

Review

Adverse events and treatment discontinuations of antimuscarinics for the treatment of overactive bladder in older adults: A systematic review and meta-analysis



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ABSTRACT

Introduction: Antimuscarinics should be used with caution in older adults with overactive bladder (OAB) due to anticholinergic adverse events (AEs). Systematic reviews and meta-analyses (SRMAs) have analyzed safety-related outcomes but have not specified risk in the elderly, the population at highest risk for AEs. The aim of this review is to explore and evaluate AEs and treatment discontinuations in adults 65 or older taking antimuscarinics for OAB.

Methods: Keywords were searched in MEDLINE, EMBASE, SCOPUS, and Cochrane Central Register for Controlled Trials. Randomized controlled trials (RCTs) along with sub-analyses and pooled analyses that compared antimuscarinics to placebo or another antimuscarinic were performed in February 2015. Studies assessing AEs or treatment discontinuations in a population of adults 65 or older were included. The Jadad Criteria and McHarm Tool were used to assess the quality of the trials.

Results: A total of 16 studies met the inclusion criteria. Eighty AEs and 27 reasons for treatment discontinuation were described in the included studies and further explored. Anticholinergic AEs were more common in antimuscarinics compared to placebo. Incidence of dizziness, dyspepsia, and urinary retention with fesoterodine, headache with darifenacin, and urinary tract infections with solifenacin were significantly higher compared to placebo. Treatment discontinuation due to AEs and dry mouth were higher in the antimuscarinics when compared to placebo in older adults.

Conclusions: Treatment for overactive bladder using antimuscarinics in adults aged 65 or older resulted in significant increases in risk for several AEs compared to placebo including anticholinergic and non-anticholinergic AEs.

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Abbreviations: AE, adverse event; OAB, overactive bladder; ER, extended release; IR, immediate release; NNH, number needed to harm; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial; SRMA, systematic review and meta-analysis.

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1. Introduction

Overactive bladder (OAB) is a condition that can negatively impact quality of life in older adults. The prevalence of OAB in epidemiological studies increases with age (Gomelsky, 2009; Milsom, Stewart, & Thuroff, 2000; Tubaro, 2004). Signs and symptoms of OAB such as urinary frequency, urgency, nocturia, and incontinence affect 25% of adults aged 60 or older (Scheife and Takeda, 2005; Wagg, Verdejo, & Molander, 2010). There are several oral and non-oral treatment options for patients with OAB which include antimuscarinics (oxybutynin, tolterodine, trospium, darifenacin, solifenacin, fesoterodine) and a beta-3 agonist (mirabegron) (Kraus, Bavendam, Brake, & Griebing, 2010; Macdiarmid, 2008). These medications are all viable options for the elderly. However, providers should be cautioned in using these medications due to adverse drug events (AEs) including dry mouth, blurry vision, and constipation in antimuscarinics as well as hypertension in beta-3 agonists (Sternberg et al., 2011). These AEs may contribute to non-adherence or discontinuation of the prescribed medication, which can lead to a return of OAB symptoms and a reduction in quality of life (Benner et al., 2010).

Several systematic reviews and meta-analyses have evaluated the use of medications in the treatment of OAB (Chapple et al., 2008; Chapple et al., 2015; Cui et al., 2014; Herbison, Hay-Smith, Ellis, & Moore, 2003; Huang, Zong, Zhou, & Zhang, 2015; Kessler et al., 2011; Luo, Liu, Han, Wei, & Shen, 2012; Madhuvrata, Cody, Ellis, Herbison, & Hay-Smith, 2012; Novara et al., 2008; Paquette, Gou, & Tannenbaum, 2011; Reynolds et al., 2015; Roxburgh, Cook, & Dublin, 2007; Wu et al., 2014; Wyndaele, Schneider, MacDiarmid, Scholfield, & Arumi, 2014). These reviews compared OAB medications to placebo and/or to other OAB medications, either directly or indirectly, using prospective randomized, non-randomized, and retrospective observational trials. Current systematic reviews have only described the individual studies with regards to the use of OAB medications in the elderly. No systematic review has used a meta-analytical technique to broadly explore safety outcomes in the elderly. The goal of this systematic review is to perform exploratory analyses of AEs and treatment discontinuations in oral and non-oral medications used to treat OAB in studies with patients aged 65 or older.

2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used for reporting this review. Institutional review board approval was not required for this review.

2.1. Literature search

Studies involving patients aged 65 or older with OAB or urge urinary incontinence who received either an antimuscarinic (oxybutynin, tolterodine, trospium, solifenacin, darifenacin,

fesoterodine) or a beta-3 agonist (mirabegron) were included. Randomized-controlled trials (RCTs) of one agent versus another agent or placebo (including studies with \geq two treatment arms), sub-analysis of a parent RCT, or pooled-results of two or more parent RCTs were included (Paquette et al., 2011). A parent study was defined as the original publication(s) in which a sub-analysis or pooled analysis was derived. Studies less than 4 weeks in duration, those evaluating antimuscarinics in combination with alpha-blockers for lower urinary tract symptoms, populations in which neurogenic bladder or conditions other than OAB were studied, and any language other than English were excluded by title or abstract.

The following electronic databases were searched: MEDLINE (PubMed interface), EMBASE, SCOPUS, and Cochrane Central Register for Controlled Trials. The basic search strategy used derivations of the following strategy (*aged* AND [*antimuscarinic agents* OR *beta-3 agonists* OR *oxybutynin* OR *tolterodine* OR *trospium* OR *darifenacin* OR *solifenacin* OR *fesoterodine* OR *mirabegron*]). MeSH and Emtree terms were used for MEDLINE and EMBASE, respectively, and the full search strategy is described in Appendix A. Duplicates were removed and non-relevant studies were removed based on title and abstract (SMV); relevant full-text articles were identified. Two of the four authors (SMV, PMS, CDK, BFT) independently screened each full-text article using the pre-established criteria after a team training exercise. Studies were excluded for the following reasons: 1) did not report original data, 2) did not include an overactive bladder medication, 3) no comparator arm, 4) used a non-standard dose, route, and frequency (e.g., antimuscarinic combination therapy), 5) conducted in subjects without overactive bladder, 6) assessed only quality of life outcomes, 7) trial was less than 4 weeks in duration, 8) was not a randomized, controlled trial, 9) studies with outcomes that did not differentiate by age, 10) did not report safety outcomes, and 11) used a duplicate population. Any conflicts were resolved by consensus of the two authors.

2.2. Data extraction

As this was an exploratory analysis, all AEs and treatment discontinuations reported in any included study were identified and collected by two authors (SMV, CDK) after a team training exercise. Any conflicts were resolved by consensus of the two authors. Once confirmed, a data extraction sheet was created. Study characteristics were extracted which included the last name of the first author, year published, journal, study type, study duration, overactive bladder medication and comparator, number of subjects, age cut points, OAB inclusion criteria, percent female, location of study, AEs, and treatment discontinuations as previously defined. Authors were contacted by email when all necessary data was not available in the manuscript; no additional data was incorporated from authors contacted by email. Two of four authors (SMV, PMS, CDK, BFT) independently extracted each

study using the pre-established criteria after an additional training exercise. Any conflicts were resolved by consensus of the two authors. As AEs and treatment discontinuations were reported as dichotomous variables within the study, the timing of such events could not be assessed.

2.3. Quality assessment

The Jadad Criteria was used to appraise the risk of bias within the included studies (Jadad et al., 1996). For pooled analyses and sub-analyses studies, the parent studies were scored when available. The McMaster tool for assessing quality of harms assessment and reporting in study reports (McHarm Tool) was used to examine the consistency in reporting of AEs (Santaguida and Raina, 2008). Each study was extracted independently by two of four authors (SMV, PMS, CDK, BFT) using the pre-established criteria to create the Jadad Criteria Score and complete the McHarm Tool after an additional training exercise. A study with a Jadad Criteria score of 4 or greater was considered high quality. Any conflicts were resolved by consensus of the two authors.

2.4. Data synthesis

The studies were synthesized using the above criteria and included the risk of bias and quality. These studies were assessed for heterogeneity using the I^2 statistic; as a conservative estimate, random-effects models were used for all analyses. If the I^2 statistic is <25%, then the authors reported no heterogeneity. If the I^2 statistic is $\geq 25\%$ then it will be denoted in the tables and the value reported out in the manuscript. Given that only four studies with four separate medications reported outcomes by differing doses, doses within each medication category were collapsed (Foote, Glavind, Kralidis, & Wyndaele, 2005; Kraus, Ruiz-Cerda, Martire, Wang, & Wagg, 2010; Malone-Lee, Walsh, & Maugourd, 2001; Wagg, Wyndaele, & Sieber, 2006). Medications were compared to placebo and any active comparator in separate analyses. Individual AEs and treatment discontinuations were described in rate ratios in an overall analysis and an analysis stratified by specific medication. For statistically significant AEs and treatment discontinuations, number needed to harm (NNH) were also calculated.

The lack of standardization in the reporting of AEs across studies was accounted for by combining similar AEs extracted from an individual study based on symptomatology to improve power in secondary analyses similar to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (2009; Kessler et al., 2011).

3. Results

The search retrieved a total of 26,166 studies, of which 228 full-text studies were reviewed for inclusion in the systematic review (Fig. 1). The most common reasons for exclusion were outcomes not being differentiated by age or a lack of a comparator arm. Seventeen studies (7 RCTs, 3 sub-analyses of RCTs, and 7 pooled analyses of RCTs) made the inclusion criteria in which AEs were reported in the 65 or older population. Safety endpoints could not be extracted from one pooled analysis of RCTs (Griebing, Kraus, Richter, Glasser, & Carlsson, 2009) as AEs were reported graphically; therefore, 16 studies were used in these analyses (Chapple, DuBeau, Ebinger, Rebeda, & Viegas, 2007; Dubeau et al., 2014; DuBeau, Morrow, Kraus, Creanga, & Bavendam, 2012; Foote et al., 2005; Herschorn et al., 2011; Kraus, Ruiz-Cerda et al., 2010; Lackner, Wyman, McCarthy, Monigold, & Davey, 2008; Malone-Lee et al., 2001; Minassian et al., 2007; Sand et al., 2011; Sand, Miklos, Ritter, & Appell, 2004; Szonyi, Collas, Ding, & Malone-Lee, 1995; Wagg et al., 2006; Wagg et al., 2013; Wagg et al., 2014; Zinner, Mattiasson, & Stanton, 2002).

Study characteristics and Jadad Criteria Score (Table 1) and McHarm Tool (Appendix B) were calculated from the included studies. The parent RCTs of the sub-analyses and pooled analyses, when available, were extracted to assess study duration, OAB inclusion criteria, location of study, Jadad Criteria Score (Table 1), and McHarm Tool (Appendix B) (Appell et al., 2001; Cardozo et al., 2004; Chapple et al., 2004; Chapple et al., 2005; Chapple, Rechberger et al., 2004; Chapple, Van Kerrebroeck et al., 2007; Dmochowski et al., 2008; Herschorn et al., 2010; Herschorn et al., 2013; Herschorn, Swift et al., 2010; Kaplan et al., 2011; Khullar et al., 2013; Nitti et al., 2007; Nitti et al., 2013; Staskin, Sand, Zinner, & Dmochowski, 2007; Van Kerrebroeck, Kreder, Jonas, Zinner, & Wein, 2001). The parent studies (3 studies) from one pooled analysis were unable to be assessed by the authors as the results were unpublished (Foote et al., 2005).

3.1. Study quality

Five of the 7 RCTs studies and 10 of the 16 parent studies evaluated were of high quality (Table 1). The quality of AEs reporting in the RCTs and the parent studies reporting was assessed using the McHarm Tool (Appendix B). Specifically, question 11 of the McHarm Tool asked “Did the authors specify if the harms reported encompass ALL the events collected, or a selected SAMPLE?” The authors answered either no or unclear to this question in all evaluated studies. Of the 23 studies that were evaluated (7 RCTs and 16 parent studies) for reporting all events, 14 studies defined their parameters for reporting specific AEs (i.e., only if $\geq 2\%$ in any group). It was unclear what proportion of AEs were reported in the remaining 9 studies.

3.2. Overactive bladder medications

The 16 included studies included analyses on oxybutynin immediate-release (IR) (Herschorn et al., 2011; Minassian et al., 2007; Szonyi et al., 1995), oxybutynin extended-release (ER) (Lackner et al., 2008; Minassian et al., 2007; Sand et al., 2004; Sand et al., 2011), tolterodine IR (Malone-Lee et al., 2001; Sand et al., 2004), tolterodine ER (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002), trospium ER (Sand et al., 2011), solifenacin (Herschorn et al., 2011; Wagg et al., 2006), darifenacin (Chapple et al., 2007; Foote et al., 2005), fesoterodine (DuBeau et al., 2012; Dubeau et al., 2014; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013), and mirabegron (Wagg et al., 2014). Thirteen studies were placebo controlled. Two studies compared solifenacin and oxybutynin ER to oxybutynin IR (Herschorn et al., 2011; Minassian et al., 2007), one study compared oxybutynin ER to tolterodine IR (Sand et al., 2004), and one study compared fesoterodine to tolterodine ER (DuBeau et al., 2012). One study compared tolterodine ER, fesoterodine, mirabegron, and placebo (Wagg et al., 2014). Using this study, the authors compared tolterodine ER to fesoterodine, fesoterodine and tolterodine ER to the same cohort of placebo. Additionally, this was the only study to assess mirabegron (compared to placebo and compared to tolterodine ER) (Wagg et al., 2014). Due to the differing mechanism of action and AEs relative to antimuscarinics, mirabegron was not incorporated into the meta-analysis as the differences in AEs and treatment discontinuations were already reported.

In these analyses, 4188 subjects (3952 subjects in placebo-controlled trials) aged 65 or older were randomized to antimuscarinic medications for 4 to 12 weeks and 3026 were randomized to placebo. The number of subjects randomized to antimuscarinic treatment was oxybutynin IR (n=88), oxybutynin ER (n=115), tolterodine IR (n=194), tolterodine ER (n=992), trospium ER (n=85), solifenacin (n=650), darifenacin (n=650), fesoterodine (n=1591).

