a systematic review and meta-analysis

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Background

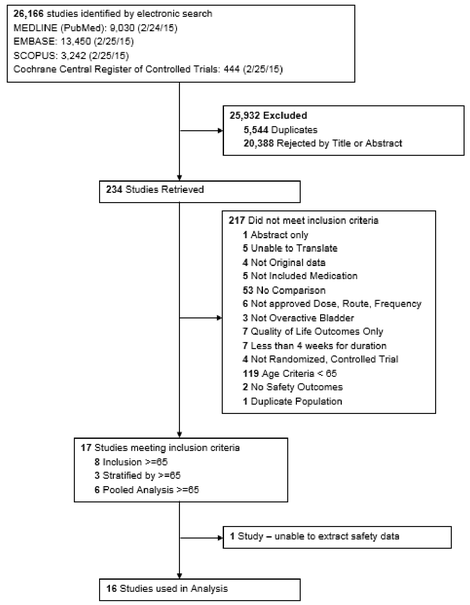
- Signs and symptoms of overactive bladder (OAB) such as urinary frequency, urgency, nocturia, and incontinence affect 25% of adults aged 60 or older.
- Treatment options for the elderly include oxybutynin, tolterodine, trospium, darifenacin, solifenacin, fesoterodine, and mirabegron.
- Providers should be cautioned in using these medications due to adverse drug events (ADEs) including dry mouth, blurry vision, and constipation in antimuscarinics.
- Several systematic reviews and meta-analyses have evaluated the use of medications used to treat OAB.
- No systematic review has used meta-analytical technique to broadly explore safety outcomes based on age.
- The goal of this systematic review is to perform exploratory analyses of harms (ADEs and treatment discontinuations) in self-administered medications used to treat OAB in studies with patients aged 65 or older.

Methods

- Randomized-controlled trials (RCTs), sub-analysis of a parent RCT, or pooled analysis of two or more RCTs in patients aged 65 or older with OAB and received antimuscarinic or beta-3 agonist were included.
- An abbreviated version of the search strategy (aged AND [antimuscarinic agents OR beta-3 agonists OR oxybutynin OR tolterodine OR trospium OR darifenacin OR solifenacin OR fesoterodine OR mirabegron]) was used in MEDLINE (PubMed), EMBASE, SCOPUS, and Cochrane Central Register for Controlled Trials.
- All harms reported in all included studies were identified and collected.
- Data extraction and quality assessment (Jadad Criteria and McHarm Tool) were independent collected by two authors
- Random effects models were used for all analyses
- Data synthesis
  - Harms were collected independent of dose
  - Tolterodine immediate-release (IR) and extended-release (ER) were combined
  - Oxybutynin IR and ER were not combined due to differences in adverse events
  - Harms were combined based on symptomatology to improve power
- Forest plots were created for all harms, odds ratios described harms in overall analyses and stratified by individual antimuscarinic .
- Number needed to harm (NNH) were calculated for statistically significant harms.

Determination of Studies

Figure 1: Determination of studies



Results

Table 1: Characteristics of Included and Parent Studies

First Author and Year of Publication	Study Type	Duration (Weeks)	Drug 1 (n)	Drug 2 (n)	Placebo-Controlled (n)	Age	Percent Females %(n)	JADAD Criteria Score
Szonyi (1995)[7]	RCT	6	Oxy IR (28)	--	Yes (26)	≥70	93.3 (56)	4
Malone-Lee (2001)[8]	RCT	4	Tolt IR (134)	--	Yes (43)	≥65	65.0 (115)	3
Zinner (2002)[9]	SA of RCT	--	Tolt ER (214)	--	Yes (223)	≥65	74.4 (325)	--
Van Kerrebroeck (2001)[10]	--	12	--			--	--	5
Sand (2004)[11]	SA of RCT	--	Oxy ER (51)	Tolt IR (60)	No	≥65	100 (111)	--
Appell (2001)[12]	--	12	--			--	--	4
Foote (2005)*[13]	Pooled RCT	--	Dari (207)	--	Yes (110)	≥65	77.6 (246)	--
Wagg (2006)[14]	Pooled RCT	.	Soli (623)		Yes (422)	≥65	74.7(781)	--
Cardozo (2004)[15]	--	12	--			--	--	3
Chapple (2004)[16]	--	12	--			--	--	3
Chapple (2004)[17]	--	4	--			--	--	3
Chapple (2004)[18]	--	12	--			--	--	5
Minassian (2007)[19]	RCT	12	Oxy ER (38)	Oxy IR (30)	No	≥65	100 (72)	2
Chapple (2007)[20]	RCT	12	Dari (266)	--	Yes (133)	≥ 65	76.6 (306)	5
Lackner (2008)[21]	RCT	4	Oxy ER (26)	--	Yes (24)	≥65	100 (50)	5
Kraus (2010)[22]	Pooled RCT	--	Feso (370)	--	Yes (178)	≥65	70.9 (389)	--
Chapple (2007)[23]	--	12	--			--	--	3
Nitti (2007)[24]	--	12	--			--	--	4
Herschorn (2011)[25]	SA of RCT	--	Soli (27)	Oxy IR (30)	No	≥65	77.2 (44)	--
Herschorn (2010)[26]	--	8	--			--	--	5
Sand (2010)[27]	Pooled RCT	.	Tros ER (85)		Yes (58)	≥75	73.4 (105)	--
Dmochowski (2008)[28]	--	12	--			--	--	3
Staskin (2007)[29]	--	12	--			--	--	5
DuBeau (2012)[30]	Pooled RCT	--	Feso (546)	Tolt ER (586)	Yes (306)	≥65	78.4 (1128)	--
Herschorn (2009)[31]	--	12	--			--	--	5
Kaplan (2010)[32]	--	12	--			--	--	5
Wagg (2013)[33]	RCT	12	Feso (392)	--	Yes (393)	≥65	53.2 (418)	5
Wagg (2014)[34]	Pooled RCT	.	Tolt ER (192)	--	Yes (521)	≥65	65.2 (465)	--
Khullar (2013)[35]	--	12	--			--	--	4
Nitti (2012)[36]	--	12	--			--	--	5
Herschorn (2013)[37]	--	12	--			--	--	3
DuBeau (2014)[38]	RCT	12	Feso (293)	--	Yes (283)	≥65	82.0 (461)	5

