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Adherence and persistence to oral medication in patients with overactive bladder (OAB) in a real-world setting – a systematic literature review

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ABSTRACT

Purpose To evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) in a real-world setting.

Materials and Methods Systematic literature searches of six electronic publication databases were performed to identify database studies of OAB patients treated with antimuscarinics and/or mirabegron. Studies reporting persistence and adherence data solely from patient interviews or subjective questionnaires were excluded. Reference lists of identified studies and relevant systematic reviews were assessed to identify additional relevant studies.

Results The search identified 3897 studies, of which 30 were selected for extraction. Overall, persistence ranged from 5–47%. In studies reporting data for antimuscarinics and mirabegron (n=3), persistence at 1 year was 12–25% and 32–38%, respectively. Median time to discontinuation was <5 months for antimuscarinics (except one study [6.5 months]) and 5.6–7.4 months for mirabegron. The proportion of patients adherent at 1 year varied between 15–44%. In studies reporting adherence for antimuscarinics and mirabegron, adherence was higher with mirabegron (mean medication possession ratio (MPR): 0.59 vs 0.41–0.53; mean proportion of days covered: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19–0.49). Reported determinants of persistence and adherence included female gender, older age group, using an extended-release formulation and treatment experience.

Conclusion Most patients with OAB discontinued oral OAB pharmacotherapy and were non-adherent 1 year after treatment initiation. However, mirabegron was associated with greater persistence and adherence compared to antimuscarinics, supporting mirabegron as a first-line pharmacological treatment option for patients with OAB.

STRENGTHS AND LIMITATIONS

- This systematic literature review includes data for mirabegron, which was approved in 2013 and not covered in previous systematic reviews examining persistence and adherence to overactive bladder medication.

- Only observational database studies were included in this study, providing a more accurate picture of rates of adherence and persistence to overactive bladder medication, which are generally lower in routine clinical practice compared to randomized clinical trials.

- This systematic literature review provides a global picture of adherence and persistence to OAB medication based on the inclusion of data from Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States.

- Although determinants of persistence and adherence were evaluated in this study, other factors such as influence persistence with treatment in patients with overactive bladder including patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed.

- The definitions and calculations of persistence and adherence were not uniform across the literature and the terms were often used interchangeably, limiting the ability to compare across studies.

INTRODUCTION

Overactive bladder (OAB) is defined as a condition with characteristic symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.[1] OAB affects 11.8–24.7% of adults in North America and Europe, and the prevalence increases with age.[2] In addition to age, risk factors for developing OAB include diabetes, UTIs and obesity.[3 4]

OAB symptoms are associated with a negative impact on health-related quality of life (HRQoL) and a significant economic burden. Indeed, bothersome OAB symptoms may lead to depression and anxiety, and sleep disturbances, which can adversely affect a patient's daily, social and professional functioning.[5 6] Whilst the cost of pharmaceutical treatment represents only a small fraction of the total therapy cost, the provision of containment products (eg, pads), treatment for clinical depression, nursing home stays and loss of productivity due to work absenteeism are the main cost drivers in OAB.[7 8] For example, the total annual cost of OAB was estimated to be $24.9 billion in the United States in 2007[9] and €9.7 billion across five European countries (Germany, Italy, Spain, Sweden and the United Kingdom) and Canada in 2005.[8]

Behavioural and lifestyle modifications are routinely the initial treatment strategy for OAB, and pharmacotherapy is recommended only if conservative management is not effective.[10] As OAB is a chronic condition, it is important that patients continue with treatment to control symptoms.[11] Lack of adherence and persistence to medication are considered the leading causes of preventable morbidity in patients with chronic conditions[12 13] and are also associated with greater indirect costs.[13] Although antimuscarinics are the current mainstay of oral pharmacotherapy, they are often associated with bothersome anticholinergic side effects, such as dry mouth and constipation; tolerability is one of the most common reasons for treatment discontinuation.[11 14-17] In a systematic review of antimuscarinic treatment in

patients with OAB, rates of discontinuation at 12 weeks ranged from 4–31% in clinical trials and 43–83% in medical claims databases.[16]

The other class of oral pharmacotherapy approved for the treatment of OAB is β_3-adrenergic receptor agonists. Mirabegron is currently the only commercially available agent of this class licensed in countries across Europe, North America and Asia.[18-20] Due to a distinct mechanism of action, the incidence of typical anticholinergic side effects with mirabegron is generally similar to placebo,[21] which may translate into better treatment persistence.[22 23] In addition, results of a recent economic analysis found that increased persistence with mirabegron treatment vs antimuscarinics was associated with reduced healthcare resource use and work hours lost, resulting in lower total costs.[24]

In general, rates of persistence and adherence with antimuscarinics and mirabegron are typically lower in routine clinical practice compared to interventional clinical trials.[11 25] To help identify factors affecting long-term persistence and adherence to OAB pharmacotherapy, a contemporary, comprehensive review of real-world evidence is needed. As mirabegron was a relatively new OAB treatment, it was not included in previous systematic reviews. Therefore, the current analysis aims to systematically review prospective and retrospective observational database studies conducted with antimuscarinics and/or mirabegron to determine the rates and determinants of persistence and adherence.

METHODS

This systematic literature review (SLR) was conducted in accordance with guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[26] The protocol for the review was registered *a priori* with the International Prospective Register of Systematic Reviews (registered January 18, 2017 with PROSPERO CRD42017059894).

Searches were performed April 27, 2017 *via* the following electronic databases: Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied

Health Literature (CINAHL); MEDLINE; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; and the Centre for Reviews and Dissemination (CRD) database. The search terms were persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [Title], AND "bladder" OR "overactive bladder" OR "OAB" OR urin* OR incontinen* [Title], OR oxybutynin OR tolterodine OR fesoterodine OR trospium OR darifenacin OR solifenacin OR propiverine OR imidafenacin OR mirabegron OR flavoxate OR hyoscyamin* OR anticholinerg* OR antimuscarin* [Title].

All search results were exported into EndNote Web (Thomas Reuter, CA, USA) bibliography software and duplicates removed electronically and manually. The full electronic search strategy is outlined in the Supplemental information.

Inclusion and exclusion criteria

Inclusion criteria were: prospective and retrospective observational database studies investigating persistence and adherence to oral medication for the treatment of OAB in adults, which were published on any date, in a peer-reviewed source. Exclusion criteria were: abstract unavailable; studies not yet fully completed; randomised controlled trials (RCTs); systematic reviews; narrative literature reviews; conference papers; single case studies/reports; studies investigating OAB medication among only healthy, asymptomatic participants; studies from which oral-only OAB persistence/adherence results cannot be isolated from other results (ie, transdermal patches); and studies containing patients aged <18 years (where the data pertaining to these patients could not be removed from the results). Populations with lower urinary tract symptoms due to stress incontinence and benign prostatic hyperplasia were also excluded.

Study selection

Duplicates were removed and title and abstract screening was performed by two independent researchers (PS and GY). Full-text articles were obtained and studies were

excluded if they did not meet the inclusion criteria.[26] Any disagreement in study selection was resolved through discussion and consultation with another member of the project team (FF) where necessary. During screening, open-label extension studies of RCTs were excluded as the trial designs were unlikely to reflect a real-world setting. Studies using data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were directly recorded rather than extracted from supplemental patient interviews or subjective questionnaires. The literature search was supplemented by screening for potential additional relevant studies identified from the reference lists of eligible articles.

Data extraction

Parameters that may affect persistence or adherence were collected, including patient characteristics (age and sex); interventions (initial [index] OAB drug and formulation) and comorbidities. The definitions, outcomes and determinants of treatment persistence and adherence were also collected, where reported. The extracted data were evaluated by one researcher and verified by a second researcher.

RESULTS

Brief overview of studies

Overall, 3897 articles were identified from the literature search; 3,614 were screened for title/abstract and 75 assessed for eligibility (figure 1). A total of 30 articles were included in the SLR (supplementary table 1), including three identified from reference lists.[27-29]

The data were collected from patients treated in Europe (12 studies) and North America (18 studies) (supplementary table 1) and were included in the analysis. The number of participants included in the published studies ranged from 377 to 103 250. Where stated, the mean age of the participants ranged from 44 to 80 years and the duration of follow-up ranged from 6 months to 7 years. Interventions included bethanechol, darifenacin,

fesoterodine, flavoxate, hyoscyamine, imipramine, mirabegron, oxybutynin, propiverine, solifenacin, tolterodine and trospium chloride. Definitions of adherence and persistence differed across the studies (supplementary table 1). In general, medication possession rate (MPR) or proportion of days covered (PDC) by prescription were typically used as a surrogate for adherence to drug. Persistence was typically defined as the proportion of patients continuing therapy/refilling prescriptions for the follow-up period (without discontinuing the index drug or switching to other OAB drug[s]) and/or the median time to discontinuation (TTD).

Persistence

Overall, persistence rates decreased over time, regardless of agent (supplementary table 2).

Antimuscarinic studies

Data for persistence (or discontinuation) at approximately 6 months was available in 14 articles[28-41] which reported data on antimuscarinics only. Yeaw 2009 was an exception due to the inclusion of bethanechol (a muscarinic receptor agonist), which accounted for <1.5% of the pharmacy claims for OAB medications.[29] The proportion of patients persistent at 6 months was <50% except for the studies of Sicras-Mainar *et al*,[36-38] where persistence ranged from 57–71%. In addition, two studies reported discontinuation rates of 6–43% after 1 month of initial treatment.[35 41]

At 1 year, persistence rates for antimuscarinics, in 19 studies, ranged from around 5% up to 47%.[15 23 30 32 34 36 37 39 40 42-49] Median TTD was <5 months (30 to 128 days) for all medications across all studies,[15 23 28 32 42 49 50] with the exception of Krhut *et al*[34] (6.5 months). At 2 years, over 75% of patients discontinued treatment.[30 32 44 50 51] Rates of treatment switching were infrequently reported, and where provided, were ≤17% of patients.[28 31 33 42 47 50 51]

Antimuscarinic and mirabegron studies

In all four studies, a greater proportion of patients persisted with mirabegron compared with antimuscarinics. In one study, persistence rates for tolterodine and mirabegron at 6 months were 19% and 35%, respectively.[27] Persistence at 1 year ranged from 12–25% for antimuscarinics and from 32–38% for mirabegron, as reported in three studies[15 23 49] and was significantly greater with mirabegron vs antimuscarinics in two studies.[15 23] Overall, mirabegron, solifenacin and fesoterodine were associated with the highest rates of persistence.[15 23]

Median TTD (or median persistence) in the overall study populations was longer with mirabegron (5.6–7.4 months) compared with the assessed antimuscarinics (1.0–3.6 months).[15 23 27 49]

Adherence

Adherence rates to all OAB medications reduced over time in all studies and varied across studies (supplementary table 2).

Antimuscarinic studies

At 1 year, the proportion of adherent patients varied between 1%[41] and 36%,[42] across those studies that provided these data. Few studies reported adherence beyond 1 year. However, Sears *et al* reported that 34% of patients were adherent at the end of 3 years,[52] which was comparable to the adherence rates reported by some other studies at just 1 year.[42 47]

Antimuscarinic and mirabegron studies

In the three studies, adherence at 1 year was significantly higher in patients receiving mirabegron compared with antimuscarinics (mean MPR: 0.59 vs 0.41 to 0.53; mean PDC: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19 to 0.49).[15 23 49] The proportion of patients adherent at 1 year was also greater with mirabegron compared with antimuscarinics (mean MPR ≥0.80: 43% vs 22–35%; mean PDC ≥0.80: 44% vs 31%).[15 23]

Determinants of persistence and adherence

Determinants of persistence and adherence were reported in 24 of the 30 studies. As expected, most studies reported medication type as a determinant of persistence/adherence (figure 2; supplementary table 2). In general, persistence and adherence were higher in: older patients compared with younger patients;[23 27 28 30-33 40 42-45 47 50 53] female patients compared with their male counterparts,[28 30 33 43-45 53] except in one study;[52] patients receiving extended-release (ER) formulations compared with immediate-release formulations;[42 50] and treated patients compared to treatment naïve patients (or untreated in the pre-index period [6 months or 1 year]).[15 23 30] Comorbidities, including diabetes, Parkinson's disease, epilepsy, dementia, multiple sclerosis and hypertension, were correlated with increased treatment persistence and adherence;[43 44 53] exceptions were chronic obstructive pulmonary disease and migraine.[44 53]

Other reported determinants of favorable persistence and adherence included higher treatment doses;[30] low daily quantity of tablets,[31] absence of UTI; higher baseline OAB costs;[33] treatment by urologists vs gynecologists/general practitioners; the absence of side effects (headache, stomach upset and glaucoma);[44] White vs Black, Hispanic and Asian patients and patients of other ethnicities;[41 45] lower medication co-payment;[45] and use of fewer medications.[41]

DISCUSSION

This systematic review provides an overview of persistence and adherence with oral pharmacotherapies used to treat patients with OAB in real-life clinical practice. A wealth of data were collected from 30 observational studies performed in Europe and North America totaling over 500 000 patients. A number of key findings were identified, including greater persistence and adherence with mirabegron vs antimuscarinics,[15 23 27 49] in females vs males,[28 33 43 45 53] in older vs younger patients,[23 27 28 30-33 40 42-45 47 50 53] and in previously treated vs untreated patients.[15 23 30]

Across the studies, persistence appeared to reduce very quickly after initiation of treatment for all OAB therapies, with low rates (<50%) already evident at 1 month.[27 35 41] Longer follow-up periods showed that large proportions of patients discontinued treatment by 1 year (62–100%)[15 23 29 32 39-41 43 44 50] and by the end of 3 years, less than 10% of patients continued on any antimuscarinic.[50] These steep reductions in rates of persistence over time were mirrored by the reported adherence rates.

The chronic nature of OAB means that long-term use of medication is essential to manage OAB symptoms and improve health outcomes. It is therefore important for patients to receive first-line treatment that has a good efficacy-tolerability profile and evidence of favorable persistence vs other treatment options. Among the antimuscarinics, solifenacin and fesoterodine were generally associated with better persistence and adherence.[15 23 37 47] In studies that assessed both mirabegron and antimuscarinics, persistence with mirabegron was statistically significantly greater ($p<0.001$).[15 23 27] Adherence to mirabegron was also greater; however, mean/median MPR values in the overall mirabegron populations did not indicate medication adherence (<0.80). Although these studies did not directly assess the reason(s) for the observed benefits of mirabegron, proposed reasons include lower rates of bothersome anticholinergic adverse events, particularly dry-mouth, compared with antimuscarinics and unmet expectations of antimuscarinic treatment.[15 23 27]

It is well established that poor medication persistence and adherence reduces the ability to achieve optimum clinical benefits and limits treatment success, especially for chronic conditions such as OAB.[12-14 40] The unwillingness of patients to continue to take long-term treatment has been observed across many chronic conditions, with non-adherence to medication observed in ~50% of patients.[12] An analysis across six chronic conditions found 1-year persistence and adherence rates to be low for all conditions, and lowest for OAB medications (antimuscarinics),[29] suggesting an unmet treatment need. However, this study was performed prior to the availability of mirabegron for use in routine clinical practice, and therefore an updated analysis of persistence in chronic conditions might be warranted.

As alluded to above, persistence and adherence to treatment is expected to improve outcomes for patients with OAB. Two studies have reported that patients compliant and adherent to OAB medication experienced significantly improved urinary symptoms and HRQoL compared with patients who were non-persistent.[54 55] These data are consistent with studies describing other chronic diseases, such as diabetes and depression, where good adherence resulted in improved health outcomes[13 56] as well as reduced complications and disability, and improved HRQoL and life expectancy.[57] Moreover, greater persistence and adherence to treatment for OAB is associated with significantly lower medical, sick leave and short-term disability costs.[45] Indeed, economic models based on real-world inputs suggest that improved persistence with mirabegron translates into benefits of reduced healthcare resource use, and lower direct and indirect costs of treatment compared with antimuscarinics.[24 58] Additionally, mirabegron is reported to be cost effective vs six antimuscarinics from commercial and Medicare perspectives in the United States, due to fewer projected adverse events and comorbidities, and data suggesting better persistence.[59]

Independent variables for treatment discontinuation were studied by at least half of the papers included in our literature review, of which sex, age, comorbidities and previous experience of OAB medications were shown to be important factors in more than two studies. Only six studies reported switch-rates and although these were low, the treatment strategy of cycling antimuscarinic agents in patients who do not achieve symptom relief is common in clinical practice. Yet recent analysis of real-world data suggests that switching antimuscarinics may provide sub-optimal care.[51] In contrast, switching to mirabegron from antimuscarinic therapy has proved beneficial in over 50% of patients with OAB in an observational study.[60]

This review represents a large pooled analysis of real-world data for persistence and adherence to oral OAB medication across different geographical locations (Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States); however, there were no identifiable trends between data and countries. The definitions and

calculations of persistence and adherence were not uniform across the literature and the terms were often used interchangeably. This lack of consistency led to some limitations on the ability to compare across studies. Other limitations to performing cross-study comparisons or pooled analyses in this SLR include differences in the individual study populations and/or study designs, resulting in considerable variations between data. For example, the median TTD for oxybutynin ER and tolterodine ER were determined to be 5.1 and 5.5 months, respectively, by one study,[50] but only 60 and 56 days, respectively, by another study.[15]

Furthermore, it is very difficult to capture the specific reasons for treatment discontinuation from prescription-driven or medical claim data rather than patient-derived data.[15] The current review excluded data from RCTs to better reflect patient behavior in the general OAB population in real-life clinical practice.[11] Only one paper included in our review reported that antimuscarinic side effects were significantly associated with discontinuation,[44] despite reports that such side effects are bothersome and a common reason for discontinuation of antimuscarinic treatment.[11 16 25] Additional factors that could not be assessed by our study, but can influence persistence with treatment in OAB patients are patient expectations, appropriate counselling and patient satisfaction with treatment.[11 14 25]

In addition to the limitations listed above, it should be noted that Sicras-Mainar *et al*[36 37] reported data on the same patient group (in terms of demographics and the timeframe/geographical source). This is also the case for two studies published by Sicras-Mainar *et al* in 2013 and 2014.[48 61] Also, this SLR excluded data on non-oral pharmacotherapies (eg, onabotulinum toxin A) and combination mirabegron plus antimuscarinic therapies, where additional efficacy has been reported compared to the monotherapies.[62] Further research on persistence and adherence to these OAB therapies is needed to better evaluate current treatment options. Additional studies are also required to improve our understanding of persistence and adherence in OAB, including qualitative studies to examine the reasons for discontinuation and real-world studies to examine

resource use associated with OAB medication in relation to adherence and persistence. As OAB is a chronic disease, clinicians should not only take into consideration the efficacy and side effects of an agent when deciding on treatment options, but also ensure that realistic patient expectations from treatment are set through patient education and counselling. The patient's life-style should also be considered as this is likely to impact adherence and persistence with OAB therapy.

CONCLUSIONS

Persistence and adherence were greater with mirabegron compared with antimuscarinics, and appeared to be greater with solifenacin and fesoterodine compared with other antimuscarinics. In addition, greater persistence and adherence were generally observed in patients who were female, older, treatment-experienced and receiving ER formulations. Together with the efficacy and tolerability data from clinical trials, these real-world data suggest a benefit from using mirabegron as first-line oral pharmacotherapy for patients with OAB.

Contributorship Statement

GY, PS, JN, ZH, ES and FF were involved in conceptualisation and design of the study and critical review of the manuscript. FF, PS and GY performed the data extraction. All authors approved the final manuscript as submitted.

Competing Interests

ZH, JN and ES are employed by Astellas. FF has received a grant from Astellas for study design, data extraction and manuscript development.

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Data Sharing Statement

The search strategy and all data supporting this study are provided as supplementary information accompanying this paper.

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Abbreviations and Acronyms

ER = extended-release

HRQoL = health-related quality of life

MPR = medication possession rate

OAB = overactive bladder

PDC = proportion of days covered

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs = randomised controlled trials

SLR = systematic literature review

TTD = time to discontinuation

UTI = urinary tract infection

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FIGURE LEGENDS

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

*Studies were excluded for the following reasons: outcome measure(s) of persistence and/or adherence, relevant to this systematic review (such as medication possession rate, proportion of days covered, discontinuation rate), were not presented within the full text of the article (n=17); adherence/persistence data were drawn from surveys, interviews or self-reports (n=13); cohort contained a portion of patients under 18 years of age (who could not be removed or isolated from results/data) (n=7); participants had prior awareness/knowledge of partaking in a study related to OAB medication (ie, open-label extension to a study or prior written consent) (n=6); a full article text was not available (ie, only a conference abstract) or the full text was not in English; or non-oral OAB medications were included within the presented results (and could not be removed or isolated from results/data) (n=1)

§Three of these studies were identified by reviewing reference lists of included studies and relevant systematic literature reviews

Figure 2 Frequency for reported determinants of discontinuation

*In one study the relationship was not statistically significant

**Includes dose, formulation, race, prior infection, financial burden, prescriber profession, side effects, medication co-payment and polypharmacy

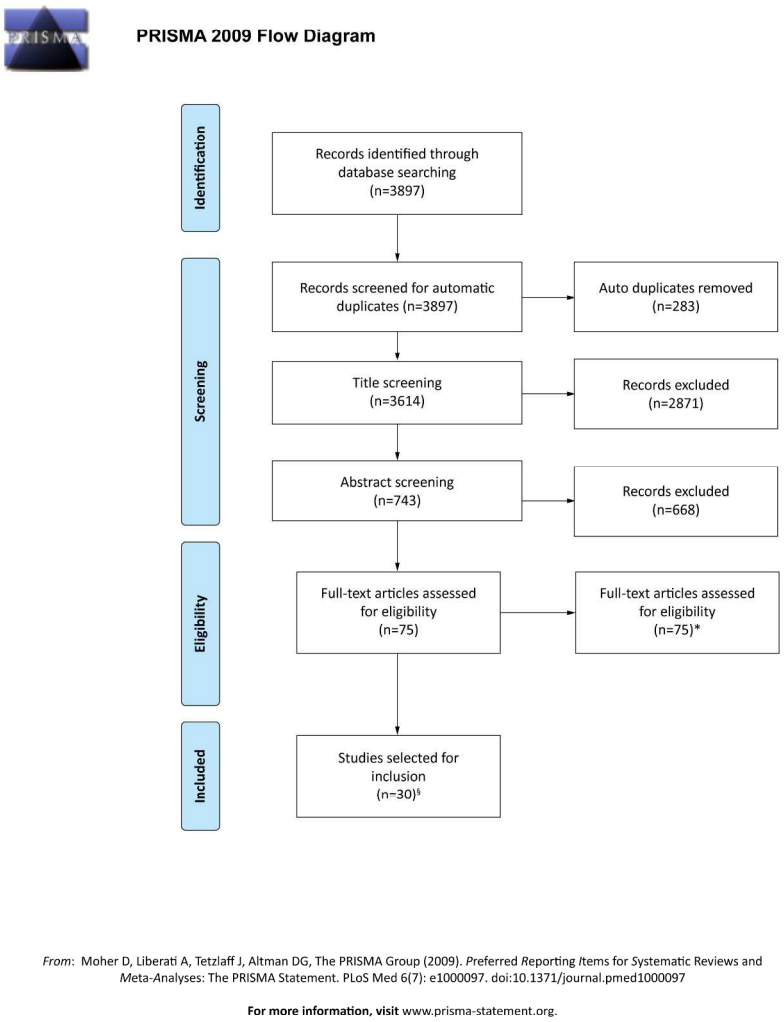

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

215x279mm (300 x 300 DPI)

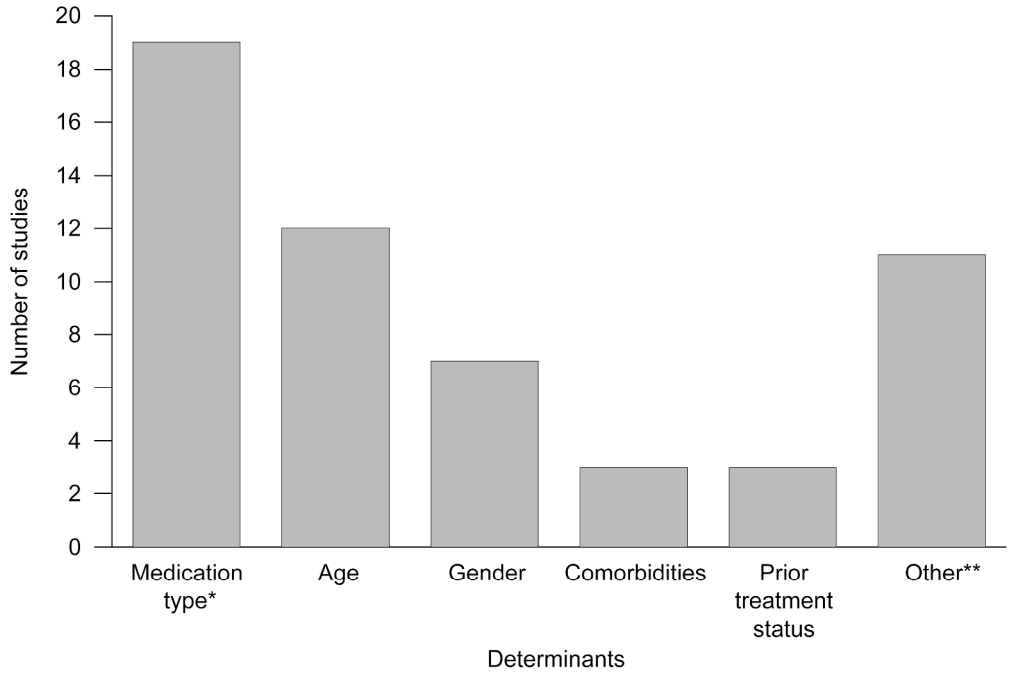

Figure 2 Frequency for reported determinants of discontinuation

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Supplemental Table 1: Patient characteristics, interventions and definitions/variables of persistence, adherence and discontinuation reported in the studies.