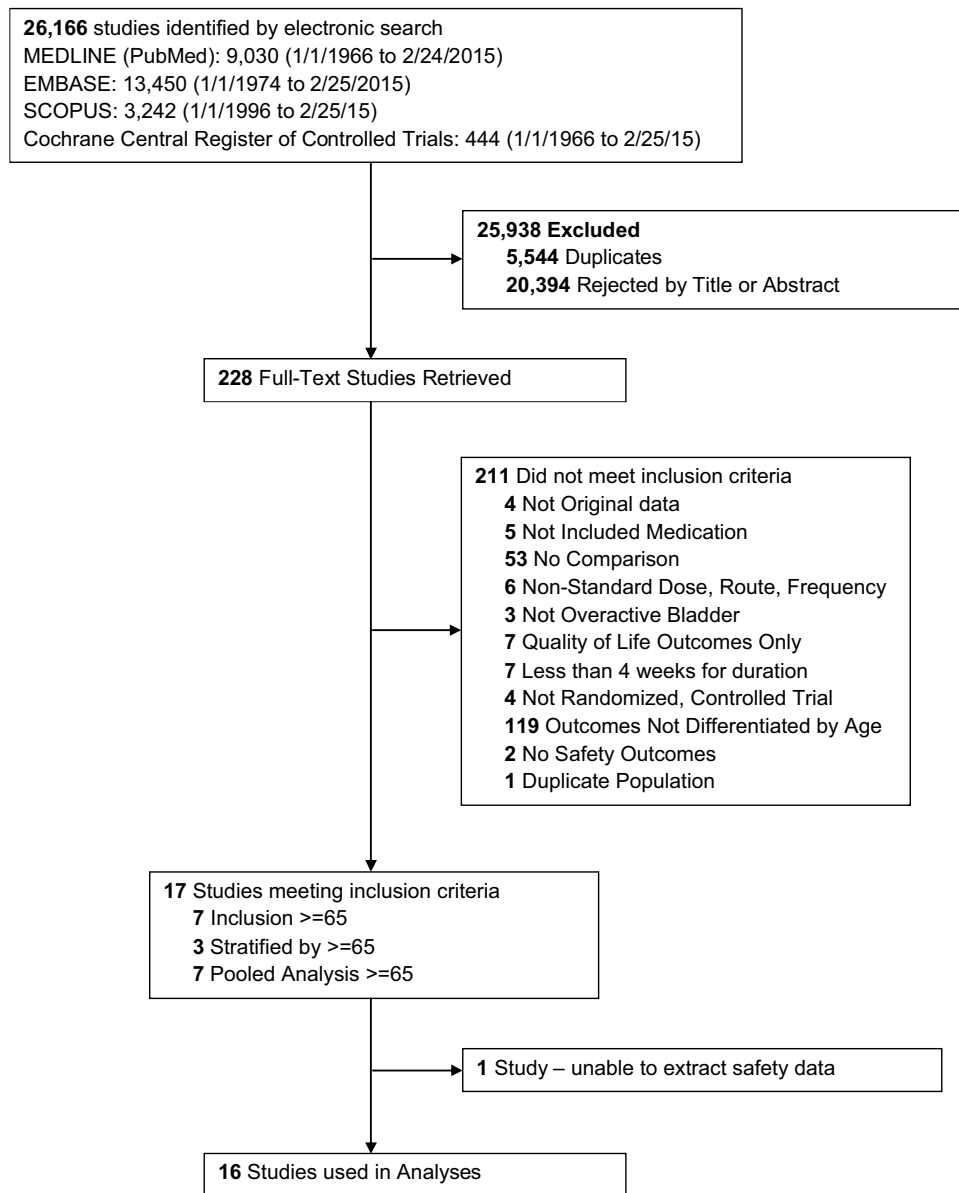


Fig. 1. Determination of studies.

From the overall 16 studies included for analyses, there were 80 distinct reports of AEs and 27 distinct reports of treatment discontinuation. Many AEs reported severity of disease (i.e., mild to moderate urinary tract infection and severe urinary tract infection) without defining severity levels. As standard nomenclature was not routinely used, many AEs appeared to be very similar (i.e., vision disorder and blurry vision) which likely increased the number that were explored.

Outcomes for all AEs and treatment discontinuations for antimuscarinics versus placebo (Appendices C and E) and antimuscarinic versus antimuscarinic (Appendices D and F) are described regardless of being statistically significant. There were 14 statistically significant AEs (Table 2), two statistically significant treatment discontinuations (Table 4), and one statistically significant combined AEs (Appendix G) in the antimuscarinic versus placebo analyses. There were four statistically significant AEs (Table 3), one statistically significant treatment discontinuation (Table 5), and no statistically significant combined AEs (Appendix H) in the antimuscarinic versus antimuscarinic analyses.

3.3. Adverse events

3.3.1. Antimuscarinics versus placebo

Statistically significant rates for AEs and NNH for antimuscarinics compared to placebo are described in Table 2. The proportion of subjects with any AEs was 53.8% in those receiving an antimuscarinic compared to 41.7% in subjects receiving placebo. There was also an increase in treatment-related AEs which was more narrowly defined as adverse outcomes likely related to the study drug in studies assessing darifenacin and trospium ER.

Ten percent of subjects receiving an antimuscarinic experienced constipation compared to 3.3% receiving placebo [$I^2 = 46.1\%$]. Darifenacin (18.0%), solifenacin (15.4%), fesoterodine (8.5%), and tolterodine (4.8%) had significantly higher rates of constipation among subjects receiving antimuscarinics compared to placebo. Within the same studies, 25% of subjects receiving an antimuscarinic experienced dry mouth compared to 5.3% of subjects receiving placebo [$I^2 = 73.9\%$]. There was a significantly higher rate of dry mouth with no heterogeneity among subjects in tolterodine ER

Table 1
Characteristics of Included and Parent Studies.

First Author and Year of Publication	Journal	Study Type	Duration (Weeks)	Drug 1 (n)	Drug 2 (n)	Placebo-Controlled (n)	Age	Duration of OAB Symptoms	Frequency (Inclusion)	Urgency (Inclusion)	Percent Females% (n)	Location	Country	JADAD Criteria Score
Szonyi (1995)(Szonyi et al., 1995)	<i>Age Ageing</i>	RCT	6	Oxybutynin IR (28)	-	Yes (26)	≥70	Not noted	"Frequency"	"Urgency"	93.3 (56)	Ambulatory	England	4
Malone-Lee (2001) (Malone-Lee et al., 2001)	<i>J Am Geriatr Soc</i>	RCT	4	Tolterodine IR (134)	-	Yes (43)	≥65	Not noted	≥8/24 h	"Urgency"	65.0 (115)	Ambulatory	Multinational	3
Zinner (2002)(Zinner et al., 2002)	<i>J Am Geriatr Soc</i>	SA of RCT	-	Tolterodine ER (214)	-	Yes (223)	≥65	-	-	-	74.4 (325)	-	-	-
Van Kerrebroeck (2001) (Van Kerrebroeck et al., 2001)	<i>Urology</i>	-	12	-	-	-	≥6 months	≥8/24 h	≥5 UUI episodes/week	-	-	Not Noted	Multinational	5
Sand (2004)(Sand et al., 2004)	<i>Int Urogynecol J</i>	SA of RCT	-	Oxybutynin ER (51)	Tolterodine IR (60)	No	≥65	-	-	-	100 (111)	-	-	-
Appell (2001)(Appell et al., 2001)	<i>Mayo Clin Proc</i>	-	12	-	-	-	Not noted	≥10/24 h	7-50 UUI episodes/week	-	-	Not Noted	USA	4
Foote (2005)*(Foote et al., 2005)	<i>Eur Urol</i>	Pooled RCT	-	Darifenacin (207)	-	Yes (110)	≥65	-	-	-	77.6 (246)	-	-	-
Wagg (2006)(Wagg et al., 2006)	<i>Am J Geriatr Pharmacother</i>	Pooled RCT	-	Solifenacin (623)	-	Yes (422)	≥65	-	-	-	74.7(781)	-	-	-
Cardozo (2004)(Cardozo et al., 2004)	<i>J Urol</i>	-	12	-	-	-	≥3 months	≥8/24 h	≥1 urge or incontinent episode/day	-	-	Not Noted	Multinational	3
Chapple (2004)(Chapple, Rechberger et al., 2004)	<i>BJU Int</i>	-	12	-	-	-	≥3 months	≥8/24 h	≥1 urge or incontinent episode/day	-	-	Not Noted	Multinational	3
Chapple (2004)(Chapple et al., 2004)	<i>BJU Int</i>	-	4	-	-	-	Not Noted	≥8/24 h	≥1 urge or incontinent episode/day	-	-	Not Noted	Not Noted	3
Chapple (2005)(Chapple et al., 2005)	<i>Eur Urol</i>	-	12	-	-	-	≥3 months	≥8/24 h	≥1 urge or incontinent episode/day	-	-	Not Noted	Not Noted	5
Minassian (2007) (Minassian et al., 2007)	<i>J Obstet Gynaecol Can</i>	RCT	12	Oxybutynin ER (38)	Oxybutynin IR (30)	No	≥65	Not noted	≥8/24 h	≥1 urge episode/week	100 (72)	Ambulatory	Canada	2
Chapple (2007)(Chapple et al., 2007)	<i>Curr Med Res Opin</i>	RCT	12	Darifenacin (266)	-	Yes (133)	≥65	≥6 months	≥10/24 h	≥1 UUI episodes/day	76.6 (306)	Ambulatory	Multinational	5
Lackner (2008)(Lackner et al., 2008)	<i>J Am Geriatr Soc</i>	RCT	4	Oxybutynin ER (26)	-	Yes (24)	≥65	Not noted	≥4/8 h	Nocturia > 2 night; Staff or patient reported urgency	100 (50)	LTCF	USA	5
Kraus (2010)(Kraus, Ruiz-Cerda et al., 2010)	<i>Urology</i>	Pooled RCT	-	Fesoterodine (370)	-	Yes (178)	≥65	-	-	-	70.9 (389)	-	-	-
Chapple (2007)(Chapple, Van Kerrebroeck et al., 2007)	<i>Eur Urol</i>	-	12	-	-	-	≥6 months	≥8/24 h	≥6 urgency episodes or ≥3 UUI episodes/day	-	-	Not Noted	Multinational	3
Nitti (2007)(Nitti et al., 2007)	<i>J Urol</i>	-	12	-	-	-	≥3 months	≥8/24 h	≥1 urge episodes and/or ≥1 UUI episodes/day	-	-	Not Noted	USA	4
Herschorn (2011) (Herschorn et al., 2011)	<i>Curr Med Res Opin</i>	SA of RCT	-	Solifenacin (27)	Oxybutynin IR (30)	No	≥65	-	-	-	77.2 (44)	-	-	-
Herschorn (2010) (Herschorn et al., 2010)	<i>J Urol</i>	-	8	-	-	-	Not noted	≥8/24 h	> 1 urge episode/day	-	-	Not Noted	Canada	5
Sand (2011)(Sand et al., 2011)	<i>BJU Int</i>	Pooled RCT	-	Trospium ER (85)	-	Yes (58)	≥75	-	-	-	73.4 (105)	-	-	-
Dmochowski (2008) (Dmochowski et al., 2008)	<i>Urology</i>	-	12	-	-	-	≥6months	≥10/24 h	≥1 severe urgency/day and ≥1 UUI episode/day	-	-	Not Noted	USA	3
Staskin (2007)(Staskin et al., 2007)	<i>J Urol</i>	-	12	-	-	-	≥6 months	≥10/24 h	≥1 severe urgency/ 3 days or 1 UUI episode/day	-	-	Not Noted	USA	5
DuBeau (2012)(DuBeau et al., 2012)	<i>Neurol Urodyn BJU Int</i>	Pooled RCT	-	Fesoterodine (546)	Tolterodine ER (586)	Yes (306)	≥65	-	-	-	78.4 (1128)	-	-	-
		-	12	-	-	-	≥3 months	≥8/24 h	≥1 UUI episodes/day	-	-	Not Noted	Not noted	5

Table 1 (Continued)

First Author and Year of Publication	Journal	Study Type	Duration (Weeks)	Drug 1 (n)	Drug 2 (n)	Placebo-Controlled (n)	Age OAB Symptoms	Duration of OAB Symptoms	Frequency (Inclusion)	Urgency (Inclusion)	Percent Females% (n)	Location	Country	JADAD Criteria Score
Herschorn (2010) (Herschorn, Swift et al., 2010)														
Kaplan (2011)(Kaplan et al., 2011)	<i>BJU Int</i>	-	12				-	≥3 months	≥8/24h	≥1 UUI episodes/day	-	Not Noted	Multinational	5
Wagg (2013)(Wagg et al., 2013)	<i>J Am Geriatr Soc</i>	RCT	12	Fesoterodine (392)	-	Yes (393)	≥65	≥3 months	≥8/24h	≥3 urge episode/day	53.2 (418)	Ambulatory	Multinational	5
Wagg (2014)(Wagg et al., 2014)	<i>Age Ageing</i>	Pooled RCT		Tolterodine ER (192)	-	Yes (521)	≥65	-	-	-	65.2 (465)	-	-	-
Khullar (2013)(Khullar et al., 2013)	<i>Eur Urol</i>	-	12				-	≥3 months	≥8/24h	≥1 urge episode/day	-	Not Noted	Multinational	4
Nitti (2013)(Nitti et al., 2013)	<i>J Urol</i>	-	12				-	≥3 months	≥8/24h	≥1 urge episode/day	-	Not Noted	Multinational	5
Herschorn (2013) (Herschorn et al., 2013)	<i>Urology</i>	-	12				-	≥3 months	≥8/24h	≥3 urge episode/day	-	Not Noted	Multinational	3
DuBeau (2014)(DuBeau et al., 2014)	<i>J Urol</i>	RCT	12	Fesoterodine (293)	-	Yes (283)	≥65	≥3 months	≥8/24h	UUI 2–15 episodes/day	82.0 (461)	Not Noted	USA	5

* = unable to obtain parent studies.

ER = extended release; IR = immediate release; LTCF = long-term care facility; RCT = Randomized, Controlled Trial; SA = sub-analysis; UUI = urge urinary incontinence; USA = United States of America. Under the "First Author and Year of Publication" columns, included studies are bolded and parent studies not bolded.

(6.1%), darifenacin (23.8%), solifenacin (26.0%), and fesoterodine (29.4%) groups. A significantly higher proportions of subjects receiving an antimuscarinic experienced mild, mild-moderate, moderate, and severe dry mouth when compared to placebo.

There was no overall increase rate of dizziness in antimuscarinics compared to placebo; however, in three fesoterodine studies there was over a higher rate of dizziness (2.5%) compared to placebo (1%). Subjects receiving fesoterodine had significantly higher rate of dyspepsia (2.7%) compared to placebo (0.6%). In a subsequent analysis in which all gastrointestinal AEs were combined (abdominal pain, anorexia, dyspepsia, gastrointestinal AEs, gastroesophageal reflux disorder, heartburn), there was no significant difference in antimuscarinics (4.6%) compared to placebo (2.7%); however, in the three fesoterodine studies that assessed any of these AEs, there was a significantly higher rate of gastrointestinal AEs (3.1%) compared to placebo (1.1%) (Appendix G). There was no overall difference in headache between subjects receiving antimuscarinic compared to placebo; however, a higher rate was seen in the three studies in which subjects received tolterodine ER (1.7%) compared to placebo (0.7%). There was an overall higher rate of urinary retention in subjects receiving antimuscarinics (1.3%) compared to placebo (0.4%) and a higher rate in the four studies which assessed subjects receiving fesoterodine (1.7%) compared to placebo (0.2%). There was an increased rate of urinary tract infections in one study comparing solifenacin (6.0%) to placebo (3.1%); however, there was no difference in antimuscarinics (3.7%) overall versus placebo (2.8%).

3.3.2. Head-to-head trials

Statistically significant rate of AEs and NNH for an antimuscarinic compared to another antimuscarinic are described in Table 3. In these comparator studies, solifenacin exhibited a lower rate of AEs (70.4% versus 96.7%), treatment-related AEs (60.3% versus 86.7%), and dry mouth (37.0% versus 80.0%) compared to oxybutynin IR, respectively. Subjects receiving fesoterodine were more likely to experience AEs (54.8% versus 40.0%) and dry mouth (31.3% versus 14.7%) compared to tolterodine ER. There were no significant AEs when outcomes were combined based on symptomatology (Appendix G).

