yes	Yes	Yes
Cardozo et al. ²⁷	Unclear	Unclear	Unclear	Yes
Karram et al. ²⁸	Unclear	Unclear	Unclear	Yes
But et al. ²⁹	Yes	Unclear	Unclear	Yes

 Table 2
 Quality assessment of included trials

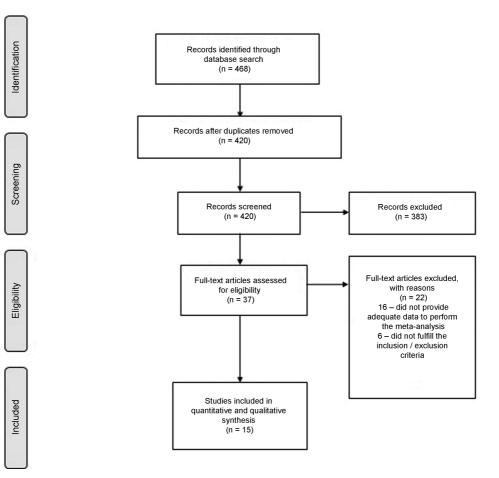


Fig. 1 Flowchart for the trial identification and selection process.

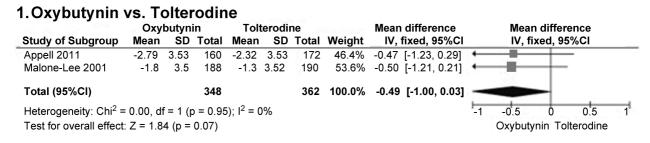


Fig. 2 Forest plot - mean difference in decrease in urge urinary incontinence (UUI) episodes per day.

Primary Outcomes

Mean decrease in UUI episodes per day

For this outcome, it was only possible to perform a comparison between oxybutynin and tolterodine. The MD in the mean decrease in UUI episodes per day was higher for patients that used oxybutynin than for those that used tolterodine (MD = -0.49; 95% CI: -1.00, 0.03; I2 = 0; p = 0.07); however, this difference was not significant (**Fig. 2**).

· Mean decrease in the number of micturitions per day

We were able to perform the following comparisons: oxybutynin versus tolterodine; tolterodine (and its different doses) versus placebo; different doses of tolterodine; and solifenacin versus placebo. We found significant differences that favored tolterodine 1 mg when compared with placebo (MD = -0.55; 95% CI: -1.08, -0.02; I2 = 0; p = 0.04); tolterodine 2 mg versus placebo (MD = -0.57; 95% CI: -0.82, -0.32; I2 = 0; *p* < 0.001); and tolterodine 4 mg versus placebo (MD = -0.66; 95% CI: -0.85, -0.47; I2 = 0; p < 0.001). Moreover, significant differences favored the use of solifenacin when compared with placebo (MD = -0.77; 95% CI: -1.09, -0.45; I2 = 0; p < 0.001) (**Fig. 3**). All of these outcome data were pooled from each study using a Mantel-Haenszel model, and a fixed-effects model was applied, as there was no heterogeneity (I2 = 0) among the studies. For all other available comparisons for this outcome (oxybutynin versus tolterodine; tolterodine 2 mg versus tolterodine 1 mg; and tolterodine 4 mg versus tolterodine 2 mg), the MD was not significant, as presented in **Fig. 3**.

Secondary Outcomes

Mean decrease in incontinence episodes per day

Significant differences were found that favored tolterodine 2 mg when compared with placebo (MD = -0.45; 95% CI: -0.76, -0.14; I2 = 0; p = 0.005); tolterodine 4 mg versus placebo (MD = -0.46; 95% CI: -0.83, -0.08; I2 = 0; p = 0.02); and solifenacin versus placebo (MD = -0.77; 95% CI: -1.09, -0.45; I2 = 0; p < 0.001) (**Fig. 4**). All of these outcome data were pooled from each study using a Mantel–Haenszel model, and a fixed-effects model was applied, as there was no heterogeneity (I2 = 0) among the studies. We did not find significant differences across any of the other available comparisons (oxybuty-nin versus tolterodine; tolterodine 1 mg versus placebo;

tolterodine 2 mg versus tolterodine 1 mg; and tolterodine 4 mg versus tolterodine 2 mg).

• Dry mouth

There were significant differences and higher RRs in patients treated with oxybutynin when compared with tolterodine (RR = 1.49; 95% CI: 1.06, 2.10; I2 = 84%; p = 0.02); tolterodine 1 mg versus placebo (RR = 2.33; 95% CI: 1.26, 4.29; I2 = 84%; p = 0.02); tolterodine 2 mg versus placebo (RR = 3.72; 95% CI: 3.05, 4.54; I2 = 0%; p < 0.001); tolterodine 4 mg versus placebo (RR = 2.88; 95% CI: 2.40, 3.45; I2 = 0%; p < 0.001); tolterodine 2 mg versus placebo (RR = 2.88; 95% CI: 2.40, 3.45; I2 = 0%; p < 0.001); tolterodine 2 mg versus tolterodine 1 mg (RR =1.69; 95% CI: 1.26, 2.28; I2 = 0%; p < 0.001), and solifenacin versus placebo (RR =3.73; 95% CI: 1.80, 7.77; I2 =0%; p < 0.001). The group of patients that used tolterodine 4 mg exhibited a lower risk (RR = 0.79; 95% CI: 0.68, 0.92; I2 = 0%; p = 0.02) when compared with tolterodine 2 mg. All of these results are presented in **~Fig. 5**.

Constipation

The findings indicated that there was a significant difference and a higher RR in patients treated with tolterodine 2 mg versus those treated with placebo (RR = 1.61; 95% CI: 1.11, 2.32; I2 = 0%; p = 0.01), and those treated with tolterodine 4 mg versus placebo (RR = 1.52; 95% CI: 1.11, 2.09; I2 = 0%; p = 0.009). We did not find significant differences across any of the other available comparisons (oxybutynin versus tolterodine; solifenacin versus placebo). All of these results are presented in **- Fig. 6**.

· Withdrawals resulting from drug-related adverse effects

We did not find statistical differences in any of the available comparisons (oxybutynin versus tolterodine, p = 0.18; tolterodine 1 mg versus placebo, p = 0.47; tolterodine 2 mg versus placebo, p = 0.32; tolterodine 4 mg versus placebo, p = 0.13; tolterodine 2 mg versus tolterodine 1 mg, p = 0.59; tolterodine 4 mg versus tolterodine 2 mg, p = 0.92; and solifenacin versus placebo, p = 0.67) when evaluating the risk of withdrawals due to drug-related adverse effects.

Discussion

To our knowledge, this is the first comprehensive review featuring a pooled analysis that has addressed the question of efficacy and the main adverse effects of all antimuscarinic drugs available in Brazil for the treatment of OAB.