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Brostrøm and Hallas (2009)[1] Odense University Pharmacoepidemio-logical Database (OPED); Denmark) (1999–2006)	n=2477 Male: n=836 (33.8%) Female: n=1641 (66.2%) Mean age: 68.3 years[a]	Any prescription of OAB medication: flavoxate (n=21) oxybutynin TD (n=48) tolterodine (n=1478) solifenacin (n=774) trospium (n=271) darifenacin (n=52)	Patients who continued taking a particular drug for up to 7 years with no more than 120-day gaps were regarded as experiencing single-treatment episodes Variables: age, gender, prior use of OAB agents and use of anti-diabetic drugs	Up to 7 years
Chancellor et al (2013)[2] IMS Lifelink Database, Connecticut; USA (2005–2008)	n=103 250 Male: n≈25 916[a] (25.1%) Female: n≈77 334[a] (74.9%) Mean (SD) age: 58.7 (15.7) years	First (new) prescription of OAB medication in adults ≥18 years: tolterodine ER (n=43 881)[a] solifenacin (n=15 488)[a] oxybutynin (n=15 075)[a] darifenacin (n=10 532)[a] oxybutynin ER (n=10 325)[a] oxybutynin TD (n=2272)[a] tolterodine (n=2581)[a] trospium (n=2478)[a] trospium ER (n=413)[a]	To be considered a discontinuation, patients were required to have a gap of at least 45 days in therapy based on fill dates and days' supply Adherence rate was defined as the proportion of patients filling more than one prescription with an MPR of ≥80%	2 years
Chapple et al (2017)[3] Clinical Practice Research Datalink (CPRD); UK (2013–2014)	n=21 996 Male: n=6513 (29.6%) Female: n=15 483 (70.4%) Mean (SD) age: 63.9 (16.3) years	First (new) prescription of OAB medication in adults ≥18 years: mirabegron (n=1203) darifenacin (n=126) fesoterodine (n=1287) flavoxate (n=144) oxybutynin ER (n=1144) oxybutynin IR (n=5779) propiverine (n=95) solifenacin (n=8191) tolterodine ER (n=1561) tolterodine IR (n=1523) trospium chloride (n=943)	Treatment was defined as discontinued if the maximum allowable gap duration was at least 1.5 times the intended duration of the most recent prescription Adherence rate was defined as mean MPR at 12 months	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
D'Souza et al (2008)[4] Undisclosed medical claims database; USA (1999–2004)	n=1117 Male: n≈206[a] (18.4%) Female: n≈911[a] (81.6%) Mean (SD) age: 55.7 (14.5) years	First index of an OAB medication in adults ≥18 years: oxybutynin ER (n=249) oxybutynin IR (n=108) tolterodine ER (n=454) tolterodine IR (n=306)	Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuing the index drug or switching to other OAB drugs Adherence rate was measured as the proportion of patients with an MPR of ≥0.80 Variables: age, gender, drug formulations and OAB-associated comorbidities (eg, falls/fractures, skin infections, UTIs, anxiety/depression)	1 year
Desgagné et al (1999)[5] Régie de l'assurance maladie du Québec (RAMQ) database; Canada (1994–1997)	n=6690 Male: n=2534 (37.9%) Female: n=4156 (62.1%) Mean age: 77.3 years[a]	Patients aged ≥65 years with at least one prescription claim (first index) of: oxybutynin (n=5718) flavoxate (n=972)	Persistence evaluated by percentage of patients refilling their initial prescription	Up to 4 years
Gomes et al (2012)[6] Canada (Ontario Drug Benefit database of prescriptions)	n=56 851[a] Male: n≈18 496 (32.5%)[a] Female: n≈38 355 (67.5%)[a] Mean age: 77.7 years[a]	Patients aged >65 years with a first index (new) claim of: oxybutynin IR (n=31 996) tolterodine ER/IR (n=24 855)	Persistence with treatment was defined by refills for the index drug within an interval defined by the duration specified on the prescription plus a 50% grace period	2 years
Gopal et al (2008)[7] UK (Health Improvement Network database of prescriptions) (1991–2005)	n=29 369 Male: n=0 (0%) Female: n=29 369 (100%) Mean (SD) age: 63.9 (16.8) years	Women aged ≥18 years prescribed anti-cholinergic medications: tolterodine IR tolterodine ER oxybutynin IR oxybutynin ER flavoxate terodiline trospium properivine solifenacin	Discontinuation was defined by no anticholinergic prescriptions issued within 90 days after the end of the last anticholinergic drug prescription Anticholinergic medications were considered discontinued at the time a patient switched to another medication or as above Variables: drug formulation	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Ivanova et al (2014)[8] OptumHealth Reporting and Insights claims database; USA (2007–2012)	n=10 318 Male: n≈2822 (27.4%)[a] Female: n≈7496 (72.6%)[a] Mean age: 51.6 years	Patients aged 18 to 64 receiving a new prescription of: darifenacin (n=970)[a] solifenacin (n=2662)[a] oxybutynin (n=2889)[a] tolterodine (n=3116)[a] trospium (n=454)[a] fesoterodine (n=227)[a]	Persisters were defined as patients who did not switch or discontinue the index antimuscarinic during the first 6 months after the treatment initiation date Discontinuation was defined by a gap of at least 60 days between refills within the first 6 months after the treatment initiation date Switching was defined as a changed prescription from the index antimuscarinic within the first 6 months after the treatment initiation date (with a gap of 60 days between the end of the day supply of the index antimuscarinic and the new antimuscarinic) Variables: age, gender, history of UTIs and index antimuscarinic	6 months
Johnston et al (2012)[9] Truven Health MarketScan® Database; USA (2004–2009)	n=73 120 Male: n=29 406 (40.2%) Female: n=43 714 (59.8%) Mean age: 69.0 years[a]	First index drug in OAB patients with or without diabetes, aged ≥18 years: darifenacin oxybutynin solifenacin tolterodine trospium	Persistence was measured as the number of days from the index date until a gap in OAB medication of ≥45 days Adherence was assessed using the interval-based (fixed time-period) MPR (adherent patients had an ≥80% MPR) Variables: age, gender and diabetes	1 year
Kalder et al (2014)[10] Disease Analyzer database (IMS Health); Germany (2005–2012)	n=26 834 Male: n≈9660[a] (36%) Female: n≈17 174[a] (64%) Mean (SD) age: 69.4 (13.2) years	First index (new) prescription in patients aged ≥18 years: darifenacin (n=1995) fesoterodine (=811) oxybutynin (n=3813) propiverine (n=2714) solifenacin (n=4844) tolterodine (n=1814) trospium (n=10 843)	Treatment discontinuation was defined as a period of 90 days without prescription of UI therapy but with at least one visit to the same doctor after 90 days Variables: age, gender, comorbidity burden (including diabetes) and antimuscarinic side-effects	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Kleinman et al (2014)[11] Human Capital Management Services [HCMS] Research Reference Database; USA (2001–2011)	n=2960 Male: n=878 (29.7%) Female: n=2082 (70.3%) Mean age: 46.6 years	First index of OAB medication in adults aged 18 to 64 years: darifenacin fesoterodine oxybutynin flavoxate[b] solifenacin tolterodine trospium hyoscyamine[b] imipramine[b]	Persistence was measured as the number of days from index UA prescription until first ≥30-day gap in UA medication supply Adherence was measured as the percentage of the annual post-index period with available medication	1 year
Krhut et al (2014)[12] Dept. of Urology and Dept. of Gynaecology and Obstetrics, University Hospital Ostrava; Czech Republic (2009–2010)	n=377 Male: n=52 (13.8%) Female: n=325 (86.2%) Mean (SD) age: 60.3 (13.8) years	First (new) index of OAB medication within patients attending hospital as an outpatient: trospium (n=189) propiverine (n=41) tolterodine ER (n=9) solifenacin (n=48) fesoterodine (n=90)	Persistence was assessed according to the patient records	1 year
Manack et al (2011)[13] Thomson Reuters MarketScan® Commericial and Medicare Supplemental Databases; USA (2002–2007)	n=46 271[c] Male: n=19 727 (42.6%) Female: n=26 544 (57.4%) Mean (SD) age: 62.5 (19.6) years	Patients with neurogenic bladder origin (such as spinal cord injury and multiple sclerosis) receiving an oral OAB medication	Continuation was defined as ≥365 days of OAB oral drug use beginning at the index date with ≤90 days between the end of therapy and end of eligibility Discontinuation was defined as ≥6 months of no OAB oral drug use between the end of therapy and the end of eligibility	1 year
Mauseth et al (2013)[14] The Norwegian Prescription Database; Norway (2004–2010)	n=32 178 Male: n=0 (0.0%) Female: n=32 178 (100.0%) No mean age reported. The majority of patients (60.5%) were aged ≥60 years	Adult patients aged ≥18 years with a first index (new) prescription of: tolterodine (n=12 389) solifenacin (n=13 682) darifenacin (n=4399) fesoterodine (n=1708)	Persistence defined as the population who had not discontinued the drug during a period of 365 days after the index date A switch was defined as a prescription for another of the drugs included in the study within 365 days after the index date Adherence was measured using MPR (sum of days of supply for all tablets purchased, except those received at the last fill, divided by the total number of days from the first to the last filling) Variables: age and initial antimuscarinic	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Nitti et al (2016)[15] Optum Database; USA (2010–2013)	n=2628 Male: n=602 (22.9%) Female: n=2026 (77.1%) Mean age: 57.3 years[a]	New and existing users aged ≥18 years treated with: mirabegron (n=380) tolterodine ER (n=2248)	Persistence was defined as a continuous supply of index drug until any 30-day period during which the patient did not have a supply of index drug Adherence: the proportion of days covered by the prescription was calculated using prescription fill dates and number of days' supply for each fill of a prescription	6 months
Pelletier et al (2009)[16] PharMetrics Patient-Centric Database; USA (2005–2006)	n=43 367 Male: n=9675 (22.3%) Female: n=33 692 (77.7%) Mean (SD) age: 51.1 (12.4) years	Adults aged ≥18 years receiving a first index (new) prescription of: tolterodine ER oxybutynin solifenacin darifenacin trospium	Adherence was measured by PDC over the 12-month post index period (adherent patients had an ≥80% PDC) Variables: age, gender and comorbidity burden (including COPD, congestive heart failure, diabetes, hypertension)	1 year
Perfetto et al (2005)[17] PharMetrics Patient-Centric Database; USA (2001–2003)	n=23 328 No patient demographics were reported	All patients with either a new diagnosis of OAB or new use of: tolterodine ER oxybutynin ER	Discontinuation rates were calculated	11 months
Sears et al (2010)[18] Military Health System; USA (2003–2006)	n=7858 Male: n=2357 (30.0%) Female: n=5501 (70.0%) Age was not reported	Military treatment facility enrollees prescribed: oxybutynin ER (n=136) oxybutynin IR (n=2003) tolterodine ER (n=4716) tolterodine IR (n=992)	Non-persistence was defined as patients who never refilled a prescription for any OAB medication during the 3-year study period Medication switch rate was calculated as the proportion of patients who changed medication or dose at least once Adherence was defined as the proportion of patients with an MPR of ≥80% Variables: gender and drug formulation	3 years
Sicras-Mainar et al (2016)[d,19] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean age: 54.0 years	Adults aged 20 to 64 with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Discontinuation was defined as when the patient switched to another active substance, another drug was added (combination) or the medication was discontinued completely or discontinued for ≥60 days without renewal and ≥2 prescriptions Compliance was calculated using MPR Variables: concomitant medication (antidepressants, antibiotics) and index drug	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sicras-Mainar et al (2015)[d,20] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean (SD) age: 54.0 (9.2) years	Adults aged ≥20 years with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Persistence was defined as the time, measured in months, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the MPR, which was evaluated from the first to the last prescription and represented the number of days of medication taken over the number of days in treatment (commencing from the start date)	1 year
Sicras-Mainar et al (2014a)[21] Primary care medical databases; Spain (2008–2010)	n=552 Male: n≈272[a] (49.2%) Female: n≈280[a] (50.8%) Mean (SD) age: 80.2 (4.0) years	Adults aged ≥75 years with a first index (new) prescription of: fesoterodine (n=58) solifenacin (n=252) tolterodine (n=212)	Persistence was defined as the time, in weeks, with no drop-out from initial treatment or with no switch to another medication at least 30 days following initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the medication use/possession rate	1 year
Sicras-Mainar et al (2014b)[e,22] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Discontinuation was defined by either the absence of prescription coverage for the initial therapy for the remainder of the 52-week follow-up period or a switch to an alternative antimuscarinic during this time-period Variables: index drug	1 year
Sicras-Mainar et al (2013)[e,23] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Persistence was defined as patients who remained on treatment during the 52-week period following the index date Compliance was defined according to ISPOR criteria and was calculated based on the MPR	1 year
Suehs et al (2016)[24] Medicare Advantage Prescription Plan - Administrative Claims Data; USA (2007–2013)	n=46 140[a] Male: n=15 479[a] (33.5%)[a] Female: n=30 661[a] (66.5%)[a] Mean age: 75.5 years[a]	Adults aged 65 to 89 years[f] with a first index (new) prescription of any antimuscarinic OAB medication	Persistence was assessed as time in days from the index date to discontinuation of index antimuscarinic treatment Adherence was assessed as PDC with the index OAB treatment over three predefined post index observation periods: 3, 6, and 12 months Treatment discontinuation was identified using a permissible gap between refills of 15 days	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sussman et al (2017)[25] Truven MarketScan® Claims Database; USA (2012–2013)	n=71 980[a] Male: n=21 225[a] (29.5%)[a] Female: n=50 755[a] (70.5%)[a] Mean age: 62.3 years[a]	Adults aged ≥18 years with a prescription of: mirabegron any anticholinergic OAB medication	Persistence was measured by evaluating treatment failure (defined as either treatment discontinuation or treatment switching). A medication supply gap of ≥30 days was used to define treatment discontinuation Adherence was defined as the PDC (ie, the number of days covered by the index therapy divided by the number of days between the index date and the end of the follow-up [365 days]). A PDC of <80% was considered nonadherent	1 year
Wagg et al (2012)[26] Prescription Database; UK (2007–2008)	n=4833 Demographics were not explicitly reported, the majority of prescriptions appeared to be issued to patients aged ≥60 years	Adults aged ≥40 years with a first index (new) prescription of: darifenacin flavoxate oxybutynin ER oxybutynin IR propiverine solifenacin tolterodine ER tolterodine IR trospium	Persistence was defined as the mean time [in days] until discontinuation (a gap in treatment exceeding 1.5 times than the length of the previous prescription without a refill)	1 year
Wagg et al (2015)[27] Canadian National Private Drug Plan Database; Canada (2013)	n=19 485 Male: n=4992 (25.6%)[a] Female: n=14 493 (74.3%)[a] Mean age not reported; the majority of patients (77.8%)[a] were aged ≥46 years	Adults aged ≥18 years with a first index (new) prescription of: mirabegron (n=1683) fesoterodine (n=1415) oxybutynin ER (n=1260) oxybutynin IR (n=5356) solifenacin (n=6032) tolterodine ER (n=3739)	Adherence was defined by the MPR over 1 year To calculate time to end of persistence (defined by a gap in therapy of ≥30 days or switching to another medication), prescription claims for a target drug were tracked for 12 months after the index claim date Variables: age, gender, treatment-naïve vs treatment-experienced, index antimuscarinic, number of coexisting medications	1 year
Wagg et al (2015)[28] IMS Brogan public and private prescription claims databases; Canada (2007–2012)	n=31 707 Male: n=9395 (29.6%)[a] Female: n=22 312 (70.4%)[a] Mean age not reported	Adult patients receiving a first index (new) prescription of: oxybutynin IR oxybutynin ER tolterodine IR tolterodine ER solifenacin darifenacin trospium flavoxate	Discontinuation was defined as patients experiencing a gap in therapy longer than 60 days	4 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Yeaw et al (2009)[29] PharMetrics Patient-Centric Database (pharmacy claims); USA (2005)	n=7722 Male: n=1686 (21.8%) Female: n=6036 (78.2%) Mean (SD) age: 43.7 (18.3) years	Adult patients receiving a first index (new) prescription of: tolterodine oxybutynin solifenacin darifenacin trospium bethanechol flavoxate hyoscyamine	Persistence was calculated for the post-index period until the patient discontinued therapy, was lost to follow-up due to disenrollment from the health plan (minimum of 12 months), or the maximum 24-month follow-up period ended, whichever event occurred first. A patient was considered persistent until an excessive gap in days supplied occurred; refill gaps of 30, 60, and 90 days were used to calculate persistence for all cohorts Adherence was measured using the PDC for each of the six drug class cohorts. This was calculated by taking patients' total days supplied of index class medications for the 360-day period following the index date and dividing by 360	2 years
Yu et al (2015)[30] California Medi-Cal administrative files; USA (1999–2002)	n=2496 Male: n=534 (21.4%) Female: n=1962 (78.6%) Mean (SD) age: 63.15 (16.14) years	Adult patients aged ≥18 years receiving a prescription of an OAB drug, including: tolterodine (n=1093) oxybutynin ER (n=524) oxybutynin (n=812) other OAB agents (n=67)	Persistence was measured by the length of continuous pharmacological treatment (patients discontinued their treatment if they failed to refill OAB/UI agents within 30 days after the expected end date of the previous prescription) Patients who switched from one agent of OAB/UI drug to another within 30 days were considered persistent on therapy. Adherence was defined as MPR over 181 days for the 6-month follow-up period Variables: age, gender, ethnicity, index drug, OAB-associated comorbidities (UTIs), medication use history, length of hospital stay and number of drug classes prescribed	1 year

COPD = chronic obstructive pulmonary disease; ER = extended release; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; IR = immediate release; MPR = medication possession ratio (measured as the proportion of days with any OAB medication on hand, over the length of the evaluation period); OAB = overactive bladder; PDC = proportion of days covered; PIM = potentially inappropriate medication; SD = standard deviation; TD = transdermal; UA = urinary antispasmodic; UI = urinary incontinence; UTIs = urinary tract infections

*The sum of the patients prescribed individual drugs may not match the total number of patients perhaps due to switching in some studies

[a]Calculated from data presented in the article; [b]used only in an OAB context; [c]26 922 continued, discontinued or restarted an OAB medication in the study period, but no demographics for this specific sub-group are reported; [d]Sicras-Mainar et al (2016)[19] and Sicras-Mainar et al (2015)[20] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [e]Sicras-Mainar et al (2014)[22] and Sicras-Mainar et al (2013)[23] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [f]this cohort was split into two groups – patients who were assigned OAB medication appropriately [non-PIM], or potentially inappropriately [PIM]. Inappropriateness was defined as patients having "drug–disease or syndrome interaction or indication of significant anticholinergic medication burden at the time of initiation of an antimuscarinic OAB treatment"

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Supplemental Table 2. Summary of adherence and persistence rates and determinants

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Brostrøm and Hallas (2009)[1]	Proportion of patients continued (all drugs except trospium chloride): <50% at 6 months <25% at 1 year <10% at ≥2 years Proportion of patients continued trospium: 46% at 6 months 36% at 1 year 22% at 2 years 16% at 3 years	Not reported	***Gender, age, medication dose, treatment status, medication type*** Retention was longer: in females; in older people; with higher doses; with previous experience of other OAB drugs; trospium vs other OAB drugs
Chancellor et al (2013)[2]	Proportion of patients discontinued at 2 years:[a] tolterodine ER: 84.7% solifenacin: 85.2% oxybutynin: 91.1% darifenacin: 85.7% oxybutynin ER: 84.0% tolterodine: 85.1% trospium: 88.1% trospium ER: 87.1% Proportion of patient switched at 2 years:[a] tolterodine ER: 5.7% solifenacin: 5.2% oxybutynin: 4.7% darifenacin: 6.0% oxybutynin ER: 6.7% tolterodine: 9.7% trospium: 6.9% trospium ER: 6.4%	Proportion of patients with MPR ≥0.80 over study period (in those filling >1 prescription): tolterodine ER: 51.1% solifenacin: 49.4% oxybutynin: 30.1% darifenacin: 51.9% oxybutynin ER: 51.8% tolterodine: 42.6% trospium: 42.4% trospium ER: 54.3%	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Chapple et al (2017)[3]	Median time to discontinuation (days): mirabegron: 169 darifenacin: 56 fesoterodine: 78 flavoxate: 30 oxybutynin ER: 60 oxybutynin IR: 35 propiverine: 56 solifenacin: 67 tolterodine ER: 56 trospium chloride: 60 Proportion of patients persistent at 1 year: mirabegron: 38% darifenacin: 16% fesoterodine: 24% flavoxate: 8.3% oxybutynin ER: 17% oxybutynin IR: 12% propiverine: 21% solifenacin: 25% tolterodine ER: 21% trospium chloride: 19%	Mean (SD) MPR at 1 year: mirabegron: 0.59 (0.33) darifenacin: 0.46 (0.34) fesoterodine: 0.53 (0.33) flavoxate: 0.44 (0.32) oxybutynin ER: 0.49 (0.32) oxybutynin IR: 0.41 (0.32) propiverine: 0.51 (0.32) solifenacin: 0.53 (0.34) tolterodine ER: 0.50 (0.34) trospium chloride: 0.48 (0.33) Proportion of patients with MPR ≥0.8 at 1 year: mirabegron: 43% darifenacin: 29% fesoterodine: 35% flavoxate: 24% oxybutynin ER: 31% oxybutynin IR: 22% propiverine: 25% solifenacin: 35% tolterodine ER: 32% trospium chloride: 29%	***Medication type*** Mirabegron was associated with a statistically significantly greater median time to discontinuation (adjusted HR range 1.31–2.31; p<0.0001 all comparisons) and 12-month persistence rates (adjusted OR range 0.18–0.71; p≤0.0001 all comparisons) vs antimuscarinics in all patients The mean MPR with mirabegron was significantly greater vs antimuscarinics in all patients (p values 0.03 to <0.0001), and in treatment-naïve subcohorts, except for flavoxate (p values 0.02 to <0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Desgagné et al (1999)[4]	Proportion of patients refilled initial prescription: Short-term[b]; oxybutynin: 39.3% flavoxate: 36.6% Long-term[c]; oxybutynin: 63.9% flavoxate: 55.5% Proportion of patients discontinued at 3 months: oxybutynin: 78% flavoxate: 83% Proportion of patients discontinued at 6-months: oxybutynin: 89% flavoxate: 94% Proportion of patients switched at 4-years: Patients without renewal of the original claim: oxybutynin: 1.3% flavoxate: 3.1% Patients with any number of renewals before switch: oxybutynin: 2.2% flavoxate: 5.9%	Not reported	***Age*** Compared with patients aged <77.5 years, those who were older were less likely to discontinue vs: 77.5–83.5 years: RR 0.90, 95% CI 0.85–0.96, p<0.001 >83.5 years: RR 0.86, 95% CI 0.81–0.92, p<0.001 ***Medication dose*** Higher quantity of tablets per day (2–4 tablets/day) was associated with increased risk of early discontinuation, compared with low daily quantity (1 tablet per day) (RR 1.45, 95% CI 1.37–1.53, p<0.001) ***Medication type*** Patients receiving flavoxate had an increased risk of discontinuation compared with those receiving oxybutynin (RR 1.13, 95% CI 1.05–1.22, p<0.001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
D'Souza et al (2008)[5]	Proportion of patients persistent at 1 year (without a gap >45 days): oxybutynin ER: 15.3% oxybutynin IR: 6.5% tolterodine ER: 15.0% tolterodine IR: 11.4% overall: 13.2% Proportion of patients not refilled index medication: oxybutynin ER: 39.4% oxybutynin IR: 59.3% tolterodine ER: 42.7% tolterodine IR: 46.1% overall: 44.5% Median time to discontinuation (days): oxybutynin ER: 34 oxybutynin IR: 0 tolterodine IR: 32 tolterodine ER: 33 overall: 31 Proportion of patients switched at 1 year: oxybutynin ER: 16.5% oxybutynin IR: 19.4% tolterodine IR: 13.7% tolterodine ER: 9.9% overall: 13.3%	Proportion of patients with MPR ≥0.80 at 1 year: oxybutynin ER: 36.1% oxybutynin IR: 14.8% tolterodine ER: 35.2% tolterodine IR: 23.5% overall: 30.3%	***Medication formulation*** Adherence with IR drugs approximately half that for ER drugs (OR 0.504, 95% CI 0.306–0.704, p<0.001) ***Age*** Patients aged ≥65 years were 1.5 times more likely to achieve an MPR ≥0.80 than patients aged <65 years