3.4. Treatment discontinuations

3.4.1. Antimuscarinic versus placebo

Statistically significant rate of treatment discontinuation and NNH for antimuscarinics compared to placebo are described in Table 4. Of the 27 reasons for discontinuation, only two were statistically significant. Treatment discontinuation due to AEs was higher in the antimuscarinic group (7.1%) compared to placebo (5.0%); however, when stratified by medication, only fesoterodine (9.4%) compared to placebo (4.9%) was statistically significant for treatment discontinuation due to an AE. Overall, the discontinuation rate due to dry mouth was higher in antimuscarinics (1.5%) compared to placebo (0.4%) and in three comparisons of fesoterodine (2.0%) when compared to placebo (0.3%).

3.4.2. Head-to-head trials

Statistically significant rate of treatment discontinuation and NNH for an antimuscarinic compared to another antimuscarinic are described in Table 4. In the antimuscarinic comparators, only fesoterodine (8.6%) had a higher rate of discontinuation due to AEs compared to tolterodine ER (2.7%).

4. Discussion

The aim of these analyses was to assess the rate of AEs and treatment discontinuations with the use of antimuscarinics in the

Table 2
Statistically Significant Adverse Events – Antimuscarinic versus Placebo.

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Malone-Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Trospium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2012; Dubeau et al., 2014; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013)
AEs	11	10	1.26 (1.12–1.43) NNH = 8.3	–	0.82 (0.38–1.78)	1.14 (0.89–1.47)	1.21 (1.00–1.45)	0.99 (0.71–1.38)	1.27 (1.09–1.48) NNH = 7.8	–	1.56(1.32–1.84) NNH = 4.9
Constipation	14	13	2.39 (1.76–3.23)* NNH = 15.4	0.99 (0.61–1.63)	4.63 (0.23–91.81)	0.96 (0.10–9.02)	1.87 (1.14–3.08) NNH = 35.5	13.03 (0.77–219.66)	2.40 (1.36–4.23)* NNH = 9.4	3.61 (2.22–5.89) NNH = 9.0	3.14(2.15–4.57) NNH = 17.5
Constipation, Mild-Moderate	1	1	3.42 (2.10–5.59) NNH = 9.7	–	–	–	–	–	–	3.42 (2.10–5.59) NNH = 9.7	–
Dizziness	9	9	1.43 (0.83–2.46)	–	0.31 (0.01–7.23)	0.64 (0.17–2.46)	1.63 (0.55–4.83)	0.14 (0.01–2.81)	1.60 (0.07–38.97)	–	2.22 (1.04–4.37) NNH = 70
Dry Mouth	14	13	3.94 (2.82–5.50)* NNH = 5.1	0.99 (0.61–1.63)	0.92 (0.06–13.95)	4.25 (1.63–11.07) NNH = 3.3	3.89 (2.08–7.27)* NNH = 8.1	3.07 (0.69–13.70)	5.82 (3.11–10.90) NNH = 5.1	5.49 (3.51–8.59) NNH = 4.7	4.88 (3.81–6.26) NNH = 4.2
Dry Mouth, Mild	2	2	5.57 (3.65–8.49) NNH = 5.5	–	–	–	–	–	–	–	5.57 (3.65–8.49) NNH = 5.5
Dry Mouth, Mild-Moderate	1	2	5.49 (3.46–8.70) NNH = 5	–	–	–	–	–	–	5.49 (3.46–8.70) NNH = 5	–
Dry Mouth, Moderate	2	2	4.00 (1.92–8.34) NNH = 20.0	–	–	–	–	–	–	–	4.00 (1.92–8.34) NNH = 20.0
Dry Mouth, Severe	4	4	4.80 (1.65–13.95) NNH = 73.3	–	–	–	–	–	–	5.42 (0.68–13.95) NNH = 96.2	4.59 (1.32–15.94) NNH = 64.0
Dyspepsia	7	7	2.01 (0.82–4.90)*	–	0.31 (0.01–7.23)	0.40 (0.11–1.43)	1.74 (0.42–7.18)	–	5.31 (0.69–40.97)	–	4.12 (1.59–10.63) NNH = 47.8
Headache	10	9	1.62 (0.95–2.79)*	–	2.78 (0.12–65.08)	2.57 (0.33–19.95)	1.97 (1.07–3.65) NNH = 99.0	–	0.11 (0.01–2.20)	–	1.46 (0.52–3.63)
Treatment-related AEs	2	2	1.96 (1.39–2.76) NNH = 5.8	–	–	–	–	1.67 (0.83–3.36)	2.06 (1.39–3.06) NNH = 5.2	–	–
Urinary Retention	10 [†] (8)	9 [†] (8)	3.60 (1.67–7.76) NNH = 95.1	–	2.78 (0.12–65.08)	†	2.08 (0.19–22.82) [†]	3.43 (0.17–70.17)	–	2.48 (0.70–8.85)	6.02 (1.81–20.00) * NNH = 65.6
Urinary Tract Infection	8	8	1.17 (0.81–1.71)	–	–	–	0.87 (0.40–1.89)	3.43 (0.17–70.17)	0.18 (0.01–4.33)	1.93 (1.04–3.58) NNH = 35.0	1.02 (0.61–1.70)

* = I² > 25%; † = Adverse Event noted in Study but 0 count.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; NNH = Number Needed to Harm; RR = rate ratio.

Table 3
Statistically Significant Adverse Events – Antimuscarinic versus Tolterodine IR/ER or Oxybutynin IR.

Outcome	Total Comparisons/ Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI) (Minassian et al., 2007)	Solifenacin RR (95% CI) (Herschorn et al., 2011)	Total Studies		Fesoterodine RR (95% CI) (DuBeau et al., 2012)
					Oxybutynin ER RR (95% CI) (Sand et al., 2004)	Tolterodine ER RR (95% CI)	
Versus Oxybutynin IR			Versus Tolterodine IR			Versus Tolterodine ER	
AEs	2	0.78 (0.61–0.98) NNH = 6.0	0.94 (0.59–1.49)	0.73 (0.56–0.94) NNH = 3.9	0	–	1 1.37 (1.21–1.55) NNH = 6.7
Dry Mouth	2	0.56 (0.38–0.83) NNH = 3.3	0.69(0.40–1.18)	0.46 (0.27–0.78) NNH = 2.3	1	1.18 (0.72–1.93)	1 2.13 (1.69–2.69) NNH = 6.0
Dry Mouth, Moderate	1	0.05 (0.00–0.86) NNH = 3	–	0.05 (0.00–0.86) NNH = 3	0	–	0 –
Treatment-related AEs	1	0.68 (0.49–0.96) NNH = 3.6	–	0.68 (0.49–0.96) NNH = 3.6	0	–	0 –

Only reported if both studies reported outcomes.

* = I² > 25%.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; NNH = Number Needed to Harm; RR = rate ratio.

Table 4
Statistically Significant Treatment Discontinuations – Antimuscarinic versus Placebo.

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Tropium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2012; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013)
AEs	13	12	1.41 (1.12–1.78)	–	2.78 (0.12–4.57)	3.53 (0.47–26.56)	1.02 (0.67–1.56)	1.14 (0.28–4.57)	0.78 (0.42–1.48)	1.44 (0.89–2.33)	1.96 (1.45–2.64) [50,47,51]
Dry Mouth	6	5	3.01 (1.18–7.68)	–	–	0.64 (0.06–6.91)	2.61 (0.31–22.25)	–	2.51 (0.12–51.90)	–	4.79 (1.16–19.74) [50,47,51]

* = $I^2 > 25\%$; † = Adverse Event noted in Study but 0 count.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; NNH = Number Needed to Harm; RR = rate ratio.

Table 5
Statistically Significant Reasons for Treatment Discontinuation – Antimuscarinic versus Tolterodine IR/ER or Oxybutynin IR.

Outcome	Total Comparisons/ Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI) (Minassian et al., 2007)		Solifenacin RR (95% CI) (Herschorn et al., 2011)		Total Studies	Oxybutynin ER RR (95% CI) (Sand et al., 2004)		Total Studies	Fesoterodine RR (95% CI) (DuBeau et al., 2012)	
			Versus Oxybutynin IR		Versus Tolterodine IR			Versus Tolterodine ER				
AEs	1	0.40 (0.15–1.12)	0.40 (0.15–1.12)	0.40 (0.15–1.12)	0.40 (0.15–1.12)	1	1.08 (0.52–2.23)	1	3.15 (1.81–5.49)	1	3.15 (1.81–5.49)	NNH = 17.0

* = $I^2 > 25\%$; † = Adverse Event noted in Study but 0 count, AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; NNH = Number Needed to Harm; RR = rate ratio.

group of patients who are most likely to experience OAB. With a known lack of studies specific to older adults, sub-analyses and pooled analyses were included to increase the number of subjects similar to a previous systematic review and meta-analysis of antimuscarinics in older adults (Paquette et al., 2011). Data from the parent studies were used to assess for OAB inclusion criteria, location of study, and quality of studies. There were 18 comparisons from 16 studies which assessed several antimuscarinic agents used for the treatment of OAB. A majority of studies were placebo-controlled while only 4 studies included direct comparisons to two antimuscarinic agents. In general, these studies were very similar in the included age (as only two studies used a minimum age inclusion criterion older than 65), OAB inclusion criteria (minor differences exist between duration of OAB symptoms, frequency, and urgency), proportion of females in trials (all were >50%), and location of the trial (all studies except for one was in a non-institutionalized setting). Two-thirds of RCTs and parent studies were of high-quality using the Jadad criteria.

Current guidelines recommend the use of any antimuscarinic or beta-3 agonist as first-line drug treatment for OAB as efficacy among the two different classes are considered to be similar (Gormley, Lightner, Faraday, & Vasavada, 2015; Thuroff et al., 2011). The approach to treating OAB in healthy older adults is similar to younger adults; however, frail older adults may have increased challenges as comorbidities, functional or cognitive deficits, and concomitant medications play a greater role in their management (Thuroff et al., 2011). Additionally, antimuscarinics in frail older adults may have a higher rate of AEs especially in the setting of polypharmacy (Geoffrion, 2012; Gormley et al., 2015).

In these analyses, AEs occurred at a higher rate in the antimuscarinic arms (53.8%) compared to placebo (41.7%) in this older adult population. Additionally, the discontinuation rate was also higher in the antimuscarinic group (7.1%) versus placebo (5.0%). This difference may be attributed to the higher rates of AEs. However, these studies are limited to up to 12 weeks of duration in patients who are willing to participate in a clinical trial and may not represent true rates of AEs and treatment discontinuation.

These findings show higher rates of anticholinergic AEs with antimuscarinics when compared to placebo in older adults. The overall rates of constipation and dry mouth in the antimuscarinic arms of these studies were 10% and 25%, respectively. Subjects in the darifenacin (18.0%) and solifenacin (15.4%) arms had the highest rates of constipation. The rates of dry mouth were also highest in the fesoterodine (29.4%), solifenacin (26.0%), and darifenacin (23.8%) arms. Compared to tolterodine ER (14.7%), there was a two-fold increase in dry mouth in subjects receiving fesoterodine (31.3%) suggesting a potential difference in rates of adverse outcomes between two antimuscarinics in older adults. This pooled analysis, which compared fesoterodine to tolterodine ER, suggested better efficacy in the fesoterodine arm with a statistically significant increase in dry mouth when compared to tolterodine ER (DuBeau et al., 2012). Fesoterodine is a pro-drug of tolterodine with doses of 4 mg and 8 mg compared to tolterodine with doses of 2 mg and 4 mg. There was a 3-fold and 4.8-fold increase rate of treatment discontinuation due to dry mouth observed in all antimuscarinics and fesoterodine, respectively, relative to placebo meaning dry mouth is bothersome enough to withdrawal from trials.

Older adults receiving fesoterodine (2.5%) were more likely to experience dizziness compared to placebo (1%). One alternative reason, beyond a true difference, for a higher rate of dizziness may be due to the increase sample size of subjects randomized to fesoterodine as 40% of subjects in the treatment arm were on fesoterodine in this analysis of older adults; therefore, it may be the only antimuscarinic with an adequate sample size needed to detect this difference. Conversely, there was no overall difference in the rate of dizziness in antimuscarinics compared to placebo. Another reason is the impact of age and/or frailty on the outcome of dizziness. DuBeau and colleagues assessed fesoterodine (n = 281) versus placebo (n = 281) in a vulnerable older adult population, defined by a Vulnerable Elders Survey score of 3 or more; however, the rate of dizziness in this population was 1.1% in the treatment arm (DuBeau et al., 2014). Kraus and colleagues showed an age-related increase in dizziness in older adults compared to younger

adults which may suggest and age-related increase in dizziness (Kraus, Ruiz-Cerda et al., 2010). Additionally, there may be differences in identifying and classifying dizziness as safety outcomes were a part of the secondary analysis. Dizziness was the only significant cognitive- or functional-related AE in the study population. A previous meta-systematic review investigated the rate of central nervous system AEs, including dizziness, in older adults (Paquette et al., 2011). Similar, low rates of dizziness were identified in the antimuscarinics evaluated except of oxybutynin (3.0%) and propiverine (3.2%) (fesoterodine was not yet approved); however, within this analysis central nervous system AEs were not measured and may be underreported. Although the rate is low, dizziness may contribute to falls and fall-related fractures which may negatively impact quality of life.

Older adults randomized to fesoterodine were at 4-fold rate of dyspepsia compared to placebo (2.7% versus 0.6%) which was not noted in any other antimuscarinic sub-analysis. In a previous systematic review, the proportion of subjects receiving antimuscarinics (4.7%) was higher than patients receiving placebo (2.1%) (Chapple et al., 2008). This may be due to the anticholinergic properties of antimuscarinics causing reduced lower esophageal pressures which can present as dyspepsia (Peters, 1989). The difference identified in fesoterodine and not the other antimuscarinics may be due to the sample size of the fesoterodine population and the use of fesoterodine in a frail population.

Headache was not significant in the overall analysis; however, there was a two-fold rate of headache with tolterodine ER (2.7%) compared to placebo (1.7%) in three studies which contained information on approximately 1000 subjects in both treatment and placebo arms. Authors of a previous systematic review were unable to determine the mechanistic difference between tolterodine and other antimuscarinics in regards to headache and differences may be due to chance (Chapple et al., 2008).

Urinary retention was also significantly higher in the overall antimuscarinic group (1.3%) compared to placebo (0.3%), especially in subjects receiving fesoterodine (1.7%) compared to placebo (0.2%). In general, males are likely to be at a higher risk of urinary retention, especially at advancing age, due to the risk of benign prostatic enlargement (Emberton and Anson, 1999). However, one oxybutynin ER study of women only in the long-term care setting, two fesoterodine studies, and one trospium study reported urinary retention separately by sex (Dubeau et al., 2014; Lackner et al., 2008; Wagg et al., 2013; Zinner et al., 2002). The overall proportion of males (0.7%) and females (1.1%) with urinary retention was similar suggesting urinary retention is not an AE that affects only men; however, the risk of urinary retention in men is likely underestimated due to the exclusion of men with bladder outlet obstruction in these RCTs.