Obudu at O 1		utynin	F - 4 - F		rodine	T - 4 - 4	141-1-1-1		in difference	Mean difference
Study of Subgroup	Mean	SD 1		Mean	SD		Weight		fixed, 95%Cl	IV, fixed, 95%Cl
Appell 2011	-3.53		160	-2.87	6.44	172	0.0%		[-2.06, 0.74]	
Drutz 1999 Lee 2002	-2 -1.8	2.3 4.2	41 116	-2 -2.6	2.5 2.9	70 112	0.0% 0.0%		[-0.92, 0.92] [-0.13, 1.73]	
Malone-Lee 2001	-1.8 -1.7	4.2 0.07		-2.6 -1.7	2.9 0.07	190	0.0% 99.9%		[-0.13, 1.73] [-0.01, 0.01]	2 C C C C C C C C C C C C C C C C C C C
	-1.7	0.07		-1.7	0.07					
Total (95%CI)			505			544	100.0%	0.00	[-0.01, 0.01]	
Heterogeneity: Chi ² = 3.6	67, df = 3 (p	o = 0.30); I ² = 18	3%						-1 -0.5 0 0.5
Test for overall effect: Z =	= 0.02 (p =	0.99)								Oxybutynin Tolterodine
2. Tolterodine 1m	na vs. I	Place	bo							
		rodine		F	lacebo			Mea	n difference	Mean difference
Study of Subgroup	Mean	and the second			ו SD		Weight		fixed, 95%Cl	IV, fixed, 95%Cl
Jacquetin 2001	-1.4	2.8		-1.2		51	32.6%	-0.20	[-1.13, 0.73]	
Millardi 1999 Van Kerrebroeck 1998	-2.3 -0.4	3 2.1		-1.4 -0.1		64 16	46.9% 20.5%	-0.90 0.30	[-1.67, -0.13]	
	-0.4	Ζ.		-0.1	1				[-1.47, 0.87]	
Total (95%CI)			235			131	100.0%	-0.55	[-1.08, -0.02]	
Heterogeneity: Chi ² = 1.5	51, df = 2 (p	o = 0.47); I ² = 09	%						-1 -0.5 0 0.5
Test for overall effect: Z =	= 2.03 (p =	0.04)								Tolterodine 1mg Placebo
3. Tolterodine 2m	na ve I	Place	ho							
		terodin			Plac	ebo		Mea	n difference	Mean difference
Study of Subgroup	Mean		Total	Mean		Total	Weight		fixed, 95%Cl	IV, fixed, 95%Cl
Chapple 2004	-1.88	3	250	-1.2	3.26	253	20.8%		[-1.23, -0.13]	•==
Drutz 1999	-2	2.5	70	-1.1	2.9	36	5.0%	-0.90	[-2.01, 0.21]	+
Jacquetin 2001	-1.4	4.3	103	-1.2	2.7	51	5.0%	-0.20	[-1.31, 0.91]	
Millardi 1999	-2.3	2.1	129	-1.4	2.3	64	13.9%		[-1.57, -0.23]	•
Swift 2003 Van Kerrebroeck 1998	-1.7 -0.1	2.9 1.8	408 17	-1.2 -0.1	2.9 1	410 16	39.4% 6.4%		[-0.90, -0.10] [-0.99, 0.99]	Not an and a second
Van Kerrebroeck 1996	-0.1 -1.7	1.0 3.3	514	-0.1 -1.2	2.9	57	6.4% 9.6%		[-0.99, 0.99] [-1.31, 0.31]	1000 Con
		2.0			2.0				shi ush da	
Total (95%CI)			1491			887	100.0%	-0.57	[-0.82, -0.32]	
Heterogeneity: Chi ² = 3.2	28, df = 6 (p = 0.77	'); I ² = 0	%						-1 -0.5 0 0.5
Test for overall effect: Z										Tolterodine 2 mg Placebo
1 Taltaradina Am			ha							
4. Tolterodine 4m		rodine		i i i	Placebo			Mer	n difference	Mean difference
	rone	June								wean unterence
Study of Subaroup	Mean	SD			ו SD	Total	Weight	IV. 1	fixed, 95%Cl	IV, fixed. 95%CI
Study of Subgroup Khullar 2004	Mean -2.1	SD 2.4	Tota	l Mear		Total 258	Weight 30.5%	and the second se	fixed, 95%Cl	IV, fixed, 95%Cl
the last to be a set of the last to be a			Tota	I Mean ∋ -1.3	2.3		30.5%	-0.80 [fixed, 95%Cl -1.14, -0.46] -1.13, -0.27]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998	-2.1 -1.9 -0.3	2.4 3.4 2.2	Tota 569 417	I Mear 9 -1.3 7 -1.2 5 -0.1	2.3 2.9 1	258 410 16	30.5% 19.4% 2.4%	-0.80 [-0.70 [-0.20	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001	-2.1 -1.9 -0.3 -1.8	2.4 3.4 2.2 3.4	Total 569 417 15 507	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2	2.3 2.9 1 2.9	258 410 16 507	30.5% 19.4% 2.4% 23.7%	-0.80 [-0.70 [-0.20 -0.60 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a	-2.1 -1.9 -0.3 -1.8 -2	2.4 3.4 2.2 3.4 3.1	Tota 569 417 15 507 292	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 5 -0.1 7 -1.2 2 -1.4	2.3 2.9 1 2.9 3.1	258 410 16 507 284	30.5% 19.4% 2.4% 23.7% 14.0%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001	-2.1 -1.9 -0.3 -1.8	2.4 3.4 2.2 3.4	Tota 569 417 15 507 292	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4	2.3 2.9 1 2.9 3.1	258 410 16 507	30.5% 19.4% 2.4% 23.7%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a	-2.1 -1.9 -0.3 -1.8 -2	2.4 3.4 2.2 3.4 3.1	Tota 569 417 15 507 292	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9	2.3 2.9 1 2.9 3.1	258 410 16 507 284	30.5% 19.4% 2.4% 23.7% 14.0% 9.9%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI)	-2.1 -1.9 -0.3 -1.8 -2 -1.4	2.4 3.4 2.2 3.4 3.1 3.7	Tota 569 417 2 15 507 292 214 2014	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 I -0.9	2.3 2.9 1 2.9 3.1	258 410 16 507 284 223	30.5% 19.4% 2.4% 23.7% 14.0% 9.9%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10]	
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b	-2.1 -1.9 -0.3 -1.8 -2 -1.4	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90	Tota 569 417 212 202 212 2014 0); I ² = 0	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 I -0.9	2.3 2.9 1 2.9 3.1	258 410 16 507 284 223	30.5% 19.4% 2.4% 23.7% 14.0% 9.9%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10]	IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p <	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000	$\begin{array}{c c} \hline Tota \\ \hline Tota \\ \hline 56\% \\ 417 \\ 216 \\ 507 \\ 292 \\ 214 \\ 2014 \\ 0); \ ^2 = 0 \\ 1) \end{array}$	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 4 -0.9 5 -0.1	2.3 2.9 1 2.9 3.1 2.9 3.1 2.6	258 410 16 507 284 223	30.5% 19.4% 2.4% 23.7% 14.0% 9.9%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10]	
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p <	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 < 0.0000 Folter	Total 569 417 517 417 507 292 214 2014 2); 1 ² = 0 1); 1); rodin	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 % Part of the second se	2.3 2.9 2.9 2.9 3.1 2.6	258 410 16 507 284 223 1698	30.5% 19.4% 2.4% 23.7% 14.0% 9.9%	-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 -	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47]	-1 -0.5 0.5 Tolterodine 4mg Placebo
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p <	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000	Total 569 417 507 292 2014 0); I ² = 0 1) rodin 2mg Total	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 % Market	2.3 2.9 2.9 2.9 3.1 2.6 g	258 410 16 507 284 223 1698	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - -0.60 [-0.60 [-0.50 -	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10]	
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 54, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4	2.4 3.4 2.2 3.4 3.1 3.7 \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	Total 569 417 507 292 2014 2014 2015 1); 12 = 0 1); 12 = 0 1); 12 = 0 1); 12 = 0 1); 12 = 0 10 Total 103	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Understand Wean Tolter Mean -1.4	g 2.3 2.9 1 2.9 3.1 2.6 g rodine 2.8	258 410 16 507 284 223 1698 1mg Tota 97	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50 -0.66 [-0.66 [-0.66 [-0.66 [-0.66 [-0.66 [-0.66 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] an difference fixed, 95%Cl [-1.00, 1.00]	1 -0.5 0 0.5 Tolterodine 4mg Placebo
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOLterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3	2.4 3.4 2.2 3.4 3.1 3.7 \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	Total 569 417 507 212 2014 2015 2014 2015 <td>Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 N Tolter Mean -1.4 -1.4 -2.3</td> <td>2.3 2.9 1 2.9 3.1 2.6 g odine 2.6</td> <td>258 410 16 507 284 223 1698 1mg Tota 97 123</td> <td>30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%</td> <td>-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50 - -0.66 [-0.50 - -0.66 [-0.50 - -0.66 [</td> <td>-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47]</td> <td>1 -0.5 0 0.5 Tolterodine 4mg Placebo</td>	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 N Tolter Mean -1.4 -1.4 -2.3	2.3 2.9 1 2.9 3.1 2.6 g odine 2.6	258 410 16 507 284 223 1698 1mg Tota 97 123	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50 - -0.66 [-0.50 - -0.66 [-0.50 - -0.66 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47]	1 -0.5 0 0.5 Tolterodine 4mg Placebo
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 54, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4	2.4 3.4 2.2 3.4 3.1 3.7 \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	Total 569 417 507 292 2014 2014 2015 1); 12 = 0 1); 12 = 0 1); 12 = 0 1); 12 = 0 1); 12 = 0 10 Total 103	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Understand Wean Tolter Mean -1.4	g 2.3 2.9 1 2.9 3.1 2.6 g rodine 2.8	258 410 16 507 284 223 1698 1mg Tota 97 123	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 -0.60 [-0.60 [-0.50 - -0.66 [-0.50 - -0.66 [-0.50 - -0.66 [-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] an difference fixed, 95%Cl [-1.00, 1.00]	1 -0.5 0 0.5 Tolterodine 4mg Placebo
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOLterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3	2.4 3.4 2.2 3.4 3.1 3.7 \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	Total 569 417 507 212 2014 2015 2014 2015 <td>Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 N Tolter Mean -1.4 -1.4 -2.3</td> <td>2.3 2.9 1 2.9 3.1 2.6 g odine 2.6</td> <td>258 410 16 507 284 223 1698 1mg Tota 97 123</td> <td>30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%</td> <td>-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30</td> <td>-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47]</td> <td>1 -0.5 0 0.5 Tolterodine 4mg Placebo</td>	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 4 -0.9 N Tolter Mean -1.4 -1.4 -2.3	2.3 2.9 1 2.9 3.1 2.6 g odine 2.6	258 410 16 507 284 223 1698 1mg Tota 97 123	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47]	1 -0.5 0 0.5 Tolterodine 4mg Placebo
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI)	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1	2.4 3.4 2.2 3.4 3.1 3.7 • 0.900 • 0.0000 Tolte: rodine 2 SD 4.3 2.1 1.8	Total 569 417 569 417 507 2014 2014 2011 2014 2011 2012 2014 2014 2014 2011 2014 <td>Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Tolter Mean -1.4 -2.3 -0.4</td> <td>2.3 2.9 1 2.9 3.1 2.6 g odine 2.6</td> <td>258 410 16 507 284 223 1698 1698 1698 97 123 15</td> <td>30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%</td> <td>-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30</td> <td>-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00] [-0.64, 0.64] [-1.06, 1.66]</td> <td>-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI</td>	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Tolter Mean -1.4 -2.3 -0.4	2.3 2.9 1 2.9 3.1 2.6 g odine 2.6	258 410 16 507 284 223 1698 1698 1698 97 123 15	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -1.00 , 1.00] [-0.64, 0.64] [-1.06, 1.66]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92	Total 569 417 569 417 507 2014 2014 2011 2014 2011 2012 2014 2014 2014 2011 2014 <td>Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Tolter Mean -1.4 -2.3 -0.4</td> <td>2.3 2.9 1 2.9 3.1 2.6 g odine 2.6</td> <td>258 410 16 507 284 223 1698 1698 1698 97 123 15</td> <td>30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%</td> <td>-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30</td> <td>-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00 [-1.00, 1.00] [-1.06, 1.66]</td> <td>-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI</td>	Mear 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Tolter Mean -1.4 -2.3 -0.4	2.3 2.9 1 2.9 3.1 2.6 g odine 2.6	258 410 16 507 284 223 1698 1698 1698 97 123 15	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00 [-1.00, 1.00] [-1.06, 1.66]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: $Chi^2 = 1.6$ Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: $Chi^2 = 0.$ Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 1G VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p =	2.4 3.4 3.4 3.1 3.7 p = 0.90 c 0.0000 Tolte: rodine 2 <u>SD</u> 4.3 2.1 1.8 (p = 0.92 = 0.87)	$\begin{array}{c} {\bf Total} \\ {\bf 569} \\ {\bf 417} \\ {\bf 569} \\ {\bf 500} \\ {\bf 292} \\ {\bf 2014} \\ {\bf 2014} \\ {\bf 0); \ l^2 = 0 \\ {\bf 10} \\ {\bf rodin} \\ {\bf rodin} \\ {\bf 103} \\ {\bf 129} \\ {\bf 17} \\ {\bf 249} \\ {\bf 2); \ l^2 = 0 \end{array}$	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 -0.9 -1.4 -0.4 -0.4 -0.4 -0.4	2.3 2.9 1 2.9 3.1 2.9 2.9 2.6 SE 2.6 3 2.1	258 410 16 507 284 223 1698 1698 1698 97 123 15	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - 0.60 [-0.60 [-0.50 - -0.66 [-0.66 [.0.66 [.0.60 - .0.00 0.00 0.30	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00 [-1.00, 1.00] [-1.06, 1.66]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: $Chi^2 = 1.6$ Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: $Chi^2 = 0.$ Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS.	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000 Tolter rodine 2 <u>SD</u> 4.3 2.1 1.8 (<i>p</i> = 0.92 = 0.87) Tolter	Total 566 417 568 417 18 507 292 2014 2017 2018 2019 1003 103 129 17 249 22); 1 ² = 0 rodin	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Image: Comparison of the second	2.3 2.9 1 2.9 3.1 2.9 2.9 2.6 SE 2.6 3 2.1	258 410 16 507 284 223 1698 1mg Tota 97 123 15 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 - -0.60 [-0.60 [-0.50 - -0.66 [-0.66 [-0.66 [0.00 0.00 0.30 0.00 6 0.04	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] [-1.00, 1.00] [-0.64, 0.64] [-0.46, 0.54]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. Tolterodine 4m	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS.	2.4 3.4 3.4 3.1 3.7 p = 0.90 c 0.0000 Tolte: rodine 2 <u>SD</u> 4.3 2.1 1.8 (p = 0.92 = 0.87)	Total 4 566 4 16 507 18 202 214 2014 292 211 2014 2011 101 rodin rodin 2011 103 103 129 17 249 20; 1 ² = 0 rodin rodin rodin	Mean 9 -1.3 9 -1.2 5 -0.1 7 -1.2 7 -1.2 2 -1.4 % Market	2.3 2.9 1 2.9 3.1 2.6 3.1 2.6 9 odine 2.8 2.1 9 2.1	258 410 16 507 284 223 1698 1698 1698 97 123 15 235	30.5% 19.4% 2.4% 32.7% 14.0% 9.9% 100.0%	-0.80 [-0.70] -0.20 - -0.60 [-0.60] -0.50 - -0.66 [.0.00 0.00 0.30 6 0.04	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -1.100, 1.00] [-1.00, 1.00] [-1.00, 1.66] [-1.06, 1.66] [-0.46, 0.54]	Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: $Chi^2 = 1.6$ Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: $Chi^2 = 0.$ Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. TolterOf	2.4 3.4 2.2 3.4 3.1 3.7 c 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 5.0 (0.0000 Folter 1.8 (p = 0.92 5.0 (0.0000 Folter 1.8 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 Folter 5.0 (0.9000 (0.9000) (Total 566 417 568 417 18 507 292 2014 2017 2018 2019 1003 103 129 17 249 22); 1 ² = 0 rodin	Mean 9 -1.3 7 -1.2 5 -0.1 7 -1.2 2 -1.4 % Image: Comparison of the second	2.3 2.9 1 2.9 3.1 2.9 2.9 2.6 SE 2.6 3 2.1	258 410 16 507 284 223 1698 1698 1698 97 123 15 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0%	-0.80 [-0.70 [-0.20 [-0.60 [-0.50 - -0.66 [-0.66 [.0.00 0.00 0.30 0.30 6 0.04	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] [-1.00, 1.00] [-0.64, 0.64] [-0.46, 0.54]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%Cl) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%Cl) Heterogeneity: Chi ² = 0.7 Test for overall effect: Z 5. Tolterodine 4m Study of Subgroup Van Kerrebroeck 1998 Yan Kerrebroeck 1998 Yan Kerrebroeck 1998	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 = 0.87) Folter 0.87) Folter 0.87) Folter	Total + 566 + 567 + 567 + 11 + 507 292 214 2014 2014 2017 2014 101 103 102 17 249 17 249 201 rodin 17 rodin 17 7 749 10 17 Total 17	Mean 9 -1.3 9 -1.2 5 -0.1 7 -1.2 7 -1.2 4 -0.9 We Mean -0.13 -0.9 Mean -1.4 -0.4 -0.4 9% Tolter Mean -0.4	2.3 2.9 1 2.9 3.1 2.6 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	258 410 16 507 284 223 1698 1698 1698 1701 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% 100.0% 39.2% 21.2%	-0.80 [-0.70] -0.60 [-0.60 [-0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50]	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-1.00, 1.00] [-0.64, 0.64] [-1.06, 1.66] [-0.46, 0.54] an difference fixed, 95%Cl	Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.7 Test for overall effect: Z 5. TOIterodine 4m Study of Subgroup Swift 2003	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolterc Mean -1.9	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 = 0.87) Folter SD 3.4	Total + 566 + 567 + 567 + 129 - 214 2014 2014 101 101 103 129 17 249 22); 1 ² = 0 10 roddin mg rotal 417	Mean 9 -1.3 9 -1.2 5 -0.1 7 -1.2 7 -1.2 2 -1.4 % • Mean -1.4 -2.3 -0.4 % • Tolter Mean -1.7 •	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 3.1 2.6 SD 2.9 2.9 2.9	258 410 16 507 284 223 1698 Total 97 123 15 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2%	-0.80 [-0.70] -0.60 [-0.60] -0.66 [-0.50 -0.66 [-0.50 -0.66 [0.00 0.30 0.30 0.30 0.30 0.30 0.30 0.3	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] [-1.00, 1.00] [-0.64, 0.64] [-1.06, 1.66] [-0.46, 0.54] -0.46, 0.54]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS. Tolterc Mean -1.9 -3	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000 Tolter rodine 2 <u>SD</u> 4.3 2.1 1.8 (p = 0.92 = 0.87) Tolter Dolter 0.87) Tolter 0.87) SD 3.4 2.2	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.2 -0.12 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -2.3 -0.4 % E 2mm Tolter Mean -1.7 -0.4	2.3 2.9 2.9 3.1 2.9 3.1 2.9 2.9 2.9 2.6 Odine 2.6 SD 2.9 1.8	258 410 16 507 284 223 1698 Total 123 15 235 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5%	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-0.64, 0.64] [-0.46, 0.54] -0.46, 0.54] -0.63, 0.23] [-4.30, -1.50] [-0.51, 0.31]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI)	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 10 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS. Tolter Mean -1.9 -3 -1.8	2.4 3.4 2.2 3.4 3.1 3.7 P = 0.90 0.0000 Tolter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 = 0.87) Tolter Dolter 50 3.4 2.2 3.4	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 2.6 9 00ine 2.8 9 2.1 9 00ine 3.2 2.1	258 410 16 507 284 223 1698 Total 123 15 235 235 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% 100.0% 39.2% 21.2%	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00] [-0.64, 0.64] [-0.64, 0.54] -0.46, 0.54] -0.63, 0.23] [-0.30, 2.33] [-4.30, -1.50]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. Tolterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0.	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS. Tolter Mean -1.9 -1.8 50; Chi ² =	2.4 3.4 2.2 3.4 3.1 3.7 coline 2 colono0 Folter codine 2 SD 4.3 2.1 1.8 Colone 2 SD 3.4 2.2 3.4 2.2 3.4 2.2 3.4	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 2.6 9 00ine 2.8 9 2.1 9 00ine 3.2 2.1	258 410 16 507 284 223 1698 Total 123 15 235 235 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5%	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-0.64, 0.64] [-0.46, 0.54] -0.46, 0.54] -0.63, 0.23] [-4.30, -1.50] [-0.51, 0.31]	Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 5. Tolterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 (p vS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p =	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 = 0.87) Folter odine 4 SD 3.4 14.23, d = 0.11)	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 2.6 9 00ine 2.8 9 2.1 9 00ine 3.2 2.1	258 410 16 507 284 223 1698 Total 123 15 235 235 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5%	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-0.64, 0.64] [-0.46, 0.54] -0.46, 0.54] -0.63, 0.23] [-4.30, -1.50] [-0.51, 0.31]	-1 -0.5 0 0.5 Tolterodine 4mg Placebo Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 5. Tolterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 (p vS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p =	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 c 0.0000 Folter rodine 2 SD 4.3 2.1 1.8 (p = 0.92 = 0.87) Folter odine 4 SD 3.4 14.23, d = 0.11)	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 2.6 9 00ine 2.8 9 2.1 9 00ine 3.2 2.1	258 410 16 507 284 223 1698 Total 123 15 235 235 235 235	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5%	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.50] -0.50 [-0.50] -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-0.64, 0.64] [-0.46, 0.54] -0.46, 0.54] -0.63, 0.23] [-4.30, -1.50] [-0.51, 0.31]	Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0. Total (95%CI) Heterogeneity: Tau ² = 0. Total (95%CI)	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p =	$\begin{array}{c} 2.4\\ 3.4\\ 3.4\\ 2.2\\ 3.4\\ 3.1\\ 3.7\\ p = 0.90\\ 0.0000\\ \hline \textbf{Folter}\\ \textbf{rodine 2}\\ \textbf{sp}\\ \textbf{a}.3\\ 2.1\\ 1.8\\ p = 0.92\\ \textbf{s}.0\\ \textbf{s}.3\\ 2.1\\ 1.8\\ \textbf{s}.3\\ 2.1\\ 1.8\\ \textbf{s}.3\\ 2.1\\ 3.4\\ 2.2\\ 3.4\\ 3.4\\ 3.4\\ 3.4\\ 3.4\\ 3.4\\ 3.4\\ 3.4$	Total + 566 + 567 + 567 + 11 + 500 202 21 2014 2012 2011 103 103 129 107 103 129 17 107 249 202); I ² = 0 0 roddin 129 107 249 507 507 939 if = 2 (p	Mean 9 -1.3 9 -1.2 5 -0.1 7 -1.2 7 -1.2 2 -1.4 % • H Mean -1.4 -2.3 -0.4 • 9% E Email 1.1.7 -0.1 -1.7 -0.4 9% • 1.1.7 = 0.0000	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.6 SD 2.9 1.8 3.3 3.3 8); ² = {	258 410 16 507 284 223 1698 1698 704 123 15 235 235 235 235 235 235 235 235 235 23	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0%	-0.80 [-0.70] -0.60 [-0.60 [-0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.60 -0.50 -0.50 -0.60 -0.50 -	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] [-1.00, 1.00] [-0.64, 0.64] [-1.00, 1.66] [-0.46, 0.54] -0.46, 0.54] -1.00, 1.03] [-0.46, 0.54] -1.00, 1.03] [-0.51, 0.31] [-1.64, 0.18] -1.64, 0.18]	Mean difference IV, fixed, 95%Cl Mean difference IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.7 Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p = Solift Mean	2.4 3.4 2.2 3.4 3.1 3.7 P = 0.90 Colter rodine 2 SD 4.3 2.1 1.8 P = 0.92 = 0.87) Tolter solution 3.4 2.2 3.4 3.4 2.2 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4	Total Form - Total - Total - Total - Total - Total	Mean -1.3 -1.13 -1.2 -0.11 7 -1.2 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -0.9 Mean -1.7 -0.1 -1.7 = 0.0000 Pla Mean	2.3 2.3 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.2 2.9 1.8 3.3 3.3 8); 1 ² = 4 cebo SD T	258 410 16 507 284 223 1698 Total 408 17 514 939 36%	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5% 100.0% Veight	-0.80 [-0.70] -0.60 [-0.60 [-0.50] -0.66 [-0.50] -0.60 [-0.50] -0.50] -0.60 [-0.50] -0.50] -0.50 [-0.50] -0.50 [-0.50] -0.73 [-0.73] -0.73 [-0.73]	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-1.00, 1.00] [-0.64, 0.64] [-1.06, 1.66] [-0.46, 0.54] -0.46, 0.54] -0.46, 0.54] -0.46, 0.54] -1.64, 0.18] -1.64, 0.18]	Mean difference IV, fixed, 95%CI
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.: Test for overall effect: Z 6. Tolterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z 7. Solifenacin vs. Study of Subgroup Cardozo 2008	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p = Solif Mean -2.1	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 0.0000 Folter rodine 2 SD 3.4 2.2 3.4 14.23, d 14.23, d 14.23, d 2.6	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -2.3 -0.4 % E 2mm Tolter Mean -1.7 -0.1 -1.7 = 0.0000 Pla Mean -1.3	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 3.1 2.6 2.6 2.6 2.6 2.1 2.7 2.9 1.8 3.3 8); l ² = { 8 5D 2.9 1.8 3.3 2.9 2.9 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2	258 410 507 284 223 1698 1698 97 123 15 235 235 235 235 235 235 235 235 235 23	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5% 100.0% Veight 57.5%	-0.80 [-0.70] -0.60 [-0.60 [-0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.73 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.60 [-0.50 -0.60 [-0.50 -0.	-1.14, -0.46] -1.13, -0.27] -1.42, 1.02] -0.99, -0.21] -1.11, -0.09] -1.11, -0.09] -1.11, -0.09] -1.11, -0.09] -1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00] -0.64, 0.64] -1.00, 1.00] -0.64, 0.64] -1.00, 1.00] -0.64, 0.54] -1.00, 1.00] -0.63, 0.23] -4.30, -1.50] -0.51, 0.31] -1.64, 0.18] -1.64, 0.18] -1.64, 0.73]	Mean difference IV, fixed, 95%Cl Mean difference IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.7 Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0.7 Test for overall effect: Z 7. SOIifenacin vs. Study of Subgroup	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p = Solif Mean -2.1	2.4 3.4 2.2 3.4 3.1 3.7 P = 0.90 Colter rodine 2 SD 4.3 2.1 1.8 P = 0.92 = 0.87) Tolter solution 3.4 2.2 3.4 3.4 2.2 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4 3.4	Total Form - Total - Total - Total - Total - Total	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -2.3 -0.4 -% E 2mm Tolter Mean -1.7 -0.1 -1.7 = 0.0000 Pla Mean -1.3	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 3.1 2.6 2.6 2.6 2.6 2.1 2.7 2.9 1.8 3.3 8); l ² = { 8 5D 2.9 1.8 3.3 2.9 2.9 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.9 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.9 2.6 1.2 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2	258 410 507 284 223 1698 1698 97 123 15 235 235 235 235 235 235 235 235 235 23	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5% 100.0% Veight	-0.80 [-0.70] -0.60 [-0.60 [-0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.50 -0.66 [-0.73 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.20 -0.60 [-0.50 -0.60 [-0.50 -0.	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-1.00, 1.00] [-0.64, 0.64] [-1.06, 1.66] [-0.46, 0.54] -0.46, 0.54] -0.46, 0.54] -0.46, 0.54] -1.64, 0.18] -1.64, 0.18]	Mean difference IV, fixed, 95%Cl Mean difference IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. TOIterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0. Test for overall effect: Z 6. TOIterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z = 7. SOIifenacin vs. Study of Subgroup Cardozo 2008 Karram 2009	-2.1 -1.9 -0.3 -1.8 -2 -1.4 54, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 19 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p = Solif Mean -2.1	2.4 3.4 2.2 3.4 3.1 3.7 p = 0.90 0.0000 Folter rodine 2 SD 3.4 2.2 3.4 14.23, d 14.23, d 14.23, d 2.6	Total + 566 + 567 + 567 + 11 + 507 2292 212 2014 2014 2017 2011 rodin 103 103 129 17 249 2012 229 121 249 rotal 417 507 939 91f = 2 (p 704 502 348	Mean -1.3 -1.3 -1.3 -1.2 -0.12 -0.12 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.2 -1.4 -2.3 -0.4 % E 2mm Tolter Mean -1.7 -0.1 -1.7 = 0.0000 Pla Mean -1.3	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 1.8 3.3 3.3 8); 1 ² = 8 Cebo SD T 2.7 3.3	258 410 16 507 284 223 1698 Total 408 17 514 408 17 514 939 939 36%	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5% 100.0% Veight 57.5% 42.5%	-0.80 [-0.70] -0.60 [-0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.73] -0.80 -0.73	-1.14, -0.46] -1.13, -0.27] [-1.42, 1.02] -0.99, -0.21] -1.11, -0.09] [-1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.64, 0.64] [-1.00, 1.00] [-0.64, 0.64] [-1.00, 1.66] [-0.46, 0.54] -0.63, 0.23] [-4.30, -1.50] [-0.51, 0.31] [-1.64, 0.18] -1.64, 0.18] -1.64, 0.18]	Mean difference IV, fixed, 95%Cl Mean difference IV, fixed, 95%Cl
Khullar 2004 Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Zinner 2002a Zinner 2002b Total (95%CI) Heterogeneity: Chi ² = 1.6 Test for overall effect: Z 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Heterogeneity: Chi ² = 0.: Test for overall effect: Z 6. Tolterodine 4m Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z 7. Solifenacin vs. Study of Subgroup Cardozo 2008	-2.1 -1.9 -0.3 -1.8 -2 -1.4 64, df = 5 (= 6.83 (p < 19 VS. Tolter Mean -1.4 -2.3 -0.1 16, df = 2 (= 0.16 (p = 10 VS. Tolter Mean -1.9 -3 -1.8 50; Chi ² = = 1.58 (p = Place Soliff Mean -2.1 -2.67	2.4 3.4 2.2 3.4 3.1 3.7 P = 0.90 Colter rodine 2 SD 4.3 2.1 1.8 P = 0.92 = 0.87) Folter odine 4 SD 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.2 3.4 2.1 5 D D D D D D D D D D	$\begin{tabular}{ c c c c c } \hline Total \\ \hline Tot$	Mean -1.3 -1.2 -1.2 -0.1 7 -1.2 -0.1 7 -1.2 -0.1 % % model Mean -1.3 -1.3 -1.3	2.3 2.9 2.9 3.1 2.9 3.1 2.9 3.1 2.9 3.1 2.9 2.9 1.8 3.3 3.3 8); 1 ² = 8 Cebo SD T 2.7 3.3	258 410 16 507 284 223 1698 Total 408 17 514 939 939 36% total V 2216 3337	30.5% 19.4% 2.4% 23.7% 14.0% 9.9% 100.0% 100.0% 100.0% 100.0% Weight 39.2% 21.2% 39.5% 100.0% Veight 57.5%	-0.80 [-0.70] -0.60 [-0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.66 [-0.50] -0.20 -2.90 -0.10 -0.73 Mea IV, 1 -0.80 -0.73	-1.14, -0.46] -1.13, -0.27] -1.42, 1.02] -0.99, -0.21] -1.11, -0.09] -1.11, -0.09] -1.11, -0.09] -1.11, -0.09] -1.10, 0.10] -0.85, -0.47] -0.85, -0.47] -0.85, -0.47] -1.00, 1.00] -0.64, 0.64] -1.00, 1.00] -0.64, 0.64] -1.00, 1.00] -0.64, 0.54] -1.00, 1.00] -0.63, 0.23] -4.30, -1.50] -0.51, 0.31] -1.64, 0.18] -1.64, 0.18] -1.64, 0.73]	Mean difference IV, fixed, 95%Cl Mean difference IV, fixed, 95%Cl