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gomes et al (2012)[6]	Median time to discontinuation (days): oxybutynin: 68 tolterodine: 128 Proportion of patients persistent at: 6 months oxybutynin: 30.6% tolterodine: 42.9% 1 year oxybutynin: 18.9% tolterodine: 27.3% 18 months oxybutynin: 13.1% tolterodine: 18.9% 2 years: oxybutynin: 9.4% tolterodine: 13.6%	Not reported	***Medication type*** Over the 2-year follow-up, the time to discontinuation was longer with tolterodine than oxybutynin (p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gopal et al (2008)[7]	Over 3 years, 91% of 49,419 episodes of medication prescription resulted in discontinuation Cumulative incidence of discontinuation at 6 months, 1 year, 2 years and 3 years (unadjusted): Overall: 58.8, 77.2, 87.5, 92.0% Cumulative incidence of discontinuation, at 6 months, 1 year, 2 years and 3 years (adjusted for age, year of initiation, switch, number of previous drug classes, number of prior episodes and smoking status): oxybutynin: 71, 86, 94, 96% oxybutynin ER: 57, 80, 93, 97% tolterodine: 61, 81, 92, 95% tolterodine ER: 54, 76, 91, 97% trospium: 56, 80, 94, 98% propiverine: 61, 84, 95, 98% solifenacin: 53, 91, 98, 99% terodiline: 89, 99%, N/A, N/A flavoxate: 85, 96, 99, 99% Median time to discontinuation (months): oxybutynin: 4.67 oxybutynin ER: 5.13 tolterodine: 5.47 tolterodine ER: 5.37 trospium: 5.47 propiverine: 5.43 solifenacin: 5.00 terodiline: 4.00 flavoxate: 4.00 overall: 4.76 Overall switch rate: 15%	Not reported	***Medication formulation*** In comparison with the multiple-dosing drug classes at 6 months, both oxybutynin ER (57%, 95% CI 55.1–59.2) and tolterodine ER (54%, 95% CI 52.3–57.4) had lower incidences of discontinuation ***Medication type*** Trospium and tolterodine were associated with the longest median time to discontinuation (5.47 months each), followed by propiverine (5.43 months) and solifenacin (5.0 months). Terodiline and flavoxate had the shortest median time to discontinuation (4 months each)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Ivanova et al (2014)[8]	Proportion of patients discontinued at 6 months: 61.0% Proportion of patients switched at 6 months: 8.0% Proportion of patients persistent at 6 months: 31.0% Proportion of patients discontinued at 6 months: oxybutynin: 30.6% tolterodine: 30.5% solifenacin: 24.5% darifenacin: 8.4% trospium: 4.1% fesoterodine: 1.9% Mean time to discontinuation: 54.7 days 42.7% of patients never refilled their indexed prescription	Not reported	***Age*** Patients who discontinued (50.5 years) or switched (52.6 years) medication were significantly younger than those who persisted (53.4 years; p<0.001) Increasing age was associated with reduced odds of discontinuation (adjusted OR 0.97, 95% CI 0.96–0.97, p<0.0001) ***Gender*** Being male was associated with greater odds of discontinuation (adjusted OR 1.11, 95% CI 1.00–1.23, p=0.0475) ***Medication type*** Patients who persisted with medication contained a significantly higher proportion of solifenacin users than those in groups who switched or discontinued (30.1% vs 19.7% vs 24.5%, respectively, p<0.001) and a lower proportion of oxybutynin (22.6% vs 29.6% vs 30.6%, respectively, p<0.001) Compared to patients treated with solifenacin, patients were significantly more likely to discontinue when treated with tolterodine (adjusted OR 1.30, 95% CI 1.16–1.45, p<0.0001) or oxybutynin (adjusted OR 1.80, 95% CI1.59–2.03, p<0.0001) ***Presence of infection*** Patients with UTI were more likely to discontinue compared with those without UTI (adjusted OR 1.31, 95% CI 1.19–1.45, p<0.0001) ***Financial burden*** Patients with lower log of baseline OAB-related costs were more likely to discontinue (adjusted OR 0.96, 95% CI 0.94–0.98, p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Johnston et al (2012)[9]	Mean time of continuation at 1 year (days): diabetic: 164 not diabetic: 146.9 (p<0.001 difference) Proportion of patients discontinued at 1 year: diabetic: 71.5% not diabetic: 76.2% (p<0.001 difference)	Mean MPR at 1 year; diabetic: 0.473 not diabetic: 0.424 (p<0.001 difference)	***Age and gender*** The odds of adherence generally increase with age, and females had higher odds of adherence than men ***Diabetes*** The diabetes cohort had greater odds of achieving an MPR ≥0.80 (OR 1.215, 95% CI 1.169–1.263, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period The diabetes cohort had greater odds of filling a second OAB medication prescription (OR 1.166, 95% CI 1.127–1.205, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kalder et al (2014)[10]	Proportion of patients discontinued at: 1 year: 74.8% 2 years: 77.6% 3 years: 87%	Not reported	***Gender*** At 3 years, there was a significantly higher risk of discontinuation in male than female patients (HR 1.14, 95% CI 1.11–1.18, p<0.001) ***Age*** Discontinuation was higher in younger patients than older patients: ≤60 years: 89.7% 61–70 years: 87.9% 71–80 years: 86.8% >80 years: 83.0% ***Prescriber's profession*** Discontinuation rate was higher in patients treated by gynecologists and general practitioners compared with urologists (HR 1.60 [95% CI 1.52–1.67] p<0.001; HR 1.24 [95% CI 1.20–1.29] p<0.001) ***Side effects*** A higher risk of discontinuation in patients experiencing side effects: headache: HR 1.27, 95% CI 1.12–1.43, p=0.002 stomach upset: HR 1.20, 95% CI 1.12–1.27, p<0.001 glaucoma: HR 1.46, 95% CI 1.16–1.84, p<0.001 ***Medication type*** Patients using propiverine (HR 0.94, 95% CI 0.88–0.99, p=0.022) or solifenacin (HR 0.93, 95% CI 0.87–0.98, p=0.003) had a significantly lower risk of treatment discontinuation compared with oxybutynin. However, the absolute difference was relatively small ***Comorbidities*** Diabetes, Parkinson's disease, epilepsy, dementia, and multiple sclerosis was associated with a lowered risk of treatment discontinuation A prior diagnosis of migraine was associated with a higher risk of treatment discontinuation

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kleinman et al (2014)[11]	Median time until a ≥30-day medication gap: 64 days Proportion of patients persistent: beyond 1 month: 70% at 9 months: 10% at 1 year: 5%	Proportion of patients with PDC ≤10% at 1 year: 45.4% Proportion of patients with PDC ≥80% at 1 year: 12.7%	***Gender*** Compared to the group with PDC ≥80%, the group with PDC <80% contained a lower proportion of females (69.5% vs 76.3%, p=0.006) ***Age*** Compared to those with PDC ≥80%, patients with PDC <80% were younger (mean age: 46.18 years vs 49.79 years, p<0.001) ***Race*** Compared to the group with a PDC ≥80%, the group with PDC <80% contained a lower proportion of White patients (38.6% vs 50.0%, p<0.001) and higher proportion of Black and Hispanic patients (6.7% vs 3.7%, p=0.025; 11.6% vs 6.3%, p=0.002) ***Medication co-payment*** Compared to the group with a PDC ≥80%, those with PDC <80% paid a higher mean medication co-payment ($20.15 vs $14.68, p<0.001)
Krhut et al (2014)[12]	Median (SD) time to discontinuation: 6.53 (3.84) months Proportion of patients persistent at: 3 months: 59.7% 6 months: 39.3% 9 months: 33.6% 1 year: 27.2%	Not reported	***Medication type*** Persistence was significantly higher in patients treated with anticholinergic medication with an ER formulation than in patients treated with IR anticholinergics (ER: 7.10 [SD 3.90] months vs IR: 6.18 [SD 3.75] months, p=0.023)
Manack et al (2011)[13]	Mean (SD) duration of therapy: 201.9 (120.9) days Proportion of patients that: continued OAB medication ≥1 year: 28.9% discontinued OAB medication and did not restart[d]: 37.5% discontinued and restarted OAB medication[e]: 33.5%	Not reported	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Mauseth et al (2013)[14]	Proportion of patients persistent at 1 year: tolterodine: 39.0% solifenacin: 39.4% darifenacin: 34.3% fesoterodine: 29.1% overall: 38.0% Proportion of patients switched at 1 year: tolterodine: 12.0% overall: 10.3% Proportion of patients filled only one prescription: 31.9%	Mean MPR at 1 year: 0.62[f] Proportion of patients with MPR ≥0.80[f] at 1 year: tolterodine: 33.7% solifenacin: 35.7% darifenacin: 37.0% fesoterodine: 38.5% overall: 35.2%	***Age*** Persistence was lowest in the age group 18–39 years (20.9%), generally increased with age, and was highest in the age groups 70–79 years (43.5%) and ≥80 years (43.3%) ***Medication type*** At 1 year, persistence was highest for tolterodine (39.0%) and solifenacin (39.4%), both of which entered the market first. Persistence for darifenacin and fesoterodine, which were launched later, was 34.3% and 29.1%, respectively
Nitti et al (2016)[15]	Proportion of patients persistent at: 1 month; mirabegron: 68.4% tolterodine ER: 47.1% 3 months; mirabegron: 48.7% tolterodine ER: 28.6% 6 months; mirabegron: 34.7% tolterodine ER: 18.5% Median persistence (days): mirabegron: 170 tolterodine ER: 90	Not reported	***Age*** Compared with patients aged <65 years, patients aged ≥65 years were less likely to discontinue over 6 months with tolterodine (HR 0.88, 95% CI 0.80–0.96, p=0.0064) and mirabegron (HR 0.68, 95% CI 0.52–0.90, p=0.0068) ***Prior treatment*** Compared to patients without prior use of OAB medication, patients with prior OAB medication use were less likely to discontinue over 6 months with tolterodine (HR 0.76, 95% CI 0.68–0.85), p<0.0001) and mirabegron (HR 0.68, 95% CI 0.53–0.88, p=0.0025) ***Medication type*** The risk of discontinuation was lower with mirabegron compared with tolterodine (HR 0.72, 95% CI 0.61–0.85, p<0.0001)
Pelletier et al (2009)[16]	Not reported	Mean cohort PDC at 1 year: 0.32 Proportion of patients with PDC ≥0.80 at 1 year: 14.4%	***Demographics (gender, age, comorbidities)***[g] Female and older subjects were more likely to adhere. Those with a history of hypertension, diabetes, or multiple sclerosis were more adherent. Subjects with COPD were less adherent

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Perfetto et al (2005)[17]	Cumulative discontinuation rates at: 1 month; tolterodine ER: 6% oxybutynin ER: 11% 3 months; tolterodine ER: 55% oxybutynin ER: 62% 6 months; tolterodine ER: 69% oxybutynin ER: 76% 11 months; tolterodine ER: 79% oxybutynin ER: 85% Overall, at 11 months, 21% of patients remained on tolterodine ER and 15% of patients remained on oxybutynin ER	Not reported	Not reported
Sears et al (2010)[18]	Proportion of patients without prescription refills over 3 years: 35.1% Median persistence (days): overall: 273 patients with at least 1 refill: 582 Overall medication persistence duration was 273 days when all cases were analyzed and 582 days when those with at least 1 refill were analyzed	Median MPR at 3 years: oxybutynin 5 mg IR: 0.68 oxybutynin 5 mg ER: 0.83 oxybutynin 10 mg ER: 0.84 tolterodine 1 mg IR: 0.71 tolterodine 2 mg IR: 0.73 tolterodine 2 mg ER: 0.88 tolterodine 4 mg ER: 0.89 overall: 0.82 Proportion of patients with MPR ≥0.80 at 3 years: 34.0%	***Gender*** Male patients had a higher median MPR than female patients (0.86 vs 0.81, p<0.001) Medication adherence was higher in males than in females (0.370 vs 0.328, p<0.001) Of patients refilling their prescription at least once, the median number of days persisted was longer in females than in males (606.0 days vs 547.0 days, p=0.01) ***Medication type*** Of patients refilling their prescription at least once, median medication persistence was longest in 5 mg oxybutynin IR (634 days, 95% CI 596.1–671.9) and lowest with 10 mg oxybutynin ER (504 days, 95% CI 137.0–871.0)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2016)[19]	Proportion of patients persistent (without switching or experiencing a gap of >60 days) at: 6 months; fesoterodine: 71.4% solifenacin: 67.1% tolterodine: 64.8% 1 year; fesoterodine: 40.2% solifenacin: 34.7% tolterodine: 33.6%	Mean MPR at 1 year was: 0.880, 0.877 or 0.875, depending upon geographical location	***Medication type*** Persistence at 6 months and 1 year was statistically significantly higher with fesoterodine than solifenacin and tolterodine ($p<0.05$). Persistence at 1 year was significantly lower with solifenacin than fesoterodine ($p<0.01$)
Sicras-Mainar et al (2015)[f,20]	Proportion of patients persistent at: 3 months: 86.2% 6 months: 67.6% 9 months: 48.4% 1 year: 35.9% Mean (SD) treatment duration (without stopping, switching or a gap >30 days): fesoterodine: 8.1 solifenacin: 7.8 tolterodine: 7.7 overall: 7.9	Mean MPR at 1 year: fesoterodine: 0.900 solifenacin: 0.870 tolterodine: 0.861 overall: 0.877	Not reported
Sicras-Mainar et al (2014)[21]	Proportion of patients persistent (without switching or experiencing a gap of >30 days): 3 months; fesoterodine: 94.8% solifenacin: 76.2% tolterodine: 70.8% 6 months; fesoterodine: 70.7% solifenacin: 59.5% tolterodine: 57.1% 1 year; fesoterodine: 46.6% solifenacin: 36.5% tolterodine: 33.5%	Mean MPR at 1 year: fesoterodine: 0.907 solifenacin: 0.935 tolterodine: 0.936	***Medication type*** At 3 months, persistence was higher with fesoterodine than with tolterodine and solifenacin

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2014)[g,22]	Proportion of patients persistent at 1 year: fesoterodine: 35.8% solifenacin: 31.9% tolterodine: 30.9%	Mean MPR at 1 year: fesoterodine: 0.937 solifenacin: 0.948 tolterodine: 0.935	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found. However, adjusted HRs for remaining on treatment at 1 year significantly favored fesoterodine compared with solifenacin (HR 1.24 [95% CI 1.05–1.47]; p=0.011) and tolterodine (HR 1.28 [95% CI 1.07–1.52]; p=0.006)
Sicras-Mainar et al (2013)[g,23]		Mean MPR at 1 year: fesoterodine: 0.945 solifenacin: 0.954 tolterodine: 0.946	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found
Suehs et al (2016)[24]	Proportion of patients not refilling their index medication: PIM: 41.4% Non-PIM: 47.8% (p<0.01) Mean number of days persistent (before discontinuation or experiencing a gap >15 days): PIM: 87.6 Non-PIM: 80.9 (p<0.001) Proportion of patients persistent at: 3 months; PIM: 23.9% Non-PIM: 20.3% 6 months; PIM: 13.2% Non-PIM: 11.4% 1 year; PIM: 5.1% Non-PIM: 4.5% (all p<0.001 differences)	Mean PDC at: 3 months; PIM: 0.62 Non-PIM: 0.59 6 months; PIM: 0.45 Non-PIM: 0.42 1 year; PIM: 0.32 Non-PIM: 0.30 (all p<0.001 differences) Proportion of patients with PDC ≥0.80: 3 months; PIM: 37.0% Non-PIM: 35.0% 6 months; PIM: 23.3% Non-PIM: 19.7% 1 year; PIM: 12.7% Non-PIM: 10.7% (all p<0.001 differences)	***Medication use appropriateness*** At 1 year, there was no statistical difference between PIM status and OAB treatment discontinuation in the multivariable adjusted model based on the primary analysis definition (15-day definition OR 0.977, 95% CI 0.891–1.072, p=0.63; 30-day definition OR 0.939, 95% CI 0.871–1.013, p=0.10)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sussman et al (2017)[25]	Proportion of patients discontinued at 1 year (gap of ≥30 days): mirabegron: 67.1% anticholinergic: 84.1% Median time to discontinuation (days): mirabegron: 131 anticholinergic: 30	Mean PDC: mirabegron: 0.66 anticholinergic: 0.55 Proportion of patients with PDC ≥0.80 at 1 year: mirabegron: 43.6% anticholinergic: 30.9%	***Medication type*** Users of mirabegron appeared to achieve greater persistence and adherence at 1 year than users of anticholinergics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2012)[26]	Time (days) to discontinuation (or a gap >1.5 times the length of the previous prescription without a refill): darifenacin: 135.9 flavoxate: 77.4 oxybutynin ER: 146.7 oxybutynin IR: 119.3 propiverine: 141.1 solifenacin: 158.7 (5 mg); 216.0 (10 mg) tolterodine ER: 156.7 tolterodine IR: 151.7 trospium: 138.5 Proportion of patients persistent at 3 months: darifenacin: 52% flavoxate: 28% oxybutynin ER: 44% oxybutynin IR: 40% propiverine: 47% solifenacin: 58% tolterodine ER: 47% tolterodine IR: 46% trospium: 42% Proportion of patients persistent at 6 months: darifenacin: 30% flavoxate: 16% oxybutynin ER: 35% oxybutynin IR: 29% propiverine: 36% solifenacin: 46% tolterodine ER: 36% tolterodine IR: 33% trospium: 33% Proportion of patients persistent at 1 year: darifenacin: 17.4% flavoxate: 13.5% oxybutynin ER: 26.1% oxybutynin IR: 21.7% propiverine: 26.8% solifenacin: 35% tolterodine ER: 28.2% tolterodine IR: 24.1% trospium: 25.9%	Not reported	***Age*** Over 1 year, the majority of patients aged ≥60 years were more likely to persist than younger patients. Graphical results only ***Medication type*** Patients receiving solifenacin spent the longest mean duration on therapy compared with other OAB medications

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[27]	Proportion of patients persistent at 1 year (without switching or experiencing a gap ≥30 days): mirabegron: 31.7% fesoterodine: 21.0% oxybutynin ER: 18.9% oxybutynin IR: 13.8% solifenacin: 22.0% tolterodine ER: 19.7% Median duration of treatment (days): mirabegron: 221 solifenacin: 108 fesoterodine: 100 tolterodine ER: 100 oxybutynin ER: 100 oxybutynin IR: 75 Proportion of patients persistent at 1 year: treatment-naïve:19.0% treatment-experienced: 30.0% Median days on therapy: treatment-naïve: 90 treatment-experienced: 205	Median MPR at 1 year: mirabegron: 0.645 fesoterodine: 0.492 oxybutynin ER: 0.328 oxybutynin IR: 0.186 solifenacin: 0.459 tolterodine ER: 0.454	***Age*** As age increased, median MPR increased for OAB medications: <46 years: 0.273 45–64 years: 0.372 ≥65 years: 0.492 (p<0.001 difference compared to ≥65 years) ***Treatment status*** Patients with prior experience of OAB medication use achieved a higher MPR than treatment-naïve patients (0.546 vs 0.328, p<0.001) ***Medication type*** Compared with antimuscarinics, patients taking mirabegron demonstrated greater persistence and statistically significantly greater adherence (64.5% vs 18.6%–49.2%, p<0.001) than those taking antimuscarinics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[28]	Proportion of patients persistent at 6 months: <40% Proportion of patients discontinued at 4 years: oxybutynin: 93% tolterodine IR: 90% tolterodine ER: 90% solifenacin: 90% darifenacin: 91% trospium: 94% flavoxate: 98% overall: 91.4% Median duration of first-line treatment (days): oxybutynin: 60 tolterodine IR: 90 tolterodine ER: 100 solifenacin: 106 darifenacin: 91 trospium: 90 flavoxate: 10	Not reported	***Medication type*** Initial treatment with solifenacin, darifenacin, tolterodine ER and tolterodine was associated with a significantly lower risk of discontinuation compared with oxybutynin as the first medication (HRs 0.68, 0.72, 0.77 and 0.84, respectively; p<0.001 vs oxybutynin for each) Patients receiving flavoxate as initial treatment had a significantly higher risk of discontinuation compared with those who received oxybutynin (HR 2.48, p<0.0001) There was no statistically significant difference in the risk of discontinuation with trospium as first-line compared with oxybutynin (p=0.1074) ***Age*** Compared with patients aged 40–64 years, patients aged <20, 20–39, 65–74 and ≥75 years had a higher risk of discontinuation (HRs 1.08–1.19, all p≤0.0022) ***Gender*** Males had a slightly higher risk of discontinuation than females (HR 1.03, 95% CI 1.00–1.06, p=0.0341)
Yeaw et al (2009)[29]	Proportion of patients remaining on therapy (without a refill gap >60 days) at: 6 months: 28% 1 year: 18%	Proportion of patients with mean MPR at 1 year: 35%	Not reported
Yu et al (2005)[30]	Proportion of patients without index prescription refill within the first 6 months: 36.9% Proportion of patients discontinued at: 1 month: 42.7% 2 months: 66.8% 5 months days: 77.6% 9 months: 86.3% At a 1-year follow-up, the rate of discontinuation was increased to 88.6%	Mean MPR at: 6 months: 0.34 1 year: 0.22 Proportion of patients with MPR ≥0.80 at: 6 months: 4.9% 1 year: 0.7%	***Medication type*** Compared with oxybutynin, patients receiving tolterodine were less likely to have discontinued at 6 months (HR 0.74, 95% CI 0.67–0.81, p<0.01) ***Polypharmacy*** The use of multiple drugs was associated with a higher risk of discontinuation by the 6-month follow up (HR 1.26, 95% CI 1.09–1.46, p<0.01) Other significant predictors of higher persistence included: White ethnicity, previous hospitalization length, and starting treatment with tolterodine

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ER = extended release; HR = hazard ratio; IR = immediate release; MPR = medication possession ratio; OAB = overactive bladder; OR = odds ratio; PIM = potentially inappropriate medication; PDC = proportion of days covered; RR = risk ratio; SD = standard deviation; UTIs = urinary tract infections

*In cases where reported values differ from published values, they were derived from the published data; [a]cohort discontinuation percentages are also quoted for 3, 6, 12 and 18 months. However, these figures included some non-oral OAB medications. Therefore, these have not been included; [b]within 1.5x the duration of the initial prescription; [c]over a 4-year period; [d]stopped receiving an OAB medication for ≥6 months between end of therapy and end of the study's eligibility period; [e]stopped receiving an OAB medication for <6 months before restarting an OAB medication; [f]patients who filled only one prescription were given an MPR of zero; [g]no exact figures were quoted within the article text

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Supplemental Information

Literature Search Strategies

The following databases were searched;

- Allied and Complementary Database [AMED] (via OVID)
- Cumulative Index to Nursing and Allied Health Literature [CINAHL] (via EBSCOhost)
- MEDLINE (via EBSCOhost)
- Database of Reviews of Effects [DARE] (via CRD, University of York)
- Health Technology Assessment [HTA] (via CRD, University of York)
- Centre for Reviews and Dissemination [CRD] (via CRD, University of York)

The searches were conducted on the 24th April 2017

The date span of the searches;

- AMED – 1985 to April 2017
- CINAHL – 1937 to April 2017
- MEDLINE – 1946 to April 2017
- DARE / HTA / CRD – 1994 to April 2017

	Searches (AMED)*	
1	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
2	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
3	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
4	(#1 AND #2 OR #3)	18
	Searches (CINAHL & MEDLINE)*	
5	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
6	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
7	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–

8	(#5 AND #6 OR #7)	3,855
	Searches (DARE / HTA / CRD)*	
9	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
10	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
11	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
12	(#9 AND #10 OR #11)	24
13	Total from #4, #8 and #12	3,897
14	Remove duplicates from 13 using EndNoteWeb	**3,614**

* Boolean operators were used. No other limits or filters were applied to each database.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Suppl.Info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A*
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Suppl. Tables 1 and 2

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A*
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, 26
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Suppl. Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14, 15

N/A, not applicable

PRISMA 2009 Checklist

*** A risk of bias tool for database studies is not available**

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Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review

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Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review

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ABSTRACT

Purpose To evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) in a real-world setting.

Materials and Methods Systematic literature searches of six electronic publication databases were performed to identify observational studies of OAB patients treated with antimuscarinics and/or mirabegron. Studies obtaining persistence and adherence data from sources other than electronic prescription claims were excluded. Reference lists of identified studies and relevant systematic reviews were assessed to identify additional relevant studies.

Results The search identified 3897 studies, of which 30 were included. Overall, persistence ranged from 5–47%. In studies reporting data for antimuscarinics and mirabegron (n=3), 1-year persistence was 12–25% and 32–38%, respectively. Median time to discontinuation was <5 months for antimuscarinics (except one study [6.5 months]) and 5.6–7.4 months for mirabegron. The proportion of patients adherent at 1 year varied between 15–44%. In studies reporting adherence for antimuscarinics and mirabegron, adherence was higher with mirabegron (mean medication possession ratio (MPR): 0.59 vs 0.41–0.53; mean proportion of days covered: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19–0.49). Reported determinants of persistence and adherence included female gender, older age group, use of extended-release formulation and treatment experience.

Conclusion Most patients with OAB discontinued oral OAB pharmacotherapy and were non-adherent 1 year after treatment initiation. In general, mirabegron was associated with greater persistence and adherence compared to antimuscarinics. Combined with existing clinical trial evidence, this real-world review merits consideration of mirabegron for first-line pharmacological treatment among patients with OAB.

The protocol for this systemic review is registered with PROSPERO: CRD42017059894

STRENGTHS AND LIMITATIONS

- This systematic literature review includes data for mirabegron, which was approved in 2013 and not covered in previous systematic reviews examining persistence and adherence to overactive bladder medication (OAB).
- Only observational database studies were included in this study, with the intention to provide a more accurate picture of rates of adherence and persistence to OAB medication, which are generally lower in routine clinical practice compared to randomized clinical trials.
- This systematic literature review provides a global picture of adherence and persistence to OAB medication based on the inclusion of data from Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States.
- Although determinants of persistence and adherence were evaluated in this study, the influence of other factors such as patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed.
- The definitions and calculations of persistence and adherence were not uniform across the literature. These terms were often used interchangeably, limiting the ability to compare across studies.

INTRODUCTION

Overactive bladder (OAB) is defined as a condition with characteristic symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.[1] OAB affects 11.8–24.7% of adults in North America and Europe, and the prevalence increases with age.[2] In addition to age, risk factors for developing OAB include diabetes, UTIs and obesity.[3 4]

OAB symptoms are associated with a negative impact on health-related quality of life (HRQoL) and a significant economic burden. Indeed, bothersome OAB symptoms may lead to depression and anxiety, and sleep disturbances, which can adversely affect a patient's daily, social and professional functioning.[5 6] Whilst the cost of pharmaceutical treatment represents only a small fraction of the total therapy cost, the provision of containment products (eg, pads), treatment for clinical depression, nursing home stays and loss of productivity due to work absenteeism are the main cost drivers in OAB.[7 8] For example, the total annual cost of OAB was estimated to be $24.9 billion in the United States in 2007[9] and €9.7 billion across five European countries (Germany, Italy, Spain, Sweden and the United Kingdom) and Canada in 2005.[8]

Behavioural and lifestyle modifications are routinely the initial treatment strategy for OAB, and pharmacotherapy is recommended only if conservative management is not effective.[10] As OAB is a chronic condition, it is important that patients continue with treatment to control symptoms.[11] Lack of persistence (time from treatment initiation to discontinuation),[12] and adherence (extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen)[12] to medication are considered the leading causes of preventable morbidity in patients with chronic conditions;[13 14] they are also associated with greater indirect costs.[14] Studies have reported that patients compliant and adherent to OAB medication experienced significantly improved urinary symptoms and

HRQoL compared with patients who were non-persistent [15 16]. Although antimuscarinics are the current mainstay of oral pharmacotherapy, they are often associated with bothersome anticholinergic side effects, such as dry mouth and constipation; tolerability is one of the most common reasons for treatment discontinuation.[11 17-20] In a systematic review of antimuscarinic treatment in patients with OAB, rates of discontinuation at 12 weeks ranged from 4–31% in clinical trials and 43–83% in medical claims databases.[19]

The other class of oral pharmacotherapy approved for the treatment of OAB is β_3-adrenergic receptor agonists. Mirabegron is currently the only commercially available agent of this class licensed in countries across Europe, North America and Asia.[21-23] Due to mirabegron's mechanism of action, the incidence of side effects typically reported with antimuscarinic treatment are low with mirabegron and generally similar to placebo,[24] which may translate into better treatment persistence.[25 26] In addition, results of a recent economic analysis found that increased persistence with mirabegron treatment vs antimuscarinics was associated with reduced healthcare resource use and work hours lost, resulting in lower total costs.[27]

In general, rates of persistence and adherence with antimuscarinics and mirabegron are typically lower in routine clinical practice compared to interventional clinical trials.[11 28] To help identify factors affecting long-term persistence and adherence to OAB pharmacotherapy, a contemporary, comprehensive review of real-world evidence is needed. As mirabegron was a relatively new OAB treatment, it was not included in previous systematic reviews. Therefore, the current analysis aims to systematically review prospective and retrospective observational database studies conducted with antimuscarinics and/or mirabegron to determine the rates and determinants of persistence and adherence.