There was nearly a two-fold increase in urinary tract infections in solifenacin (5.9%) compared to placebo (3.1%); however, there was no difference when evaluating all antimuscarinics versus placebo regarding urinary tract infections. The significant difference in solifenacin and placebo may be due to an adequate sample size to detect a difference, random chance, or mechanistically, solifenacin is different from other antimuscarinics which may contribute to urinary tract infections.

4.1. Limitations

There are limitations to the study design. RCTs along with pooled and sub-analyses were the only study types included. These outcomes may not be generalizable to a clinical setting and may underrepresent the true rate of AEs and treatment discontinuations as there is the potential that subjects with higher risks of AEs and treatment discontinuations would be excluded for the study (Loke, Price, & Herxheimer, 2007). Observational studies were not

incorporated due to potential for inconsistent collection of AEs and treatment discontinuations across studies. Open-label studies with no comparator were not included for analysis as it may be difficult to discern between AEs and treatment discontinuations and the impact of aging. The duration of studies were 12 weeks or less; therefore, the authors cannot assess AEs and treatment discontinuations that may occur after continued use of antimuscarinics beyond 12 weeks. This may not allow enough time for a subject to develop and be identified with cognitive-related AEs as these may not present until beyond three months (Han, Agostini, & Allore, 2008). Many studies did not describe a standardized way of identifying or reporting AEs or treatment discontinuations. While the majority reported any AEs that occurred in at least 5% of the subjects, there is a potential of not being able to identify all AEs across these studies, which may lead to an under identification of AEs and treatment discontinuations. Using the McHarm tool, the authors were able to be explicit on the differences in reporting AEs across studies. Similar terms, as previously described by Kessler, were used to combine potentially related AEs based on symptomatology (Kessler et al., 2011); however, no new significant AEs were detected. Efficacy was not analyzed in the systematic review and meta-analysis; therefore the authors cannot assess if the benefits of medications outweigh the risks of the various types of AEs. However, previous clinical guidelines suggest similar efficacy outcomes across antimuscarinics (Geoffrion, 2012; Gormley et al., 2015; Thuroff et al., 2011). Heterogeneity was not further explored beyond stratification of antimuscarinics as this was an exploratory analysis to identify AEs and treatment discontinuations that can be tested in future observational studies. Mirabegron and non-oral antimuscarinics (i.e., oxybutynin patch, oxybutynin gel) were not incorporated into these analyses. Only one study has assessed mirabegron in older adults (DuBeau et al., 2012) and no studies have evaluated non-oral antimuscarinics in older adults. These medications may have a differing AE profile. The authors did not assess for publication bias using funnel plots; however, since AEs were secondary outcomes, with the exception of one study (Herschorn et al., 2011), the publication of these studies were less dependent on positive or negative results in the safety outcomes compared to primary efficacy outcomes.

4.2. Strengths

Despite these limitations, there were many strengths to the study. This is the second review to aggregate RCTs, pooled analyses of RCTs, and sub-analyses of RCTs AEs of antimuscarinics (Paquette et al., 2011) and the first to perform an analysis of AEs beyond central-nervous system AEs with a large enough sample size to potentially detect differences in treatment groups that may not be able to be detected using individual studies. As RCTs were used in this analyses and not observational studies, the results are not impacted by channeling bias due to the random allocation of treatment and not on the preferential use of one medication over another based on clinical presentation and pre-existing comorbid conditions (Petri and Urquhart, 1991). The study also identified non-anticholinergic AEs which may not be routinely associated with antimuscarinics. Similar AEs were combined based on symptomatology to further explore AEs. Future studies to further explore less well-documented antimuscarinic AEs using pharmacoepidemiological techniques should be performed. Properly attributing AEs to antimuscarinics may help identify alternative therapies and avoid prescribing cascades (Rochon and Gurwitz, 1997).

5. Conclusion

Treatment for overactive bladder using antimuscarinics in adults aged 65 or older resulted in significant increase risk of

several AEs compared to placebo including both anticholinergic (e.g., dry mouth, constipation) and non-anticholinergic (e.g., dyspepsia, dizziness, headaches) AEs. Pharmacoepidemiology studies are needed to confirm AEs described in these analyses in a clinical setting. Differences in AEs, dry mouth, and discontinuation rates due to AEs were identified in head-to-head trials.

Conflict of interest

Scott Martin Vouri – Nothing to Disclose.
Clark D. Kebodeaux – Nothing to Disclose.
Paul M. Stranges – Nothing to Disclose.
Besu F. Teshome – Nothing to Disclose.

Authors' contribution

SM Vouri – Project development, data extraction, quality assessment, data synthesis, manuscript writing, manuscript revision.

CD Kebodeaux – Data extraction, quality assessment, manuscript writing, manuscript revision.

PM Stranges – Data extraction, quality assessment, manuscript writing, manuscript revision.

BF Teshome – Data extraction, quality assessment, manuscript writing, manuscript revision.

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Appendix A. Complete Search Strategy

PubMed

("aged" OR "Aged"[Mesh] OR "elderly" OR "aged, 80 and over"[Mesh] OR "aged, 80 and over" OR "oldest old" OR "nonagenarian*" OR "octogenarian*" OR "centenarian*" OR "frail elderly"[Mesh] OR "frail elder*" OR "functionally-impaired elderly" OR "frail older adult*" OR "retire*" OR "septuagenarian*" OR "sexagenarian*" OR "geriatric*" OR "senior citizen") AND ("Muscarinic Antagonists"[Mesh] OR "Antagonists, Muscarinic" OR "Antimuscarinics" OR "Antimuscarinic Agents" OR "Agents, Antimuscarinic" OR "Cholinergic Muscarinic Antagonists" OR "Antagonists, Cholinergic Muscarinic" OR "Muscarinic Antagonists, Cholinergic" OR "Antimuscarinic agent" OR "antimuscarinic drug" OR "muscarinic blocker" OR "muscarinic blocking agent" OR "muscarinic receptor antagonist" OR "muscarinic receptor blocker" OR "oxybutynin" [Supplementary Concept] OR "oxybutynin" OR "K9P6MC7092" OR "Zatur" OR "Contimin" OR "Cystonorm" OR "Ditropan" OR "Dridase" OR "Cystrin" OR "Dresplan" OR "Driptane" OR "gelnique" OR "Gen-Oxybutynin" OR "Novo-Oxybutynin" OR "Nu-Oxybutyn" OR "Oxyb AbZ" OR "Oxybutin Holsten" OR "Oxybutynin Heumann" OR "Oxybutynin Hexal" OR "oxybutynin hydrochloride" OR "oxybutynin chloride" OR "Oxybutynin Stada" OR "oxybutynin von ct" OR "Oxybutynin-Puren" OR "Oxybutynin-ratiopharm" OR "Oxymedin" OR "Oxytrol" OR "PMS-Oxybutynin"

OR "Pollakis" OR "Renamel" OR "Ryol" OR "Spasmex" OR "Oxybutynin" OR "Spasyt" OR "Tavor" OR "Oxybugamma" OR "Apo-Oxybutynin" OR "tolterodine" [Supplementary Concept] OR "WHE7A56U7K" OR "PHA-686464B" OR "Urotrol" OR "Detrol" OR "Unidet" OR "Detrusitol" OR "tolterodine tartrate" OR "trospium chloride" [Supplementary Concept] OR "trospium chloride" OR "1E6682427E" OR "azoniaspiro compound XVII" OR "Spasmex" OR "Uraton" OR "Spasmolyt" OR "Spasmo-Urgenin TC" OR "Spasmo-lyt" OR "Spasmo-Rhoival TC" OR "Trospi" OR "Ceris" OR "Uraplex" OR "Spasmo-Urgenin" OR "Sanctura" OR "solifenacin" [Supplementary Concept] OR "solifenacin" OR "A8910SQJ1U" OR "YM905" OR "YM 905" OR "solifenacin succinate" OR "vesicare" OR "darifenacin" [Supplementary Concept] OR "darifenacin" OR "darifenacin" OR "darifenacin" OR "darifenacin hydrochloride" OR "Enablex" OR "UK-88525" OR "darifenacin hydrobromide" OR "Emselex" OR "APG9819VLM" OR "fesoterodine" [Supplementary Concept] OR "fesoterodine" OR "621G617227" OR "toviaz" OR "fesoterodine fumarate" OR "Mirabegron" OR "mirabegron" [Supplementary Concept] OR "MVR3JL3B2V" OR "Betanis" OR "YM 178" OR "YM-178" OR "Adrenergic beta-3 Receptor Agonists")

EMBASE

('aged'/exp OR 'aged' OR 'frail elderly'/exp OR 'very elderly'/exp OR 'very elderly' OR 'geriatrics'/exp OR 'geriatrics' OR 'geriatric patient'/exp OR 'geriatric patient' OR 'elderly' OR 'aged, 80 and over' OR 'oldest old' OR 'nonagenarian' OR 'nonagenarians' OR 'octogenarian' OR 'octogenarians' OR 'centenarian' OR 'centenarians' OR 'frail elder' OR 'frail elders' OR 'frail elderly' OR 'functionally-impaired elderly' OR 'frail older adult' OR 'frail older adults' OR 'retiree' OR 'septuagenarian' OR 'septuagenarians' OR 'sexagenarian' OR 'sexagenarians' OR 'geriatric' OR 'senior citizen') AND ('muscarinic receptor blocking agent'/exp OR 'Antagonists, Muscarinic' OR 'Antimuscarinics' OR 'Antimuscarinic Agents' OR 'Agents, Antimuscarinic' OR 'Cholinergic Muscarinic Antagonists' OR 'Antagonists, Cholinergic Muscarinic' OR 'Muscarinic Antagonists, Cholinergic' OR 'Antimuscarinic agent' OR 'antimuscarinic drug' OR 'muscarinic antagonist' OR 'muscarinic antagonists' OR 'muscarinic blocker' OR 'muscarinic blocking agent' OR 'muscarinic receptor antagonist' OR 'muscarinic receptor blocker' OR 'muscarinic receptor antagonist' OR 'oxybutynin'/exp OR 'anturo' OR 'cystonorm' OR 'cystrin' OR 'delifon' OR 'ditropan' OR 'ditropan xl' OR 'diutropin' OR 'dridase' OR 'driptane' OR 'esoxybutynin' OR 'esoxybutynin chloride' OR 'frenurin' OR 'gelnique' OR 'iliaden' OR 'kentera' OR 'kl 007' OR 'kl1007' OR 'lenditro' OR 'lyrinel xl' OR 'mj 4309 1' OR 'mj 43091' OR 'mj43091' OR 'mutum cr' OR 'nefryl' OR 'novitropan' OR 'oxibutinin' OR 'oxibutynin' OR 'oxyban' OR 'oxybutinin' OR 'oxybutinin chloride' OR 'oxybutyn' OR 'oxybutyn chloride' OR 'oxybutynin chlorhydrate' OR 'oxybutynin chloride' OR 'oxybutynin hydrochloride' OR 'oxytrol' OR 'oxytrol for women' OR 'oyrobin' OR 'pollakis' OR 'reteven' OR 'tropan' OR 'uricont' OR 'uroflax' OR 'urotrol' OR 'zatur ge' OR 'Zatur' OR 'Contimin' OR 'Cystonorm' OR 'Dresplan' OR 'Driptane' OR 'gelnique' OR 'Gen-Oxybutynin' OR 'Novo-Oxybutynin' OR 'Nu-Oxybutyn' OR 'Oxyb AbZ' OR 'Oxybutin Holsten' OR 'Oxybutynin AL' OR 'Oxybutynin AZU' OR 'Oxybutynin Heumann' OR 'Oxybutynin Hexal' OR 'oxybutynin hydrochloride' OR 'Oxybutynin Stada' OR 'oxybutynin von ct' OR 'Oxybutynin-Puren' OR 'Oxybutynin-ratiopharm' OR 'Oxymedin' OR 'Pollakis' OR 'Renamel' OR 'Ryol' OR 'Spasmex' OR 'Spasyt' OR 'Tavor' OR 'Oxybugamma' OR 'Apo-Oxybutynin' OR 'tolterodine'/exp OR 'detrol' OR 'detrol la' OR 'detrusitol' OR 'pnu 200583' OR 'pnu200583' OR 'tolterodine tartrate' OR 'WHE7A56U7K' OR 'PHA-686464B' OR 'Urotrol' OR 'Unidet' OR 'trospium chloride'/exp OR 'regurin' OR 'sanctura' OR 'sanctura xr' OR 'spasmex' OR 'spasmo urgenin' OR 'spasmo-lyt' OR 'spasmolyt' OR 'spasmourgenin' OR 'trospium chloride' OR

'1E6682427E' OR 'azoniaspiro compound XVII' OR "Spasmex" OR 'Uraton' OR "Spasmo-Urgenin TC" OR 'Spasmo-Rhoival TC' OR "Trospi" OR 'Ceris' OR "Uraplex" OR 'Spasmo-Urgenin' OR "Sanctura" OR 'solifenacin/exp OR 'solifenacin succinate' OR "vesicare" OR 'vesikur' OR "ym 53705" OR 'ym 905' OR "ym53705" OR 'ym905' OR "A8910SQJ1U" OR 'darifenacin/exp OR 'darifenacin hydrobromide' OR "emselex" OR 'enablex' OR "uk 88525" OR 'uk 88525 04' OR "uk 88525-04" OR 'uk88525' OR "uk88525 04" OR "UK-88525" OR 'APG9819VLM' OR 'fesoterodine/exp OR "fesoterodine fumarate" OR 'fesoterodine hydrogen fumarate' OR "spm 907" OR 'spm907' OR "toviaz" OR '621G617227' OR 'mirabegron/exp OR "betanis" OR 'betmiga' OR "myrbetriq" OR 'sc 211912' OR 'sc211912' OR 'ym 178' OR 'ym178' OR 'MVR3JL3B2V' OR 'YM-178' OR 'Adrenergic beta-3 Receptor Agonists')