Fig. 3 Forest plot – mean difference in decrease in the number of micturitions per day.

1. Oxybutynin vs. Tolterodine

	Favo	urs Oxyt	outyni	Tolter	odine			Mean difference		Mean dif	ference	
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%CI		IV, rando	m, 95%Cl	
Appell 2011	-3.07	4.14	160	-2.53	4.17	172	29.0%	-0.54 [-1.43, 0.35]	+	-		1.1
Drutz 1999	-1.7	1.7	39	-1.7	2	60	33.0%	0.00 [-0.74, 0.74]			÷	
Lee 2002	-1.4	1.8	116	-2.2	2.3	112	38.1%	0.80 [0.26, 1.34]				\rightarrow
Total (95%CI)			315			344	100.0%	0.15 [-0.64, 0.94]				-
Heterogeneity: Tau ² = 0.	.35; Chi ² =	7.34, df =	= 2 (p =	0.03); I ²	= 73%				-			-
Test for overall effect: Z	= 0.37 (p =	0.71)	u.						-1	-0.5 Oxybutyn	0 0.5 in Tolterodine	1

2. Tolterodine 1mg vs. Placebo

	Toltero	odine 1r	ng	P	acebo)		Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%CI	IV, fixed, 95%Cl
Millardi 1999	-1.7	2.8	109	-1.3	2.5	55	87.6%	-0.40 [-1.24, 0.44]	+
Van Kerrebroeck 1998	-1.2	3.9	15	-1.9	2.2	16	12.4%	0.70 [-1.55, 2.95]	• <u> </u>
Total (95%CI)			124			71	100.0%	-0.26 [-1.05, 0.53]	
Heterogeneity: Chi ² = 0.	81, df = 1 (p	= 0.37);	$I^2 = 0\%$						
Test for overall effect: Z	= 0.65 (p = 0	0.51)							-1 -0.5 0 0.5 Tolterodine 1mg Placebo

3. Tolterodine 2mg vs. Placebo

	,	1000							
	Tolt	erodin	e 2mg	Р	lacebo			Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%CI	IV, fixed, 95%Cl
Chapple 2004	-1.14	2.15	157	-0.76	2.26	153	40.0%	-0.38 [-0.87, 0.11]	
Drutz 1999	-1.7	2	39	-1	2.2	33	10.1%	-0.70 [-1.68, 0.28]	• <u> </u>
Mllardi 1999	-1.7	2.5	117	-1.3	2.5	55	15.0%	-0.40 [-1.20, 0.40]	+
Swift 2003	-1.44	5.89	408	-1.03	5.74	410	15.2%	-0.41 [-1.21, 0.39]	• • • • • • • • • • • • • • • • • • •
Van Kerrebroeck 1998	-2.4	3.5	17	-1.9	2.2	16	2.5%	-0.50 [-2.48, 1.48]	+
Van Kerrebroeck 2001	-1.51	6.38	514	-0.99	5.81	507	17.2%	-0.52 [-1.27, 0.23]	· · · · · · · · · · · · · · · · · · ·
Total (95%CI)			1252			1174	100.0%	-045 [-0.76, -0.14]	-
Heterogeneity: Chi ² = 0.39,	df = 5 (r)	b = 1.00	$1^{2} = 1^{2}$	0%					
Test for overall effect: $Z = 2$				0,0					-1 -0.5 0 0.5 Tolterodine 2mg Placebo