METHODS

This systematic literature review (SLR) was conducted in accordance with guidelines for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [29]. The protocol for the

review was registered *a priori* with the International Prospective Register of Systematic Reviews (registered January 18, 2017 with PROSPERO CRD42017059894).

Searches were performed April 27, 2017 *via* the following electronic databases: Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied Health Literature (CINAHL); MEDLINE; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; and the Centre for Reviews and Dissemination (CRD) database. The search terms were persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [Title], AND "bladder" OR "overactive bladder" OR "OAB" OR urin* OR incontinen* [Title], OR oxybutynin OR tolterodine OR fesoterodine OR trospium OR darifenacin OR solifenacin OR propiverine OR imidafenacin OR mirabegron OR flavoxate OR hyoscyamin* OR anticholinerg* OR antimuscarin* [Title].

All search results were exported into EndNote Web (Thomas Reuter, CA, USA) bibliography software and duplicates removed electronically and manually. The full electronic search strategy is outlined in the Supplemental information.

Patient and public involvement

Patients and or the public were not involved in this study.

Inclusion and exclusion criteria

Inclusion criteria were: prospective and retrospective observational database studies investigating persistence and adherence to oral medication for the treatment of OAB in adults, conducted in any geographical location and published on any date, within a peer-reviewed source. Exclusion criteria were: abstract unavailable; studies not yet fully completed; randomised controlled trials (RCTs); systematic reviews; narrative literature reviews; conference papers; single case studies/reports; studies investigating OAB medication among only healthy, asymptomatic participants; studies from which oral-only

OAB persistence/adherence results cannot be isolated from other results (ie, transdermal patches); and studies containing patients aged <18 years (where the data pertaining to these patients could not be removed from the results) and studies not published in English. Populations with lower urinary tract symptoms due to stress incontinence and benign prostatic hyperplasia were also excluded.

Study selection

Duplicates were removed and title and abstract screenings were performed by two independent researchers (PS and GY). Full-text articles were obtained and studies were excluded if they did not meet the inclusion criteria.[30] Any disagreement in study selection was to be resolved through discussion and consultation with another member of the project team (FF) where necessary. During screening, open-label extension studies of RCTs were excluded as the trial designs were unlikely to reflect a real-world setting. Studies utilising data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were determined from prescription claims data rather than extracted from supplemental patient interviews, patient-supplied pill counts or subjective questionnaires. The literature search was supplemented by screening for potential additional relevant studies identified from the reference lists of eligible articles.

Data extraction

Parameters that may affect persistence or adherence were collected, including patient characteristics (age and sex); interventions (initial [index] OAB drug and formulation) and comorbidities. The definitions, outcomes and determinants of treatment persistence and adherence were also collected, where reported. The extracted data were evaluated by one researcher and verified by a second researcher.

Data analysis

A descriptive analysis of extracted results is presented. No meta-analysis was planned due to the expected heterogeneity of reporting methodologies and data across studies.

RESULTS

Brief overview of studies

Overall, 3897 articles were identified from the literature search; 3,614 were screened for title/abstract and 75 were assessed for eligibility (figure 1). Thirty articles were included in the SLR (supplementary table 1), including three identified from reference lists.[31-33] The articles described the findings of 28 independent studies. There was nil disagreement between the two independent researchers (PS, GY) during the screening process.

The data were collected from patients treated in Europe (12 studies) and North America (18 studies) (supplementary table 1) and were included in the analysis. The number of participants included in the published studies ranged from 377 to 103 250. Where stated, the mean age of the participants ranged from 44 to 80 years and the duration of follow-up ranged from 6 months to 7 years. Prescribed antimuscarinic interventions for patients with OAB included darifenacin, fesoterodine, flavoxate, hyoscyamine, imipramine, oxybutynin, propiverine, solifenacin, tolterodine and trospium chloride. Mirabegron was prescribed in four studies.[18 31 32 34] Uncommon oral interventions included imipramine, a tricyclic anti-depressant with an unknown mechanism of action in the context of OAB,[35] and bethanechol, a muscarinic receptor agonist.[33] The methods used to quantify adherence and persistence differed across the studies (supplementary table 1). In general, medication possession rate (MPR) or proportion of days covered (PDC) by prescription were typically used as a measure of adherence to a drug. Persistence was typically defined as the proportion of patients continuing therapy/refilling prescriptions for the follow-up period (without discontinuing the index drug or switching to other OAB drug[s]) and/or the median time to discontinuation (TTD).

Persistence

Overall, persistence rates decreased over time, regardless of agent (supplementary table 2).

Antimuscarinic studies

Data for persistence (or discontinuation) at approximately 6 months was available in 14 articles[32 33 36-47] which reported data on antimuscarinics only. Yeaw 2009 was an exception due to the inclusion of bethanechol (a muscarinic receptor agonist), which accounted for <1.5% of the pharmacy claims for OAB medications.[33] The proportion of patients persistent at 6 months was <50% except for the studies of Sicras-Mainar *et al*,[42-44] where persistence ranged from 57–71%. In addition, two studies reported discontinuation rates of 6–43% after 1 month of initial treatment.[41 47]

At 1 year, persistence rates for antimuscarinics across 19 studies ranged from around 5% up to 47%.[18 26 34-36 38 40 42 43 45 46 48-53] Median TTD was <5 months (30 to 128 days) for all medications across all studies,[18 26 32 34 38 48 54] with the exception of Krhut *et al*[40] (6.5 months). At 2 years, over 75% of patients discontinued treatment.[36 38 50 54 55] Rates of treatment switching were infrequently reported, and where provided, were ≤17% of patients.[32 37 39 48 52 54 55]

Antimuscarinic and mirabegron studies

In all four studies, a greater proportion of patients persisted with mirabegron compared with antimuscarinics. In one study, persistence rates for tolterodine and mirabegron at 6 months were 19% and 35%, respectively.[31] Persistence at 1 year ranged from 8–25% for antimuscarinics and from 32–38% for mirabegron, as reported in three studies.[18 26 34]Where tested inferentially, 1-year persistence was statistically significantly greater with mirabegron compared to antimuscarinics ($p < 0.0001$), with the exception of oxybutynin ($p = 0.002$).[18] The risk of discontinuing within 1 year was also greater with antimuscarinics compared to mirabegron ($p < 0.001$).[18 32] Overall, mirabegron, solifenacin and fesoterodine were associated with the highest rates of persistence.[18 26]

Across the four studies, 40–81% and 83–96% of the mirabegron and antimuscarinic patient cohorts were treatment naïve, having received no OAB drug for at least 6 months prior to

their first index of OAB treatment.[18 31 32 34] Studies typically found that treatment-naive patients prescribed mirabegron or antimuscarinics had lower persistence than treatment-experienced patients prescribed the same OAB treatments. In the three studies that assessed persistence in treatment-experienced and treatment-naïve populations, persistence was higher with mirabegron treatment (significantly in two studies) compared with antimuscarinics.[18 31 32]

Median TTD in the overall study populations was longer with mirabegron (5.6–7.4 months) compared with the assessed antimuscarinics (1.0–3.6 months).[18 26 31 34]

Adherence

Adherence rates to all OAB medications reduced over time in all studies and varied across studies (supplementary table 2).

Antimuscarinic studies

At 1 year, the proportion of adherent patients varied between 1%[47] and 36%,[48] across those studies that provided these data. Few studies reported adherence beyond 1 year. However, Sears *et al* reported that 34% of patients were adherent at the end of 3 years,[56] which was comparable to the adherence rates reported by some other studies at just 1 year.[48 52]

Antimuscarinic and mirabegron studies

In the three studies, adherence at 1 year was significantly higher in patients receiving mirabegron compared with antimuscarinics (mean MPR: 0.59 vs 0.41 to 0.53; mean PDC: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19 to 0.49).[18 26 34] The proportion of patients adherent at 1 year was also greater with mirabegron compared with antimuscarinics (mean MPR ≥0.80: 43% vs 22–35%; mean PDC ≥0.80: 44% vs 31%).[18 26] Within treatment-naïve patients specifically, adherence was greater with mirabegron compared to antimuscarinics 0.59 vs. 0.39–0.51, p values 0.02 to <0.0001).[18]

Determinants of persistence and adherence

Determinants of persistence and adherence were reported in 24 of the 30 studies. As expected, most studies reported medication type as a determinant of persistence/adherence (figure 2; supplementary table 2). In general, persistence and adherence were higher in: older patients compared with younger patients;[26 31 32 35-39 46 48-50 52 54 57] female patients compared with their male counterparts,[32 35 36 39 49 50 57] except in one study;[56] patients receiving extended-release (ER) formulations compared with immediate-release formulations;[48 54] and treated patients compared to treatment naïve patients (or untreated in the pre-index period [6 months or 1 year]).[18 26 36] Comorbidities, including diabetes, Parkinson's disease, epilepsy, dementia, multiple sclerosis and hypertension, were correlated with increased treatment persistence and adherence;[49 50 57] exceptions were chronic obstructive pulmonary disease and migraine.[50 57]

Other reported determinants of favorable persistence and adherence included higher treatment doses;[36] low daily quantity of tablets,[37] absence of UTI; higher baseline OAB costs;[39] treatment by urologists vs gynecologists/general practitioners; the absence of side effects (headache, stomach upset and glaucoma);[50] White vs Black, Hispanic and Asian patients and patients of other ethnicities;[35 47] lower medication co-payment;[35] and use of fewer medications.[47]

DISCUSSION

This systematic review provides an overview of persistence and adherence with oral pharmacotherapies used to treat patients with OAB in real-life clinical practice. A wealth of data were collected from 30 articles, which described 28 observational studies performed in Europe and North America totaling over 500 000 patients. A number of key findings were identified, including greater persistence and adherence with mirabegron vs antimuscarinics,[18 26 31 34] in females vs males,[32 35 39 49 57] in older vs younger patients,[26 31 32 35-39 46 48-50 52 54 57] and in previously treated vs untreated patients.[18 26 36]

Across the studies, persistence appeared to reduce very quickly after initiation of treatment for all OAB therapies, with low rates (<50%) already evident at 1 month.[31 41 47] Longer follow-up periods showed that large proportions of patients discontinued treatment by 1 year (62–100%)[18 26 33 38 45-47 49 50 54] and by the end of 3 years, less than 10% of patients continued on any antimuscarinic.[54] These steep reductions in rates of persistence over time were mirrored by the reported adherence rates.

The chronic nature of OAB means that consistent and long-term use of medication is essential to manage OAB symptoms and improve health outcomes. It is therefore important for patients to receive a first-line treatment that has a good efficacy-tolerability profile and evidence of favorable persistence and adherence vs other treatment options. Among the antimuscarinics, solifenacin and fesoterodine were generally associated with better persistence and adherence.[18 26 43 52] In studies that assessed both mirabegron and antimuscarinics, persistence in the mirabegron cohorts, including the treatment-naïve populations, was statistically significantly greater ($p<0.001$).[18 26 31] Due to the recommended treatment sequence for OAB [10 58], the majority of patients that receive mirabegron are treatment-experienced; however, these studies suggest a benefit of mirabegron treatment regardless of treatment status. Adherence to mirabegron was also greater; however, mean/median MPR values in the overall mirabegron populations did not indicate medication adherence (MPR/PDC<0.80). Although these studies did not directly assess the reason(s) for the observed benefits of mirabegron, proposed reasons include a distinct mechanism of action, lower rates of bothersome anticholinergic adverse events, particularly dry-mouth, compared with antimuscarinics and unmet expectations of antimuscarinic treatment.[18 26 31]

It is well established that poor medication persistence and adherence reduces the ability to achieve optimum clinical benefits and limits treatment success, especially for chronic conditions such as OAB.[13 14 17 46] The unwillingness of patients to continue to take long-term treatment has been observed across many chronic conditions, with non-adherence to medication observed in ~50% of patients.[13] An analysis across six chronic conditions found

1-year persistence and adherence rates to be low for all conditions, and lowest for OAB medications (antimuscarinics),[33] suggesting an unmet treatment need. However, this study was performed prior to the availability of mirabegron for use in routine clinical practice, and therefore an updated analysis of persistence in chronic conditions might be warranted.

As alluded to above, persistence and adherence to treatment is expected to improve outcomes for patients with OAB. In two studies, better OAB treatment persistence and adherence were associated with improved clinical outcomes and HRQoL compared with patients who were non-persistent.[15 16] These data are consistent with studies describing other chronic diseases, such as diabetes and depression, where good adherence resulted in improved health outcomes[14 59] as well as reduced complications and disability, and improved HRQoL and life expectancy.[60] Moreover, greater persistence and adherence to treatment for OAB is associated with significantly lower medical, sick leave and short-term disability costs.[35] Indeed, economic models based on real-world inputs suggest that improved persistence with mirabegron translates into benefits of reduced healthcare resource use, and lower direct and indirect costs of treatment compared with antimuscarinics.[27 61] Additionally, mirabegron is reported to be cost effective vs six antimuscarinics from commercial and Medicare perspectives in the United States, due to fewer projected adverse events and comorbidities, and data suggesting better persistence.[62]

Independent variables for treatment discontinuation were studied by at least half of the papers included in our literature review, of which sex, age, comorbidities and previous experience of OAB medications were shown to be important factors in more than two studies. Only six studies reported switch-rates and although these were low, the treatment strategy of cycling antimuscarinic agents in patients who do not achieve symptom relief is common in clinical practice. Yet recent analysis of real-world data suggests that switching antimuscarinics may provide sub-optimal care.[55] In contrast, switching to mirabegron from antimuscarinic therapy has proved beneficial in over 50% of patients with OAB in an observational study.[63]

This review represents a large pooled analysis of real-world data for persistence and adherence to oral OAB medication across different geographical locations (Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States); however, there were no identifiable trends between data and countries. The definitions and calculations of persistence and adherence were not uniform across the literature and the terms were often used interchangeably. This lack of consistency led to some limitations on the ability to compare across studies. Other limitations to performing cross-study comparisons or pooled analyses in this SLR include differences in the individual study populations and/or study designs, resulting in considerable variations between data. For example, the median TTD for oxybutynin ER and tolterodine ER were determined to be 5.1 and 5.5 months, respectively, by one study,[54] but only 60 and 56 days, respectively, by another study.[18]

Furthermore, it is very difficult to capture the specific reasons for treatment discontinuation from prescription-driven or medical claim data rather than patient-derived data.[18] The current review excluded data from RCTs to better reflect patient behavior in the general OAB population in real-life clinical practice.[11] Only one paper included in our review reported that antimuscarinic side effects were significantly associated with discontinuation,[50] despite reports that such side effects are bothersome and a common reason for discontinuation of antimuscarinic treatment.[11 19 28] Additional factors that could not be assessed by our study, but can influence persistence with treatment in OAB patients are patient expectations, appropriate counselling and patient satisfaction with treatment.[11 17 28]

In addition to the limitations listed above, it should be noted that Sicras-Mainar *et al*[42 43] reported data on the same patients (in terms of demographics and the timeframe/geographical source). This is also the case for two studies published by Sicras-Mainar *et al* in 2013 and 2014.[53 64] Also, this SLR excluded data on non-oral pharmacotherapies (eg, onabotulinum toxin A) and combination mirabegron plus antimuscarinic therapies, where additional efficacy has been reported compared to the

monotherapies.[65] Further research on persistence and adherence to these OAB therapies is needed to better evaluate current treatment options. Additional studies are also required to improve our understanding of persistence and adherence in OAB, including qualitative studies to examine the reasons for discontinuation and real-world studies to examine resource use associated with OAB medication in relation to adherence and persistence. As OAB is a chronic disease, clinicians should not only take into consideration the efficacy and side effects of an agent when deciding on treatment options, but also ensure that realistic patient expectations from treatment are set through patient education and counselling. The patient's life-style should also be considered as this is likely to impact adherence and persistence with OAB therapy.

CONCLUSIONS

Persistence and adherence were greater with mirabegron compared with antimuscarinics, and appeared to be greater with solifenacin and fesoterodine compared with other antimuscarinics. In addition, greater persistence and adherence were generally observed in patients who were female, older, treatment-experienced and receiving ER formulations. Together with the efficacy and tolerability data from clinical trials, real-world data examined in this review warrants consideration of using mirabegron as first-line oral pharmacotherapy for patients with OAB.

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Contributorship Statement

GY, PS, JN, ZH, ES and FF were involved in conceptualisation and design of the study and critical review of the manuscript. FF, PS and GY performed the data extraction. All authors approved the final manuscript as submitted.

Competing Interests

JN and ES are employed by Astellas Pharma Inc. ZH was employed by Astellas Pharma Inc. as the time of the study. FF has received a grant from Astellas for study design, data extraction and manuscript development.

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Data Sharing Statement

The search strategy and all data supporting this study are provided as supplementary information accompanying this paper.

Abbreviations and Acronyms

ER = extended-release

HRQoL = health-related quality of life

MPR = medication possession rate

OAB = overactive bladder

PDC = proportion of days covered

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs = randomised controlled trials

SLR = systematic literature review

TTD = time to discontinuation

UTI = urinary tract infection

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FIGURE LEGENDS

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

*Studies were excluded for the following reasons: outcome measure(s) of persistence and/or adherence, relevant to this systematic review (such as medication possession rate, proportion of days covered, discontinuation rate), were not presented within the full text of the article (n=17); adherence/persistence data were drawn from surveys, interviews or self-reports (n=13); cohort contained a portion of patients under 18 years of age (who could not be removed or isolated from results/data) (n=7); participants had prior awareness/knowledge of partaking in a study related to OAB medication (ie, open-label extension to a study or prior written consent) (n=6); a full article text was not available (ie, only a conference abstract) or the full text was not in English (n=1); or non-oral OAB medications were included within the presented results (and could not be removed or isolated from results/data) (n=1)

§Three of these studies were identified by reviewing reference lists of included studies and relevant systematic literature reviews

Figure 2 Frequency for reported determinants of discontinuation

*In one study the relationship was not statistically significant

**Includes dose, formulation, race, prior infection, financial burden, prescriber profession, side effects, medication co-payment and polypharmacy

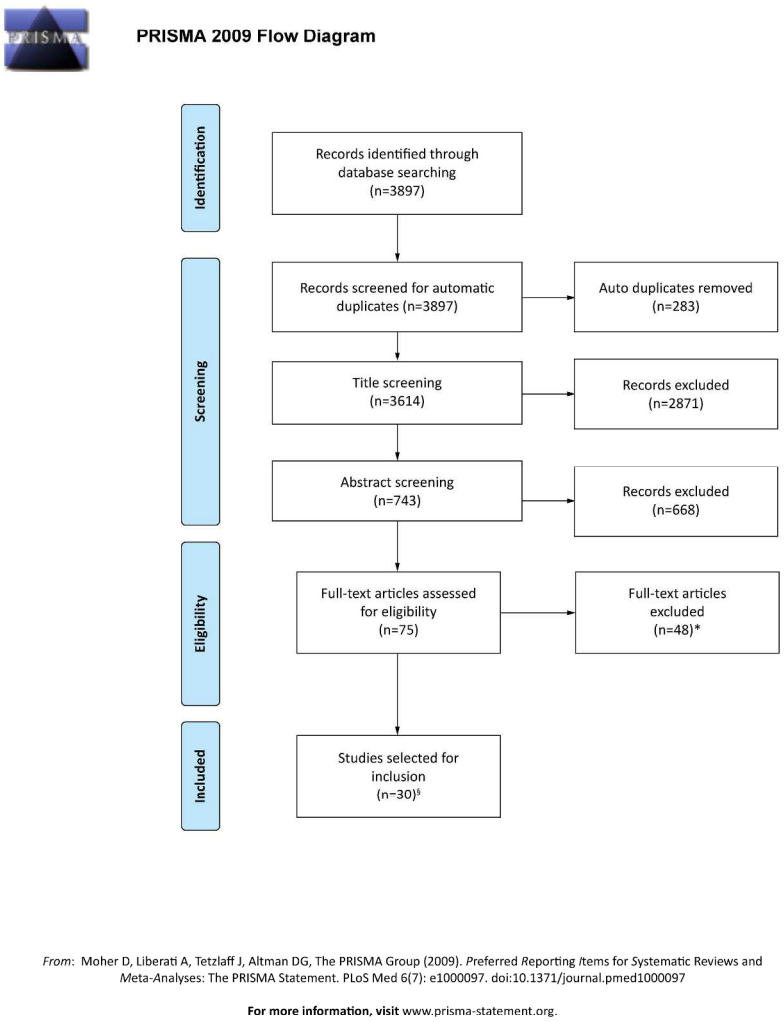

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

279x361mm (300 x 300 DPI)

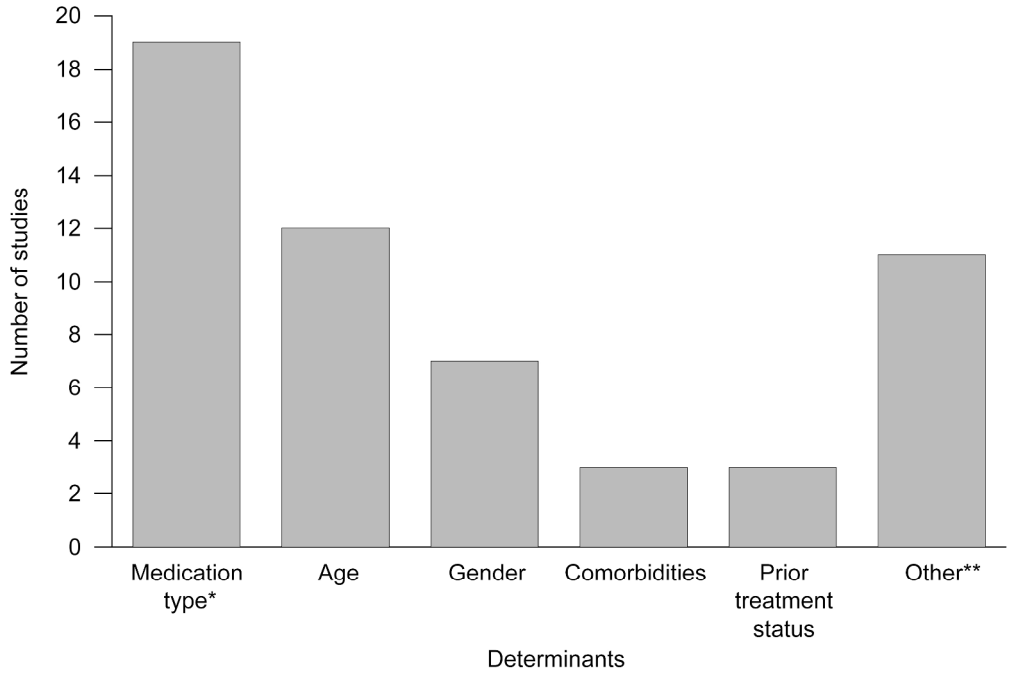

Figure 2 Frequency for reported determinants of discontinuation

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Supplemental Table 1: Patient characteristics, interventions and definitions/variables of persistence, adherence and discontinuation reported in the studies.