SCOPUS

(TITLE-ABS-KEY("aged") OR TITLE-ABS-KEY("elderly") OR TITLE-ABS-KEY("aged, 80 and over") OR TITLE-ABS-KEY("oldest old") OR TITLE-ABS-KEY("nonagenarian**") OR TITLE-ABS-KEY("octogenarian**") OR TITLE-ABS-KEY("centenarian**") OR TITLE-ABS-KEY("frail elder**") OR TITLE-ABS-KEY("functionally-impaired elderly") OR TITLE-ABS-KEY("frail older adult**") OR TITLE-ABS-KEY("retire**") OR TITLE-ABS-KEY("septuagenarian**") OR TITLE-ABS-KEY("sexagenarian**") OR TITLE-ABS-KEY("geriatric**") OR TITLE-ABS-KEY("senior citizen") OR TITLE-ABS-KEY("very elderly") OR TITLE-ABS-KEY("geriatric patient")) AND (TITLE-ABS-KEY("Muscarinic Antagonists") OR TITLE-ABS-KEY("Antagonists, Muscarinic") OR TITLE-ABS-KEY("Antimuscarinics") OR TITLE-ABS-KEY("Antimuscarinic Agents") OR TITLE-ABS-KEY("Agents, Antimuscarinic") OR TITLE-ABS-KEY("Cholinergic Muscarinic Antagonists") OR TITLE-ABS-KEY("Antagonists, Cholinergic Muscarinic") OR TITLE-ABS-KEY("Muscarinic Antagonists, Cholinergic") OR TITLE-ABS-KEY("Antimuscarinic agent") OR TITLE-ABS-KEY("antimuscarinic drug") OR TITLE-ABS-KEY("muscarinic blocker") OR TITLE-ABS-KEY("muscarinic blocking agent") OR TITLE-ABS-KEY("muscarinic receptor antagonist") OR TITLE-ABS-KEY("muscarinic receptor blocker") OR TITLE-ABS-KEY("oxybutynin") OR TITLE-ABS-KEY("K9P6MC7092") OR TITLE-ABS-KEY("Zatur") OR TITLE-ABS-KEY("Contimin") OR TITLE-ABS-KEY("Cystonorm") OR TITLE-ABS-KEY("Ditropan") OR TITLE-ABS-KEY("Dridase") OR TITLE-ABS-KEY("Cystrin") OR TITLE-ABS-KEY("Dresplan") OR TITLE-ABS-KEY("Driptane") OR TITLE-ABS-KEY("gelnique") OR TITLE-ABS-KEY("Gen-Oxybutynin") OR TITLE-ABS-KEY("Novo-Oxybutynin") OR TITLE-ABS-KEY("Nu-Oxybutyn") OR TITLE-ABS-KEY("Oxyb AbZ") OR TITLE-ABS-KEY("Oxybutin Holsten") OR TITLE-ABS-KEY("Oxybuton") OR TITLE-ABS-KEY("Oxybutynin AL") OR TITLE-ABS-KEY("Oxybutynin AZU") OR TITLE-ABS-KEY("Oxybutynin Heumann") OR TITLE-ABS-KEY("Oxybutynin Hexal") OR TITLE-ABS-KEY("oxybutynin hydrochloride") OR TITLE-ABS-KEY("oxybutynin chloride") OR TITLE-ABS-KEY("oxybutynin Stada") OR TITLE-ABS-KEY("oxybutynin von ct") OR TITLE-ABS-KEY("Oxybutynin-Puren") OR TITLE-ABS-KEY("Oxybutynin-ratiopharm") OR TITLE-ABS-KEY("Oxymedin") OR TITLE-ABS-KEY("Oxytrol") OR TITLE-ABS-KEY("PMS-Oxybutynin") OR TITLE-ABS-KEY("Pollakisu") OR TITLE-ABS-KEY("Renamel") OR TITLE-ABS-KEY("Ryol") OR TITLE-ABS-KEY("Spasmex") OR TITLE-ABS-KEY("Oxybutynin") OR TITLE-ABS-KEY("Spasyt") OR TITLE-ABS-KEY("Tavor") OR TITLE-ABS-KEY("Oxybugamma") OR TITLE-ABS-KEY("Apo-Oxybutynin") OR TITLE-ABS-KEY("tolterodine") OR TITLE-ABS-KEY("WHE7A56U7K") OR TITLE-ABS-KEY("PHA-686464B") OR TITLE-ABS-KEY("Urotrol") OR TITLE-ABS-KEY("Detrol") OR TITLE-ABS-KEY("Unidet") OR TITLE-ABS-KEY("Detrusitol") OR TITLE-ABS-KEY("tolterodine tartrate") OR TITLE-ABS-KEY("trospium chloride") OR TITLE-ABS-KEY("trospium chloride") OR TITLE-ABS-KEY("1E6682427E") OR

TITLE-ABS-KEY("azoniaspiro compound XVII") OR TITLE-ABS-KEY("Spasmex") OR TITLE-ABS-KEY("Uraton") OR TITLE-ABS-KEY("Spasmolyt") OR TITLE-ABS-KEY("Spasmo-Urgenin TC") OR TITLE-ABS-KEY("Spasmo-lyt") OR TITLE-ABS-KEY("Spasmo-Rhoival TC") OR TITLE-ABS-KEY("Trospi") OR TITLE-ABS-KEY("Ceris") OR TITLE-ABS-KEY("Uraplex") OR TITLE-ABS-KEY("Spasmo-Urgenin") OR TITLE-ABS-KEY("Sanctura") OR TITLE-ABS-KEY("solifenacin") OR TITLE-ABS-KEY("solifenacin") OR TITLE-ABS-KEY("A8910SQJ1U") OR TITLE-ABS-KEY("YM905") OR TITLE-ABS-KEY("YM 905") OR TITLE-ABS-KEY("solifenacin succinate") OR TITLE-ABS-KEY("vesicare") OR TITLE-ABS-KEY("darifenacin") OR TITLE-ABS-KEY("darifenacin") OR TITLE-ABS-KEY("darifenacine") OR TITLE-ABS-KEY("darifenacin hydrochloride") OR TITLE-ABS-KEY("Enablex") OR TITLE-ABS-KEY("UK-88525") OR TITLE-ABS-KEY("darifenacin hydrobromide") OR TITLE-ABS-KEY("Emselex") OR TITLE-ABS-KEY("APG9819VLM") OR TITLE-ABS-KEY("fesoterodine") OR TITLE-ABS-KEY("fesoterodine") OR TITLE-ABS-KEY("621G617227") OR TITLE-ABS-KEY("toviaz") OR TITLE-ABS-KEY("fesoterodine fumarate") OR TITLE-ABS-KEY("Adrenergic beta-3 Receptor Agonists") OR TITLE-ABS-KEY("Mirabegron") OR TITLE-ABS-KEY("Mirabegron") OR TITLE-ABS-KEY("MVR3JL3B2V") OR TITLE-ABS-KEY("Betanis") OR TITLE-ABS-KEY("YM 178") OR TITLE-ABS-KEY("YM-178"))

COCHRAN RCTs

("aged" OR "Aged" OR "elderly" OR "aged, 80 and over" OR "aged, 80 and over" OR "oldest old" OR "nonagenarian**" OR "octogenarian**" OR "centenarian**" OR "frail elderly"[Mesh] OR "frail elder**" OR "functionally-impaired elderly" OR "frail older adult**" OR "retire**" OR "septuagenarian**" OR "sexagenarian**" OR "geriatric**" OR "senior citizen") AND ("Muscarinic Antagonists" OR "Antagonists, Muscarinic" OR "Antimuscarinics" OR "Antimuscarinic Agents" OR "Agents, Antimuscarinic" OR "Cholinergic Muscarinic Antagonists" OR "Antagonists, Cholinergic Muscarinic" OR "Muscarinic Antagonists, Cholinergic" OR "Antimuscarinic agent" OR "antimuscarinic drug" OR "muscarinic blocker" OR "muscarinic blocking agent" OR "muscarinic receptor antagonist" OR "muscarinic receptor blocker" OR "oxybutynin" OR "oxybutynin" OR "K9P6MC7092" OR "Zatur" OR "Contimin" OR "Cystonorm" OR "Ditropan" OR "Dridase" OR "Cystrin" OR "Dresplan" OR "Driptane" OR "gelnique" OR "Gen-Oxybutynin" OR "Novo-Oxybutynin" OR "Nu-Oxybutyn" OR "Oxyb AbZ" OR "Oxybutin Holsten" OR "Oxybuton" OR "Oxybutynin AL" OR "Oxybutynin AZU" OR "Oxybutynin Heumann" OR "Oxybutynin Hexal" OR "oxybutynin hydrochloride" OR "oxybutynin chloride" OR "Oxybutynin Stada" OR "oxybutynin von ct" OR "Oxybutynin-Puren" OR "Oxybutynin-ratiopharm" OR "Oxymedin" OR "Oxytrol" OR "PMS-Oxybutynin" OR "Pollakisu" OR "Renamel" OR "Ryol" OR "Spasmex" OR "Oxybutynin" OR "Spasyt" OR "Tavor" OR "Oxybugamma" OR "Apo-Oxybutynin" OR "tolterodine" OR "WHE7A56U7K" OR "PHA-686464B" OR "Urotrol" OR "Detrol" OR "Unidet" OR "Detrusitol" OR "tolterodine tartrate" OR "trospium chloride" OR "trospium chloride" OR "1E6682427E" OR "azoniaspiro compound XVII" OR "Spasmex" OR "Uraton" OR "Spasmolyt" OR "Spasmo-Urgenin TC" OR "Spasmo-lyt" OR "Spasmo-Rhoival TC" OR "Trospi" OR "Ceris" OR "Uraplex" OR "Spasmo-Urgenin" OR "Sanctura" OR "solifenacin" OR "solifenacin" OR "A8910SQJ1U" OR "YM905" OR "YM 905" OR "solifenacin succinate" OR "vesicare" OR "darifenacin" OR "darifenacin" OR "darifenacine" OR "darifenacin hydrochloride" OR "Enablex" OR "UK-88525" OR "darifenacin hydrobromide" OR "Emselex" OR "APG9819VLM" OR "fesoterodine" OR "fesoterodine" OR "621G617227" OR "toviaz" OR "fesoterodine fumarate" OR "Mirabegron" OR "mirabegron" OR "MVR3JL3B2V" OR "Betanis" OR "YM 178" OR "YM-178" OR "Adrenergic beta-3 Receptor Agonists")

Appendix B. McMaster Tool for Assessing Quality of Harms Assessments and Reporting in Study Reports (McHarm) of Included and Parent Studies

First Author and Year of Publication	McHarm Question 1	McHarm Question 2	McHarm Question 3	McHarm Question 4	McHarm Question 5	McHarm Question 6	McHarm Question 7	McHarm Question 8	McHarm Question 9	McHarm Question 10	McHarm Question 11	McHarm Question 11 Explanation	McHarm Question 12	McHarm Question 13	McHarm Question 14	McHarm Question 15
Szonyi (1995)(Szonyi et al., 1995)	Y	N	Y	Y	Y	Y	N	N	N	N	U	Not Discussed	Y	N	Y	N
Malone-Lee (2001) (Malone-Lee et al., 2001)	N	N	N	N	N	Y	N	N	N	N	U	Not Discussed	Y	Y	Y	Y
Zinner (2002)(Zinner et al., 2002)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Van Kerrebroeck (2001)(Van Kerrebroeck et al., 2001)	Y	N	Y	Y	N	Y	N	N	N	N	N	AE in $\geq 5\%$ in any group	Y	N	Y	N
Sand (2004)(Sand et al., 2004)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Appell (2001)(Appell et al., 2001)	N	N	N	N	Y	U	N	N	Y	N	U	Not Discussed	Y	N	Y	Y
Foote (2005)(Foote et al., 2005)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wagg (2006)(Wagg et al., 2006)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardozo (2004) (Cardozo et al., 2004)	N	N	N	Y	Y	N	N	N	Y	N	U	Not Discussed	Y	N	Y	N
Chapple (2004) (Chapple, Rechberger et al., 2004)	N	N	N	Y	Y	N	N	N	Y	N	U	Not Discussed	Y	N	Y	N
Chapple (2004) (Chapple et al., 2004)	N	Y	N	Y	N	Y	N	N	N	N	N	Possible or probable AE in $\geq 3\%$ in any group	Y	Y	Y	N
Chapple (2005) (Chapple et al., 2005)	N	N	Y	N	Y	N	Y	N	Y	N	U	Not Discussed	Y	N	Y	N
Minassian (2007) (Minassian et al., 2007)	N	N	N	N	N	Y	N	N	N	N	U	Not Discussed	Y	Y	Y	N
Chapple (2007) (Chapple et al., 2007)	N	N	N	Y	N	Y	N	N	N	N	N	AE in $\geq 5\%$ in any group	Y	Y	Y	Y
Lackner (2008) (Lackner et al., 2008)	N	N	Y	Y	Y	N	Y	N	Y	Y	U	Not Discussed	Y	Y	Y	Y
Kraus (2010)(Kraus, Ruiz-Cerda et al., 2010)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chapple (2007) (Chapple, Van Kerrebroeck et al., 2007)	N	N	N	N	Y	U	Y	N	Y	N	N	Treatment-emergent AE in $\geq 2\%$ in any group	Y	Y	Y	N
Nitti (2007)(Nitti et al., 2007)	N	N	N	Y	N	Y	N	N	N	N	N	AE in $\geq 2\%$ in any group	Y	Y	Y	N
Herschorn (2011) (Herschorn et al., 2011)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Y	N	N	N	Y	N	N	N	Y	Y	U	Not Discussed	Y	Y	Y	Y

Herschorn (2010) (Herschorn et al., 2010)																	
Sand (2011)(Sand et al., 2011)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dmochowski (2008) (Dmochowski et al., 2008)	N	N	N	Y	N	Y	N	N	N	N	N	N	Not Discussed	N	Y	Y	Y
Staskin (2007)(Staskin et al., 2007)	N	N	N	N	N	Y	N	N	Y	N	N	Possible AE in $\geq 1\%$ in active drug group	Y	Y	Y	Y	N
DuBeau (2012) (DuBeau et al., 2012)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Herschorn (2010) (Herschorn, Swift et al., 2010)	N	N	N	Y	N	Y	N	N	N	N	N	Treatment-emergent AE in $\geq 2\%$ in active drug group with higher incidence than placebo	Y	Y	Y	Y	N
Kaplan (2011)(Kaplan et al., 2011)	N	N	Y	N	Y	N	N	N	N	N	N	Treatment-emergent AE in $\geq 2\%$ in active drug group with higher incidence than placebo	Y	N	Y	Y	N
Wagg (2013)(Wagg et al., 2013)	N	N	N	Y	N	Y	N	N	N	N	N	AE in $\geq 2\%$ in any group	Y	Y	Y	Y	N
Wagg (2014)(Wagg et al., 2014)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Khullar (2012)(Khullar et al., 2013)	Y	N	Y	Y	N	Y	N	N	N	N	N	AE in $\geq 2\%$ in any group	Y	Y	Y	Y	N
Nitti (2012)(Nitti et al., 2013)	Y	N	N	Y	N	Y	N	N	N	N	N	AE in $\geq 2\%$ in any group	Y	N	Y	Y	N
Herschorn (2013) (Herschorn et al., 2013)	Y	N	N	N	N	Y	N	N	N	Y	N	AE in $\geq 2\%$ in any group	Y	Y	Y	Y	N
DuBeau (2014) (Dubeau et al., 2014)	N	N	N	Y	N	Y	N	N	N	N	N	AE in $\geq 1\%$ in any group	Y	Y	Y	Y	N

AE = Adverse Event; N = No; U = Unclear; Y = Yes; * = Parent studies were not available for review.

Under the "First Author and Year of Publication" columns, included studies are bolded and parent studies not bolded.

McHarm Question 1: Were the harms PRE-DEFINED using standardized or precise definitions?

McHarm Question 2: Were SERIOUS events precisely defined?

McHarm Question 3: Were SEVERE events precisely defined?

McHarm Question 4: Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?

McHarm Question 5: Was the mode of harms collection specified as ACTIVE?

McHarm Question 6: Was the mode of harms collection specified as PASSIVE?

