Long-Term Adherence to Antimuscarinic Therapy in Everyday Practice: A Systematic Review

Paul W. Veenboer*,† and J. L. H. Ruud Bosch‡

From the Department of Urology, University Medical Centre Utrecht, Utrecht, The Netherlands

Purpose: Antimuscarinic drug treatment is known to have side effects and, consequently, poor adherence in therapeutic regimens. In this systematic review we study the long-term (greater than 6 months) adherence to antimuscarinic drugs in daily clinical practice, and identify factors contributing to poor adherence and persistence.

Materials and Methods: This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A literature search was performed using PubMed® and Embase™ using synonyms for incontinence, overactive bladder and antimuscarinics combined with synonyms for medication adherence. We chose to include only pharmaceutical database studies (using prescription/insurance claim data) and patient self-report studies, using established pharmacoepidemiological parameters such as persistence rate and medication possession rate.

Results: A total of 1,245 titles were screened, of which 102 abstracts were assessed. Fourteen studies were ultimately included, comprising 190,279 unique patients (mean age 69.5 years). Regardless of which specific antimuscarinic drug is studied, persistence rates are usually poor. Considering all drugs together, median persistence rates were 12.0% to 39.4% (with an outlier of 75.5%) at 12 months, 8.0% to 15.0% at 18 months and 6.0% to 12.0% at 24 months. At 36 months persistence rates ranged from 0.0% (darifenacin) to 16.0% (trospium). Mean reported medication possession rates were also low, with a mean of 0.37 at 12 months. Risk factors for discontinuation were identified, with the most important being younger age group, use of oxybutynin and use of immediate release formulations.

Conclusions: Improvement in adherence and persistence with antimuscarinic medication should be an important goal in the development of new drugs for overactive bladder and urinary incontinence.

Key Words: muscarinic antagonists, cholinergic antagonists, urinary incontinence, medication adherence, patient compliance

Abbreviations and Acronyms

IR = immediate release

MPR = medication possession rate

OAB = overactive bladder

RCT = randomized controlled trial

UI = urinary incontinence

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* Correspondence: Department of Urology, University Medical Center Utrecht, Room 04.236, PO Box 85500, 3508 GA Utrecht, The Netherlands (telephone: 31-887553348; e-mail: P.W.Veenboer-2@umcutrecht.nl).

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‡ Financial interest and/or other relationship with GSK.

ANTIMUSCARINIC medication is the cornerstone of the medical treatment of UI and OAB. Targeting the M3 and M2 subtypes of the muscarinic anticholinergic receptor, these drugs aim to reduce the parasympathetic activity that normally triggers detrusor muscle contractions. Antimuscarinics are known to cause anticholinergic side effects. These side effects may result in discontinuation of therapy and, thus, poor adherence, ie the extent to which a patient follows medical instructions. Adherence is a synonym of compliance, and is best measured by medication possession

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rate or adherence ratio and by persistence (ie the duration from initiation to discontinuation of therapy).[1] The terminology is briefly explained in figure 1.

Furthermore, if a drug does not fulfill the expectations of a patient (ie it does not reduce OAB or UI symptoms), patients might stop taking the prescribed pills. A systematic review published in 2011 (including articles up to 2009) focused primarily on RCTs lasting 12 weeks, which already showed high discontinuation rates (4% to 31%).[2] Sexton et al also looked at several database studies and found 12-week discontinuation rates of 43% to 83%. However, since 2009 much new evidence has been published on this topic. Although one might expect adherence to antimuscarinic therapy to be poor, the exact discontinuation rates after a longer followup (more than 12 weeks) have not been well investigated.

RCTs do not always provide a reliable overview of therapy compliance because they often involve a period of only 4 to 12 weeks, after which no more data are collected, thus giving rise to an important bias. Extension trials of RCTs might continue for a longer time but are still prone to an important selection bias. These extension trials are often voluntary and patients persisting on medication are those with a positive experience with the drug. Furthermore, patients in (extension) trials in everyday practice have to pay for the medication themselves, which could be seen as a financial bias. The only studies that would be free of this kind of bias are pharmacoepidemiological studies. However, to our knowledge no systematic reviews on adherence to antimuscarinic therapy are currently available.

Three main questions are addressed in this review. How good is compliance (continuous measure) and persistence (discrete measure) per antimuscarinic during a period of at least 6 months? 2) Which factors determine whether a patient will discontinue his/her medication? 3) What reasons do patients give for discontinuation of antimuscarinic treatment?

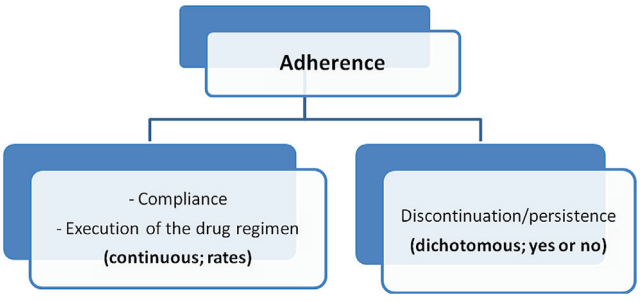

Figure 1. Brief overview of pharmacoepidemiological terminology

METHODS

This review was performed following PRISMA guidelines.[3] Studies were selected if they included adult (older than 18 years) patients with OAB (ICD-9: 596.51) and UI (ICD-9: 788.3). The preferred study types were database studies and self-report studies that investigated persistence and adherence. The study period had to cover at least 6 months. Open label extension studies of previous RCTs were excluded from analysis as were nonsystematic reviews. We chose to exclude extension trials because of the inherent risk of selection bias.

The search was performed on December 28, 2012 using PubMed and Embase. The complete search syntaxes can be found in the supplementary Appendix (http://jurology.com/). Results were limited to adult patients (older than 18 years) and studies published in the last 10 years. Only English language papers were selected. Many of the synonyms used previously by the National Institute for Health and Care Excellence were used and adapted when necessary.[4]

Duplicates were removed and title screening was performed by 1 author (PWV). Abstract screening was done by both authors independently, after which an agreement was reached concerning which papers to include. All selected papers were thoroughly examined by both authors to assess their relevance to the present review. Several pharmacoepidemiological parameters of measures for persistence and measures for compliance were collected from the selected studies.

Measures for Persistence

Persistence is calculated from the index date until the patient discontinues treatment or is lost to followup, or the maximum followup period has ended, whichever occurs first.[1,5] The rate of persistence is the number of patients who persist in using medication during a certain period. In some studies this is also called the continuation rate, which is the same as 1-discontinuation rate. If possible, persistence rates were collected for 6, 12, 18, 24, 30 and 36 months. The number of patients who never received a refill after the initial (index) prescription was included in many papers, and can be seen as a measure for early discontinuation.

Measures for Compliance

Medication possession rate. This is the total number of days of medication dispensed, except for the last refill, divided by the number of days between the first date on which medication was dispensed and the last refill date.[6]

Percentage of days covered. This figure is similar to the MPR but is calculated differently. It adds the number of days prescribed and gives a more conservative measure than MPR. It differs from MPR in that it credits the patients with finishing the current fill of medication before starting the next refill, which is not always the case. The difference between the percentage of days covered and MPR is especially important when multiple drugs are