4. Tolterodine 4mg vs. Placebo

	Tolter	odine 4	mg	Р	lacebo			Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%Cl	IV, fixed, 95%Cl
Khullar 2004	-0.68	4.72	569	-0.57	5.21	258	25.6%	-0.11 [-0.85, 0.63]	
Swift 2003	-1.69	6.79	417	-1.03	5.74	410	19.4%	-0.66 [-1.52, 0.20]	• • • • • • • • • • • • • • • • • • •
Van Kerrebroeck 1998	-1.5	1.7	15	-1.9	2.2	16	7.5%	0.40 [-0.98, 1.78]	
Van Kerrebroeck 2001	-1.69	6.72	507	-0.99	5.81	507	23.8%	-0.70 [-1.47, 0.07]	• •
Zinner 2002a	-1.71	6.64	292	-1.06	5.89	284	13.6%	-0.65 [-1.67, 0.37]	+
Zinner 2002b	-1.64	6.87	214	-0.9	5.66	223	10.2%	-0.74 [-1.92, 0.44]	•
Total (95%CI)			2014			1698	100.0%	-0.46 [-0.83, 0.08]	-
Heterogeneity: Chi ² = 3.2	7. df = 5 (c	= 0.66	$ ^2 = 0$	%					
Test for overall effect: Z =									-1 -0.5 0 Tolterodine 4mg Placel

5. Tolterodine 2mg vs. Tolterodine 1mg

	Toltero	dine 2	mg	Toltero	dine 1	mg		Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%CI	IV, fixed, 95%CI
Millardi 1999	-1.7	2.5	117	-1.7	2.8	109	93.3%	0.00 [-0.69, 0.69]	
Van Kerrebroeck 1998	-2.4	3.5	17	-1.2	3.9	15	6.7%	-1.20 [-3.78, 1.38]	\leftarrow \rightarrow
Total (95%CI)			134			124	100.0%	-0.08 [-0.75, 0.59]	
Heterogeneity: Chi ² = 0.7			8); I ² = C)%					-1 -0.5 0 0.5
Test for overall effect: Z	= 0.24 (p =	0.81)							Tolterodine 2mg Tolterodine 1mg

6. Tolterodine 4mg vs. Tolterodine 2mg

	Tolter	odine 4	mg	Tolter	odine 2	mg		Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%Cl	IV, fixed, 95%CI
Swift 2003	-1.69	6.79	417	-1.44	5.89	408	42.1%	-0.25 [-1.12, 0.62]	·
Van Kerrebroeck 1998	-1.5	1.7	15	-2.4	3.5	17	9.0%	0.90 [-0.97, 2.77]	· · · · · · · · · · · · · · · · · · ·
Van Kerrebroeck 2001	-1.69	6.72	507	-1.51	6.38	514	48.9%	-0.18 [-0.98, 0.62]	· · · · · · · · · · · · · · · · · · ·
Total (95%CI)			939			939	100.0%	-0.11 [-0.67, 0.45]	
Heterogeneity: Chi ² = 1.2	25. df = 2 ((p = 0.5)	4); $I^2 = C$)%					
Test for overall effect: Z			,,						-0.5 -0.25 0 0.25 0.5 Tolterodine 4mg Tolterodine 2mg

7. Solifenacin vs. Placebo

	Soli	fenaciı	ı	Pla	cebo			Mean difference	Mean difference
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, fixed, 95%Cl	IV, fixed, 95%Cl
Cardozo 2008	-2.1	2.6	502	-1.3	2.7	216	57.5%	-0.80 [-1.23, -0.37]	+ <u>-</u>
Karram 2009	-2.67	3.31	348	-1.94	3.3	337	42.5%	-0.73 [-1.23, -0.23]	
Total (95%CI)			850			553	100.0%	-0.77 [-1.09, -0.45]	•
Heterogeneity: Chi ² = 0			83); I ² =	0%		555	100.070	-0.77 [-1.00, -0.40]	-1 -0.5 0 0.5
Test for overall effect: Z	<u>z</u> = 4.68 (p	< 0.00	001)						Solifenacin Placebo