McHarm Question 7: Did the study specify WHO collected the harms?

McHarm Question 8: Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?

McHarm Question 9: Did the study specify the TIMING and FREQUENCY of collection of the harms?

McHarm Question 10: Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?

McHarm Question 11: Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?

McHarm Question 12: Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?

McHarm Question 13: Was the TOTAL NUMBER of participants affected by harms specified for each study arm?

McHarm Question 14: Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?

McHarm Question 15: Did the author(s) specify the type of analyses undertaken for harms data?

Appendix C. Adverse Events – Antimuscarinic versus Placebo

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Malone-Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Trospium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2014; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013)
Abdominal Pain	3	3	0.83 (0.25–2.74)	–	2.78 (0.12–65.08)	0.96 (0.20–4.60)	–	–	–	–	0.33 (0.03–3.19)
Abnormal Accommodation	1	1	0.64 (0.06–6.91)	–	–	0.64 (0.06–6.91)	–	–	–	–	–
AEs	11	10	1.26 (1.12–1.43)	–	0.82 (0.38–1.78)	1.14 (0.89–1.47)	1.21 (1.00–1.45)	0.99(0.71–1.38)	1.27(1.09–1.48)	–	1.56(1.32–1.84)
AEs, Severe	1	1	0.88 (0.30–2.63)	–	–	0.88 (0.30–2.63)	–	–	–	–	–
Anorexia	1	1	0.92 (0.06–13.95)	–	0.92 (0.06–13.95)	–	–	–	–	–	–
Arthralgia	1	1	1.00 (0.20–4.91)	–	–	–	–	–	–	–	1.00 (0.20–4.91)
Atrial Fibrillation	1	1	1.51 (0.06–36.71)	–	–	–	–	–	1.51 (0.06–36.71)	–	–
Back Pain	2	2	1.22 (0.03–43.25)*	–	–	–	–	–	–	–	1.22 (0.03–43.25)*
Balance Disorder	1	1	2.41 (0.12–49.99)	–	–	–	–	–	–	–	2.41 (0.12–49.99)
Blurred Vision	2	2	0.39 (0.04–3.71)*	0.77 (0.5–1.19)	–	–	–	–	–	–	0.09 (0.01–1.64)
Bronchitis	1	1	0.20 (0.02–1.70)	–	–	–	–	–	–	–	0.20 (0.02–1.70)
Cardiovascular Disease AEs	1	1	4.80 (0.26–88.40)	–	–	–	–	–	4.80 (0.26–88.40)	–	–
Cognitive AEs	2† (0)	1† (0)	–	–	–	–	†	–	–	–	†
Confusional State	2	2	0.95(0.10–8.95)	–	0.31 (0.01–7.23)	–	–	–	–	–	3.0 (0.12–7.33)
Constipation	14	13	2.39 (1.76–3.23)*	0.99 (0.61–1.63)	4.63 (0.23–91.81)	0.96 (0.10–9.02)	1.87 (1.14–3.08)	13.03 (0.77–219.66)	2.40 (1.36–4.23)*	3.61 (2.22–5.89)	3.14(2.15–4.57)
Constipation, Mild	2	2	2.73 (0.88–8.49)	–	2.78 (0.12–65.08)	–	–	–	–	–	2.73 (0.81–9.18)
Constipation, Mild-Moderate	1	1	3.42 (2.10–5.59)	–	–	–	–	–	–	3.42 (2.10–5.59)	–
Constipation, Moderate	2	2	6.56 (0.80–53.64)	–	2.78 (0.12–65.08)	–	–	–	–	–	13.30 (0.78–217.90)
Constipation, Severe	3	3	2.76 (0.58–13.05)	–	–	–	–	–	–	7.46 (0.58–13.05)	1.84 (0.29–11.63)
Contusion	1	1	1.50 (0.25–8.91)	–	–	–	–	–	–	–	1.50 (0.25–8.91)
Cough	2	2	1.77 (0.47–6.61)*	–	0.92 (0.47–6.61)	–	–	–	–	–	3.50 (0.73–16.7)
Diarrhea	8	7	1.20 (0.56–2.56)*	–	–	1.28 (0.28–5.82)	2.80 (0.19–41.56)*	0.10 (0.01–1.86)	–	–	1.26 (0.42–3.79)
Dizziness	9	9	1.43 (0.83–2.46)	–	0.31 (0.01–7.23)	0.64 (0.17–2.46)	1.63 (0.55–4.83)	0.14 (0.01–2.81)	1.60 (0.07–38.97)	–	2.22 (1.04–4.37)
Dry Eyes	2	2	1.78 (0.47–6.69)	–	–	–	–	–	–	–	1.78 (0.47–6.69)
Dry Mouth	14	13	3.94 (2.82–5.50)*	0.99 (0.61–1.63)	0.92 (0.06–13.95)	4.25 (1.63–11.07)	3.89 (2.08–7.27)*	3.07 (0.69–13.70)	5.82 (3.11–10.90)	5.49 (3.51–8.59)	4.88 (3.81–6.26)
Dry Mouth, Mild	2	2	5.57 (3.65–8.49)	–	–	–	–	–	–	–	5.57 (3.65–8.49)
Dry Mouth, Mild-Moderate	1	1	5.49 (3.46–8.70)	–	–	–	–	–	–	5.49 (3.46–8.70)	–
Dry Mouth, Moderate	2	2	4.00 (1.92–8.34)	–	–	–	–	–	–	–	4.00 (1.92–8.34)
Dry Mouth, Severe	4	4	4.80 (1.65–13.95)	–	–	–	–	–	–	5.42 (0.68–13.95)	4.59 (1.32–15.94)
Dry Skin	1	1	0.77 (0.50–1.19)	0.77 (0.50–1.19)	–	–	–	–	–	–	–
Dry Throat	2	2	1.89 (0.60–5.89)	–	–	–	–	–	–	–	1.89 (0.60–5.89)
Dyspepsia	7	7	2.01 (0.82–4.90)*	–	0.31 (0.01–7.23)	0.40 (0.11–1.43)	1.74 (0.42–7.18)	–	5.31 (0.69–40.97)	–	4.12 (1.59–10.63)
Dysuria	2	2	1.02 (0.27–3.92)	–	0.31 (0.01–7.23)	–	–	–	–	–	1.33 (0.30–5.90)
Edema	2	2	1.02 (0.46–2.25)	–	–	–	1.04 (0.34–3.18)	–	–	–	1.00 (0.33–3.06)
Facial Drop	1	1	0.31 (0.01–7.23)	–	0.31 (0.01–7.23)	–	–	–	–	–	–
Fall	2	2	0.89 (0.37–2.18)	–	0.46 (0.04–4.77)	–	–	–	–	–	1.00 (0.38–2.63)
Fatigue	3	3	1.21 (0.50–2.93)	–	0.31 (0.01–7.23)	–	–	–	–	–	1.39 (0.49–3.92)
Flatulence	1	1	1.36 (0.13–14.70)	–	–	–	–	1.36 (0.13–14.70)	–	–	–
Gastroesophageal Reflux Disorder	1	1	3.00 (0.31–28.67)	–	–	–	–	–	–	–	3.00 (0.31–28.67)
Headache	10	9	1.62 (0.95–2.79)*	–	2.78 (0.12–65.08)	2.57 (0.33–19.95)	1.97 (1.07–3.65)	–	0.11 (0.01–2.20)	–	1.46 (0.52–3.63)
Heartburn	1	1	1.13 (0.71–1.79)	1.13 (0.71–1.79)	–	–	–	–	–	–	–
Hypertension	4	4	1.27 (0.85–1.91)	–	–	–	1.45 (0.92–2.27)	–	–	–	0.75 (0.30–1.87)
Increased Post-Void Residual Volume	1	1	3.00 (0.12–73.33)	–	–	–	–	–	–	–	3.00 (0.12–73.33)
Influenza	4	3	0.83 (0.25–2.83)*	–	–	–	2.61 (0.58–11.84)	–	–	–	0.54 (0.13–2.23)
Insomnia	2	2	3.28 (0.79–13.66)	–	–	–	2.61 (0.51–13.28)	–	–	–	7.00 (0.36–134.90)
Memory Impairment	1	1	5.00 (0.24–103.68)	–	–	–	–	–	–	–	5.00 (0.24–103.68)
Muscle Spasms	1	1	0.11 (0.01–2.05)	–	–	–	–	–	–	–	0.11 (0.01–2.05)
Nasal Dryness	1	1	2.78 (0.12–65.08)	–	2.78 (0.12–65.08)	–	–	–	–	–	–

Nasopharyngitis	4	4	1.40 (0.82–2.39)	–	–	–	1.46 (0.59–3.61)	–	–	–	1.37 (0.71–2.66)
Nausea	6	6	1.32 (0.67–2.60)	–	2.78 (0.12–65.08)	0.96 (0.10–9.02)	0.35 (0.04–3.31)	–	–	–	1.53 (0.71–3.32)
Nervous System AE	2	2	1.18 (0.38–3.63)	–	–	1.28 (0.28–5.82)	–	–	1.06 (0.20–5.71)	–	–
Nervousness	1	1	2.78 (0.12–65.08)	–	2.78 (0.12–65.08)	–	–	–	–	–	–
Pain in Extremity	1	1	0.16 (0.01–2.74)	–	–	–	0.16 (0.01–2.74)	–	–	–	–
Palpitations	1	1	0.20 (0.01–4.15)	–	–	–	–	–	–	–	0.20 (0.01–4.15)
Paranoia	1	1	0.31 (0.01–7.23)	–	0.31 (0.01–7.23)	–	–	–	–	–	–
Pruritus	1	1	5.00 (0.24–103.68)	–	–	–	–	–	–	–	5.00 (0.24–103.68)
Rash	2	2	0.60 (0.03–11.15)*	–	2.78 (0.12–65.08)	–	–	–	–	–	0.14 (0.01–2.75)
Renal Colic	1	1	1.51 (0.06–36.71)	–	–	–	–	–	1.51 (0.06–36.71)	–	–
Serious AEs	11	10	0.83 (0.58–1.19)	–	–	0.96 (0.10–9.02)	0.59 (0.22–1.57)*	0.14 (0.01–2.81)	0.68 (0.15–3.02)	0.85 (0.23–3.13)	1.10 (0.67–1.81)
Sinusitis	2	2	0.64 (0.00–168.55)*	–	–	–	–	–	–	–	0.64 (0.00–168.55)*
Somnolence	4† (3)	4† (3)	0.87 (0.19–4.09)*	–	0.31 (0.01–7.23)	–	2.08 (0.53–8.23)	†	–	–	0.2 (0.01–4.15)
Toothache	1	1	2.41 (0.12–49.99)	–	–	–	–	–	–	–	2.41 (0.12–49.99)
Treatment-related AEs	2	2	1.96 (1.39–2.76)	–	–	–	–	1.67 (0.83–3.36)	2.06 (1.39–3.06)	–	–
Treatment-related Glaucoma	1† (0)	1† (0)	–	–	–	–	–	–	†	–	–
Upper Respiratory Tract Infection	2	2	0.96 (0.11–8.30)*	–	–	–	–	–	–	–	0.96 (0.11–8.30)*
Urinary Retention	10† (8)	9† (8)	3.60 (1.67–7.76)	–	2.78 (0.12–65.08)	†	2.08 (0.19–22.82)†	3.43 (0.17–70.17)	–	2.48 (0.70–8.85)	6.02 (1.81–20.00)*
Urinary Tract Infection	8	8	1.17 (0.81–1.71)	–	–	–	0.87 (0.40–1.89)	3.43 (0.17–70.17)	0.18 (0.01–4.33)	1.93 (1.04–3.58)	1.02 (0.61–1.70)
Urinary Tract Infection, Mild-Moderate	1	1	1.93 (1.04–3.58)	–	–	–	–	–	–	1.93 (1.04–3.58)	–
Urinary Tract Infection, Severe	1† (0)	1† (0)	–	–	–	–	–	–	–	†	–
Urticaria	1	1	3.00 (0.12–73.33)	–	–	–	–	–	–	–	3.00 (0.12–73.33)
Vertigo	1† (0)	1† (0)	–	–	–	–	–	†	–	–	–
Visual Disturbance	3† (1)	3† (1)	7.29 (0.38–140.36)	–	†	–	7.29 (0.38–140.36)	†	–	–	–
Vomiting	2	2	0.72 (0.10–5.09)	–	2.78 (0.12–65.08)	–	0.35 (0.04–3.31)	–	–	–	–

* = I² > 25%; † = Adverse Event noted in Study but 0 count.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; RR = rate ratio.

Appendix D. Adverse Events – Antimuscarinic versus Tolterodine IR/ER or Oxybutynin IR

Outcome	Total Comparisons/Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI)[44]	Solifenacin RR (95% CI)[48]	Total Studies	Oxybutynin ER RR (95% CI)[41]	All Studies RR (95% CI)	Fesoterodine OR (95% CI)[50]
	Versus Oxybutynin IR				Versus Tolterodine IR		Versus Tolterodine ER	
Abdominal Pain	1	0.37 (0.02–8.69)	–	0.37 (0.02–8.69)	0	–	0	–
AEs	2	0.78 (0.61–0.98)	0.94 (0.59–1.49)	0.73 (0.56–0.94)	0	–	1	1.37 (1.21–1.55)
AEs, Mild	1	1.78 (0.66–4.78)	–	1.78 (0.66–4.78)	0	–	0	–
AEs, Moderate	1	0.63 (0.33–1.17)	–	0.63 (0.33–1.17)	0	–	0	–
AEs, Severe	1	0.28 (0.06–1.20)	–	0.28 (0.06–1.20)	0	–	0	–
Back Pain	1† (0)	–	–	†	0	–	0	–
Balance Disorder	0	–	–	–	1† (0)	†	0	–
Blurred Vision	0	–	–	–	1	5.87 (0.29–119.44)	0	–
Confusional State	1	0.37 (0.02–8.69)	–	0.37 (0.02–8.69)	1† (0)	†	0	–
Constipation	1	1.85 (0.49–7.03)	–	1.85 (0.49–7.03)	1	2.06 (0.64–6.64)	1	1.24 (0.79–1.94)
Cough	1	0.56 (0.05–5.79)	–	0.56 (0.05–5.79)	0	–	0	–
Diarrhea	0	–	–	–	0	–	1	0.98 (0.44–2.21)
Dizziness	1	9.96 (0.56–176.92)	–	9.96 (0.56–176.92)	1	1.18 (0.72–1.93)	0	–
Dry Eyes	1	0.22 (0.01–4.42)	–	0.22 (0.01–4.42)	0	–	0	–
Dry Mouth	2	0.56 (0.38–0.83)	0.69(0.40–1.18)	0.46 (0.27–0.78)	1	1.18 (0.72–1.93)	1	2.13 (1.69–2.69)
Dry Mouth, Mild	1	1.27 (0.53–3.03)	–	1.27 (0.53–3.03)	0	–	0	–
Dry Mouth, Moderate	1	0.05 (0.00–0.86)	–	0.05 (0.00–0.86)	0	–	0	–
Dry Mouth, Severe	1	0.32 (0.07–1.40)	–	0.32 (0.07–1.40)	0	–	0	–
Dry Skin	1† (0)	–	–	†	0	–	0	–
Dry Throat	1† (0)	–	–	†	0	–	0	–
Dysgeusia	1	3.32 (0.14–78.25)	–	3.32 (0.14–78.25)	0	–	0	–