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Brostrøm and Hallas (2009)[1] Odense University Pharmacoepidemio-logical Database (OPED); Denmark) (1999–2006)	n=2477 Male: n=836 (33.8%) Female: n=1641 (66.2%) Mean age: 68.3 years[a]	Any prescription of OAB medication: flavoxate (n=21) oxybutynin TD (n=48) tolterodine (n=1478) solifenacin (n=774) trospium (n=271) darifenacin (n=52)	Patients who continued taking a particular drug for up to 7 years with no more than 120-day gaps were regarded as experiencing single-treatment episodes Variables: age, gender, prior use of OAB agents and use of anti-diabetic drugs	Up to 7 years
Chancellor et al (2013)[2] IMS Lifelink Database, Connecticut; USA (2005–2008)	n=103 250 Male: n≈25 916[a] (25.1%) Female: n≈77 334[a] (74.9%) Mean (SD) age: 58.7 (15.7) years	First (new) prescription of OAB medication in adults ≥18 years: tolterodine ER (n=43 881)[a] solifenacin (n=15 488)[a] oxybutynin (n=15 075)[a] darifenacin (n=10 532)[a] oxybutynin ER (n=10 325)[a] oxybutynin TD (n=2272)[a] tolterodine (n=2581)[a] trospium (n=2478)[a] trospium ER (n=413)[a]	To be considered a discontinuation, patients were required to have a gap of at least 45 days in therapy based on fill dates and days' supply Adherence rate was defined as the proportion of patients filling more than one prescription with an MPR of ≥80%	2 years
Chapple et al (2017)[3] Clinical Practice Research Datalink (CPRD); UK (2013–2014)	n=21 996 Male: n=6513 (29.6%) Female: n=15 483 (70.4%) Mean (SD) age: 63.9 (16.3) years	First (new) prescription of OAB medication in adults ≥18 years: mirabegron (n=1203) darifenacin (n=126) fesoterodine (n=1287) flavoxate (n=144) oxybutynin ER (n=1144) oxybutynin IR (n=5779) propiverine (n=95) solifenacin (n=8191) tolterodine ER (n=1561) tolterodine IR (n=1523) trospium chloride (n=943)	Treatment was defined as discontinued if the maximum allowable gap duration was at least 1.5 times the intended duration of the most recent prescription Adherence rate was defined as mean MPR at 12 months	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
D'Souza et al (2008)[4] Undisclosed medical claims database; USA (1999–2004)	n=1117 Male: n≈206[a] (18.4%) Female: n≈911[a] (81.6%) Mean (SD) age: 55.7 (14.5) years	First index of an OAB medication in adults ≥18 years: oxybutynin ER (n=249) oxybutynin IR (n=108) tolterodine ER (n=454) tolterodine IR (n=306)	Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuing the index drug or switching to other OAB drugs Adherence rate was measured as the proportion of patients with an MPR of ≥0.80 Variables: age, gender, drug formulations and OAB-associated comorbidities (eg, falls/fractures, skin infections, UTIs, anxiety/depression)	1 year
Desgagné et al (1999)[5] Régie de l'assurance maladie du Québec (RAMQ) database; Canada (1994–1997)	n=6690 Male: n=2534 (37.9%) Female: n=4156 (62.1%) Mean age: 77.3 years[a]	Patients aged ≥65 years with at least one prescription claim (first index) of: oxybutynin (n=5718) flavoxate (n=972)	Persistence evaluated by percentage of patients refilling their initial prescription	Up to 4 years
Gomes et al (2012)[6] Canada (Ontario Drug Benefit database of prescriptions)	n=56 851[a] Male: n≈18 496 (32.5%)[a] Female: n≈38 355 (67.5%)[a] Mean age: 77.7 years[a]	Patients aged >65 years with a first index (new) claim of: oxybutynin IR (n=31 996) tolterodine ER/IR (n=24 855)	Persistence with treatment was defined by refills for the index drug within an interval defined by the duration specified on the prescription plus a 50% grace period	2 years
Gopal et al (2008)[7] UK (Health Improvement Network database of prescriptions) (1991–2005)	n=29 369 Male: n=0 (0%) Female: n=29 369 (100%) Mean (SD) age: 63.9 (16.8) years	Women aged ≥18 years prescribed anti-cholinergic medications: tolterodine IR tolterodine ER oxybutynin IR oxybutynin ER flavoxate terodiline trospium properivine solifenacin	Discontinuation was defined by no anticholinergic prescriptions issued within 90 days after the end of the last anticholinergic drug prescription Anticholinergic medications were considered discontinued at the time a patient switched to another medication or as above Variables: drug formulation	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Ivanova et al (2014)[8] OptumHealth Reporting and Insights claims database; USA (2007–2012)	n=10 318 Male: n≈2822 (27.4%)[a] Female: n≈7496 (72.6%)[a] Mean age: 51.6 years	Patients aged 18 to 64 receiving a new prescription of: darifenacin (n=970)[a] solifenacin (n=2662)[a] oxybutynin (n=2889)[a] tolterodine (n=3116)[a] trospium (n=454)[a] fesoterodine (n=227)[a]	Persisters were defined as patients who did not switch or discontinue the index antimuscarinic during the first 6 months after the treatment initiation date Discontinuation was defined by a gap of at least 60 days between refills within the first 6 months after the treatment initiation date Switching was defined as a changed prescription from the index antimuscarinic within the first 6 months after the treatment initiation date (with a gap of 60 days between the end of the day supply of the index antimuscarinic and the new antimuscarinic) Variables: age, gender, history of UTIs and index antimuscarinic	6 months
Johnston et al (2012)[9] Truven Health MarketScan® Database; USA (2004–2009)	n=73 120 Male: n=29 406 (40.2%) Female: n=43 714 (59.8%) Mean age: 69.0 years[a]	First index drug in OAB patients with or without diabetes, aged ≥18 years: darifenacin oxybutynin solifenacin tolterodine trospium	Persistence was measured as the number of days from the index date until a gap in OAB medication of ≥45 days Adherence was assessed using the interval-based (fixed time-period) MPR (adherent patients had an ≥80% MPR) Variables: age, gender and diabetes	1 year
Kalder et al (2014)[10] Disease Analyzer database (IMS Health); Germany (2005–2012)	n=26 834 Male: n≈9660[a] (36%) Female: n≈17 174[a] (64%) Mean (SD) age: 69.4 (13.2) years	First index (new) prescription in patients aged ≥18 years: darifenacin (n=1995) fesoterodine (=811) oxybutynin (n=3813) propiverine (n=2714) solifenacin (n=4844) tolterodine (n=1814) trospium (n=10 843)	Treatment discontinuation was defined as a period of 90 days without prescription of UI therapy but with at least one visit to the same doctor after 90 days Variables: age, gender, comorbidity burden (including diabetes) and antimuscarinic side-effects	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Kleinman et al (2014)[11] Human Capital Management Services [HCMS] Research Reference Database; USA (2001–2011)	n=2960 Male: n=878 (29.7%) Female: n=2082 (70.3%) Mean age: 46.6 years	First index of OAB medication in adults aged 18 to 64 years: darifenacin fesoterodine oxybutynin flavoxate[b] solifenacin tolterodine trospium hyoscyamine[b] imipramine[b]	Persistence was measured as the number of days from index UA prescription until first ≥30-day gap in UA medication supply Adherence was measured as the percentage of the annual post-index period with available medication	1 year
Krhut et al (2014)[12] Dept. of Urology and Dept. of Gynaecology and Obstetrics, University Hospital Ostrava; Czech Republic (2009–2010)	n=377 Male: n=52 (13.8%) Female: n=325 (86.2%) Mean (SD) age: 60.3 (13.8) years	First (new) index of OAB medication within patients attending hospital as an outpatient: trospium (n=189) propiverine (n=41) tolterodine ER (n=9) solifenacin (n=48) fesoterodine (n=90)	Persistence was assessed according to the patient records	1 year
Manack et al (2011)[13] Thomson Reuters MarketScan® Commericial and Medicare Supplemental Databases; USA (2002–2007)	n=46 271[c] Male: n=19 727 (42.6%) Female: n=26 544 (57.4%) Mean (SD) age: 62.5 (19.6) years	Patients with neurogenic bladder origin (such as spinal cord injury and multiple sclerosis) receiving an oral OAB medication	Continuation was defined as ≥365 days of OAB oral drug use beginning at the index date with ≤90 days between the end of therapy and end of eligibility Discontinuation was defined as ≥6 months of no OAB oral drug use between the end of therapy and the end of eligibility	1 year
Mauseth et al (2013)[14] The Norwegian Prescription Database; Norway (2004–2010)	n=32 178 Male: n=0 (0.0%) Female: n=32 178 (100.0%) No mean age reported. The majority of patients (60.5%) were aged ≥60 years	Adult patients aged ≥18 years with a first index (new) prescription of: tolterodine (n=12 389) solifenacin (n=13 682) darifenacin (n=4399) fesoterodine (n=1708)	Persistence defined as the population who had not discontinued the drug during a period of 365 days after the index date A switch was defined as a prescription for another of the drugs included in the study within 365 days after the index date Adherence was measured using MPR (sum of days of supply for all tablets purchased, except those received at the last fill, divided by the total number of days from the first to the last filling) Variables: age and initial antimuscarinic	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Nitti et al (2016)[15] Optum Database; USA (2010–2013)	n=2628 Male: n=602 (22.9%) Female: n=2026 (77.1%) Mean age: 57.3 years[a]	New and existing users aged ≥18 years treated with: mirabegron (n=380) tolterodine ER (n=2248)	Persistence was defined as a continuous supply of index drug until any 30-day period during which the patient did not have a supply of index drug Adherence: the proportion of days covered by the prescription was calculated using prescription fill dates and number of days' supply for each fill of a prescription	6 months
Pelletier et al (2009)[16] PharMetrics Patient-Centric Database; USA (2005–2006)	n=43 367 Male: n=9675 (22.3%) Female: n=33 692 (77.7%) Mean (SD) age: 51.1 (12.4) years	Adults aged ≥18 years receiving a first index (new) prescription of: tolterodine ER oxybutynin solifenacin darifenacin trospium	Adherence was measured by PDC over the 12-month post index period (adherent patients had an ≥80% PDC) Variables: age, gender and comorbidity burden (including COPD, congestive heart failure, diabetes, hypertension)	1 year
Perfetto et al (2005)[17] PharMetrics Patient-Centric Database; USA (2001–2003)	n=23 328 No patient demographics were reported	All patients with either a new diagnosis of OAB or new use of: tolterodine ER oxybutynin ER	Discontinuation rates were calculated	11 months
Sears et al (2010)[18] Military Health System; USA (2003–2006)	n=7858 Male: n=2357 (30.0%) Female: n=5501 (70.0%) Age was not reported	Military treatment facility enrollees prescribed: oxybutynin ER (n=136) oxybutynin IR (n=2003) tolterodine ER (n=4716) tolterodine IR (n=992)	Non-persistence was defined as patients who never refilled a prescription for any OAB medication during the 3-year study period Medication switch rate was calculated as the proportion of patients who changed medication or dose at least once Adherence was defined as the proportion of patients with an MPR of ≥80% Variables: gender and drug formulation	3 years
Sicras-Mainar et al (2016)[d,19] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean age: 54.0 years	Adults aged 20 to 64 with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Discontinuation was defined as when the patient switched to another active substance, another drug was added (combination) or the medication was discontinued completely or discontinued for ≥60 days without renewal and ≥2 prescriptions Compliance was calculated using MPR Variables: concomitant medication (antidepressants, antibiotics) and index drug	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sicras-Mainar et al (2015)[d,20] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean (SD) age: 54.0 (9.2) years	Adults aged ≥20 years with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Persistence was defined as the time, measured in months, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the MPR, which was evaluated from the first to the last prescription and represented the number of days of medication taken over the number of days in treatment (commencing from the start date)	1 year
Sicras-Mainar et al (2014a)[21] Primary care medical databases; Spain (2008–2010)	n=552 Male: n≈272[a] (49.2%) Female: n≈280[a] (50.8%) Mean (SD) age: 80.2 (4.0) years	Adults aged ≥75 years with a first index (new) prescription of: fesoterodine (n=58) solifenacin (n=252) tolterodine (n=212)	Persistence was defined as the time, in weeks, with no drop-out from initial treatment or with no switch to another medication at least 30 days following initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the medication use/possession rate	1 year
Sicras-Mainar et al (2014b)[e,22] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Discontinuation was defined by either the absence of prescription coverage for the initial therapy for the remainder of the 52-week follow-up period or a switch to an alternative antimuscarinic during this time-period Variables: index drug	1 year
Sicras-Mainar et al (2013)[e,23] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Persistence was defined as patients who remained on treatment during the 52-week period following the index date Compliance was defined according to ISPOR criteria and was calculated based on the MPR	1 year
Suehs et al (2016)[24] Medicare Advantage Prescription Plan - Administrative Claims Data; USA (2007–2013)	n=46 140[a] Male: n=15 479[a] (33.5%)[a] Female: n=30 661[a] (66.5%)[a] Mean age: 75.5 years[a]	Adults aged 65 to 89 years[f] with a first index (new) prescription of any antimuscarinic OAB medication	Persistence was assessed as time in days from the index date to discontinuation of index antimuscarinic treatment Adherence was assessed as PDC with the index OAB treatment over three predefined post index observation periods: 3, 6, and 12 months Treatment discontinuation was identified using a permissible gap between refills of 15 days	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sussman et al (2017)[25] Truven MarketScan® Claims Database; USA (2012–2013)	n=71 980[a] Male: n=21 225[a] (29.5%)[a] Female: n=50 755[a] (70.5%)[a] Mean age: 62.3 years[a]	Adults aged ≥18 years with a prescription of: mirabegron any anticholinergic OAB medication	Persistence was measured by evaluating treatment failure (defined as either treatment discontinuation or treatment switching). A medication supply gap of ≥30 days was used to define treatment discontinuation Adherence was defined as the PDC (ie, the number of days covered by the index therapy divided by the number of days between the index date and the end of the follow-up [365 days]). A PDC of <80% was considered nonadherent	1 year
Wagg et al (2012)[26] Prescription Database; UK (2007–2008)	n=4833 Demographics were not explicitly reported, the majority of prescriptions appeared to be issued to patients aged ≥60 years	Adults aged ≥40 years with a first index (new) prescription of: darifenacin flavoxate oxybutynin ER oxybutynin IR propiverine solifenacin tolterodine ER tolterodine IR trospium	Persistence was defined as the mean time [in days] until discontinuation (a gap in treatment exceeding 1.5 times than the length of the previous prescription without a refill)	1 year
Wagg et al (2015)[27] Canadian National Private Drug Plan Database; Canada (2013)	n=19 485 Male: n=4992 (25.6%)[a] Female: n=14 493 (74.3%)[a] Mean age not reported; the majority of patients (77.8%)[a] were aged ≥46 years	Adults aged ≥18 years with a first index (new) prescription of: mirabegron (n=1683) fesoterodine (n=1415) oxybutynin ER (n=1260) oxybutynin IR (n=5356) solifenacin (n=6032) tolterodine ER (n=3739)	Adherence was defined by the MPR over 1 year To calculate time to end of persistence (defined by a gap in therapy of ≥30 days or switching to another medication), prescription claims for a target drug were tracked for 12 months after the index claim date Variables: age, gender, treatment-naïve vs treatment-experienced, index antimuscarinic, number of coexisting medications	1 year
Wagg et al (2015)[28] IMS Brogan public and private prescription claims databases; Canada (2007–2012)	n=31 707 Male: n=9395 (29.6%)[a] Female: n=22 312 (70.4%)[a] Mean age not reported	Adult patients receiving a first index (new) prescription of: oxybutynin IR oxybutynin ER tolterodine IR tolterodine ER solifenacin darifenacin trospium flavoxate	Discontinuation was defined as patients experiencing a gap in therapy longer than 60 days	4 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Yeaw et al (2009)[29] PharMetrics Patient-Centric Database (pharmacy claims); USA (2005)	n=7722 Male: n=1686 (21.8%) Female: n=6036 (78.2%) Mean (SD) age: 43.7 (18.3) years	Adult patients receiving a first index (new) prescription of: tolterodine oxybutynin solifenacin darifenacin trospium bethanechol flavoxate hyoscyamine	Persistence was calculated for the post-index period until the patient discontinued therapy, was lost to follow-up due to disenrollment from the health plan (minimum of 12 months), or the maximum 24-month follow-up period ended, whichever event occurred first. A patient was considered persistent until an excessive gap in days supplied occurred; refill gaps of 30, 60, and 90 days were used to calculate persistence for all cohorts Adherence was measured using the PDC for each of the six drug class cohorts. This was calculated by taking patients' total days supplied of index class medications for the 360-day period following the index date and dividing by 360	2 years
Yu et al (2015)[30] California Medi-Cal administrative files; USA (1999–2002)	n=2496 Male: n=534 (21.4%) Female: n=1962 (78.6%) Mean (SD) age: 63.15 (16.14) years	Adult patients aged ≥18 years receiving a prescription of an OAB drug, including: tolterodine (n=1093) oxybutynin ER (n=524) oxybutynin (n=812) other OAB agents (n=67)	Persistence was measured by the length of continuous pharmacological treatment (patients discontinued their treatment if they failed to refill OAB/UI agents within 30 days after the expected end date of the previous prescription) Patients who switched from one agent of OAB/UI drug to another within 30 days were considered persistent on therapy. Adherence was defined as MPR over 181 days for the 6-month follow-up period Variables: age, gender, ethnicity, index drug, OAB-associated comorbidities (UTIs), medication use history, length of hospital stay and number of drug classes prescribed	1 year

COPD = chronic obstructive pulmonary disease; ER = extended release; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; IR = immediate release; MPR = medication possession ratio (measured as the proportion of days with any OAB medication on hand, over the length of the evaluation period); OAB = overactive bladder; PDC = proportion of days covered; PIM = potentially inappropriate medication; SD = standard deviation; TD = transdermal; UA = urinary antispasmodic; UI = urinary incontinence; UTIs = urinary tract infections

*The sum of the patients prescribed individual drugs may not match the total number of patients perhaps due to switching in some studies

[a]Calculated from data presented in the article; [b]used only in an OAB context; [c]26 922 continued, discontinued or restarted an OAB medication in the study period, but no demographics for this specific sub-group are reported; [d]Sicras-Mainar et al (2016)[19] and Sicras-Mainar et al (2015)[20] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [e]Sicras-Mainar et al (2014)[22] and Sicras-Mainar et al (2013)[23] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [f]this cohort was split into two groups – patients who were assigned OAB medication appropriately [non-PIM], or potentially inappropriately [PIM]. Inappropriateness was defined as patients having "drug–disease or syndrome interaction or indication of significant anticholinergic medication burden at the time of initiation of an antimuscarinic OAB treatment"

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Supplemental Table 2. Summary of adherence and persistence rates and determinants

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Brostrøm and Hallas (2009)[1]	Proportion of patients continued (all drugs except trospium chloride): <50% at 6 months <25% at 1 year <10% at ≥2 years Proportion of patients continued trospium: 46% at 6 months 36% at 1 year 22% at 2 years 16% at 3 years	Not reported	***Gender, age, medication dose, treatment status, medication type*** Retention was longer: in females; in older people; with higher doses; with previous experience of other OAB drugs; trospium vs other OAB drugs
Chancellor et al (2013)[2]	Proportion of patients discontinued at 2 years:[a] tolterodine ER: 84.7% solifenacin: 85.2% oxybutynin: 91.1% darifenacin: 85.7% oxybutynin ER: 84.0% tolterodine: 85.1% trospium: 88.1% trospium ER: 87.1% Proportion of patient switched at 2 years:[a] tolterodine ER: 5.7% solifenacin: 5.2% oxybutynin: 4.7% darifenacin: 6.0% oxybutynin ER: 6.7% tolterodine: 9.7% trospium: 6.9% trospium ER: 6.4%	Proportion of patients with MPR ≥0.80 over study period (in those filling >1 prescription): tolterodine ER: 51.1% solifenacin: 49.4% oxybutynin: 30.1% darifenacin: 51.9% oxybutynin ER: 51.8% tolterodine: 42.6% trospium: 42.4% trospium ER: 54.3%	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Chapple et al (2017)[3]	Median time to discontinuation (days): mirabegron: 169 darifenacin: 56 fesoterodine: 78 flavoxate: 30 oxybutynin ER: 60 oxybutynin IR: 35 propiverine: 56 solifenacin: 67 tolterodine ER: 56 trospium chloride: 60 Proportion of patients persistent at 1 year: mirabegron: 38% darifenacin: 16% fesoterodine: 24% flavoxate: 8.3% oxybutynin ER: 17% oxybutynin IR: 12% propiverine: 21% solifenacin: 25% tolterodine ER: 21% trospium chloride: 19%	Mean (SD) MPR at 1 year: mirabegron: 0.59 (0.33) darifenacin: 0.46 (0.34) fesoterodine: 0.53 (0.33) flavoxate: 0.44 (0.32) oxybutynin ER: 0.49 (0.32) oxybutynin IR: 0.41 (0.32) propiverine: 0.51 (0.32) solifenacin: 0.53 (0.34) tolterodine ER: 0.50 (0.34) trospium chloride: 0.48 (0.33) Proportion of patients with MPR ≥0.8 at 1 year: mirabegron: 43% darifenacin: 29% fesoterodine: 35% flavoxate: 24% oxybutynin ER: 31% oxybutynin IR: 22% propiverine: 25% solifenacin: 35% tolterodine ER: 32% trospium chloride: 29%	***Medication type*** Mirabegron was associated with a statistically significantly greater median time to discontinuation (adjusted HR range 1.31–2.31; p<0.0001 all comparisons) and 12-month persistence rates (adjusted OR range 0.18–0.71; p≤0.0001 all comparisons) vs antimuscarinics in all patients The mean MPR with mirabegron was significantly greater vs antimuscarinics in all patients (p values 0.03 to <0.0001), and in treatment-naïve subcohorts, except for flavoxate (p values 0.02 to <0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Desgagné et al (1999)[4]	Proportion of patients refilled initial prescription: Short-term[b]; oxybutynin: 39.3% flavoxate: 36.6% Long-term[c]; oxybutynin: 63.9% flavoxate: 55.5% Proportion of patients discontinued at 3 months: oxybutynin: 78% flavoxate: 83% Proportion of patients discontinued at 6-months: oxybutynin: 89% flavoxate: 94% Proportion of patients switched at 4-years: Patients without renewal of the original claim: oxybutynin: 1.3% flavoxate: 3.1% Patients with any number of renewals before switch: oxybutynin: 2.2% flavoxate: 5.9%	Not reported	***Age*** Compared with patients aged <77.5 years, those who were older were less likely to discontinue vs: 77.5–83.5 years: RR 0.90, 95% CI 0.85–0.96, p<0.001 >83.5 years: RR 0.86, 95% CI 0.81–0.92, p<0.001 ***Medication dose*** Higher quantity of tablets per day (2–4 tablets/day) was associated with increased risk of early discontinuation, compared with low daily quantity (1 tablet per day) (RR 1.45, 95% CI 1.37–1.53, p<0.001) ***Medication type*** Patients receiving flavoxate had an increased risk of discontinuation compared with those receiving oxybutynin (RR 1.13, 95% CI 1.05–1.22, p<0.001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
D'Souza et al (2008)[5]	Proportion of patients persistent at 1 year (without a gap >45 days): oxybutynin ER: 15.3% oxybutynin IR: 6.5% tolterodine ER: 15.0% tolterodine IR: 11.4% overall: 13.2% Proportion of patients not refilled index medication: oxybutynin ER: 39.4% oxybutynin IR: 59.3% tolterodine ER: 42.7% tolterodine IR: 46.1% overall: 44.5% Median time to discontinuation (days): oxybutynin ER: 34 oxybutynin IR: 0 tolterodine IR: 32 tolterodine ER: 33 overall: 31 Proportion of patients switched at 1 year: oxybutynin ER: 16.5% oxybutynin IR: 19.4% tolterodine IR: 13.7% tolterodine ER: 9.9% overall: 13.3%	Proportion of patients with MPR ≥0.80 at 1 year: oxybutynin ER: 36.1% oxybutynin IR: 14.8% tolterodine ER: 35.2% tolterodine IR: 23.5% overall: 30.3%	***Medication formulation*** Adherence with IR drugs approximately half that for ER drugs (OR 0.504, 95% CI 0.306–0.704, p<0.001) ***Age*** Patients aged ≥65 years were 1.5 times more likely to achieve an MPR ≥0.80 than patients aged <65 years

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gomes et al (2012)[6]	Median time to discontinuation (days): oxybutynin: 68 tolterodine: 128 Proportion of patients persistent at: 6 months oxybutynin: 30.6% tolterodine: 42.9% 1 year oxybutynin: 18.9% tolterodine: 27.3% 18 months oxybutynin: 13.1% tolterodine: 18.9% 2 years: oxybutynin: 9.4% tolterodine: 13.6%	Not reported	***Medication type*** Over the 2-year follow-up, the time to discontinuation was longer with tolterodine than oxybutynin (p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gopal et al (2008)[7]	Over 3 years, 91% of 49,419 episodes of medication prescription resulted in discontinuation Cumulative incidence of discontinuation at 6 months, 1 year, 2 years and 3 years (unadjusted): Overall: 58.8, 77.2, 87.5, 92.0% Cumulative incidence of discontinuation, at 6 months, 1 year, 2 years and 3 years (adjusted for age, year of initiation, switch, number of previous drug classes, number of prior episodes and smoking status): oxybutynin: 71, 86, 94, 96% oxybutynin ER: 57, 80, 93, 97% tolterodine: 61, 81, 92, 95% tolterodine ER: 54, 76, 91, 97% trospium: 56, 80, 94, 98% propiverine: 61, 84, 95, 98% solifenacin: 53, 91, 98, 99% terodiline: 89, 99%, N/A, N/A flavoxate: 85, 96, 99, 99% Median time to discontinuation (months): oxybutynin: 4.67 oxybutynin ER: 5.13 tolterodine: 5.47 tolterodine ER: 5.37 trospium: 5.47 propiverine: 5.43 solifenacin: 5.00 terodiline: 4.00 flavoxate: 4.00 overall: 4.76 Overall switch rate: 15%	Not reported	***Medication formulation*** In comparison with the multiple-dosing drug classes at 6 months, both oxybutynin ER (57%, 95% CI 55.1–59.2) and tolterodine ER (54%, 95% CI 52.3–57.4) had lower incidences of discontinuation ***Medication type*** Trospium and tolterodine were associated with the longest median time to discontinuation (5.47 months each), followed by propiverine (5.43 months) and solifenacin (5.0 months). Terodiline and flavoxate had the shortest median time to discontinuation (4 months each)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Ivanova et al (2014)[8]	Proportion of patients discontinued at 6 months: 61.0% Proportion of patients switched at 6 months: 8.0% Proportion of patients persistent at 6 months: 31.0% Proportion of patients discontinued at 6 months: oxybutynin: 30.6% tolterodine: 30.5% solifenacin: 24.5% darifenacin: 8.4% trospium: 4.1% fesoterodine: 1.9% Mean time to discontinuation: 54.7 days 42.7% of patients never refilled their indexed prescription	Not reported	***Age*** Patients who discontinued (50.5 years) or switched (52.6 years) medication were significantly younger than those who persisted (53.4 years; p<0.001) Increasing age was associated with reduced odds of discontinuation (adjusted OR 0.97, 95% CI 0.96–0.97, p<0.0001) ***Gender*** Being male was associated with greater odds of discontinuation (adjusted OR 1.11, 95% CI 1.00–1.23, p=0.0475) ***Medication type*** Patients who persisted with medication contained a significantly higher proportion of solifenacin users than those in groups who switched or discontinued (30.1% vs 19.7% vs 24.5%, respectively, p<0.001) and a lower proportion of oxybutynin (22.6% vs 29.6% vs 30.6%, respectively, p<0.001) Compared to patients treated with solifenacin, patients were significantly more likely to discontinue when treated with tolterodine (adjusted OR 1.30, 95% CI 1.16–1.45, p<0.0001) or oxybutynin (adjusted OR 1.80, 95% CI1.59–2.03, p<0.0001) ***Presence of infection*** Patients with UTI were more likely to discontinue compared with those without UTI (adjusted OR 1.31, 95% CI 1.19–1.45, p<0.0001) ***Financial burden*** Patients with lower log of baseline OAB-related costs were more likely to discontinue (adjusted OR 0.96, 95% CI 0.94–0.98, p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Johnston et al (2012)[9]	Mean time of continuation at 1 year (days): diabetic: 164 not diabetic: 146.9 (p<0.001 difference) Proportion of patients discontinued at 1 year: diabetic: 71.5% not diabetic: 76.2% (p<0.001 difference)	Mean MPR at 1 year; diabetic: 0.473 not diabetic: 0.424 (p<0.001 difference)	***Age and gender*** The odds of adherence generally increase with age, and females had higher odds of adherence than men ***Diabetes*** The diabetes cohort had greater odds of achieving an MPR ≥0.80 (OR 1.215, 95% CI 1.169–1.263, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period The diabetes cohort had greater odds of filling a second OAB medication prescription (OR 1.166, 95% CI 1.127–1.205, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kalder et al (2014)[10]	Proportion of patients discontinued at: 1 year: 74.8% 2 years: 77.6% 3 years: 87%	Not reported	***Gender*** At 3 years, there was a significantly higher risk of discontinuation in male than female patients (HR 1.14, 95% CI 1.11–1.18, p<0.001) ***Age*** Discontinuation was higher in younger patients than older patients: ≤60 years: 89.7% 61–70 years: 87.9% 71–80 years: 86.8% >80 years: 83.0% ***Prescriber's profession*** Discontinuation rate was higher in patients treated by gynecologists and general practitioners compared with urologists (HR 1.60 [95% CI 1.52–1.67] p<0.001; HR 1.24 [95% CI 1.20–1.29] p<0.001) ***Side effects*** A higher risk of discontinuation in patients experiencing side effects: headache: HR 1.27, 95% CI 1.12–1.43, p=0.002 stomach upset: HR 1.20, 95% CI 1.12–1.27, p<0.001 glaucoma: HR 1.46, 95% CI 1.16–1.84, p<0.001 ***Medication type*** Patients using propiverine (HR 0.94, 95% CI 0.88–0.99, p=0.022) or solifenacin (HR 0.93, 95% CI 0.87–0.98, p=0.003) had a significantly lower risk of treatment discontinuation compared with oxybutynin. However, the absolute difference was relatively small ***Comorbidities*** Diabetes, Parkinson's disease, epilepsy, dementia, and multiple sclerosis was associated with a lowered risk of treatment discontinuation A prior diagnosis of migraine was associated with a higher risk of treatment discontinuation