Study of Subgroup	Tolterodi Oxybutynin Events To		rodine s Tota	l Weig	aht N		sk ratio Idom, 95%Cl	Risk M-H, rando	
Appell 2011		185 6				0.80	[0.62, 1.15]		
Drutz 1999		112 3				1.97	[1.49, 2.62]	22	-
Lee 2002		112 3				1.80	[1.35, 2.40]		-
Malone-Lee 2001		188 7				1.60	[1.31, 2.02]		•
Maj0110-L00 2001	114	55 1	190	, 20.0		1.02	[1.01, 2.02]		
Total (95%CI) Total events	315	500 21:	607 3	7 100.0	0%	1.49	[1.06, 2.10]		<u> </u>
Heterogeneity: Tau ² = 0.1				² = 84%				0.01 0.1	1 10 1
Test for overall effect: Z =								Tolterodine	Oxybutynin
2. Tolterodine 1mg	g vs. Plac		Placebo			Ri	sk ratio	Risk	ratio
Study of Subgroup	Events	Total E	vents T			M-H, f	ixed, 95%Cl	M-H, fixe	
Jacquetin 2001	20	97			27.2%		[1.09, 11.24]		
Millardi 1999	29	123	8	64	72.8%	1.89	[0.92, 3.88]		-
Total (95%CI)		220		115	100.0%	2.33	[1.26, 4.29]		-
	49	220	11	. 13	100.070	2.33	[1.20, 4.23]		
Total events		07) 12 001	H 68					0.01 0.1 1	10 1
Heterogeneity: Chi ² = 0.8								Placebo	Tolterodine 1m
Test for overall effect: Z =	: 2.70 (p = 0.00	7)							
3. Tolterodine 2mg	g vs. Plac	ebo							
	Tolterodi	ne 2mg	Placet				Risk ratio		ratio
Study of Subgroup	Events	Total	the second s	and the second se	Weight		fixed, 95%Cl	M-H, fix	ed, 95%Cl
Chapple 2004	49	263	13	267	11.6%	3.83	[2.13, 6.88]		
Drutz 1999	33	109	8	56	9.5%	2.12	[1.05, 4.28]		
Jacquetin 2001	35	103	3	51	3.6%	5.78	[1.87, 17.89]		
Millardi 1999	50	129	8	64	9.6%	3.10			
			-				[1.57, 6.14]		-
Swift 2003	127	407	33	410	29.6%	3.88	[2.71, 5.54]	· · · · ·	
Van Kerrebroeck 1998	3	18	1	19	0.9%	3.17	[0.36, 27.72]		-
Van Kerrebroeck 2001	156	512	39	507	35.2%	3.96	[2.85, 5.50]		
				· • - ·					•
Total (95%CI)		1541		1374	100.0%	3.72	[3.05, 4.54]		
Total events	453		105					H +	<u> </u>
Heterogeneity: Chi ² = 3.54	4. $df = 6 (n = 0)$	(74): $I^2 = 0\%$						0.01 0.1	1 10 1
Test for overall effect: Z =								Placebo	Tolterodine 2n
Study of Subgroup Khullar 2004	Events 112	Total 569	Events 23	Total 258	Weight 22.0%	<u>м-н,</u> 2.21	fixed, 95%Cl [1.45, 3.37]	M-H, fix	ed, 95%Cl
Swift 2003	105	415	33	410	23.1%	3.14	[2.18, 4.54]		-
Van Kerrebroeck 1998	3	17	1	19	0.7%	3.35	[0.38, 29.26]		
Van Kerrebroeck 2001	118	505	39	507	27.1%	3.04	[2.16, 4.27]		
Zinner 2002a	66	291	23	285	16.2%	2.81	[1.80, 4.39]		
Zinner 2002b	52	214	16	200	10.2%	3.37	[1.99, 5.72]		7.00
	52	214	10	222	10.370	5.57	[1.55, 5.72]		•
Total (95%CI)		2011		1701	100.0%	2.88	[2.40, 3.45]	<u> </u>	
Total events	,456	aa) 1 ² aay	135					0.01 0.1	1 10 1
Heterogeneity: Chi ² = 2.20	0, af = 5 (p = 0	.82); 1 = 0%							
	11 17 (0 - 0 0							Placebo	Tolterodine 4m
Test for overall effect: Z =		0001)						Placebo	l olterodine 4m
Test for overall effect: Z = 5. Tolterodine 2mg	g vs. Tolt	0001) erodine 2mg T	1mg				Risk ratio	Risk	ratio
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup	g vs. Tolt Tolterodine Events	0001) erodine 2mg T Total	1mg olterodine Events	Tota	al Weigh	t M-H	l, fixed, 95%Cl	Risk	
Test for overall effect: Z = 5. Tolterodine 2m Study of Subgroup Jacquetin 2001	g vs. Tolt Tolterodine Events 35	0001) erodine 2mg T Total 103	1mg Tolteroding Events 20	Tota 9	7 40.5%	t M-H %	 fixed, 95%Cl 1.65 [1.03, 2.65] 	Risk	ratio
Test for overall effect: Z = 5. Tolterodine 2m Study of Subgroup Jacquetin 2001 Millardi 1999	g vs. Tolt Tolterodine Events 35 50	0001) erodine 2mg T Total 103 129	1mg folterodine Events 20 29	Tota 91 123	7 40.5% 3 58.4%	t M-H % %	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42]	Risk	ratio ted, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2m Study of Subgroup Jacquetin 2001	g vs. Tolt Tolterodine Events 35	0001) erodine 2mg T Total 103	1mg Tolteroding Events 20	Tota 9	7 40.5% 3 58.4%	t M-H % %	 fixed, 95%Cl 1.65 [1.03, 2.65] 	Risk	ratio ted, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2m 5. Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998	g vs. Tolt Tolterodine Events 35 50	0001) erodine 2mg T Total 103 129 18	1mg folterodine Events 20 29	Tota 97 123 16	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk	ratio ted, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI)	g vs. Tolt Tolterodine Events 35 50 3	0001) erodine 2mg T Total 103 129	1mg folterodine Events 20 29 0	Tota 91 123	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42]	Risk	ratio ted, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events	g vs. Tolt Tolterodine Events 35 50 3 88	0001) erodine 2mg T Total 103 129 18 250	1mg folterodine Events 20 29	Tota 97 123 16	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk M-H, fix	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.83	g vs. Tolt <u>Tolterodine</u> <u>Events</u> 35 50 3 88 2, df = 2 (p = 0.	0001) erodine 2mg T Total 103 129 18 250 66); l ² = 0%	1mg folterodine Events 20 29 0	Tota 97 123 16	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk M-H, fix	ratio red, 95%CI
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events	g vs. Tolt <u>Tolterodine</u> <u>Events</u> 35 50 3 88 2, df = 2 (p = 0.	0001) erodine 2mg T Total 103 129 18 250 66); l ² = 0%	1mg Folterodine Events 20 29 0	Tota 97 123 16	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk M-H, fix	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z =	g vs. Tolt Tolterodine Events 35 50 3 8 8 2, df = 2 (p = 0 3.47 (p = 0.00	0001) erodine 2mg T Total 103 129 18 250 66); I ² = 0% 05)	1mg folteroding Events 20 29 0 49	Tota 97 123 16	7 40.5% 3 58.4% 6 1.0%	t M-H % % % 6.2	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk M-H, fix	ratio red, 95%CI
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z =	g vs. Tolt Tolterodine <u>Events</u> 35 50 3 2, df = 2 (p = 0. 347 (p = 0.00 g vs. Tolt	0001) erodine 2 2mg T Total 103 129 18 250 66); I ² = 0% 05) erodine	1mg olterodine 20 29 0 49 2mg	97 123 16 230	7 40.5% 3 58.4% 6 1.0%	t <u>M-</u> H % % 6.2 % ·	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70]	Risk M-H, fix 0.01 0.1 Tolterodine 1mg	ratio ted, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z =	g vs. Tolt Tolterodine Events 35 50 3 88 2, df = 2 (p = 0 : 3.47 (p = 0.00 g vs. Tolt Tolterodine	0001) erodine 2mg T Total 103 129 18 250 66); I ² = 0% 05) erodine 4mg T	1mg ioiterodine 20 29 0 49 29g 0 49	Tota 9 123 16 230	7 40.59 3 58.49 6 1.09 6 100.09	t <u>M-H</u> % % 6.2 % ·	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 16 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 xatio	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup	g vs. Tolt Tolterodine Events 35 50 3 88 2, df = 2 (p = 0 3.47 (p = 0.00) g vs. Tolt Tolterodine Events	0001) erodine Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T Total	1mg folterodine 20 29 0 49 29g 0 49	Tota 9 12: 16 23 23 e 2mg Total	7 40.59 3 58.49 6 1.09 6 100.09 Weight	t <u>M-H</u> % 6.2 % ·	 fixed, 95%Cl fixed, 1.03, 2.65] fi.64 [1.12, 2.42] f6 [0.35, 112.70] f.69 [1.26, 2.28] fi.69 [1.26, 2.68] fixed, 95%Cl 	Risk M-H, fix 0.01 0.1 Tolterodine 1mg	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003	g vs. Tolt Tolterodine <u>Events</u> 35 50 3 88 2, df = 2 (p = 0, : 3.47 (p = 0.00 g vs. Tolt <u>Tolterodine</u> <u>Events</u> 105	0001) erodine 2 2mg T Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T Total 415	1mg folterodinu Events 20 29 0 49 49 2mg olterodine Events 127	Tota 97 123 18 230 230 230 230 230 230 230 230 230 230	7 40.59 3 58.49 6 1.09 6 100.09 Weight 44.8%	t M-H % % 6.2 % • F M-H, 0.8	 fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 66 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [5, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0. 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3	0001) erodine 2 mg T Total 129 18 250 66); I ² = 0% 05) erodine 4mg T Total 415 17	1mg folteroding Events 20 29 0 49 49 2mg olteroding Events 20 29 0 49	Tota 97 123 18 230 e 2mg Total 407 18	7 40.59 3 58.49 6 1.09 6 100.09 Weight 44.8% 1.0%	t M-H % % 6.2 % • F M-H, 0.8 1.00	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70] 1.69 [1.26, 2.28] Risk ratio fixed, 95%Cl [0.65, 1.01] 6 [0.25, 4.54]	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003	g vs. Tolt Tolterodine <u>Events</u> 35 50 3 88 2, df = 2 (p = 0, : 3.47 (p = 0.00 g vs. Tolt <u>Tolterodine</u> <u>Events</u> 105	0001) erodine 2 2mg T Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T Total 415	1mg folterodinu Events 20 29 0 49 49 2mg olterodine Events 127	Tota 97 123 18 230 230 230 230 230 230 230 230 230 230	7 40.59 3 58.49 6 1.09 6 100.09 Weight 44.8%	t M-H % % 6.2 % • F M-H, 0.8 1.00	 fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 66 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [5, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0. 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3	0001) erodine 2 2mg T Total 103 129 18 250 666); I ² = 0% 05) erodine 4mg T Total 415 17 505	1mg folteroding Events 20 29 0 49 49 2mg olteroding Events 20 29 0 49	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	 H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 166 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.65 [1.26, 2	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI)	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0. 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118	0001) erodine 2 mg T Total 129 18 250 66); I ² = 0% 05) erodine 4mg T Total 415 17	1mg folteroding Events 20 29 0 49 49 2mg olteroding Events 20 29 0 49	Tota 97 123 18 230 e 2mg Total 407 18	7 40.59 3 58.49 6 1.09 6 100.09 Weight 44.8% 1.0%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 6 [0.35, 112.70] 1.69 [1.26, 2.28] Risk ratio fixed, 95%Cl [0.65, 1.01] 6 [0.25, 4.54]	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk	ratio red, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8 Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events	g vs. Tolt Tolterodine Events 35 50 3 8 2, df = 2 (p = 0 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 226	$\begin{array}{c} \text{0001} \\ \text{erodine} \\ \text{rod} \\ $	1mg folteroding Events 20 29 0 49 49 2mg olteroding Events 20 29 0 49	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	 H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 166 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.65 [1.26, 2	Risk M-H, fix	ratio (ed, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI)	g vs. Tolt Tolterodine Events 35 50 3 8 2, df = 2 (p = 0 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 226	$\begin{array}{c} \text{0001} \\ \text{erodine} \\ \text{rod} \\ $	1mg olterodine 29 0 49 2mg olterodine Events 127 3 156	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	 H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 166 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.65 [1.26, 2	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk M-H, fixe	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8 Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events	g vs. Tolt Tolterodine Events 35 50 3 88 2, df = 2 (p = 0, 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0, 226 9, df = 2 (p = 0, 105 3 118	0001) erodine Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T. Total 415 17 505 937 87); l ² = 0%	1mg olterodine 29 0 49 2mg olterodine Events 127 3 156	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	 H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 166 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.65 [1.26, 2	Risk M-H, fix	ratio (ed, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8 Totterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events Heterogeneity: Chi ² = 0.2 Total or verall effect: Z =	g vs. Tolt Tolterodine Events 35 50 3 8 2, df = 2 (p = 0 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0 3.47 (p = 0.00 g vs. Tolt 108 108 108 108 108 108 108 108	0001) erodine Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T. Total 415 17 505 937 87); l ² = 0%	1mg olterodine 29 0 49 2mg olterodine Events 127 3 156	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % % 6.2 % ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	 H, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 166 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.65 [1.26, 2	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk M-H, fixe	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8 Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events Heterogeneity: Chi ² = 0.2 Total events Heterogeneity: Chi ² = 0.2 Test for overall effect: Z =	g vs. Tolt Tolterodine Events 35 50 3 88 2, df = 2 (p = 0. 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0. 3.41 (p = 0.00 9, df = 2 (p = 0. 3.11 (p = 0.00 Placebo	$\begin{array}{c} \text{0001} \\ \text{erodine} \\ \text{rod} \\ $	1mg olterodine 20 29 0 49 2mg olterodine 20 29 0 127 3 156 286	Tota 9; 122 12 230 230 e 2mg Total 407 18 512	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2%	t M-H % % 6.2 % 6.2 % 6.2 % 6.2 % 6.2 % 6.2 % % 6.2 % % % 6.2 % % % % % % % % % % % % % % % % % % %	 4, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 16 [0.35, 112.70] 1.69 [1.26, 2.28] 	Risk M-H, fix	ratio red, 95% CI
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total events Heterogeneity: Chi ² = 0.22 Total (95%CI) Total events Heterogeneity: Chi ² = 0.22 Test for overall effect: Z = 7. Solifenacin vs.	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0, 3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0, -3.47 (p = 0.00 g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0, -3.11 (p = 0.00 Placebo Solifenacin	0001) erodine Total 103 129 18 250 66); l ² = 0% 05) erodine 4mg T. Total 415 17 505 937 87); l ² = 0% 2) Place	1mg olterodinc 20 29 0 49 2mg olterodinc Events 127 3 156 286	Tota 97 123 124 230 230 230 407 18 512 937	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2% 100.0%	t M-H % % 6.2 % - % M-H, 0.8 1.00 0.7 1.07 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.	 4, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 16 [0.35, 112.70] 1.69 [1.26, 2.28] 	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk M-H, fixe 0.1 0.2 0.5 Tolterodine 2mg Risk	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events Heterogeneity: Chi ² = 0.2; Test for overall effect: Z = 7. Solifenacin vs. Study of Subgroup	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0, 0) g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0, 0) 9, df = 2 (p = 0, 0) 3, 118 226 9, df = 2 (p = 0, 0) Solifenacin Events To	0001) erodine 2 mg T Total 129 18 250 66); l ² = 0% 05) erodine 4mg T Total 415 17 505 937 87); l ² = 0% 2) Play paid Event	1mg otterodine Events 20 29 0 49 2mg otterodine Events 126 286 286 286	Tota 97 123 16 230 e 2mg Total 407 18 512 937 937	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2% 100.0% ht M-I	nt M-H % % % 6.2 % - FI, 0.8 1.00 0.7 1.00 0.00 0	 fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 66 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [0.25, 4.54] 7 [0.62, 0.94] 2 [0.68, 0.92] ratio om, 95%Cl 	Risk M-H, fix	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8: Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events Heterogeneity: Chi ² = 0.22 Total (95%CI) Total events Heterogeneity: Chi ² = 0.22 Test for overall effect: Z = 7. Solifenacin vs.	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0, 0) g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0, 0) 9, df = 2 (p = 0, 0) 3, 118 226 9, df = 2 (p = 0, 0) Solifenacin Events To	0001) erodine 2 mg T Total 129 18 250 66); l ² = 0% 05) erodine 4mg T Total 415 17 505 937 87); l ² = 0% 2) Play paid Event	1mg olterodinc 20 29 0 49 2mg olterodinc Events 127 3 156 286	Tota 97 123 16 230 e 2mg Total 407 18 512 937 937	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2% 100.0% ht M-I	nt M-H % % % 6.2 % - FI, 0.8 1.00 0.7 1.00 0.00 0	 4, fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 16 [0.35, 112.70] 1.69 [1.26, 2.28] 	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk M-H, fixe 0.1 0.2 0.5 Tolterodine 2mg Risk	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl
Test for overall effect: Z = 5. Tolterodine 2mg Study of Subgroup Jacquetin 2001 Millardi 1999 Van Kerrebroeck 1998 Total (95%CI) Total events Heterogeneity: Chi ² = 0.8; Test for overall effect: Z = 5. Tolterodine 4mg Study of Subgroup Swift 2003 Van Kerrebroeck 1998 Van Kerrebroeck 2001 Total (95%CI) Total events Heterogeneity: Chi ² = 0.2; Test for overall effect: Z = 7. Solifenacin vs. Study of Subgroup	g vs. Tolt Tolterodine Events 35 50 3 2, df = 2 (p = 0.0) g vs. Tolt Tolterodine Events 105 3 118 9, df = 2 (p = 0.0) Placebo Solifenacin Events To 80 50 50 50 3 118 11	0001) erodine 2 mg T 103 129 18 250 66); l ² = 0% 05) erodine 4mg T Total 415 17 505 937 87); l ² = 0% 937 87); l ² = 0% 2) Plat 505	1mg otterodine Events 20 29 0 49 2mg otterodine Events 126 286 286 286	Tota 9 122 16 230 e 2mg Total 407 18 512 937 Weigl 38.3	7 40.5% 3 58.4% 6 1.0% 6 100.0% Weight 44.8% 1.0% 54.2% 100.0% ht M-I 3%	t M-H % % % 6.2 % % 6.2 % % % % % % % % % % % % % % % % % % %	 fixed, 95%Cl 1.65 [1.03, 2.65] 1.64 [1.12, 2.42] 66 [0.35, 112.70] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [1.26, 2.28] 1.69 [0.25, 4.54] 7 [0.62, 0.94] 2 [0.68, 0.92] ratio om, 95%Cl 	Risk M-H, fix 0.01 0.1 Tolterodine 1mg Risk M-H, fixe 0.1 0.2 0.5 Tolterodine 2mg Risk	ratio ratio 1 10 1 Tolterodine 2n d, 95%Cl