*= unable to obtain parent studies

Table 2: Significant Adverse Outcomes – Antimuscarinic versus Placebo

Outcome	Total Comparisons	All Studies	Oxy IR[7]	Oxy ER[21]	Tolt IR/ER[8,9,30,34]	Tros[27]	Dari[13,20]	Soli[14]	Feso[22,30,33,38]
		Odds Ratio (95% Confidence Interval)							
Adverse Events	11	1.26 (1.12-1.43) NNH = 8.3	--	0.82 (0.38-1.78)	1.13 (1.02-1.24)[8,9,30,34] NNH = 27.0	0.99(0.71-1.38)	1.27(1.09-1.48)[13,20] NNH = 7.8	--	1.56(1.32-1.84)[30,33,38] NNH =4.9
Constipation	14	2.39 (1.76-3.23)* NNH =15.4	0.99 (0.61-1.63)	4.63 (0.23-91.81)	1.81 (1.11-2.95)[8,9,30,34] NNH =20.4	13.03 (0.77-219.66)	2.40 (1.36-4.23)*[13,20] NNH =9.4	3.61 (2.22-5.89) NNH =9.0	3.14(2.15-4.57)[22,30,33,38] NNH = 17.5
Constipation, Mild-Moderate	1	3.42 (2.10-5.59) NNH=9.7	--	--	--	--	--	3.42 (2.10-5.59) NNH=9.7	--
Dizziness	9	1.43 (0.83-2.46)	--	0.31 (0.01-7.23)	1.16 (0.49-2.79)[8,9,34]	0.14 (0.01-2.81)	1.60 (0.07-38.97)[20]	--	2.22 (1.04-4.37)[22,33,38] NNH =70
Dry Mouth	14	3.94 (2.82-5.50)* NNH =5.1	0.99 (0.61-1.63)	0.92 (0.06-13.95)	3.89 (2.37-6.41)*[8,9,30,34] NNH =6.7	3.07 (0.69-13.70)	5.82 (3.11-10.90)[13,20] NNH =5.1	5.49 (3.51-8.59) NNH =4.7	4.88 (3.81-6.26)[22,30,33,38] NNH = 4.2
Dry Mouth, Mild	2	5.57 (3.65-8.49) NNH =5.5	--	--	--	--	--	--	5.57 (3.65-8.49)[22,33] NNH =5.5
Dry Mouth, Mild-Moderate	1	5.49 (3.46-8.70) NNH=5.0	--	--	--	--	--	5.49 (3.46-8.70) NNH=5.0	--
Dry Mouth, Moderate	2	4.00 (1.92-8.34) NNH =20.0	--	--	--	--	--	--	4.00 (1.92-8.34)[22,33] NNH =20.0
Dry Mouth, Severe	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)[22,33,38] NNH =64.0
Dyspepsia	7	2.01 (0.82-4.90)*	--	0.31 (0.01-7.23)	0.81 (0.19-3.41)*[8,9]	--	5.31 (0.69-40.97)[13]	--	4.12 (1.59-10.63)[22,33,38] NNH =47.8
Headache	10	1.62 (0.95-2.79)*	--	2.78 (0.12-65.08)	2.02 (1.12-3.63)[8,9,30,34] NNH =73.0	--	0.11 (0.01-2.20)[13]	--	1.46 (0.52-3.63)[22,30,33,38]
Treatment-related Adverse Events	2	1.96 (1.39-2.76) NNH =5.8	--	--	--	1.67 (0.83-3.36)	2.06 (1.39-3.06)[20] NNH = 5.2	--	--
Urinary Retention	10† (8)	3.60 (1.67-7.76) NNH =95.1	--	2.78 (0.12-65.08)	2.08 (0.19-22.82)[8(†),9,30(†)]	3.43 (0.17-70.17)	--	2.48 (0.70-8.85)	6.02 (1.81-20.00)*[22,30,33,38] NNH =65.6
Urinary Tract Infection	8	1.17 (0.81-1.71)	--	--	0.87 (0.40-1.89)[9,34]	3.43 (0.17-70.17)	0.18 (0.01-4.33)[20]	1.93 (1.04-3.58) NNH=35.0	1.02 (0.61-1.70)[22,33,38]

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

DISCUSSION

- This was the first study to explore harms from antimuscarinic medications in the elderly using RCTs, sub-analyses of RCT, and pooled analyses of RCTs
- The risk of dizziness in fesoterodine was significantly higher than placebo
- Older adults may be more vulnerable to this ADEs which may contribute to falls
- The risk for dyspepsia in fesoterodine was significantly higher than placebo
- Urinary retention was significantly higher in subjects receiving any antimuscarinic or fesoterodine compared to placebo
- Future pharmacoepidemiological studies can further explore these ADEs outside RCTs

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LEGEND

CI = confidence interval; Dari = darifenacin; ER = extended-release; Feso = fesoterodine; IR = immediate-release; NNH = number need to harm; Oxy = oxybutynin; RCT = randomized-controlled trial; SA = sub-analysis; Soli = solifenacin; Tolt = tolterodine; Tros = trospium

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