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kleinman et al (2014)[11]	Median time until a ≥30-day medication gap: 64 days Proportion of patients persistent: beyond 1 month: 70% at 9 months: 10% at 1 year: 5%	Proportion of patients with PDC ≤10% at 1 year: 45.4% Proportion of patients with PDC ≥80% at 1 year: 12.7%	***Gender*** Compared to the group with PDC ≥80%, the group with PDC <80% contained a lower proportion of females (69.5% vs 76.3%, p=0.006) ***Age*** Compared to those with PDC ≥80%, patients with PDC <80% were younger (mean age: 46.18 years vs 49.79 years, p<0.001) ***Race*** Compared to the group with a PDC ≥80%, the group with PDC <80% contained a lower proportion of White patients (38.6% vs 50.0%, p<0.001) and higher proportion of Black and Hispanic patients (6.7% vs 3.7%, p=0.025; 11.6% vs 6.3%, p=0.002) ***Medication co-payment*** Compared to the group with a PDC ≥80%, those with PDC <80% paid a higher mean medication co-payment ($20.15 vs $14.68, p<0.001)
Krhut et al (2014)[12]	Median (SD) time to discontinuation: 6.53 (3.84) months Proportion of patients persistent at: 3 months: 59.7% 6 months: 39.3% 9 months: 33.6% 1 year: 27.2%	Not reported	***Medication type*** Persistence was significantly higher in patients treated with anticholinergic medication with an ER formulation than in patients treated with IR anticholinergics (ER: 7.10 [SD 3.90] months vs IR: 6.18 [SD 3.75] months, p=0.023)
Manack et al (2011)[13]	Mean (SD) duration of therapy: 201.9 (120.9) days Proportion of patients that: continued OAB medication ≥1 year: 28.9% discontinued OAB medication and did not restart[d]: 37.5% discontinued and restarted OAB medication[e]: 33.5%	Not reported	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Mauseth et al (2013)[14]	Proportion of patients persistent at 1 year: tolterodine: 39.0% solifenacin: 39.4% darifenacin: 34.3% fesoterodine: 29.1% overall: 38.0% Proportion of patients switched at 1 year: tolterodine: 12.0% overall: 10.3% Proportion of patients filled only one prescription: 31.9%	Mean MPR at 1 year: 0.62[f] Proportion of patients with MPR ≥0.80[f] at 1 year: tolterodine: 33.7% solifenacin: 35.7% darifenacin: 37.0% fesoterodine: 38.5% overall: 35.2%	***Age*** Persistence was lowest in the age group 18–39 years (20.9%), generally increased with age, and was highest in the age groups 70–79 years (43.5%) and ≥80 years (43.3%) ***Medication type*** At 1 year, persistence was highest for tolterodine (39.0%) and solifenacin (39.4%), both of which entered the market first. Persistence for darifenacin and fesoterodine, which were launched later, was 34.3% and 29.1%, respectively
Nitti et al (2016)[15]	Proportion of patients persistent at: 1 month; mirabegron: 68.4% tolterodine ER: 47.1% 3 months; mirabegron: 48.7% tolterodine ER: 28.6% 6 months; mirabegron: 34.7% tolterodine ER: 18.5% Median persistence (days): mirabegron: 170 tolterodine ER: 90	Not reported	***Age*** Compared with patients aged <65 years, patients aged ≥65 years were less likely to discontinue over 6 months with tolterodine (HR 0.88, 95% CI 0.80–0.96, p=0.0064) and mirabegron (HR 0.68, 95% CI 0.52–0.90, p=0.0068) ***Prior treatment*** Compared to patients without prior use of OAB medication, patients with prior OAB medication use were less likely to discontinue over 6 months with tolterodine (HR 0.76, 95% CI 0.68–0.85), p<0.0001) and mirabegron (HR 0.68, 95% CI 0.53–0.88, p=0.0025) ***Medication type*** The risk of discontinuation was lower with mirabegron compared with tolterodine (HR 0.72, 95% CI 0.61–0.85, p<0.0001)
Pelletier et al (2009)[16]	Not reported	Mean cohort PDC at 1 year: 0.32 Proportion of patients with PDC ≥0.80 at 1 year: 14.4%	***Demographics (gender, age, comorbidities)***[g] Female and older subjects were more likely to adhere. Those with a history of hypertension, diabetes, or multiple sclerosis were more adherent. Subjects with COPD were less adherent

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Perfetto et al (2005)[17]	Cumulative discontinuation rates at: 1 month; tolterodine ER: 6% oxybutynin ER: 11% 3 months; tolterodine ER: 55% oxybutynin ER: 62% 6 months; tolterodine ER: 69% oxybutynin ER: 76% 11 months; tolterodine ER: 79% oxybutynin ER: 85% Overall, at 11 months, 21% of patients remained on tolterodine ER and 15% of patients remained on oxybutynin ER	Not reported	Not reported
Sears et al (2010)[18]	Proportion of patients without prescription refills over 3 years: 35.1% Median persistence (days): overall: 273 patients with at least 1 refill: 582 Overall medication persistence duration was 273 days when all cases were analyzed and 582 days when those with at least 1 refill were analyzed	Median MPR at 3 years: oxybutynin 5 mg IR: 0.68 oxybutynin 5 mg ER: 0.83 oxybutynin 10 mg ER: 0.84 tolterodine 1 mg IR: 0.71 tolterodine 2 mg IR: 0.73 tolterodine 2 mg ER: 0.88 tolterodine 4 mg ER: 0.89 overall: 0.82 Proportion of patients with MPR ≥0.80 at 3 years: 34.0%	***Gender*** Male patients had a higher median MPR than female patients (0.86 vs 0.81, p<0.001) Medication adherence was higher in males than in females (0.370 vs 0.328, p<0.001) Of patients refilling their prescription at least once, the median number of days persisted was longer in females than in males (606.0 days vs 547.0 days, p=0.01) ***Medication type*** Of patients refilling their prescription at least once, median medication persistence was longest in 5 mg oxybutynin IR (634 days, 95% CI 596.1–671.9) and lowest with 10 mg oxybutynin ER (504 days, 95% CI 137.0–871.0)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2016)[19]	Proportion of patients persistent (without switching or experiencing a gap of >60 days) at: 6 months; fesoterodine: 71.4% solifenacin: 67.1% tolterodine: 64.8% 1 year; fesoterodine: 40.2% solifenacin: 34.7% tolterodine: 33.6%	Mean MPR at 1 year was: 0.880, 0.877 or 0.875, depending upon geographical location	***Medication type*** Persistence at 6 months and 1 year was statistically significantly higher with fesoterodine than solifenacin and tolterodine ($p<0.05$). Persistence at 1 year was significantly lower with solifenacin than fesoterodine ($p<0.01$)
Sicras-Mainar et al (2015)[f,20]	Proportion of patients persistent at: 3 months: 86.2% 6 months: 67.6% 9 months: 48.4% 1 year: 35.9% Mean (SD) treatment duration (without stopping, switching or a gap >30 days): fesoterodine: 8.1 solifenacin: 7.8 tolterodine: 7.7 overall: 7.9	Mean MPR at 1 year: fesoterodine: 0.900 solifenacin: 0.870 tolterodine: 0.861 overall: 0.877	Not reported
Sicras-Mainar et al (2014)[21]	Proportion of patients persistent (without switching or experiencing a gap of >30 days): 3 months; fesoterodine: 94.8% solifenacin: 76.2% tolterodine: 70.8% 6 months; fesoterodine: 70.7% solifenacin: 59.5% tolterodine: 57.1% 1 year; fesoterodine: 46.6% solifenacin: 36.5% tolterodine: 33.5%	Mean MPR at 1 year: fesoterodine: 0.907 solifenacin: 0.935 tolterodine: 0.936	***Medication type*** At 3 months, persistence was higher with fesoterodine than with tolterodine and solifenacin

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2014)[g,22]	Proportion of patients persistent at 1 year: fesoterodine: 35.8% solifenacin: 31.9% tolterodine: 30.9%	Mean MPR at 1 year: fesoterodine: 0.937 solifenacin: 0.948 tolterodine: 0.935	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found. However, adjusted HRs for remaining on treatment at 1 year significantly favored fesoterodine compared with solifenacin (HR 1.24 [95% CI 1.05–1.47]; p=0.011) and tolterodine (HR 1.28 [95% CI 1.07–1.52]; p=0.006)
Sicras-Mainar et al (2013)[g,23]		Mean MPR at 1 year: fesoterodine: 0.945 solifenacin: 0.954 tolterodine: 0.946	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found
Suehs et al (2016)[24]	Proportion of patients not refilling their index medication: PIM: 41.4% Non-PIM: 47.8% (p<0.01) Mean number of days persistent (before discontinuation or experiencing a gap >15 days): PIM: 87.6 Non-PIM: 80.9 (p<0.001) Proportion of patients persistent at: 3 months; PIM: 23.9% Non-PIM: 20.3% 6 months; PIM: 13.2% Non-PIM: 11.4% 1 year; PIM: 5.1% Non-PIM: 4.5% (all p<0.001 differences)	Mean PDC at: 3 months; PIM: 0.62 Non-PIM: 0.59 6 months; PIM: 0.45 Non-PIM: 0.42 1 year; PIM: 0.32 Non-PIM: 0.30 (all p<0.001 differences) Proportion of patients with PDC ≥0.80: 3 months; PIM: 37.0% Non-PIM: 35.0% 6 months; PIM: 23.3% Non-PIM: 19.7% 1 year; PIM: 12.7% Non-PIM: 10.7% (all p<0.001 differences)	***Medication use appropriateness*** At 1 year, there was no statistical difference between PIM status and OAB treatment discontinuation in the multivariable adjusted model based on the primary analysis definition (15-day definition OR 0.977, 95% CI 0.891–1.072, p=0.63; 30-day definition OR 0.939, 95% CI 0.871–1.013, p=0.10)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sussman et al (2017)[25]	Proportion of patients discontinued at 1 year (gap of ≥30 days): mirabegron: 67.1% anticholinergic: 84.1% Median time to discontinuation (days): mirabegron: 131 anticholinergic: 30	Mean PDC: mirabegron: 0.66 anticholinergic: 0.55 Proportion of patients with PDC ≥0.80 at 1 year: mirabegron: 43.6% anticholinergic: 30.9%	***Medication type*** Users of mirabegron appeared to achieve greater persistence and adherence at 1 year than users of anticholinergics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2012)[26]	Time (days) to discontinuation (or a gap >1.5 times the length of the previous prescription without a refill): darifenacin: 135.9 flavoxate: 77.4 oxybutynin ER: 146.7 oxybutynin IR: 119.3 propiverine: 141.1 solifenacin: 158.7 (5 mg); 216.0 (10 mg) tolterodine ER: 156.7 tolterodine IR: 151.7 trospium: 138.5 Proportion of patients persistent at 3 months: darifenacin: 52% flavoxate: 28% oxybutynin ER: 44% oxybutynin IR: 40% propiverine: 47% solifenacin: 58% tolterodine ER: 47% tolterodine IR: 46% trospium: 42% Proportion of patients persistent at 6 months: darifenacin: 30% flavoxate: 16% oxybutynin ER: 35% oxybutynin IR: 29% propiverine: 36% solifenacin: 46% tolterodine ER: 36% tolterodine IR: 33% trospium: 33% Proportion of patients persistent at 1 year: darifenacin: 17.4% flavoxate: 13.5% oxybutynin ER: 26.1% oxybutynin IR: 21.7% propiverine: 26.8% solifenacin: 35% tolterodine ER: 28.2% tolterodine IR: 24.1% trospium: 25.9%	Not reported	***Age*** Over 1 year, the majority of patients aged ≥60 years were more likely to persist than younger patients. Graphical results only ***Medication type*** Patients receiving solifenacin spent the longest mean duration on therapy compared with other OAB medications

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[27]	Proportion of patients persistent at 1 year (without switching or experiencing a gap ≥30 days): mirabegron: 31.7% fesoterodine: 21.0% oxybutynin ER: 18.9% oxybutynin IR: 13.8% solifenacin: 22.0% tolterodine ER: 19.7% Median duration of treatment (days): mirabegron: 221 solifenacin: 108 fesoterodine: 100 tolterodine ER: 100 oxybutynin ER: 100 oxybutynin IR: 75 Proportion of patients persistent at 1 year: treatment-naïve:19.0% treatment-experienced: 30.0% Median days on therapy: treatment-naïve: 90 treatment-experienced: 205	Median MPR at 1 year: mirabegron: 0.645 fesoterodine: 0.492 oxybutynin ER: 0.328 oxybutynin IR: 0.186 solifenacin: 0.459 tolterodine ER: 0.454	***Age*** As age increased, median MPR increased for OAB medications: <46 years: 0.273 45–64 years: 0.372 ≥65 years: 0.492 (p<0.001 difference compared to ≥65 years) ***Treatment status*** Patients with prior experience of OAB medication use achieved a higher MPR than treatment-naïve patients (0.546 vs 0.328, p<0.001) ***Medication type*** Compared with antimuscarinics, patients taking mirabegron demonstrated greater persistence and statistically significantly greater adherence (64.5% vs 18.6%–49.2%, p<0.001) than those taking antimuscarinics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[28]	Proportion of patients persistent at 6 months: <40% Proportion of patients discontinued at 4 years: oxybutynin: 93% tolterodine IR: 90% tolterodine ER: 90% solifenacin: 90% darifenacin: 91% trospium: 94% flavoxate: 98% overall: 91.4% Median duration of first-line treatment (days): oxybutynin: 60 tolterodine IR: 90 tolterodine ER: 100 solifenacin: 106 darifenacin: 91 trospium: 90 flavoxate: 10	Not reported	***Medication type*** Initial treatment with solifenacin, darifenacin, tolterodine ER and tolterodine was associated with a significantly lower risk of discontinuation compared with oxybutynin as the first medication (HRs 0.68, 0.72, 0.77 and 0.84, respectively; p<0.001 vs oxybutynin for each) Patients receiving flavoxate as initial treatment had a significantly higher risk of discontinuation compared with those who received oxybutynin (HR 2.48, p<0.0001) There was no statistically significant difference in the risk of discontinuation with trospium as first-line compared with oxybutynin (p=0.1074) ***Age*** Compared with patients aged 40–64 years, patients aged <20, 20–39, 65–74 and ≥75 years had a higher risk of discontinuation (HRs 1.08–1.19, all p≤0.0022) ***Gender*** Males had a slightly higher risk of discontinuation than females (HR 1.03, 95% CI 1.00–1.06, p=0.0341)
Yeaw et al (2009)[29]	Proportion of patients remaining on therapy (without a refill gap >60 days) at: 6 months: 28% 1 year: 18%	Proportion of patients with mean MPR at 1 year: 35%	Not reported
Yu et al (2005)[30]	Proportion of patients without index prescription refill within the first 6 months: 36.9% Proportion of patients discontinued at: 1 month: 42.7% 2 months: 66.8% 5 months days: 77.6% 9 months: 86.3% At a 1-year follow-up, the rate of discontinuation was increased to 88.6%	Mean MPR at: 6 months: 0.34 1 year: 0.22 Proportion of patients with MPR ≥0.80 at: 6 months: 4.9% 1 year: 0.7%	***Medication type*** Compared with oxybutynin, patients receiving tolterodine were less likely to have discontinued at 6 months (HR 0.74, 95% CI 0.67–0.81, p<0.01) ***Polypharmacy*** The use of multiple drugs was associated with a higher risk of discontinuation by the 6-month follow up (HR 1.26, 95% CI 1.09–1.46, p<0.01) Other significant predictors of higher persistence included: White ethnicity, previous hospitalization length, and starting treatment with tolterodine

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ER = extended release; HR = hazard ratio; IR = immediate release; MPR = medication possession ratio; OAB = overactive bladder; OR = odds ratio; PIM = potentially inappropriate medication; PDC = proportion of days covered; RR = risk ratio; SD = standard deviation; UTIs = urinary tract infections

*In cases where reported values differ from published values, they were derived from the published data; [a]cohort discontinuation percentages are also quoted for 3, 6, 12 and 18 months. However, these figures included some non-oral OAB medications. Therefore, these have not been included; [b]within 1.5x the duration of the initial prescription; [c]over a 4-year period; [d]stopped receiving an OAB medication for ≥6 months between end of therapy and end of the study's eligibility period; [e]stopped receiving an OAB medication for <6 months before restarting an OAB medication; [f]patients who filled only one prescription were given an MPR of zero; [g]no exact figures were quoted within the article text

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Supplemental Information

Literature Search Strategies

The following databases were searched;

- Allied and Complementary Database [AMED] (via OVID)
- Cumulative Index to Nursing and Allied Health Literature [CINAHL] (via EBSCOhost)
- MEDLINE (via EBSCOhost)
- Database of Reviews of Effects [DARE] (via CRD, University of York)
- Health Technology Assessment [HTA] (via CRD, University of York)
- Centre for Reviews and Dissemination [CRD] (via CRD, University of York)

The searches were conducted on the 24th April 2017

The date span of the searches;

- AMED – 1985 to April 2017
- CINAHL – 1937 to April 2017
- MEDLINE – 1946 to April 2017
- DARE / HTA / CRD – 1994 to April 2017

	Searches (AMED)*	
1	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
2	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
3	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
4	(#1 AND #2 OR #3)	18
	Searches (CINAHL & MEDLINE)*	
5	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
6	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
7	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–

8	(#5 AND #6 OR #7)	3,855
	Searches (DARE / HTA / CRD)*	
9	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
10	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
11	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
12	(#9 AND #10 OR #11)	24
13	Total from #4, #8 and #12	3,897
14	Remove duplicates from 13 using EndNoteWeb	**3,614**

* Boolean operators were used. No other limits or filters were applied to each database.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3–5
2	Hypothesis statement	N/A
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	6–8
5	Type of study designs used	6
6	Study population	6–7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	6-7, Figure 1, Supplemental Information
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	5–6, Supplemental Information
11	Search software used, name and version, including special features used (eg, explosion)	Supplemental Information
12	Use of hand searching (eg, reference lists of obtained articles)	6–7
13	List of citations located and those excluded, including justification	6–7, Supplemental Tables 1 and 2
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6–7
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6–7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6–7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6–7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Not performed – see response to reviewers
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
24	Provision of appropriate tables and graphics	Figures 1 and 2 and Supplemental Tables

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2 and Supplemental Tables 1 and 2
26	Table giving descriptive information for each study included	Supplemental Tables 1 and 2
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	N/A

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	N/A
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1 legend
31	Assessment of quality of included studies	Not performed – see response to reviewers
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12–14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	13-15
34	Guidelines for future research	15
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review

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Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB) – a systematic literature review

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Running head: Adherence and persistence to OAB medication

Key Words: Overactive bladder, persistence, adherence, antimuscarinics, β_3-adrenergic receptor agonists, systematic literature review

ABSTRACT

Purpose To evaluate persistence and adherence of oral pharmacotherapy used in the treatment of overactive bladder (OAB) in a real-world setting.

Materials and Methods Systematic literature searches of six electronic publication databases were performed to identify observational studies of OAB patients treated with antimuscarinics and/or mirabegron. Studies obtaining persistence and adherence data from sources other than electronic prescription claims were excluded. Reference lists of identified studies and relevant systematic reviews were assessed to identify additional relevant studies.

Results The search identified 3897 studies, of which 30 were included. Overall, persistence ranged from 5–47%. In studies reporting data for antimuscarinics and mirabegron (n=3), 1-year persistence was 12–25% and 32–38%, respectively. Median time to discontinuation was <5 months for antimuscarinics (except one study [6.5 months]) and 5.6–7.4 months for mirabegron. The proportion of patients adherent at 1 year varied between 15–44%. In studies reporting adherence for antimuscarinics and mirabegron, adherence was higher with mirabegron (mean medication possession ratio (MPR): 0.59 vs 0.41–0.53; mean proportion of days covered: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19–0.49). Reported determinants of persistence and adherence included female (sex), older age group, use of extended-release formulation and treatment experience.

Conclusion Most patients with OAB discontinued oral OAB pharmacotherapy and were non-adherent 1 year after treatment initiation. In general, mirabegron was associated with greater persistence and adherence compared to antimuscarinics. Combined with existing clinical trial evidence, this real-world review merits consideration of mirabegron for first-line pharmacological treatment among patients with OAB.

The protocol for this systemic review is registered with PROSPERO: CRD42017059894

STRENGTHS AND LIMITATIONS

- This systematic literature review includes data for mirabegron, which was approved in 2013 and not covered in previous systematic reviews examining persistence and adherence to overactive bladder medication (OAB).
- Only observational database studies were included in this study, with the intention to provide a more accurate picture of rates of adherence and persistence to OAB medication, which are generally lower in routine clinical practice compared to randomized clinical trials.
- This systematic literature review provides a global picture of adherence and persistence to OAB medication based on the inclusion of data from Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States.
- Although determinants of persistence and adherence were evaluated in this study, the influence of other factors such as patient expectations, appropriate counselling and patient satisfaction with treatment could not be assessed.
- The definitions and calculations of persistence and adherence were not uniform across the literature. These terms were often used interchangeably, limiting the ability to compare across studies.

INTRODUCTION

Overactive bladder (OAB) is defined as a condition with characteristic symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.[1] OAB affects 11.8–24.7% of adults in North America and Europe, and the prevalence increases with age.[2] In addition to age, risk factors for developing OAB include diabetes, UTIs and obesity.[3 4]

OAB symptoms are associated with a negative impact on health-related quality of life (HRQoL) and a significant economic burden. Indeed, bothersome OAB symptoms may lead to depression and anxiety, and sleep disturbances, which can adversely affect a patient's daily, social and professional functioning.[5 6] Whilst the cost of pharmaceutical treatment represents only a small fraction of the total therapy cost, the provision of containment products (eg, pads), treatment for clinical depression, nursing home stays and loss of productivity due to work absenteeism are the main cost drivers in OAB.[7 8] For example, the total annual cost of OAB was estimated to be $24.9 billion in the United States in 2007[9] and €9.7 billion across five European countries (Germany, Italy, Spain, Sweden and the United Kingdom) and Canada in 2005.[8]

Behavioural and lifestyle modifications are routinely the initial treatment strategy for OAB, and pharmacotherapy is recommended only if conservative management is not effective.[10] As OAB is a chronic condition, it is important that patients continue with treatment to control symptoms.[11] Lack of persistence (time from treatment initiation to discontinuation),[12] and adherence (extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen)[12] to medication are considered the leading causes of preventable morbidity in patients with chronic conditions;[13 14] they are also associated with greater indirect costs.[14] Studies have reported that patients compliant and adherent to OAB medication experienced significantly improved urinary symptoms and

HRQoL compared with patients who were non-persistent [15 16]. Although antimuscarinics are the current mainstay of oral pharmacotherapy, they are often associated with bothersome anticholinergic side effects, such as dry mouth and constipation; tolerability is one of the most common reasons for treatment discontinuation.[11 17-20] In a systematic review of antimuscarinic treatment in patients with OAB, rates of discontinuation at 12 weeks ranged from 4–31% in clinical trials and 43–83% in medical claims databases.[19]

The other class of oral pharmacotherapy approved for the treatment of OAB is β_3-adrenergic receptor agonists. Mirabegron is currently the only commercially available agent of this class licensed in countries across Europe, North America and Asia.[21-23] Due to mirabegron's mechanism of action, the incidence of side effects typically reported with antimuscarinic treatment are low with mirabegron and generally similar to placebo,[24] which may translate into better treatment persistence.[25 26] In addition, results of a recent economic analysis found that increased persistence with mirabegron treatment vs antimuscarinics was associated with reduced healthcare resource use and work hours lost, resulting in lower total costs.[27]

In general, rates of persistence and adherence with antimuscarinics and mirabegron are typically lower in routine clinical practice compared to interventional clinical trials.[11 28] To help identify factors affecting long-term persistence and adherence to OAB pharmacotherapy, a contemporary, comprehensive review of real-world evidence is needed. As mirabegron was a relatively new OAB treatment, it was not included in previous systematic reviews. Therefore, the current analysis aims to systematically review prospective and retrospective observational database studies conducted with antimuscarinics and/or mirabegron to determine the rates and determinants of persistence and adherence.

METHODS

This systematic literature review (SLR) was conducted in accordance with guidelines for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [29]. The protocol for the

review was registered *a priori* with the International Prospective Register of Systematic Reviews (registered January 18, 2017 with PROSPERO CRD42017059894).

Searches were performed April 27, 2017 *via* the following electronic databases: Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied Health Literature (CINAHL); MEDLINE; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; and the Centre for Reviews and Dissemination (CRD) database. The search terms were persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [Title], AND "bladder" OR "overactive bladder" OR "OAB" OR urin* OR incontinen* [Title], OR oxybutynin OR tolterodine OR fesoterodine OR trospium OR darifenacin OR solifenacin OR propiverine OR imidafenacin OR mirabegron OR flavoxate OR hyoscyamin* OR anticholinerg* OR antimuscarin* [Title].

All search results were exported into EndNote Web (Thomas Reuter, CA, USA) bibliography software and duplicates removed electronically and manually. The full electronic search strategy is outlined in the Supplemental information.