	Solifena	acin	Placel	bo		Risk ratio	Risk ratio
Study of Subgroup	Events	Total	Events	Total	Weight	M-H, random, 95%Cl	M-H, random, 95%Cl
Cardozo 2008	80	505	6	223	38.3%	5.89 [2.61, 13.30]	
Karram 2009	94	372	33	367	61.7%	2.81 [1.94, 4.07]	=
Total (95%CI)		877		590	100.0%	3.73 [1.80, 7.72]	+
Total events	174		39				
Heterogeneity: Tau ² = 0	0.19, Chi ² = 2	2.80, df =	1 (p = 0.0)	9); I ² = 6	4%		
Test for overall effect: Z	z = 3.54 (p =	0.01 0.1 1 10 100 Placebo Solifenacin					

Fig. 5 Forest plot – Risk Ratio (RR) of dry mouth.

1. Oxybutynin vs. Tolterodine

	Oxybuty	nin	Toltero	dine		Risk ratio	Risk ratio
Study of Subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95%Cl	M-H, fixed, 95%Cl
Appell 2011	13	185	12	193	42.5%	1.13 [0.53, 2.41]	
Malone-Lee 2001	11	188	16	190	57.5%		
Total (95%CI)		373		383	100.0%	0.88 [0.52, 1.49]	+
Total events	24		28				
Heterogeneity: Chi ² = 0.8 Test for overall effect: Z			0%				0.01 0.1 1 10 100 Oxybutynin Tolterodine

2. Tolterodine 2mg vs. Placebo

	Tolterodine	Placebo			Risk ratio	Risk ratio			
Study of Subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95%Cl	M-H, fixed, 95%Cl		
Chapple 2004 Jacquetin 2001	7	263 103	5 2	267 51	11.4% 6.1%	1.42 [0.46, 4.42] 0.50 [0.07, 3.41]			
Swift 2003	27	407	14	410	31.9%	1.94 [1.03, 3.65]			
Van Kerrebroeck 2001	35	512	22	507	50.6%	1.58 [0.94, 2.65]	-		
Total (95%CI)		1285		1235	100.0%	1.61 [1.11, 2.32]	•		
Total events	71		43						
Heterogeneity: $Chi^2 = 1.83$, Test for overall effect: Z = 2	0.01 0.1 1 10 10 Placebo Tolterodine 2mg								
	T lacebo Tollerodine zing								

3. Tolterodine 4mg vs. Placebo

Tolterodine 4	Place	00		Risk ratio	Risk ratio			
Events	Total	Events	Total	Weight	M-H, fixed, 95%Cl	M-H, fixed, 95%Cl		
9	569	2	258	4.5%	2.04 [0.44, 9.38]			
27	415	14	410	23.2%	1.91 [1.01, 3.58]			
30	505	22	507	36.2%	1.37 [0.80, 2.34]			
17	291	12	285	20.0%	1.39 [0.67, 2.85]			
13	214	10	222	16.2%	1.35 [0.60, 3.01]	-		
	1994		1682	100.0%	1.52 [1.11, 2.09]	•		
96		60						
Heterogeneity: $Chi^2 = 0.93$, df = 4 (p = 0.92); $i^2 = 0\%$								
60 (p = 0.009)						0.01 0.1 1 10 Placebo Tolterodine 4mg		
	Events 9 27 30 17 13 96	$9 569 27 415 30 505 17 291 13 214 1994 96 df = 4 (p = 0.92); l^2 = 0\%$	Events Total Events 9 569 2 27 415 14 30 505 22 17 291 12 13 214 10 IP94 96 60 df = 4 (p = 0.92); l ² = 0% 50%	Events Total Events Total 9 569 2 258 27 415 14 410 30 505 22 507 17 291 12 285 13 214 10 222 1994 1682 96 60 60 aff = 4 (p = 0.92); l ² = 0% 50% 50%	Events Total Events Total Weight 9 569 2 258 4.5% 27 415 14 410 23.2% 30 505 22 507 36.2% 17 291 12 285 20.0% 13 214 10 222 16.2% 1994 1682 100.0% 96 60 60 df = 4 (p = 0.92); l ² = 0% 10 225 100.0% 10	Events Total Events Total Weight M-H, fixed, 95%CI 9 569 2 258 4.5% 2.04 [0.44, 9.38] 27 415 14 410 23.2% 1.91 [1.01, 3.58] 30 505 22 507 36.2% 1.37 [0.80, 2.34] 17 291 12 285 2.0.0% 1.35 [0.60, 3.01] 13 214 10 222 16.2% 1.35 [0.60, 3.01] 994 1682 100.0% 1.52 [1.11, 2.09] 96 60 40 40 40 40		

4. Solifenacin vs. Placebo

	Solifena	Solifenacin				Risk ratio	Risk ratio
Study of Subgroup	Events	Total	Events	Total	Weight	M-H, random, 95%Cl	M-H, random, 95%Cl
Cardozo 2008	35	505	2	223	41.3%	7.73 [1.87, 31.85]	
Karram 2009	55	372	34	367	58.7%	1.60 [1.07, 2.39]	
Total (95%CI)		877		590	100.0%	3.06 [0.62, 15.17]	
Total events	90		36				20. ISBN 01. ISBN 01.
Heterogeneity: Tau ² = 1	.09, Chi ² = 4.88	0.05 0.2 1 5 20					
Test for overall effect: Z	= 1.37 (p = 0.1	Placebo Solifenacin					

Fig. 6 Forest plot – Risk Ratio (RR) of constipation.

This systematic review showed that there is no significant difference in the mean decrease in UUI episodes per day between oxybutynin and tolterodine. Although there was a trend of a higher reduction in UUI episodes with the use of oxybutynin, the difference was not statistically significant. It was not possible to perform comparisons between oxybutynin versus solifenacin, oxybutynin versus darifenacin, tolterodine versus solifenacin, tolterodine versus darifenacin, and solifenacin versus darifenacin due to limitations in data reporting (that is, studies without a measure of variation) and the lack of similarity in measures.

Regarding the decrease in the number of micturitions per day, which was another important primary outcome, the results favored tolterodine in its various dosages and solifenacin when compared with placebo. The comparison between oxybutynin and tolterodine showed no significant difference in treatment efficacy across any of the outcomes; the same was found for the comparisons of tolterodine in its various dosages. As result of the relative paucity of data that qualified for inclusion in the meta-analysis – and that directly compared pharmacological agents –, it is impossible to report definitively whether any specific agent is superior to another in terms of efficacy.

Antimuscarinic agents may be associated with adverse effects. The human bladder tissue contains M2 and M3 muscarinic receptors. The M3 subtype has been identified as the primary mediator of detrusor contraction in response to cholinergic activation.^{52,53} Different subtypes of muscarinic receptors are widely distributed in the body. M1 receptors in the brain and salivary glands are involved in cognition and in the

production of mucous saliva;^{54,55} M2 receptors in the cardiovascular system play a role in mediating heart rate and cardiac output;⁵⁶ and M5 receptors in the eye are involved in ciliary muscle contraction.^{57–59} As a result, antimuscarinic agents, which bind to some or all of these receptors, are effective in treating OAB symptoms, but they may also be associated with adverse effects such as dry mouth, constipation, cognitive impairment, tachycardia, and blurred vision.⁵⁷ This systematic review showed that oxybutynin was associated with significantly higher rates of dry mouth when compared with tolterodine. When compared with placebo, tolterodine, in its various dosages, and solifenacin were associated with significantly higher rates of dry mouth. The group of patients that used tolterodine 4 mg presented lower risk when compared with the group treated with tolterodine 2 mg. This can be explained by the fact that tolterodine 4 mg is an extended-release (ER) presentation. Compared with the immediate-release drug, tolterodine ER releases the drug in a steady and constant manner, thus lowering peaks. This translates into more constant serum concentrations and theoretically improves patient tolerability.⁶⁰ Concerning constipation, differences were not found between oxybutynin and tolterodine. Significantly high rates of constipation were found in patients treated with tolterodine 2 mg and 4 mg when compared with placebo.

The current data demonstrate that a substantial proportion of patients discontinue anticholinergic drugs, with 75–90% of patients discontinuing therapy within 12 months. Among those studies that provided information about the reasons for the discontinuation of the therapy, the most frequently cited reasons were that the medication did not work as expected, and that the medication's side effects were not desirable.⁷ We did not find a statistical difference associated with withdrawals resulting from drug-related adverse effects.

New drugs for the treatment of OAB are emerging, such as imidafenacin and tarafenacin, but they are not available in Brazil yet. Mirabegron, a β 3-adrenoreceptor agonist, has just recently been released into the Brazilian market with some promising results, especially when associated with regular antimuscarinic drugs.^{61,62}

The quality of the available evidence that supports these results is moderate. The main limitation of the available evidence concerning OAB treatment is that although there is a large amount of RCTs, it is not possible to combine all of the data in a meta-analysis due to their heterogeneity. If the goal of a meta-analysis is to estimate the MD between two treatments, then the means, sample sizes, and a measure of variation (standard deviation, standard error, or a confidence interval) are required. Thus, many of the available RCTs on OAB treatment did not contribute to the meta-analysis, and were excluded from our study. Unfortunately, we discovered a lack of high-quality evidence pertaining to the available drugs and dosages for the treatment of OAB in Brazil that can inform clinical decision making for patients and care providers.

