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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.

Contents

Abbreviations: AE, adverse event; OAB, overactive bladder; ER, extended, release; IR, immediate release; NNH, number needed to harm; PRIMSA, 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, & Griebling, 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 ≥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