Inclusion and exclusion criteria

Inclusion criteria were: prospective and retrospective observational database studies investigating persistence and adherence to oral medication for the treatment of OAB in adults, conducted in any geographical location and published on any date, within a peer-reviewed source. Exclusion criteria were: abstract unavailable; studies not yet fully completed; randomised controlled trials (RCTs); systematic reviews; narrative literature reviews; conference papers; single case studies/reports; studies investigating OAB medication among only healthy, asymptomatic participants; studies from which oral-only OAB persistence/adherence results cannot be isolated from other results (ie, transdermal patches); and studies containing patients aged <18 years (where the data pertaining to these patients could not be removed from the results) and studies not published in English.

Populations with lower urinary tract symptoms due to stress incontinence and benign prostatic hyperplasia were also excluded.

Study selection

Duplicates were removed and title and abstract screenings were performed by two independent researchers (PS and GY). Full-text articles were obtained and studies were excluded if they did not meet the inclusion criteria.[30] Any disagreement in study selection was to be resolved through discussion and consultation with another member of the project team (FF) where necessary. During screening, open-label extension studies of RCTs were excluded as the trial designs were unlikely to reflect a real-world setting. Studies utilising data from hospital records, in addition to large-scale databases, were included provided that persistence and adherence data were determined from prescription claims data rather than extracted from supplemental patient interviews, patient-supplied pill counts or subjective questionnaires. The literature search was supplemented by screening for potential additional relevant studies identified from the reference lists of eligible articles.

Data extraction

Parameters that may affect persistence or adherence were collected, including patient characteristics (age and sex); interventions (initial [index] OAB drug and formulation) and comorbidities. The definitions, outcomes and determinants of treatment persistence and adherence were also collected, where reported. The extracted data were evaluated by one researcher and verified by a second researcher.

Data analysis

A descriptive analysis of extracted results is presented. No meta-analysis was planned due to the expected heterogeneity of reporting methodologies and data across studies.

Patient and Public Involvement

Patients were not directly involved in the conduct of this study.

RESULTS

Brief overview of studies

Overall, 3897 articles were identified from the literature search; 3,614 were screened for title/abstract and 75 were assessed for eligibility (figure 1). Thirty articles were included in the SLR (supplementary table 1), including three identified from reference lists.[31-33] The articles described the findings of 28 independent studies. There was nil disagreement between the two independent researchers (PS, GY) during the screening process.

The data were collected from patients treated in Europe (12 studies) and North America (18 studies) (supplementary table 1) and were included in the analysis. The number of participants included in the published studies ranged from 377 to 103 250. Where stated, the mean age of the participants ranged from 44 to 80 years and the duration of follow-up ranged from 6 months to 7 years. Prescribed antimuscarinic interventions for patients with OAB included darifenacin, fesoterodine, flavoxate, hyoscyamine, imipramine, oxybutynin, propiverine, solifenacin, tolterodine and trospium chloride. Mirabegron was prescribed in four studies.[18 31 32 34] Uncommon oral interventions included imipramine, a tricyclic anti-depressant with an unknown mechanism of action in the context of OAB,[35] and bethanechol, a muscarinic receptor agonist.[33] The methods used to quantify adherence and persistence differed across the studies (supplementary table 1). In general, medication possession rate (MPR) or proportion of days covered (PDC) by prescription were typically used as a measure of adherence to a drug. Persistence was typically defined as the proportion of patients continuing therapy/refilling prescriptions for the follow-up period (without discontinuing the index drug or switching to other OAB drug[s]) and/or the median time to discontinuation (TTD).

Persistence

Overall, persistence rates decreased over time, regardless of agent (supplementary table 2).

Antimuscarinic studies

Data for persistence (or discontinuation) at approximately 6 months was available in 14 articles[32 33 36-47] which reported data on antimuscarinics only. Yeaw 2009 was an exception due to the inclusion of bethanechol (a muscarinic receptor agonist), which accounted for <1.5% of the pharmacy claims for OAB medications.[33] The proportion of patients persistent at 6 months was <50% except for the studies of Sicras-Mainar *et al*,[42-44] where persistence ranged from 57–71%. In addition, two studies reported discontinuation rates of 6–43% after 1 month of initial treatment.[41 47]

At 1 year, persistence rates for antimuscarinics across 19 studies ranged from around 5% up to 47%.[18 26 34-36 38 40 42 43 45 46 48-53] Median TTD was <5 months (30 to 128 days) for all medications across all studies,[18 26 32 34 38 48 54] with the exception of Krhut *et al*[40] (6.5 months). At 2 years, over 75% of patients discontinued treatment.[36 38 50 54 55] Rates of treatment switching were infrequently reported, and where provided, were ≤17% of patients.[32 37 39 48 52 54 55]

Antimuscarinic and mirabegron studies

In all four studies, a greater proportion of patients persisted with mirabegron compared with antimuscarinics. In one study, persistence rates for tolterodine and mirabegron at 6 months were 19% and 35%, respectively.[31] Persistence at 1 year ranged from 8–25% for antimuscarinics and from 32–38% for mirabegron, as reported in three studies.[18 26 34]Where tested inferentially, 1-year persistence was statistically significantly greater with mirabegron compared to antimuscarinics ($p < 0.0001$), with the exception of oxybutynin ($p = 0.002$).[18] The risk of discontinuing within 1 year was also greater with antimuscarinics compared to mirabegron ($p < 0.001$).[18 32] Overall, mirabegron, solifenacin and fesoterodine were associated with the highest rates of persistence.[18 26]

Across the four studies, 40–81% and 83–96% of the mirabegron and antimuscarinic patient cohorts were treatment naïve, having received no OAB drug for at least 6 months prior to

their first index of OAB treatment.[18 31 32 34] Studies typically found that treatment-naive patients prescribed mirabegron or antimuscarinics had lower persistence than treatment-experienced patients prescribed the same OAB treatments. In the three studies that assessed persistence in treatment-experienced and treatment-naïve populations, persistence was higher with mirabegron treatment (significantly in two studies) compared with antimuscarinics.[18 31 32]

Median TTD in the overall study populations was longer with mirabegron (5.6–7.4 months) compared with the assessed antimuscarinics (1.0–3.6 months).[18 26 31 34]

Adherence

Adherence rates to all OAB medications reduced over time in all studies and varied across studies (supplementary table 2).

Antimuscarinic studies

At 1 year, the proportion of adherent patients varied between 1%[47] and 36%,[48] across those studies that provided these data. Few studies reported adherence beyond 1 year. However, Sears *et al* reported that 34% of patients were adherent at the end of 3 years,[56] which was comparable to the adherence rates reported by some other studies at just 1 year.[48 52]

Antimuscarinic and mirabegron studies

In the three studies, adherence at 1 year was significantly higher in patients receiving mirabegron compared with antimuscarinics (mean MPR: 0.59 vs 0.41 to 0.53; mean PDC: 0.66 vs 0.55; and median MPR: 0.65 vs 0.19 to 0.49).[18 26 34] The proportion of patients adherent at 1 year was also greater with mirabegron compared with antimuscarinics (mean MPR ≥0.80: 43% vs 22–35%; mean PDC ≥0.80: 44% vs 31%).[18 26] Within treatment-naïve patients specifically, adherence was greater with mirabegron compared to antimuscarinics 0.59 vs. 0.39–0.51, p values 0.02 to <0.0001).[18]

Determinants of persistence and adherence

Determinants of persistence and adherence were reported in 24 of the 30 studies. As expected, most studies reported medication type as a determinant of persistence/adherence (figure 2; supplementary table 2). In general, persistence and adherence were higher in: older patients compared with younger patients;[26 31 32 35-39 46 48-50 52 54 57] female patients compared with their male counterparts,[32 35 36 39 49 50 57] except in one study;[56] patients receiving extended-release (ER) formulations compared with immediate-release formulations;[48 54] and treated patients compared to treatment naïve patients (or untreated in the pre-index period [6 months or 1 year]).[18 26 36] Comorbidities, including diabetes, Parkinson's disease, epilepsy, dementia, multiple sclerosis and hypertension, were correlated with increased treatment persistence and adherence;[49 50 57] exceptions were chronic obstructive pulmonary disease and migraine.[50 57]

Other reported determinants of favorable persistence and adherence included higher treatment doses;[36] low daily quantity of tablets,[37] absence of UTI; higher baseline OAB costs;[39] treatment by urologists vs gynecologists/general practitioners; the absence of side effects (headache, stomach upset and glaucoma);[50] White vs Black, Hispanic and Asian patients and patients of other ethnicities;[35 47] lower medication co-payment;[35] and use of fewer medications.[47]

DISCUSSION

This systematic review provides an overview of persistence and adherence with oral pharmacotherapies used to treat patients with OAB in real-life clinical practice. A wealth of data were collected from 30 articles, which described 28 observational studies performed in Europe and North America totaling over 500 000 patients. A number of key findings were identified, including greater persistence and adherence with mirabegron vs antimuscarinics,[18 26 31 34] in females vs males,[32 35 39 49 57] in older vs younger patients,[26 31 32 35-39 46 48-50 52 54 57] and in previously treated vs untreated patients.[18 26 36]

Across the studies, persistence appeared to reduce very quickly after initiation of treatment for all OAB therapies, with low rates (<50%) already evident at 1 month.[31 41 47] Longer follow-up periods showed that large proportions of patients discontinued treatment by 1 year (62–100%)[18 26 33 38 45-47 49 50 54] and by the end of 3 years, less than 10% of patients continued on any antimuscarinic.[54] These steep reductions in rates of persistence over time were mirrored by the reported adherence rates.

The chronic nature of OAB means that consistent and long-term use of medication is essential to manage OAB symptoms and improve health outcomes. It is therefore important for patients to receive a first-line treatment that has a good efficacy-tolerability profile and evidence of favorable persistence and adherence vs other treatment options. Among the antimuscarinics, solifenacin and fesoterodine were generally associated with better persistence and adherence.[18 26 43 52] In studies that assessed both mirabegron and antimuscarinics, persistence in the mirabegron cohorts, including the treatment-naïve populations, was statistically significantly greater ($p<0.001$).[18 26 31] Due to the recommended treatment sequence for OAB [10 58], the majority of patients that receive mirabegron are treatment-experienced; however, these studies suggest a benefit of mirabegron treatment regardless of treatment status. Adherence to mirabegron was also greater; however, mean/median MPR values in the overall mirabegron populations did not indicate medication adherence (MPR/PDC<0.80). Although these studies did not directly assess the reason(s) for an observed difference in persistence and adherence with mirabegron vs antimuscarinics, proposed reasons include lower rates of bothersome anticholinergic adverse events, particularly dry-mouth, and unmet expectations of antimuscarinic treatment.[18 26 31]

It is well established that poor medication persistence and adherence reduces the ability to achieve optimum clinical benefits and limits treatment success, especially for chronic conditions such as OAB.[13 14 17 46] The unwillingness of patients to continue to take long-term treatment has been observed across many chronic conditions, with non-adherence to

medication observed in ~50% of patients.[13] An analysis across six chronic conditions found 1-year persistence and adherence rates to be low for all conditions, and lowest for OAB medications (antimuscarinics),[33] suggesting an unmet treatment need. However, this study was performed prior to the availability of mirabegron for use in routine clinical practice, and therefore an updated analysis of persistence in chronic conditions might be warranted.

As alluded to above, persistence and adherence to treatment is expected to improve outcomes for patients with OAB. In two studies, better OAB treatment persistence and adherence were associated with improved clinical outcomes and HRQoL compared with patients who were non-persistent.[15 16] These data are consistent with studies describing other chronic diseases, such as diabetes and depression, where good adherence resulted in improved health outcomes[14 59] as well as reduced complications and disability, and improved HRQoL and life expectancy.[60] Moreover, greater persistence and adherence to treatment for OAB is associated with significantly lower medical, sick leave and short-term disability costs.[35] Indeed, economic models based on real-world inputs suggest that improved persistence with mirabegron translates into benefits of reduced healthcare resource use, and lower direct and indirect costs of treatment compared with antimuscarinics.[27 61] Additionally, mirabegron is reported to be cost effective vs six antimuscarinics from commercial and Medicare perspectives in the United States, due to fewer projected adverse events and comorbidities, and data suggesting better persistence.[62]

Independent variables for treatment discontinuation were studied by at least half of the papers included in our literature review, of which sex, age, comorbidities and previous experience of OAB medications were shown to be important factors in more than two studies. Only six studies reported switch-rates and although these were low, the treatment strategy of cycling antimuscarinic agents in patients who do not achieve symptom relief is common in clinical practice. Yet recent analysis of real-world data suggests that switching antimuscarinics may provide sub-optimal care.[55] In contrast, switching to mirabegron from

antimuscarinic therapy has proved beneficial in over 50% of patients with OAB in an observational study.[63]

This review represents a large pooled analysis of real-world data for persistence and adherence to oral OAB medication across different geographical locations (Canada, Czech Republic, Denmark, Germany, Norway, Spain, the United Kingdom and the United States); however, there were no identifiable trends between data and countries. The definitions and calculations of persistence and adherence were not uniform across the literature and the terms were often used interchangeably. This lack of consistency led to some limitations on the ability to compare across studies. Other limitations to performing cross-study comparisons or pooled analyses in this SLR include differences in the individual study populations and/or study designs, resulting in considerable variations between data. For example, the median TTD for oxybutynin ER and tolterodine ER were determined to be 5.1 and 5.5 months, respectively, by one study,[54] but only 60 and 56 days, respectively, by another study.[18]

Furthermore, it is very difficult to capture the specific reasons for treatment discontinuation from prescription-driven or medical claim data rather than patient-derived data.[18] The current review excluded data from RCTs to better reflect patient behavior in the general OAB population in real-life clinical practice.[11] Only one paper included in our review reported that antimuscarinic side effects were significantly associated with discontinuation,[50] despite reports that such side effects are bothersome and a common reason for discontinuation of antimuscarinic treatment.[11 19 28] Additional factors that could not be assessed by our study, but can influence persistence with treatment in OAB patients are patient expectations, appropriate counselling and patient satisfaction with treatment.[11 17 28]

In addition to the limitations listed above, it should be noted that Sicras-Mainar *et al*[42 43] reported data on the same patients (in terms of demographics and the timeframe/geographical source). This is also the case for two studies published by Sicras-

Mainar *et al* in 2013 and 2014.[53 64] Also, this SLR excluded data on non-oral pharmacotherapies (eg, onabotulinum toxin A) and combination mirabegron plus antimuscarinic therapies, where additional efficacy has been reported compared to the monotherapies.[65] Further research on persistence and adherence to these OAB therapies is needed to better evaluate current treatment options. Additional studies are also required to improve our understanding of persistence and adherence in OAB, including qualitative studies to examine the reasons for discontinuation and real-world studies to examine resource use associated with OAB medication in relation to adherence and persistence. As OAB is a chronic disease, clinicians should not only take into consideration the efficacy and side effects of an agent when deciding on treatment options, but also ensure that realistic patient expectations from treatment are set through patient education and counselling. The patient's life-style should also be considered as this is likely to impact adherence and persistence with OAB therapy.

CONCLUSIONS

Persistence and adherence were greater with mirabegron compared with antimuscarinics, and appeared to be greater with solifenacin and fesoterodine compared with other antimuscarinics. In addition, greater persistence and adherence were generally observed in patients who were female, older, treatment-experienced and receiving ER formulations. Together with the efficacy and tolerability data from clinical trials, real-world data examined in this review warrants consideration of using mirabegron as first-line oral pharmacotherapy for patients with OAB.

Contributorship Statement

GY, PS, JN, ZH, ES and FF were involved in conceptualisation and design of the study and critical review of the manuscript. FF, PS and GY performed the data extraction. All authors approved the final manuscript as submitted.

Competing Interests

JN and ES are employed by Astellas Pharma Inc. ZH was employed by Astellas Pharma Inc. as the time of the study. FF has received a grant from Astellas for study design, data extraction and manuscript development. GY and PS declared no conflicts.

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Data Sharing Statement

The search strategy and all data supporting this study are provided as supplementary information accompanying this paper.

Acknowledgments

Patients were not directly involved in the conduct of this study. Medical writing support was provided by Claire Chinn, PhD, and Kinnari Patel, PhD, of Bioscript Medical and funded by Astellas Pharma Global Development.

Abbreviations and Acronyms

ER = extended-release

HRQoL = health-related quality of life

MPR = medication possession rate

OAB = overactive bladder

PDC = proportion of days covered

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs = randomised controlled trials

SLR = systematic literature review

TTD = time to discontinuation

UTI = urinary tract infection

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FIGURE LEGENDS

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

*Studies were excluded for the following reasons: outcome measure(s) of persistence and/or adherence, relevant to this systematic review (such as medication possession rate, proportion of days covered, discontinuation rate), were not presented within the full text of the article (n=17); adherence/persistence data were drawn from surveys, interviews or self-reports (n=13); cohort contained a portion of patients under 18 years of age (who could not be removed or isolated from results/data) (n=7); participants had prior awareness/knowledge of partaking in a study related to OAB medication (ie, open-label extension to a study or prior written consent) (n=6); a full article text was not available (ie, only a conference abstract) or the full text was not in English (n=1); or non-oral OAB medications were included within the presented results (and could not be removed or isolated from results/data) (n=1)

§Three of these studies were identified by reviewing reference lists of included studies and relevant systematic literature reviews

Figure 2 Frequency for reported determinants of discontinuation

*In one study the relationship was not statistically significant

**Includes dose, formulation, race, prior infection, financial burden, prescriber profession, side effects, medication co-payment and polypharmacy

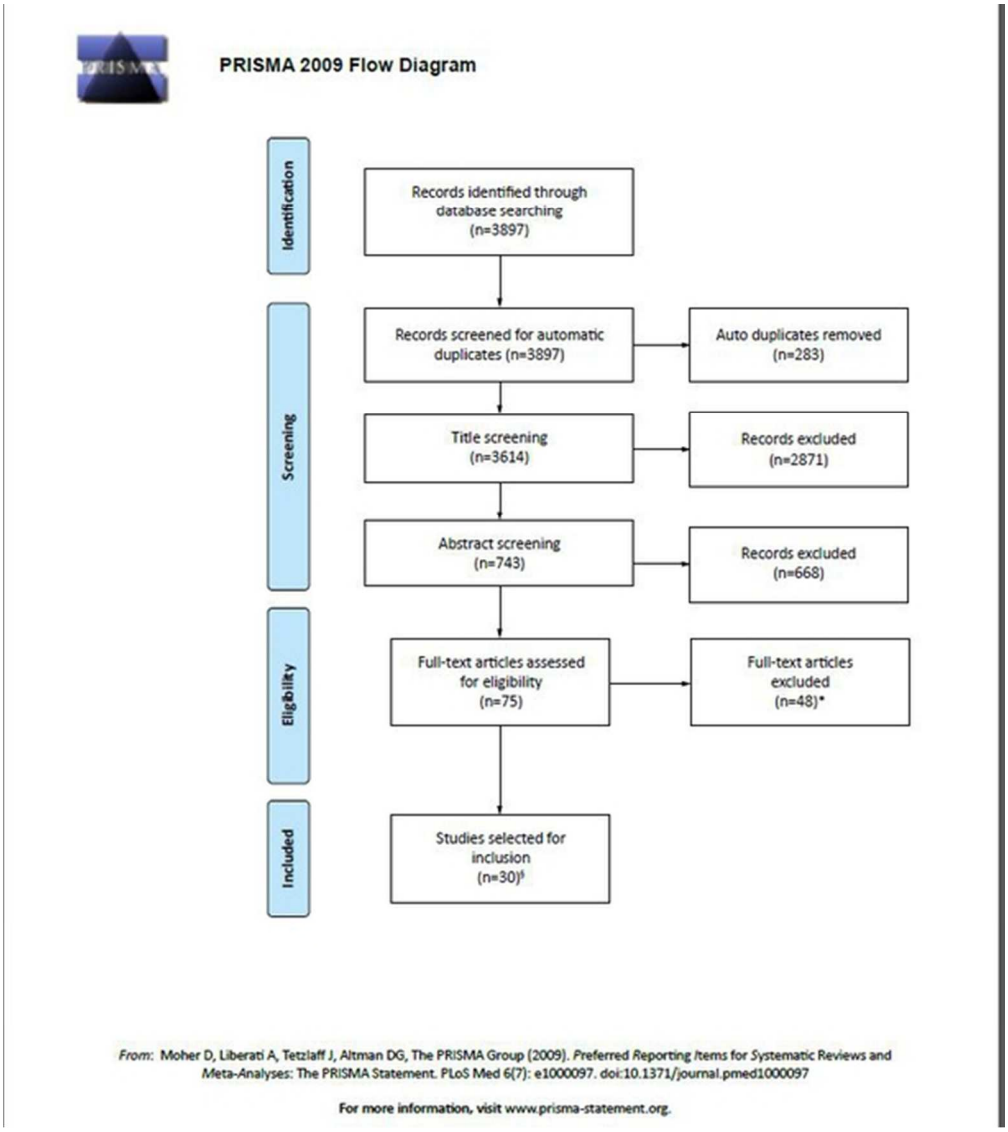

Figure 1 Search strategy and selection of studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

51x57mm (300 x 300 DPI)

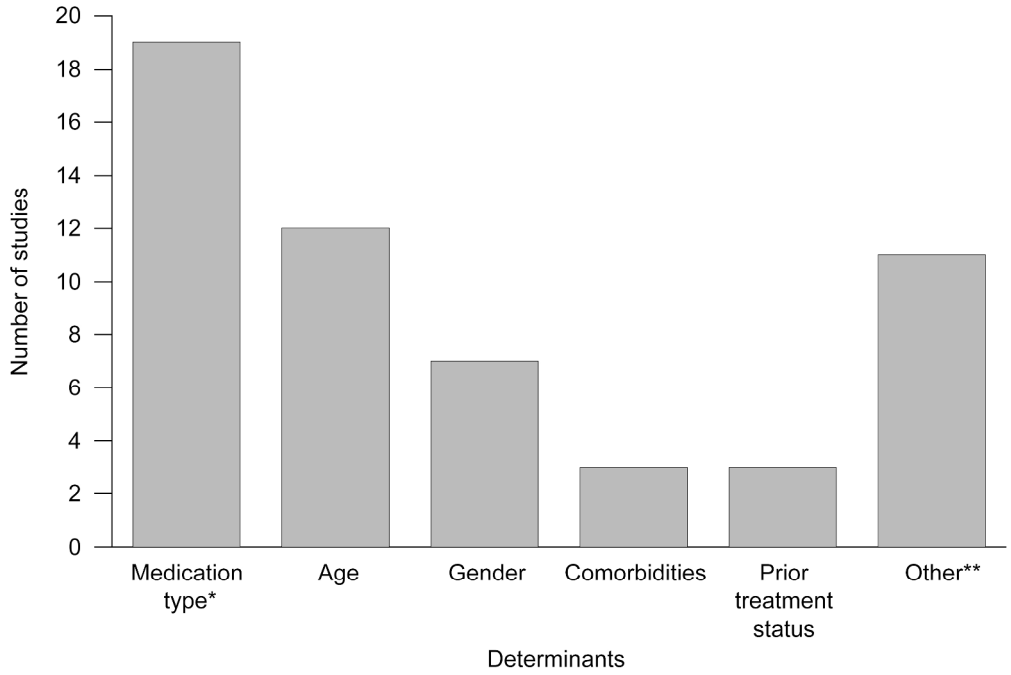

Figure 2 Frequency for reported determinants of discontinuation

273x182mm (300 x 300 DPI)

Supplemental Table 1: Patient characteristics, interventions and definitions/variables of persistence, adherence and discontinuation reported in the studies.