In summary, the results of this meta-analysis suggest that there is a moderate to high quality of evidence supporting the benefits of using anticholinergic drugs in alleviating OAB symptoms when compared with placebo. Despite its lower improvement in primary and secondary outcomes when compared with anticholinergics, the use of placebo contributed to many of the improvements in OAB symptoms. It is still not clear if any one specific drug available in Brazil has any advantage over the others. The use of these drugs is associated with adverse effects (mainly dry mouth and constipation), although the use of these agents is not related to an increase in the number of withdrawals.

References

- Haylen BT, de Ridder D, Freeman RM, et al; International Urogynecological Association; International Continence Society. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1): 4–20
- 2 Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50(6):1306–1314, discussion 1314–1315
- 3 Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20(6):327–336
- 4 Townsend MK, Minassian VA, Okereke OI, Resnick NM, Grodstein F. Urinary incontinence and prevalence of high depressive symptoms in older black versus white women. Int Urogynecol J Pelvic Floor Dysfunct 2014;25(6):823–829
- 5 Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. Int J Clin Pract 2011;65(5):567–585
- 6 Moroni RM, Magnani PS, Haddad JM, Castro RdeA, Brito LG. Conservative treatment of stress urinary incontinence: a systematic review with meta-analysis of randomized controlled trials. Rev Bras Ginecol Obstet 2016;38(2):97–111
- 7 Gormley EA, Lightner DJ, Burgio KL, et al; American Urological Association; Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol 2012;188(6, Suppl)2455–2463
- 8 Thiagamoorthy G, Cardozo L, Robinson D. Current and future pharmacotherapy for treating overactive bladder. Expert Opin Pharmacother 2016;17(10):1317–1325
- 9 Brown ET, Martin L, Dmochowski RR. New evidence in the treatment of overactive bladder. Curr Opin Obstet Gynecol 2015;27(5):366–372
- 10 Lawrence M, Guay DR, Benson SR, Anderson MJ. Immediaterelease oxybutynin versus tolterodine in detrusor overactivity: a population analysis. Pharmacotherapy 2000;20(4): 470–475
- 11 Juliato CR, Santos Júnior LC, Haddad JM, Castro RA, Lima M, Castro EB. Mesh surgery for anterior vaginal wall prolapse: a metaanalysis. Rev Bras Ginecol Obstet 2016;38(7):356–364
- 12 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535
- 13 Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Colaboration; 2011
- 14 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–560
- 15 Appell RA, Sand P, Dmochowski R, et al; Overactive Bladder: Judging Effective Control and Treatment Study Group. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive

bladder: results of the OBJECT Study. Mayo Clin Proc 2001;76(4): 358–363

- 16 Drutz HP, Appell RA, Gleason D, Klimberg I, Radomski S. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 1999;10(5):283–289
- 17 Lee JG, Hong JY, Choo MS, et al. Tolterodine: as effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. Int J Urol 2002;9(5):247–252
- 18 Malone-Lee J, Shaffu B, Anand C, Powell C. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. J Urol 2001;165(5):1452–1456
- 19 Chapple CR, Rechberger T, Al-Shukri S, et al; YM-905 Study Group. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004;93(3): 303–310
- 20 Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. Eur J Obstet Gynecol Reprod Biol 2001;98(1):97–102
- 21 Khullar V, Hill S, Laval KU, Schiøtz HA, Jonas U, Versi E. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. Urology 2004;64(2):269–274, discussion 274–275
- 22 Millard R, Tuttle J, Moore K, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol 1999;161(5):1551–1555
- 23 Swift S, Garely A, Dimpfl T, Payne C; Tolterodine Study Group. A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 2003;14(1):50–54, discussion 54–55
- 24 Van Kerrebroeck PE, Amarenco G, Thüroff JW, et al. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. Neurourol Urodyn 1998;17(5):499–512
- 25 Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A; Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001;57(3):414–421
- 26 Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. J Am Geriatr Soc 2002;50(5):799–807
- 27 Cardozo L, Hessdörfer E, Milani R, et al; SUNRISE Study Group. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int 2008;102(9): 1120–1127
- 28 Karram MM, Toglia MR, Serels SR, Andoh M, Fakhoury A, Forero-Schwanhaeuser S. Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial. Urology 2009;73(1):14–18
- 29 But I, Goldstajn MS, Oresković S. Comparison of two selective muscarinic receptor antagonists (solifenacin and darifenacin) in women with overactive bladder-the SOLIDAR study. Coll Antropol 2012;36(4):1347–1353
- 30 Armstrong RB, Dmochowski RR, Sand PK, Macdiarmid S. Safety and tolerability of extended-release oxybutynin once daily in urinary incontinence: combined results from two phase 4 controlled clinical trials. Int Urol Nephrol 2007;39(4): 1069–1077
- 31 Barkin J, Corcos J, Radomski S, et al; UROMAX Study Group. A randomized, double-blind, parallel-group comparison of controlled- and immediate-release oxybutynin chloride in urge urinary incontinence. Clin Ther 2004;26(7):1026–1036

- 32 Leung HY, Yip SK, Cheon C, et al. A randomized controlled trial of tolterodine and oxybutynin on tolerability and clinical efficacy for treating Chinese women with an overactive bladder. BJU Int 2002; 90(4):375–380
- 33 Jonas U, Höfner K, Madersbacher H, Holmdahl TH; The International Study Group. Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. World J Urol 1997;15(2):144–151
- 34 Wagg A, Dale M, Tretter R, Stow B, Compion G. Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. Eur Urol 2013;64(1):74–81
- 35 Abrams P, Kelleher C, Huels J, Quebe-Fehling E, Omar MA, Steel M. Clinical relevance of health-related quality of life outcomes with darifenacin. BJU Int 2008;102(2):208–213
- 36 Diokno AC, Appell RA, Sand PK, et al; OPERA Study Group. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc 2003;78(6):687–695
- 37 Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Efficacy of oral extended-release oxybutynin in cognitively impaired older nursing home residents with urge urinary incontinence: a randomized placebo-controlled trial. J Am Med Dir Assoc 2011;12(9):639–647
- 38 Sand PK, Miklos J, Ritter H, Appell R. A comparison of extendedrelease oxybutynin and tolterodine for treatment of overactive bladder in women. Int Urogynecol J Pelvic Floor Dysfunct 2004; 15(4):243–248
- 39 Versi E, Appell R, Mobley D, Patton W, Saltzstein D; The Ditropan XL Study Group. Dry mouth with conventional and controlledrelease oxybutynin in urinary incontinence. Obstet Gynecol 2000; 95(5):718–721
- 40 Yoo DS, Han JY, Lee KS, Choo MS. Prescription pattern of oxybutynin ER in patients with overactive bladder in real life practice: a multicentre, open-label, prospective observational study. Int J Clin Pract 2012;66(2):132–138
- 41 Chapple CR, Fianu-Jonsson A, Indig M, et al; STAR study group. Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg. Eur Urol 2007;52(4): 1195–1203
- 42 Dmochowski R, Abrams P, Marschall-Kehrel D, Wang JT, Guan Z. Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. Eur Urol 2007;51(4): 1054–1064, discussion 1064
- 43 Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z; 037 STUDY GROUP. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. Urology 2006;67(4):731–736, discussion 736
- 44 Rentzhog L, Stanton SL, Cardozo L, Nelson E, Fall M, Abrams P. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. Br J Urol 1998;81(1):42–48
- 45 Vardy MD, Mitcheson HD, Samuels TA, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a doubleblind, placebo-controlled trial. Int J Clin Pract 2009;63(12): 1702–1714
- 46 Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. Eur Urol 2004;45(4):420–429, discussion 429
- 47 Hill S, Khullar V, Wyndaele JJ, Lheritier K; Darifenacin Study Group. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive

bladder: results of a fixed dose study. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(3):239–247

- 48 Khullar V, Foote J, Seifu Y, Egermark M. Time-to-effect with darifenacin in overactive bladder: a pooled analysis. Int Urogynecol J Pelvic Floor Dysfunct 2011;22(12):1573–1580
- 49 Steers W, Corcos J, Foote J, Kralidis G. An investigation of dose titration with darifenacin, an M3-selective receptor antagonist. BJU Int 2005;95(4):580–586
- 50 Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. World J Urol 2005;23(4):248–252
- 51 Zinner N, Susset J, Gittelman M, Arguinzoniz M, Rekeda L, Haab F. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB. Int J Clin Pract 2006;60(1):119–126
- 52 Fetscher C, Fleichman M, Schmidt M, Krege S, Michel MC. M(3) muscarinic receptors mediate contraction of human urinary bladder. Br J Pharmacol 2002;136(5):641–643
- 53 Chess-Williams R. Muscarinic receptors of the urinary bladder: detrusor, urothelial and prejunctional. Auton Autacoid Pharmacol 2002;22(3):133–145
- 54 Fisher A, Michaelson DM, Brandeis R, Haring R, Chapman S, Pittel Z. M1 muscarinic agonists as potential disease-modifying agents in Alzheimer's disease. Rationale and perspectives. Ann N Y Acad Sci 2000;920:315–320

- 55 Culp DJ, Luo W, Richardson LA, Watson GE, Latchney LR. Both M1 and M3 receptors regulate exocrine secretion by mucous acini. Am J Physiol 1996;271(6 Pt 1):C1963–C1972
- 56 Bymaster FP, Carter PA, Zhang L, et al. Investigations into the physiological role of muscarinic M2 and M4 muscarinic and M4 receptor subtypes using receptor knockout mice. Life Sci 2001; 68(22–23):2473–2479
- 57 Andersson KE. Potential benefits of muscarinic M3 receptor sensitivity. Eur Urol Suppl 2002;1(4):23–28
- 58 Gil DW, Krauss HA, Bogardus AM, WoldeMussie E. Muscarinic receptor subtypes in human iris-ciliary body measured by immunoprecipitation. Invest Ophthalmol Vis Sci 1997;38(7): 1434–1442
- 59 Choppin A, Eglen RM. Pharmacological characterization of muscarinic receptors in dog isolated ciliary and urinary bladder smooth muscle. Br J Pharmacol 2001;132(4):835–842
- 60 Chung DE, Te AE. Tolterodine extended-release for overactive bladder. Expert Opin Pharmacother 2009;10(13):2181–2194
- 61 Karmarkar R, Khullar V. Emerging drugs for overactive bladder. Expert Opin Emerg Drugs 2015;20(4):613–624
- 62 Drake MJ, Chapple C, Esen AA, et al; BESIDE study investigators. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised doubleblind multicentre phase 3b study (BESIDE). Eur Urol 2016;70(1): 136–145