(Continued)

Outcome	Total Comparisons/Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI)[44]	Solifenacin RR (95% CI)[48]	Total Studies	Oxybutynin ER RR (95% CI)[41]	All Studies RR (95% CI)	Fesoterodine OR (95% CI)[50]
	Versus Oxybutynin IR				Versus Tolterodine IR		Versus Tolterodine ER	
Dyspepsia	1	7.75 (0.42–143.52)	–	7.75 (0.42–143.52)	1	2.94 (0.60–14.52)	0	–
Dysphagia	1	0.16 (0.01–2.93)	–	0.16 (0.01–2.93)	0	–	0	–
Dysphonia	1	3.32 (0.14–78.25)	–	3.32 (0.14–78.25)	0	–	0	–
Epistaxis	1 [†] (0)	–	–	†	0	–	0	–
Fatigue	1	2.22 (0.44–11.18)	–	2.22 (0.44–11.18)	0	–	0	–
Gastrointestinal	1	2.37 (0.51–10.91)	2.37 (0.51–10.91)	–	0	–	0	–
Headache	1	0.37 (0.02–8.69)	–	0.37 (0.02–8.69)	1	0.39 (0.08–1.86)	1	1.82 (0.84–3.95)
Influenza	0	–	–	–	1	–	–	0.54 (0.18–1.56)
Insomnia	0	–	–	–	1 (0) [†]	†	0	–
Nasopharyngitis	1	0.22 (0.01–4.42)	–	0.22 (0.01–4.42)	0	–	0	–
Nausea	1 [†] (0)	–	–	†	1	2.35 (0.22–25.20)	0	–
Nervousness	0	–	–	–	1	0.39 (0.02–9.39)	0	–
Serious AEs	0	–	–	–	0	–	1	2.76 (1.16–6.56) ^c
Somnolence	1	1.11 (0.07–16.91)	–	1.11 (0.07–16.91)	1	2.35 (0.22–25.20)	0	–
Treatment-related AEs	1	0.68 (0.49–0.96)	–	0.68 (0.49–0.96)	0	–	0	–
Urinary Retention	0	–	–	–	1	4.71 (0.54–40.79)	1	7.51 (0.39–145.09)
Urinary Tract Infection	1	2.22 (0.21–23.15)	–	2.22 (0.21–23.15)	0	–	0	–
Vomiting	0	–	–	–	1	3.52 (0.15–84.55)	0	–

* = I² > 25%; † = Adverse Event noted in Study but 0 count.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; RR = rate ratio.

Appendix E. Reasons for Treatment Discontinuation – Antimuscarinic versus Placebo

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Malone- Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Trospium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2012; DuBeau et al., 2014; Kraus, Ruiz- Cerdeira et al., 2010; Wagg et al., 2013)
Administrative Problems	1	1	0.50 (0.03–7.93)	–	–	–	–	–	0.50 (0.03–7.93)	–	–
AEs	13	12	1.41 (1.12–1.78)	–	2.78 (0.12–4.57)	3.53 (0.47–26.56)	1.02 (0.67–1.56)	1.14 (0.28–4.57)	0.78 (0.42–1.48)	1.44 (0.89–2.33)	1.96 (1.45–2.64)
Cognitive Function AEs	2	2	0.62 (0.03–12.30)	–	–	–	–	–	–	–	0.62 (0.03–12.30)
Constipation	7	6	1.26 (0.53–3.04)	–	–	–	0.52 (0.07–3.69)	2.06 (0.09–49.66)	1.28 (0.25–6.60)	–	1.73 (0.46–6.53)
Death	6 [†] (4)	6 [†] (4)	0.76 (0.16–3.49)	2.79 (0.12–65.66)	0.31 (0.01–7.23)	–	0.35 (0.01–8.48)	–	†	–	1.00 (0.06–15.97) [†]
Decline in Medical Condition	1	1	0.31 (0.01–7.23)	–	0.31 (0.01–7.23)	–	–	–	–	–	–
Did Not Meet Entrance Criteria	1	1	0.56 (0.25–1.25)	–	–	–	–	–	–	–	0.56 (0.25–1.25)
Dizziness	1	1	0.23 (0.01–5.52)	–	–	–	–	0.23 (0.01–5.52)	–	–	–
Dry Mouth	6	5	3.01 (1.18–7.68)	–	–	0.64 (0.06–6.91)	2.61 (0.31–22.25)	–	2.51 (0.12–51.90)	–	4.79 (1.16–19.74)
Dry Throat	1	1	2.06 (0.09–49.66)	–	–	–	–	2.06 (0.09–49.66)	–	–	–
Fall	1	1	2.79 (0.12–65.66)	2.79 (0.12–65.66)	–	–	–	–	–	–	–
Flatulence	1	1	0.23 (0.01–5.52)	–	–	–	–	0.23 (0.01–5.52)	–	–	–
Headache	2	1	2.57 (0.29–22.58)	–	–	–	1.57 (0.06–38.40)	–	–	–	3.93 (0.20–75.81)
Heartburn/GERD	1	1	2.79 (0.31–25.12)	2.79 (0.31–25.12)	–	–	–	–	–	–	–
Lost to Follow-up	4	4	2.15 (0.54–8.50)	–	–	–	1.04 (0.07–16.55)	3.43 (0.17–70.17)	3.51 (0.18–67.52)	–	2.00 (0.18–21.93)
Other	3	3	0.94 (0.42–2.14)	–	–	–	–	0.14 (0.01–2.81)	–	–	1.10 (0.47–2.58)
Protocol Violation	4	4	0.72 (0.32–1.62)	–	–	–	1.04 (0.26–4.11)	0.23 (0.01–5.52)	0.25 (0.02–2.73)	–	0.83 (0.26–2.70)
Renal Pain	1	1	2.06 (0.09–49.66)	–	–	–	–	2.06 (0.09–49.66)	–	–	–
Serious AEs	2	2	0.34 (0.06–1.97) [*]	–	–	–	0.13 (0.02–1.03)	–	0.75 (0.13–4.43)	–	–
Subject Non-Compliance	2	2	1.06 (0.41–2.72)	0.93 (0.34–2.52)	–	–	–	3.43 (0.17–70.17)	–	–	–

Total	8	8	1.07 (0.85–1.34)*	1.49 (0.56–3.95)	–	1.36 (0.49–3.83)	0.75 (0.44–1.28)	0.94 (0.40–2.19)	0.69 (0.37–1.26)	–	1.20 (0.87–1.66)
Discontinuation											
Unsatisfactory Therapeutic Effect	5	5	0.54 (0.20–1.43)*	–	–	–	0.26 (0.03–2.31)	–	0.10 (0.00–2.08)	–	0.73 (0.24–2.21)
Urinary Retention	4	4	3.44 (0.86–13.84)	–	2.78 (0.12–65.08)	–	–	2.06 (0.09–49.66)	–	–	4.32 (0.73–25.48)
Vertigo	1	1	0.31 (0.01–7.30)	0.31 (0.01–7.30)	–	–	–	–	–	–	–
Vision Blurred	2 [†] (0)	1 [†] (0)	–	–	–	–	†	–	–	–	†
Withdrew Consent	6	6	0.73 (0.45–1.17)	0.93 (0.21–4.20)	–	–	0.69 (0.20–2.43)	0.68 (0.10–4.71)	1.25 (0.25–6.36)	–	0.58 (0.22–1.50)*

* = I² > 25%; † = Adverse Event noted in Study but 0 count.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; GERD = Gastroesophageal Reflux Disorder; IR = immediate release; RR = rate ratio.

Appendix F. Reasons for Treatment Discontinuation – Antimuscarinic versus Tolterodine IR/ER or Oxybutynin IR

Outcome	Total Comparisons/ Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI) (Minassian et al., 2007)	Solifenacin RR (95% CI) (Herschorn et al., 2011)	Total Studies	Oxybutynin ER RR (95% CI) (Sand et al., 2004)	Total Studies	Fesoterodine RR (95% CI) (DuBeau et al., 2012)
	Versus Oxybutynin IR			Versus Tolterodine IR		Versus Tolterodine ER		
AEs	1	0.40 (0.15–1.12)	0.40 (0.15–1.12)	0.40 (0.15–1.12)	1	1.08 (0.52–2.23)	1	3.15 (1.81–5.49)
Constipation	0	–	–	–	0	–	1	2.15 (0.39–11.67)
Dizziness	0	–	–	–	0	–	–	–
Dry Mouth	1	0.1 (0.01–1.74)	–	0.1 (0.01–1.74)	0	–	1	2.79 (1.00–7.78)
Headache	0	–	–	–	0	–	1	3.22 (0.34–30.86)
Lost to Follow-up	0	–	–	–	1	1.76 (0.31–10.15)	0	–
Personal Reasons	0	–	–	–	1	3.53 (0.38–32.89)	0	–
Protocol Violation	0	–	–	–	1	0.39 (0.02–9.39)	0	–
Total Discontinuation	1	0.73 (0.39–1.36)	0.73 (0.39–1.36)	–	0	–	0	–
Unsatisfactory Therapeutic Effect	0	–	–	–	1	3.53 (0.38–32.89)	0	–
Vision Blurred	0	–	–	–	0	–	1 (0) [†]	†
Withdrew Consent	0	–	–	–	1	5.87 (0.29–119.44)	0	–

Only reported if both studies reported outcomes.

* = I² > 25%.

AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; OR = odds ratio.

Appendix G. Combined Adverse Events – Antimuscarinic versus Placebo

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Malone-Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Tropium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2012; Dubeau et al., 2014; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013)
^a Gastrointestinal AEs	8	8	1.52 (0.89–2.61)*	1.13 (0.71–1.79)	0.46 (0.04–4.77)	0.59 (0.23–1.50)	1.74 (0.42–7.18)]	–	5.31 (0.69–40.97)	–	2.80 (1.33–5.89)
^b Ocular/Visual AEs	7 [†] (4)	7 [†] (4)	1.32 (0.38–4.51)*	0.77 (0.50–1.19)	†	0.364 (0.06–6.91)	7.29 (0.38–140.36)]	†	†	–	5.31 (0.30–95.45)
^c Pain-related AEs	3	2	0.45 (0.15–1.35)	–	–	–	0.16 (0.01–2.74)	–	–	–	0.52 (0.13–2.05)
^d Cardiac AEs	6	6	1.28 (0.86–1.90)	–	–	–	1.45 (0.92–2.27)	–	2.84 (0.33–24.40)	–	0.57 (0.15–2.16)
^e Falls	9	9	1.29 (0.77–2.19)	–	0.31 (0.03–2.76)	0.64 (0.17–2.46)	1.63 (0.55–4.83)	0.14 (0.01–2.81)	1.60 (0.07–38.97)	–	1.76 (0.87–3.56)*
	5	4	0.88 (0.54–1.41)	–	0.92 (0.21–4.14)	–	2.61 (0.58–11.84)	–	–	–	0.76 (0.45–1.30)

(Continued)

Outcome	Total Comparisons	Total Studies	All Studies RR (95% CI)	Oxybutynin IR RR (95% CI) (Szonyi et al., 1995)	Oxybutynin ER RR (95% CI) (Lackner et al., 2008)	Tolterodine IR RR (95% CI) (Malone-Lee et al., 2001)	Tolterodine ER RR (95% CI) (DuBeau et al., 2012; Wagg et al., 2014; Zinner et al., 2002)	Trospium RR (95% CI) (Sand et al., 2011)	Darifenacin RR (95% CI) (Chapple et al., 2007; Foote et al., 2005)	Solifenacin RR (95% CI) (Wagg et al., 2006)	Fesoterodine RR (95% CI) (DuBeau et al., 2012; Dubeau et al., 2014; Kraus, Ruiz-Cerda et al., 2010; Wagg et al., 2013)
^f Respiratory tract-related AEs											
^g Neurological/Cognitive AEs	8 [†] (6)	7 [†] (6)	1.38 (0.67–2.83)	–	0.46 (0.04–4.77)	1.28 (0.28–5.82)	2.08 (0.53–8.23) [†]	†	–	–	1.76 (0.38–8.19)
^h Nasal AEs	5	5	1.24 (0.78–1.98)	–	2.78 (0.12–65.08)	–	1.46 (0.59–3.61)	–	–	–	1.13 (0.56–2.31)

* = $I^2 > 25\%$; † = Adverse Event noted in Study but 0 count, AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; RR = rate ratio.

^a = Abdominal pain, Anorexia, Dyspepsia, Gastrointestinal, Gastroesophageal Reflux Disorder, Heartburn.

^b = Abnormal Accommodation, Dry Eyes, Blurred Vision, Treatment-related Glaucoma, Visual Disturbance.

^c = Back Pain, Muscle Spasms, Pain in Extremity.

^d = Atrial Fibrillation, Cardiovascular Disease Adverse Event, Hypertension, Palpitations.

^e = Balance Disorder, Dizziness, Falls, Vertigo.

^f = Bronchitis, Cough, Influenza, Upper Respiratory Tract Infection.

^g = Cognitive Adverse Events, Confusional State, Memory Impairment, Nervous System Adverse Event, Nervousness, Somnolence.

^h = Nasal Dryness, Nasopharyngitis, Sinusitis.

Appendix H. Combined Adverse Events – Antimuscarinic versus Tolterodine IR/ER or Oxybutynin IR

Outcome	Total Comparisons/Studies	All Studies RR (95% CI)	Oxybutynin ER RR (95% CI)[44]	Solifenacin RR (95% CI)[48]	Total Studies	Oxybutynin ER RR (95% CI)[41]	Total Studies	Fesoterodine RR (95% CI)[50]
	Versus Oxybutynin IR			Versus Tolterodine IR		Versus Tolterodine ER		
^a Gastrointestinal AEs	2	2.65 (0.75–9.28)	2.37 (0.51–10.91)	3.33 (0.37–30.16)	1	2.94 (0.60–14.52)	0	–
^b Ocular/Visual AEs	1	0.22 (0.01–4.42)	–	0.22 (0.01–4.42)	1	5.87 (0.29–119.44)	0	–
^c Pain-related AEs	1 [†] (0)	–	–	†	0	–	0	–
^d Cardiac AEs	0	–	–	–	0	–	0	–
^e Falls	1	9.96 (0.56–176.92)	–	9.96 (0.56–176.92)	1	8.21 (0.43–155.33)	0	–
^f Respiratory tract-related AEs	1	0.56 (0.05–5.79)	–	0.56 (0.05–5.79)	0	–	1	0.54 (0.18–1.56)
^g Neurological/Cognitive AEs	1	0.56 (0.05–5.79)	–	0.56 (0.05–5.79)	1	1.18 (0.17–8.06)	1	5.37 (0.26–111.51)
^h Nasal AEs	1	0.07 (0.00–1.23)	–	0.07 (0.00–1.23)	0	–	0	–

* = $I^2 > 25\%$; † = Adverse Event noted in Study but 0 count, AEs = Adverse Events; CI = confidence intervals; ER = extended release; IR = immediate release; RR = rate ratio.

