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Efficacy and Adverse Events of Antimuscarinics for Treating Overactive Bladder: Network Meta-analyses

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Abstract

Context: Millions of people worldwide experience overactive bladder (OAB), and antimuscarinics are the pharmacologic treatment of choice. Several conventional meta-analyses have been published, but they fail to quantify efficacy and adverse events across drugs, dosages, formulations, and pharmaceutical forms.
Objective: To perform two network meta-analyses summarizing the efficacy and adverse events of antimuscarinics in the treatment of OAB.
Evidence acquisition: Medline and Scopus searches, previous systematic reviews, conference abstracts, book chapters, and the reference lists of relevant articles were searched. Trialists were contacted. Eligible studies were randomized trials that compared at least one antimuscarinic for treating OAB with placebo or with another antimuscarinic, and that reported efficacy and/or adverse event outcomes. Efficacy was assessed for six outcomes (perception of cure or improvement, urgency episodes per 24 h, leakage episodes per 24 h, urgency incontinence episodes per 24 h, micturitions per 24 h, and nocturia episodes per 24 h). Adverse events were assessed in seven categories according to the Common Terminology Criteria for Adverse Events. Across all outcomes, a summary efficacy and an adverse event score were computed. Two authors independently extracted data.
Evidence synthesis: For the comparison of the efficacy, 76 trials enrolling 38 662 patients were included; for adverse events, 90 trials enrolling 39 919 patients were included. In the subset of studies reporting on treatments and dosages as used in clinical practice, 40 mg/d trospium chloride, 100 mg/g per day oxybutynin topical gel, and 4 mg/d fesoterodine had the best efficacy, while higher dosages of orally administered oxybutynin and propiverine had the least favorable relationship of efficacy and adverse events.
Conclusions: This is the first study allowing trade-offs between efficacy and adverse events of various drugs and dosages in the treatment of patients with OAB. Differences among the various antimuscarinics call for careful, patient-centered management in which regimen changes should be considered.

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1. Introduction

Overactive bladder (OAB) is a widespread chronic illness that affects the lives of millions of people worldwide at all ages but is more common in the elderly, with a prevalence of up to 31% in women and 42% in men >75 yr [1]. OAB has a major impact on quality of life; it affects emotional, social, sexual, occupational, and physical aspects of daily life [2–4] and is associated with a greater risk of falls and injuries, including fractures [5], which may even lead to death. Besides the debilitating manifestations for patients, OAB also imposes a substantial economic burden, as direct annual costs are comparable to those of other chronic diseases such as dementia and diabetes mellitus [6].

Among several nonsurgical interventions, antimuscarinics are the pharmacologic treatment of choice for OAB. Various conventional systematic reviews [7–14] have assessed the efficacy of eight currently available antimuscarinics (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride). However, despite applying up-to-date systematic review methods, these conventional meta-analyses fell short in quantifying and comparing the efficacy and adverse events across different drugs, dosages, formulations, and routes of administration, because these summaries did not use all available information on reported comparisons. This shortfall is a major impediment when examining the trade-offs in a decision-analytic context.

Recently, new meta-analytic methods—network meta-analysis—have become available that allow complete assessments across different drugs [15–19]. Because the selection of a specific drug should be based on a careful assessment of its efficacy and related adverse events, a complete examination and careful benchmarking of all available drugs, formulations, and dosages is the first step in rational decision-analytic reasoning.

However, for the efficacy assessment, such an analysis is not available yet. Until recently, such an analysis was also lacking for adverse events. In 2011, Kessler and colleagues published the first network meta-analysis summarizing the most common adverse events of various antimuscarinics, dosages, and formulations [20]. The authors concluded that based on adverse events, most currently used antimuscarinics would qualify for the initial treatment of OAB. Since publication of that paper, various new study reports have been published. A new drug formulation [21] and a new OAB drug [22] also have become available.

In this paper, we describe a network meta-analysis summarizing data from all randomized comparative clinical trials assessing the efficacy of all currently used antimuscarinics for the most salient and commonly reported outcomes, and we present the results of an update of the existing network analysis on adverse events of Kessler et al. [20]. We provide efficacy and adverse events charts for all assessed medications and dosages, allowing straightforward benchmarking of antimuscarinics for treating OAB in clinical practice.

2. Evidence acquisition

The systematic reviews were done according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [23].

2.1. Search strategy

2.1.1. Efficacy data

To identify randomized controlled trials of antimuscarinics compared with placebo and head-to-head comparative trials without a placebo arm, we started with the recent Cochrane Review by Nabi et al. [13] and three recent meta-analyses by Chapple et al. [7], Novara et al. [14], and Madhuvrata et al. [12].

Secondarily, an update search from June 2005 until April 2012 was done. The Medline search employed a search algorithm, including combinations of the two MeSH terms *urinary bladder, overactive* and *muscarinic antagonists*, as well as various associated free text terms. Searches were repeated in Scopus, entering the same search terms. In addition, other relevant studies cited in the reference lists of the selected papers were considered. We also searched reference lists and conference abstracts by hand, checked relevant reviews and book chapters, and contacted manufacturers and trialists. Searches were limited to published randomized controlled trials. The search was conducted without restriction on language. The search strategies are available on request. To be included, studies had to be randomized controlled trials comparing at least one antimuscarinic for treating OAB with placebo or with another antimuscarinic. Crossover trials and studies that were described only in an abstract were not included.

2.1.2. Adverse events data

A literature search update from January 2008 to April 2012 was done to identify randomized controlled clinical studies of antimuscarinics compared with placebo or head-to-head comparisons. Electronic searches were performed in Medline using combinations of the MeSH terms *muscarinic antagonists, urinary bladder*, and *overactive*, as well as associated free text terms. Scopus was searched using the key words *antimuscarinic* AND overactive AND bladder*. In addition, we searched reference lists and conference abstracts by hand, checked relevant reviews and book chapters, and contacted manufacturers and trialists. The search strategy is available in the Appendix.

2.1.3. Selection criteria

All currently used antimuscarinics were considered. Trials with intravesical antimuscarinic administration, drugs with less direct antimuscarinic effects (such as smooth muscle relaxants, flavoxate hydrochloride, calcium channel blockers, potassium channel openers, β-adrenoceptor agonists, α-adrenoceptor antagonists, prostaglandin synthetase inhibitors, and tricyclic antidepressants), and drugs no longer used in clinical practice were excluded. In the case of multiple publications on the same patients, the most complete report was chosen for each trial. We extracted