^a = Abdominal pain, Anorexia, Dyspepsia, Gastrointestinal, Gastroesophageal Reflux Disorder, Heartburn.

^b = Abnormal Accommodation, Dry Eyes, Blurred Vision, Treatment-related Glaucoma, Visual Disturbance.

^c = Back Pain, Muscle Spasms, Pain in Extremity.

^d = Atrial Fibrillation, Cardiovascular Disease Adverse Event, Hypertension, Palpitations.

^e = Balance Disorder, Dizziness, Falls, Vertigo.

^f = Bronchitis, Cough, Influenza, Upper Respiratory Tract Infection.

^g = Cognitive Adverse Events, Confusional State, Memory Impairment, Nervous System Adverse Event, Nervousness, Somnolence.

^h = Nasal Dryness, Nasopharyngitis, Sinusitis.

Appendix I. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.archger.2016.11.006.

References

- Appell, R. A., Sand, P., Dmochowski, R., Anderson, R., Zinner, N., Lama, D., et al. (2001). Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: Results of the OBJECT Study. *Mayo Clinic Proceedings*, 76, 358–363.
- Benner, J. S., Nichol, M. B., Rovner, E. S., Jumadilova, Z., Alvir, J., Hussein, M., et al. (2010). Patient-reported reasons for discontinuing overactive bladder medication. *BJU International*, 105, 1276–1282.
- National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE).
- Cardozo, L., Lisee, M., Millard, R., van Vierssen Trip, O., Kuzmin, I., Drogendijk, T. E., et al. (2004). Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *The Journal of Urology*, 172, 1919–1924.
- Chapple, C. R., Arano, P., Bosch, J. L., De Ridder, D., Kramer, A. E., & Ridder, A. M. (2004). Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study. *BJU International*, 93, 71–77.
- Chapple, C. R., Martinez-Garcia, R., Selvaggi, L., Toozs-Hobson, P., Warnack, W., Drogendijk, T., et al. (2005). A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: Results of the STAR trial. *European Urology*, 48, 464–470.
- Chapple, C., DuBeau, C., Ebinger, U., Rebeda, L., & Viegas, A. (2007). Darifenacin treatment of patients >or= 65 years with overactive bladder: Results of a randomized, controlled, 12-week trial. *Current Medical Research and Opinion*, 23, 2347–2358.
- Chapple, C. R., Khullar, V., Gabriel, Z., Muston, D., Bitoun, C. E., & Weinstein, D. (2008). The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. *European Urology*, 54, 543–562.
- Chapple, C., Oelke, M., Kaplan, S. A., Scholfield, D., Arumi, D., & Wagg, A. S. (2015). Fesoterodine clinical efficacy and safety for the treatment of overactive bladder in relation to patient profiles: A systematic review. *Current Medical Research and Opinion*, 31, 1201–1243.
- Chapple, C. R., Rechberger, T., Al-Shukri, S., Meffan, P., Everaert, K., Huang, M., et al. (2004). Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU International*, 93, 303–310.
- Chapple, C., Van Kerrebroeck, P., Tubaro, A., Haag-Molkenteller, C., Forst, H. T., Massow, U., et al. (2007). Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *European Urology*, 52, 1204–1212.
- Cui, Y., Zong, H., Yang, C., Yan, H., & Zhang, Y. (2014). The efficacy and safety of mirabegron in treating OAB: A systematic review and meta-analysis of phase III trials. *International Urology and Nephrology*, 46, 275–284.
- Dmochowski, R. R., Sand, P. K., Zinner, N. R., & Staskin, D. R. (2008). Trospium 60 mg once daily (QD) for overactive bladder syndrome: Results from a placebo-controlled interventional study. *Urology*, 71, 449–454.
- DuBeau, C. E., Morrow, J. D., Kraus, S. R., Creanga, D., & Bavendam, T. (2012). Efficacy and tolerability of fesoterodine versus tolterodine in older and younger subjects with overactive bladder: A post hoc, pooled analysis from two placebo-controlled trials. *Neurourology and Urodynamics*, 31, 1258–1265.
- Dubeau, C. E., Kraus, S. R., Griebling, T. L., Newman, D. K., Wyman, J. F., Johnson, T. M., et al. (2014). Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: A double-blind, placebo controlled trial. *The Journal of Urology*, 191, 395–404.
- Emberton, M., & Anson, K. (1999). Acute urinary retention in men: An age old problem. *BMJ (Clinical Research Ed.)*, 318, 921–925.
- Foote, J., Glavind, K., Kralidis, G., & Wyndaele, J. J. (2005). Treatment of overactive bladder in the older patient: Pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. *European Urology*, 48, 471–477.
- Geoffroy, R. (2012). Treatments for overactive bladder: Focus on pharmacotherapy. *Journal of obstetrics and gynaecology Canada: JOGC=Journal d'obstetrique et gynecologie du Canada: JOGC*, 34, 1092–1101.
- Gomelsky, A. (2009). Urinary incontinence in the elderly female. *Annals of Long-Term Care*, 17, 41–45.
- Gormley, E. A., Lightner, D. J., Faraday, M., & Vasavada, S. P. (2015). Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *The Journal of Urology*, 193, 1572–1580.
- Griebling, T. L., Kraus, S. R., Richter, H. E., Glasser, D. B., & Carlsson, M. (2009). Tolterodine extended release is well tolerated in older subjects. *International Journal of Clinical Practice*, 63, 1198–1204.
- Han, L., Agostini, J. V., & Allore, H. G. (2008). Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *Journal of the American Geriatrics Society*, 56, 2203–2210.
- Herbison, P., Hay-Smith, J., Ellis, G., & Moore, K. (2003). Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: Systematic review. *BMJ (Clinical Research Ed.)*, 326, 841–844.
- Herschorn, S., Stothers, L., Carlson, K., Egerdie, B., Gajewski, J. B., Pommerville, P., et al. (2010). Tolerability of 5 mg solifenacin once daily versus 5 mg oxybutynin immediate release 3 times daily: Results of the VECTOR trial. *The Journal of Urology*, 183, 1892–1898.
- Herschorn, S., Pommerville, P., Stothers, L., Egerdie, B., Gajewski, J., Carlson, K., et al. (2011). Tolerability of solifenacin and oxybutynin immediate release in older (>65 years) and younger (<= 65 years) patients with overactive bladder: Sub-analysis from a Canadian, randomized, double-blind study. *Current Medical Research and Opinion*, 27, 375–382.
- Herschorn, S., Barkin, J., Castro-Diaz, D., Frankel, J. M., Espuna-Pons, M., Gousse, A. E., et al. (2013). A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta(3) adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology*, 82, 313–320.
- Herschorn, S., Swift, S., Guan, Z., Carlsson, M., Morrow, J. D., Brodsky, M., et al. (2010). Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: A head-to-head placebo-controlled trial. *BJU International*, 105, 58–66.
- Huang, W., Zong, H., Zhou, X., & Zhang, Y. (2015). Efficacy and safety of imidafenacin for overactive bladder in adult: A systematic review and meta-analysis. *International Urology and Nephrology*, 47, 457–464.
- Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., et al. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*, 17, 1–12.
- Kaplan, S. A., Schneider, T., Foote, J. E., Guan, Z., Carlsson, M., & Gong, J. (2011). Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: A prospective, head-to-head, placebo-controlled trial. *BJU International*, 107, 1432–1440.
- Kessler, T. M., Bachmann, L. M., Minder, C., Lohrer, D., Umbehr, M., Schunemann, H. J., et al. (2011). Adverse event assessment of antimuscarinics for treating overactive bladder: A network meta-analytic approach. *PUBLIC LIBRARY OF SCIENCE*, 6, e16718.
- Khullar, V., Amarenco, G., Angulo, J. C., Cambroner, J., Hoyer, K., Milsom, I., et al. (2013). Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: Results from a randomised European-Australian phase 3 trial. *European Urology*, 63, 283–295.
- Kraus, S. R., Bavendam, T., Brake, T., & Griebling, T. L. (2010). Vulnerable elderly patients and overactive bladder syndrome. *Drugs & Aging*, 27, 697–713.
- Kraus, S. R., Ruiz-Cerda, J. L., Martire, D., Wang, J. T., & Wagg, A. S. (2010). Efficacy and tolerability of fesoterodine in older and younger subjects with overactive bladder. *Urology*, 76, 1350–1357.
- Lackner, T. E., Wyman, J. F., McCarthy, T. C., Monigold, M., & Davey, C. (2008). Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. *Journal of the American Geriatrics Society*, 56, 862–870.
- Loke, Y. K., Price, D., & Herxheimer, A. (2007). Systematic reviews of adverse effects: Framework for a structured approach. *BMC Medical Research Methodology*, 7, 32.
- Luo, D., Liu, L., Han, P., Wei, Q., & Shen, H. (2012). Solifenacin for overactive bladder: A systematic review and meta-analysis. *International Urogynecology Journal*, 23, 983–991.
- Macdiarmid, S. A. (2008). Maximizing the treatment of overactive bladder in the elderly. *Reviews in Urology*, 10, 6–13.
- Madhuvrata, P., Cody, J. D., Ellis, G., Herbison, G. P., & Hay-Smith, E. J. (2012). Which anticholinergic drug for overactive bladder symptoms in adults. *The Cochrane Database of Systematic Reviews*, 1, Cd005429.
- Malone-Lee, J. G., Walsh, J. B., & Maugourd, M. F. (2001). Tolterodine: A safe and effective treatment for older patients with overactive bladder. *Journal of the American Geriatrics Society*, 49, 700–705.
- Milsom, I., Stewart, W., & Thuroff, J. (2000). The prevalence of overactive bladder. *The American Journal of Managed Care*, 6, S565–573.
- Minassian, V. A., Ross, S., Sumabat, O., Lovatsis, D., Pascali, D., Al-Badr, A., et al. (2007). Randomized trial of oxybutynin extended versus immediate release for women aged 65 and older with overactive bladder: Lessons learned from conducting a trial. *Journal of obstetrics and gynaecology Canada: JOGC=Journal d'obstetrique et gynecologie du Canada: JOGC*, 29, 726–732.
- Nitti, V. W., Dmochowski, R., Sand, P. K., Forst, H. T., Haag-Molkenteller, C., Massow, U., et al. (2007). Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *The Journal of Urology*, 178, 2488–2494.
- Nitti, V. W., Auerbach, S., Martin, N., Calhoun, A., Lee, M., & Herschorn, S. (2013). Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *The Journal of Urology*, 189, 1388–1395.
- Novara, G., Galfano, A., Secco, S., D'Elia, C., Cavalleri, S., Ficarra, V., et al. (2008). A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. *European Urology*, 54, 740–763.
- Paquette, A., Gou, P., & Tannenbaum, C. (2011). Systematic review and meta-analysis: Do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? *Journal of the American Geriatrics Society*, 59, 1332–1339.
- Peters, N. L. (1989). Snipping the thread of life. Antimuscarinic side effects of medications in the elderly. *Archives of Internal Medicine*, 149, 2414–2420.
- Petri, H., & Urquhart, J. (1991). Channeling bias in the interpretation of drug effects. *Statistics in Medicine*, 10, 577–581.
- Reynolds, W. S., McPheeters, M., Blume, J., Surawicz, T., Worley, K., Wang, L., et al. (2015). Comparative effectiveness of anticholinergic therapy for overactive

- bladder in women: A systematic review and meta-analysis. *Obstetrics and Gynecology*, 125, 1423–1432.
- Rochon, P. A., & Gurwitz, J. H. (1997). Optimising drug treatment for elderly people: The prescribing cascade. *BMJ (Clinical Research)*, 315, 1096–1099.
- Roxburgh, C., Cook, J., & Dublin, N. (2007). Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. *The Cochrane Database of Systematic Reviews*Cd003190.
- Sand, P. K., Miklos, J., Ritter, H., & Appell, R. (2004). A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *International Urogynecology Journal and Pelvic Floor Dysfunction*, 15, 243–248.
- Sand, P. K., Johnson Ii, T. M., Rovner, E. S., Ellsworth, P. I., Oefelein, M. G., & Staskin, D. R. (2011). Trospium chloride once-daily extended release is efficacious and tolerated in elderly subjects (aged >= 75 years) with overactive bladder syndrome. *BJU International*, 107, 612–620.
- Santaguida, P. L., & Raina, P. (2008). *The Development of the McHarm Quality Assessment Scale for adverse events: Delphi Consensus on important criteria for evaluating harms*. .
- Scheife, R., & Takeda, M. (2005). Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clinical Therapeutics*, 27, 144–153.
- Staskin, D., Sand, P., Zinner, N., & Dmochowski, R. (2007). Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: Results from a multicenter phase III trial. *The Journal of Urology*, 178, 978–983 [discussion 983–]974.
- Sternberg, S. A., Wershof Schwartz, A., Karunanathan, S., Bergman, H., & Mark Clarfield, A. (2011). The identification of frailty: A systematic literature review. *Journal of the American Geriatrics Society*, 59, 2129–2138.
- Szonyi, G., Collas, D. M., Ding, Y. Y., & Malone-Lee, J. G. (1995). Oxybutynin with bladder retraining for detrusor instability in elderly people: A randomized controlled trial. *Age and Ageing*, 24, 287–291.
- Thuroff, J. W., Abrams, P., Andersson, K. E., Artibani, W., Chapple, C. R., Drake, M. J., et al. (2011). EAU guidelines on urinary incontinence. *European Urology*, 59, 387–400.
- Tubaro, A. (2004). Defining overactive bladder: Epidemiology and burden of disease. *Urology*, 64, 2–6.
- Van Kerrebroeck, P., Kreder, K., Jonas, U., Zinner, N., & Wein, A. (2001). Tolterodine once-daily: Superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*, 57, 414–421.
- Wagg, A., Wyndaele, J. J., & Sieber, P. (2006). Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: A pooled analysis. *The American Journal of Geriatric Pharmacotherapy*, 4, 14–24.
- Wagg, A., Verdejo, C., & Molander, U. (2010). Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *International Journal of Clinical Practice*, 64, 1279–1286.
- Wagg, A., Khullar, V., Marschall-Kehrel, D., Michel, M. C., Oelke, M., Darekar, A., et al. (2013). Flexible-dose fesoterodine in elderly adults with overactive bladder: Results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. *Journal of the American Geriatrics Society*, 61, 185–193.
- Wagg, A., Cardozo, L., Nitti, V. W., Castro-Diaz, D., Auerbach, S., Blauwet, M. B., et al. (2014). The efficacy and tolerability of the beta3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients. *Age and Ageing*, 43, 666–675.
- Wu, T., Duan, X., Cao, C. X., Peng, C. D., Bu, S. Y., & Wang, K. J. (2014). The role of mirabegron in overactive bladder: A systematic review and meta-analysis. *Urologia Internationalis*, 93, 326–337.
- Wyndaele, J. J., Schneider, T., MacDiarmid, S., Scholfield, D., & Arumi, D. (2014). Flexible dosing with fesoterodine 4 and 8 mg: A systematic review of data from clinical trials. *International Journal of Clinical Practice*, 68, 830–840.
- Zinner, N. R., Mattiasson, A., & Stanton, S. L. (2002). Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *Journal of the American Geriatrics Society*, 50, 799–807.