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Brostrøm and Hallas (2009)[1] Odense University Pharmacoepidemio-logical Database (OPED); Denmark) (1999–2006)	n=2477 Male: n=836 (33.8%) Female: n=1641 (66.2%) Mean age: 68.3 years[a]	Any prescription of OAB medication: flavoxate (n=21) oxybutynin TD (n=48) tolterodine (n=1478) solifenacin (n=774) trospium (n=271) darifenacin (n=52)	Patients who continued taking a particular drug for up to 7 years with no more than 120-day gaps were regarded as experiencing single-treatment episodes Variables: age, gender, prior use of OAB agents and use of anti-diabetic drugs	Up to 7 years
Chancellor et al (2013)[2] IMS Lifelink Database, Connecticut; USA (2005–2008)	n=103 250 Male: n≈25 916[a] (25.1%) Female: n≈77 334[a] (74.9%) Mean (SD) age: 58.7 (15.7) years	First (new) prescription of OAB medication in adults ≥18 years: tolterodine ER (n=43 881)[a] solifenacin (n=15 488)[a] oxybutynin (n=15 075)[a] darifenacin (n=10 532)[a] oxybutynin ER (n=10 325)[a] oxybutynin TD (n=2272)[a] tolterodine (n=2581)[a] trospium (n=2478)[a] trospium ER (n=413)[a]	To be considered a discontinuation, patients were required to have a gap of at least 45 days in therapy based on fill dates and days' supply Adherence rate was defined as the proportion of patients filling more than one prescription with an MPR of ≥80%	2 years
Chapple et al (2017)[3] Clinical Practice Research Datalink (CPRD); UK (2013–2014)	n=21 996 Male: n=6513 (29.6%) Female: n=15 483 (70.4%) Mean (SD) age: 63.9 (16.3) years	First (new) prescription of OAB medication in adults ≥18 years: mirabegron (n=1203) darifenacin (n=126) fesoterodine (n=1287) flavoxate (n=144) oxybutynin ER (n=1144) oxybutynin IR (n=5779) propiverine (n=95) solifenacin (n=8191) tolterodine ER (n=1561) tolterodine IR (n=1523) trospium chloride (n=943)	Treatment was defined as discontinued if the maximum allowable gap duration was at least 1.5 times the intended duration of the most recent prescription Adherence rate was defined as mean MPR at 12 months	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
D'Souza et al (2008)[4] Undisclosed medical claims database; USA (1999–2004)	n=1117 Male: n≈206[a] (18.4%) Female: n≈911[a] (81.6%) Mean (SD) age: 55.7 (14.5) years	First index of an OAB medication in adults ≥18 years: oxybutynin ER (n=249) oxybutynin IR (n=108) tolterodine ER (n=454) tolterodine IR (n=306)	Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuing the index drug or switching to other OAB drugs Adherence rate was measured as the proportion of patients with an MPR of ≥0.80 Variables: age, gender, drug formulations and OAB-associated comorbidities (eg, falls/fractures, skin infections, UTIs, anxiety/depression)	1 year
Desgagné et al (1999)[5] Régie de l'assurance maladie du Québec (RAMQ) database; Canada (1994–1997)	n=6690 Male: n=2534 (37.9%) Female: n=4156 (62.1%) Mean age: 77.3 years[a]	Patients aged ≥65 years with at least one prescription claim (first index) of: oxybutynin (n=5718) flavoxate (n=972)	Persistence evaluated by percentage of patients refilling their initial prescription	Up to 4 years
Gomes et al (2012)[6] Canada (Ontario Drug Benefit database of prescriptions)	n=56 851[a] Male: n≈18 496 (32.5%)[a] Female: n≈38 355 (67.5%)[a] Mean age: 77.7 years[a]	Patients aged >65 years with a first index (new) claim of: oxybutynin IR (n=31 996) tolterodine ER/IR (n=24 855)	Persistence with treatment was defined by refills for the index drug within an interval defined by the duration specified on the prescription plus a 50% grace period	2 years
Gopal et al (2008)[7] UK (Health Improvement Network database of prescriptions) (1991–2005)	n=29 369 Male: n=0 (0%) Female: n=29 369 (100%) Mean (SD) age: 63.9 (16.8) years	Women aged ≥18 years prescribed anti-cholinergic medications: tolterodine IR tolterodine ER oxybutynin IR oxybutynin ER flavoxate terodiline trospium properivine solifenacin	Discontinuation was defined by no anticholinergic prescriptions issued within 90 days after the end of the last anticholinergic drug prescription Anticholinergic medications were considered discontinued at the time a patient switched to another medication or as above Variables: drug formulation	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Ivanova et al (2014)[8] OptumHealth Reporting and Insights claims database; USA (2007–2012)	n=10 318 Male: n≈2822 (27.4%)[a] Female: n≈7496 (72.6%)[a] Mean age: 51.6 years	Patients aged 18 to 64 receiving a new prescription of: darifenacin (n=970)[a] solifenacin (n=2662)[a] oxybutynin (n=2889)[a] tolterodine (n=3116)[a] trospium (n=454)[a] fesoterodine (n=227)[a]	Persisters were defined as patients who did not switch or discontinue the index antimuscarinic during the first 6 months after the treatment initiation date Discontinuation was defined by a gap of at least 60 days between refills within the first 6 months after the treatment initiation date Switching was defined as a changed prescription from the index antimuscarinic within the first 6 months after the treatment initiation date (with a gap of 60 days between the end of the day supply of the index antimuscarinic and the new antimuscarinic) Variables: age, gender, history of UTIs and index antimuscarinic	6 months
Johnston et al (2012)[9] Truven Health MarketScan® Database; USA (2004–2009)	n=73 120 Male: n=29 406 (40.2%) Female: n=43 714 (59.8%) Mean age: 69.0 years[a]	First index drug in OAB patients with or without diabetes, aged ≥18 years: darifenacin oxybutynin solifenacin tolterodine trospium	Persistence was measured as the number of days from the index date until a gap in OAB medication of ≥45 days Adherence was assessed using the interval-based (fixed time-period) MPR (adherent patients had an ≥80% MPR) Variables: age, gender and diabetes	1 year
Kalder et al (2014)[10] Disease Analyzer database (IMS Health); Germany (2005–2012)	n=26 834 Male: n≈9660[a] (36%) Female: n≈17 174[a] (64%) Mean (SD) age: 69.4 (13.2) years	First index (new) prescription in patients aged ≥18 years: darifenacin (n=1995) fesoterodine (=811) oxybutynin (n=3813) propiverine (n=2714) solifenacin (n=4844) tolterodine (n=1814) trospium (n=10 843)	Treatment discontinuation was defined as a period of 90 days without prescription of UI therapy but with at least one visit to the same doctor after 90 days Variables: age, gender, comorbidity burden (including diabetes) and antimuscarinic side-effects	3 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Kleinman et al (2014)[11] Human Capital Management Services [HCMS] Research Reference Database; USA (2001–2011)	n=2960 Male: n=878 (29.7%) Female: n=2082 (70.3%) Mean age: 46.6 years	First index of OAB medication in adults aged 18 to 64 years: darifenacin fesoterodine oxybutynin flavoxate[b] solifenacin tolterodine trospium hyoscyamine[b] imipramine[b]	Persistence was measured as the number of days from index UA prescription until first ≥30-day gap in UA medication supply Adherence was measured as the percentage of the annual post-index period with available medication	1 year
Krhut et al (2014)[12] Dept. of Urology and Dept. of Gynaecology and Obstetrics, University Hospital Ostrava; Czech Republic (2009–2010)	n=377 Male: n=52 (13.8%) Female: n=325 (86.2%) Mean (SD) age: 60.3 (13.8) years	First (new) index of OAB medication within patients attending hospital as an outpatient: trospium (n=189) propiverine (n=41) tolterodine ER (n=9) solifenacin (n=48) fesoterodine (n=90)	Persistence was assessed according to the patient records	1 year
Manack et al (2011)[13] Thomson Reuters MarketScan® Commericial and Medicare Supplemental Databases; USA (2002–2007)	n=46 271[c] Male: n=19 727 (42.6%) Female: n=26 544 (57.4%) Mean (SD) age: 62.5 (19.6) years	Patients with neurogenic bladder origin (such as spinal cord injury and multiple sclerosis) receiving an oral OAB medication	Continuation was defined as ≥365 days of OAB oral drug use beginning at the index date with ≤90 days between the end of therapy and end of eligibility Discontinuation was defined as ≥6 months of no OAB oral drug use between the end of therapy and the end of eligibility	1 year
Mauseth et al (2013)[14] The Norwegian Prescription Database; Norway (2004–2010)	n=32 178 Male: n=0 (0.0%) Female: n=32 178 (100.0%) No mean age reported. The majority of patients (60.5%) were aged ≥60 years	Adult patients aged ≥18 years with a first index (new) prescription of: tolterodine (n=12 389) solifenacin (n=13 682) darifenacin (n=4399) fesoterodine (n=1708)	Persistence defined as the population who had not discontinued the drug during a period of 365 days after the index date A switch was defined as a prescription for another of the drugs included in the study within 365 days after the index date Adherence was measured using MPR (sum of days of supply for all tablets purchased, except those received at the last fill, divided by the total number of days from the first to the last filling) Variables: age and initial antimuscarinic	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Nitti et al (2016)[15] Optum Database; USA (2010–2013)	n=2628 Male: n=602 (22.9%) Female: n=2026 (77.1%) Mean age: 57.3 years[a]	New and existing users aged ≥18 years treated with: mirabegron (n=380) tolterodine ER (n=2248)	Persistence was defined as a continuous supply of index drug until any 30-day period during which the patient did not have a supply of index drug Adherence: the proportion of days covered by the prescription was calculated using prescription fill dates and number of days' supply for each fill of a prescription	6 months
Pelletier et al (2009)[16] PharMetrics Patient-Centric Database; USA (2005–2006)	n=43 367 Male: n=9675 (22.3%) Female: n=33 692 (77.7%) Mean (SD) age: 51.1 (12.4) years	Adults aged ≥18 years receiving a first index (new) prescription of: tolterodine ER oxybutynin solifenacin darifenacin trospium	Adherence was measured by PDC over the 12-month post index period (adherent patients had an ≥80% PDC) Variables: age, gender and comorbidity burden (including COPD, congestive heart failure, diabetes, hypertension)	1 year
Perfetto et al (2005)[17] PharMetrics Patient-Centric Database; USA (2001–2003)	n=23 328 No patient demographics were reported	All patients with either a new diagnosis of OAB or new use of: tolterodine ER oxybutynin ER	Discontinuation rates were calculated	11 months
Sears et al (2010)[18] Military Health System; USA (2003–2006)	n=7858 Male: n=2357 (30.0%) Female: n=5501 (70.0%) Age was not reported	Military treatment facility enrollees prescribed: oxybutynin ER (n=136) oxybutynin IR (n=2003) tolterodine ER (n=4716) tolterodine IR (n=992)	Non-persistence was defined as patients who never refilled a prescription for any OAB medication during the 3-year study period Medication switch rate was calculated as the proportion of patients who changed medication or dose at least once Adherence was defined as the proportion of patients with an MPR of ≥80% Variables: gender and drug formulation	3 years
Sicras-Mainar et al (2016)[d,19] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean age: 54.0 years	Adults aged 20 to 64 with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Discontinuation was defined as when the patient switched to another active substance, another drug was added (combination) or the medication was discontinued completely or discontinued for ≥60 days without renewal and ≥2 prescriptions Compliance was calculated using MPR Variables: concomitant medication (antidepressants, antibiotics) and index drug	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sicras-Mainar et al (2015)[d,20] Primary care medical databases; Spain (2008–2013)	n=3094 Male: n≈1170[a] (37.8%) Female: n≈1924[a] (62.2%) Mean (SD) age: 54.0 (9.2) years	Adults aged ≥20 years with a first index (new) prescription of: fesoterodine (n=859) solifenacin (n=1330) tolterodine (n=905)	Persistence was defined as the time, measured in months, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the MPR, which was evaluated from the first to the last prescription and represented the number of days of medication taken over the number of days in treatment (commencing from the start date)	1 year
Sicras-Mainar et al (2014a)[21] Primary care medical databases; Spain (2008–2010)	n=552 Male: n≈272[a] (49.2%) Female: n≈280[a] (50.8%) Mean (SD) age: 80.2 (4.0) years	Adults aged ≥75 years with a first index (new) prescription of: fesoterodine (n=58) solifenacin (n=252) tolterodine (n=212)	Persistence was defined as the time, in weeks, with no drop-out from initial treatment or with no switch to another medication at least 30 days following initial prescription Compliance was defined according to ISPOR criteria and was calculated based on the medication use/possession rate	1 year
Sicras-Mainar et al (2014b)[e,22] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Discontinuation was defined by either the absence of prescription coverage for the initial therapy for the remainder of the 52-week follow-up period or a switch to an alternative antimuscarinic during this time-period Variables: index drug	1 year
Sicras-Mainar et al (2013)[e,23] Primary care medical databases; Spain (2008–2010)	n=1971 Male: n=821 (41.7%) Female: n=1150 (58.3%) Mean (SD) age: 70.1 (10.6) years	Adults aged ≥18 years with a first index (new) prescription of: fesoterodine (n=302) solifenacin (n=952) tolterodine (n=717)	Persistence was defined as patients who remained on treatment during the 52-week period following the index date Compliance was defined according to ISPOR criteria and was calculated based on the MPR	1 year
Suehs et al (2016)[24] Medicare Advantage Prescription Plan - Administrative Claims Data; USA (2007–2013)	n=46 140[a] Male: n=15 479[a] (33.5%)[a] Female: n=30 661[a] (66.5%)[a] Mean age: 75.5 years[a]	Adults aged 65 to 89 years[f] with a first index (new) prescription of any antimuscarinic OAB medication	Persistence was assessed as time in days from the index date to discontinuation of index antimuscarinic treatment Adherence was assessed as PDC with the index OAB treatment over three predefined post index observation periods: 3, 6, and 12 months Treatment discontinuation was identified using a permissible gap between refills of 15 days	1 year

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Sussman et al (2017)[25] Truven MarketScan® Claims Database; USA (2012–2013)	n=71 980[a] Male: n=21 225[a] (29.5%)[a] Female: n=50 755[a] (70.5%)[a] Mean age: 62.3 years[a]	Adults aged ≥18 years with a prescription of: mirabegron any anticholinergic OAB medication	Persistence was measured by evaluating treatment failure (defined as either treatment discontinuation or treatment switching). A medication supply gap of ≥30 days was used to define treatment discontinuation Adherence was defined as the PDC (ie, the number of days covered by the index therapy divided by the number of days between the index date and the end of the follow-up [365 days]). A PDC of <80% was considered nonadherent	1 year
Wagg et al (2012)[26] Prescription Database; UK (2007–2008)	n=4833 Demographics were not explicitly reported, the majority of prescriptions appeared to be issued to patients aged ≥60 years	Adults aged ≥40 years with a first index (new) prescription of: darifenacin flavoxate oxybutynin ER oxybutynin IR propiverine solifenacin tolterodine ER tolterodine IR trospium	Persistence was defined as the mean time [in days] until discontinuation (a gap in treatment exceeding 1.5 times than the length of the previous prescription without a refill)	1 year
Wagg et al (2015)[27] Canadian National Private Drug Plan Database; Canada (2013)	n=19 485 Male: n=4992 (25.6%)[a] Female: n=14 493 (74.3%)[a] Mean age not reported; the majority of patients (77.8%)[a] were aged ≥46 years	Adults aged ≥18 years with a first index (new) prescription of: mirabegron (n=1683) fesoterodine (n=1415) oxybutynin ER (n=1260) oxybutynin IR (n=5356) solifenacin (n=6032) tolterodine ER (n=3739)	Adherence was defined by the MPR over 1 year To calculate time to end of persistence (defined by a gap in therapy of ≥30 days or switching to another medication), prescription claims for a target drug were tracked for 12 months after the index claim date Variables: age, gender, treatment-naïve vs treatment-experienced, index antimuscarinic, number of coexisting medications	1 year
Wagg et al (2015)[28] IMS Brogan public and private prescription claims databases; Canada (2007–2012)	n=31 707 Male: n=9395 (29.6%)[a] Female: n=22 312 (70.4%)[a] Mean age not reported	Adult patients receiving a first index (new) prescription of: oxybutynin IR oxybutynin ER tolterodine IR tolterodine ER solifenacin darifenacin trospium flavoxate	Discontinuation was defined as patients experiencing a gap in therapy longer than 60 days	4 years

Author (year) and country (database)	Participants	Drug/intervention*	Definition of persistence/adherence/discontinuation and independent variables on persistence	Length of follow-up
Yeaw et al (2009)[29] PharMetrics Patient-Centric Database (pharmacy claims); USA (2005)	n=7722 Male: n=1686 (21.8%) Female: n=6036 (78.2%) Mean (SD) age: 43.7 (18.3) years	Adult patients receiving a first index (new) prescription of: tolterodine oxybutynin solifenacin darifenacin trospium bethanechol flavoxate hyoscyamine	Persistence was calculated for the post-index period until the patient discontinued therapy, was lost to follow-up due to disenrollment from the health plan (minimum of 12 months), or the maximum 24-month follow-up period ended, whichever event occurred first. A patient was considered persistent until an excessive gap in days supplied occurred; refill gaps of 30, 60, and 90 days were used to calculate persistence for all cohorts Adherence was measured using the PDC for each of the six drug class cohorts. This was calculated by taking patients' total days supplied of index class medications for the 360-day period following the index date and dividing by 360	2 years
Yu et al (2015)[30] California Medi-Cal administrative files; USA (1999–2002)	n=2496 Male: n=534 (21.4%) Female: n=1962 (78.6%) Mean (SD) age: 63.15 (16.14) years	Adult patients aged ≥18 years receiving a prescription of an OAB drug, including: tolterodine (n=1093) oxybutynin ER (n=524) oxybutynin (n=812) other OAB agents (n=67)	Persistence was measured by the length of continuous pharmacological treatment (patients discontinued their treatment if they failed to refill OAB/UI agents within 30 days after the expected end date of the previous prescription) Patients who switched from one agent of OAB/UI drug to another within 30 days were considered persistent on therapy. Adherence was defined as MPR over 181 days for the 6-month follow-up period Variables: age, gender, ethnicity, index drug, OAB-associated comorbidities (UTIs), medication use history, length of hospital stay and number of drug classes prescribed	1 year

COPD = chronic obstructive pulmonary disease; ER = extended release; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; IR = immediate release; MPR = medication possession ratio (measured as the proportion of days with any OAB medication on hand, over the length of the evaluation period); OAB = overactive bladder; PDC = proportion of days covered; PIM = potentially inappropriate medication; SD = standard deviation; TD = transdermal; UA = urinary antispasmodic; UI = urinary incontinence; UTIs = urinary tract infections

*The sum of the patients prescribed individual drugs may not match the total number of patients perhaps due to switching in some studies

[a]Calculated from data presented in the article; [b]used only in an OAB context; [c]26 922 continued, discontinued or restarted an OAB medication in the study period, but no demographics for this specific sub-group are reported; [d]Sicras-Mainar et al (2016)[19] and Sicras-Mainar et al (2015)[20] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [e]Sicras-Mainar et al (2014)[22] and Sicras-Mainar et al (2013)[23] relate to the same patient group in terms of demographics and the timeframe/geographical source of adherence/persistence data; [f]this cohort was split into two groups – patients who were assigned OAB medication appropriately [non-PIM], or potentially inappropriately [PIM]. Inappropriateness was defined as patients having "drug–disease or syndrome interaction or indication of significant anticholinergic medication burden at the time of initiation of an antimuscarinic OAB treatment"

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Supplemental Table 2. Summary of adherence and persistence rates and determinants

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Brostrøm and Hallas (2009)[1]	Proportion of patients continued (all drugs except trospium chloride): <50% at 6 months <25% at 1 year <10% at ≥2 years Proportion of patients continued trospium: 46% at 6 months 36% at 1 year 22% at 2 years 16% at 3 years	Not reported	***Gender, age, medication dose, treatment status, medication type*** Retention was longer: in females; in older people; with higher doses; with previous experience of other OAB drugs; trospium vs other OAB drugs
Chancellor et al (2013)[2]	Proportion of patients discontinued at 2 years:[a] tolterodine ER: 84.7% solifenacin: 85.2% oxybutynin: 91.1% darifenacin: 85.7% oxybutynin ER: 84.0% tolterodine: 85.1% trospium: 88.1% trospium ER: 87.1% Proportion of patient switched at 2 years:[a] tolterodine ER: 5.7% solifenacin: 5.2% oxybutynin: 4.7% darifenacin: 6.0% oxybutynin ER: 6.7% tolterodine: 9.7% trospium: 6.9% trospium ER: 6.4%	Proportion of patients with MPR ≥0.80 over study period (in those filling >1 prescription): tolterodine ER: 51.1% solifenacin: 49.4% oxybutynin: 30.1% darifenacin: 51.9% oxybutynin ER: 51.8% tolterodine: 42.6% trospium: 42.4% trospium ER: 54.3%	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Chapple et al (2017)[3]	Median time to discontinuation (days): mirabegron: 169 darifenacin: 56 fesoterodine: 78 flavoxate: 30 oxybutynin ER: 60 oxybutynin IR: 35 propiverine: 56 solifenacin: 67 tolterodine ER: 56 trospium chloride: 60 Proportion of patients persistent at 1 year: mirabegron: 38% darifenacin: 16% fesoterodine: 24% flavoxate: 8.3% oxybutynin ER: 17% oxybutynin IR: 12% propiverine: 21% solifenacin: 25% tolterodine ER: 21% trospium chloride: 19%	Mean (SD) MPR at 1 year: mirabegron: 0.59 (0.33) darifenacin: 0.46 (0.34) fesoterodine: 0.53 (0.33) flavoxate: 0.44 (0.32) oxybutynin ER: 0.49 (0.32) oxybutynin IR: 0.41 (0.32) propiverine: 0.51 (0.32) solifenacin: 0.53 (0.34) tolterodine ER: 0.50 (0.34) trospium chloride: 0.48 (0.33) Proportion of patients with MPR ≥0.8 at 1 year: mirabegron: 43% darifenacin: 29% fesoterodine: 35% flavoxate: 24% oxybutynin ER: 31% oxybutynin IR: 22% propiverine: 25% solifenacin: 35% tolterodine ER: 32% trospium chloride: 29%	***Medication type*** Mirabegron was associated with a statistically significantly greater median time to discontinuation (adjusted HR range 1.31–2.31; p<0.0001 all comparisons) and 12-month persistence rates (adjusted OR range 0.18–0.71; p≤0.0001 all comparisons) vs antimuscarinics in all patients The mean MPR with mirabegron was significantly greater vs antimuscarinics in all patients (p values 0.03 to <0.0001), and in treatment-naïve subcohorts, except for flavoxate (p values 0.02 to <0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Desgagné et al (1999)[4]	Proportion of patients refilled initial prescription: Short-term[b]; oxybutynin: 39.3% flavoxate: 36.6% Long-term[c]; oxybutynin: 63.9% flavoxate: 55.5% Proportion of patients discontinued at 3 months: oxybutynin: 78% flavoxate: 83% Proportion of patients discontinued at 6-months: oxybutynin: 89% flavoxate: 94% Proportion of patients switched at 4-years: Patients without renewal of the original claim: oxybutynin: 1.3% flavoxate: 3.1% Patients with any number of renewals before switch: oxybutynin: 2.2% flavoxate: 5.9%	Not reported	***Age*** Compared with patients aged <77.5 years, those who were older were less likely to discontinue vs: 77.5–83.5 years: RR 0.90, 95% CI 0.85–0.96, p<0.001 >83.5 years: RR 0.86, 95% CI 0.81–0.92, p<0.001 ***Medication dose*** Higher quantity of tablets per day (2–4 tablets/day) was associated with increased risk of early discontinuation, compared with low daily quantity (1 tablet per day) (RR 1.45, 95% CI 1.37–1.53, p<0.001) ***Medication type*** Patients receiving flavoxate had an increased risk of discontinuation compared with those receiving oxybutynin (RR 1.13, 95% CI 1.05–1.22, p<0.001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
D'Souza et al (2008)[5]	Proportion of patients persistent at 1 year (without a gap >45 days): oxybutynin ER: 15.3% oxybutynin IR: 6.5% tolterodine ER: 15.0% tolterodine IR: 11.4% overall: 13.2% Proportion of patients not refilled index medication: oxybutynin ER: 39.4% oxybutynin IR: 59.3% tolterodine ER: 42.7% tolterodine IR: 46.1% overall: 44.5% Median time to discontinuation (days): oxybutynin ER: 34 oxybutynin IR: 0 tolterodine IR: 32 tolterodine ER: 33 overall: 31 Proportion of patients switched at 1 year: oxybutynin ER: 16.5% oxybutynin IR: 19.4% tolterodine IR: 13.7% tolterodine ER: 9.9% overall: 13.3%	Proportion of patients with MPR ≥0.80 at 1 year: oxybutynin ER: 36.1% oxybutynin IR: 14.8% tolterodine ER: 35.2% tolterodine IR: 23.5% overall: 30.3%	***Medication formulation*** Adherence with IR drugs approximately half that for ER drugs (OR 0.504, 95% CI 0.306–0.704, p<0.001) ***Age*** Patients aged ≥65 years were 1.5 times more likely to achieve an MPR ≥0.80 than patients aged <65 years

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gomes et al (2012)[6]	Median time to discontinuation (days): oxybutynin: 68 tolterodine: 128 Proportion of patients persistent at: 6 months oxybutynin: 30.6% tolterodine: 42.9% 1 year oxybutynin: 18.9% tolterodine: 27.3% 18 months oxybutynin: 13.1% tolterodine: 18.9% 2 years: oxybutynin: 9.4% tolterodine: 13.6%	Not reported	***Medication type*** Over the 2-year follow-up, the time to discontinuation was longer with tolterodine than oxybutynin (p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Gopal et al (2008)[7]	Over 3 years, 91% of 49,419 episodes of medication prescription resulted in discontinuation Cumulative incidence of discontinuation at 6 months, 1 year, 2 years and 3 years (unadjusted): Overall: 58.8, 77.2, 87.5, 92.0% Cumulative incidence of discontinuation, at 6 months, 1 year, 2 years and 3 years (adjusted for age, year of initiation, switch, number of previous drug classes, number of prior episodes and smoking status): oxybutynin: 71, 86, 94, 96% oxybutynin ER: 57, 80, 93, 97% tolterodine: 61, 81, 92, 95% tolterodine ER: 54, 76, 91, 97% trospium: 56, 80, 94, 98% propiverine: 61, 84, 95, 98% solifenacin: 53, 91, 98, 99% terodiline: 89, 99%, N/A, N/A flavoxate: 85, 96, 99, 99% Median time to discontinuation (months): oxybutynin: 4.67 oxybutynin ER: 5.13 tolterodine: 5.47 tolterodine ER: 5.37 trospium: 5.47 propiverine: 5.43 solifenacin: 5.00 terodiline: 4.00 flavoxate: 4.00 overall: 4.76 Overall switch rate: 15%	Not reported	***Medication formulation*** In comparison with the multiple-dosing drug classes at 6 months, both oxybutynin ER (57%, 95% CI 55.1–59.2) and tolterodine ER (54%, 95% CI 52.3–57.4) had lower incidences of discontinuation ***Medication type*** Trospium and tolterodine were associated with the longest median time to discontinuation (5.47 months each), followed by propiverine (5.43 months) and solifenacin (5.0 months). Terodiline and flavoxate had the shortest median time to discontinuation (4 months each)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Ivanova et al (2014)[8]	Proportion of patients discontinued at 6 months: 61.0% Proportion of patients switched at 6 months: 8.0% Proportion of patients persistent at 6 months: 31.0% Proportion of patients discontinued at 6 months: oxybutynin: 30.6% tolterodine: 30.5% solifenacin: 24.5% darifenacin: 8.4% trospium: 4.1% fesoterodine: 1.9% Mean time to discontinuation: 54.7 days 42.7% of patients never refilled their indexed prescription	Not reported	***Age*** Patients who discontinued (50.5 years) or switched (52.6 years) medication were significantly younger than those who persisted (53.4 years; p<0.001) Increasing age was associated with reduced odds of discontinuation (adjusted OR 0.97, 95% CI 0.96–0.97, p<0.0001) ***Gender*** Being male was associated with greater odds of discontinuation (adjusted OR 1.11, 95% CI 1.00–1.23, p=0.0475) ***Medication type*** Patients who persisted with medication contained a significantly higher proportion of solifenacin users than those in groups who switched or discontinued (30.1% vs 19.7% vs 24.5%, respectively, p<0.001) and a lower proportion of oxybutynin (22.6% vs 29.6% vs 30.6%, respectively, p<0.001) Compared to patients treated with solifenacin, patients were significantly more likely to discontinue when treated with tolterodine (adjusted OR 1.30, 95% CI 1.16–1.45, p<0.0001) or oxybutynin (adjusted OR 1.80, 95% CI1.59–2.03, p<0.0001) ***Presence of infection*** Patients with UTI were more likely to discontinue compared with those without UTI (adjusted OR 1.31, 95% CI 1.19–1.45, p<0.0001) ***Financial burden*** Patients with lower log of baseline OAB-related costs were more likely to discontinue (adjusted OR 0.96, 95% CI 0.94–0.98, p<0.0001)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Johnston et al (2012)[9]	Mean time of continuation at 1 year (days): diabetic: 164 not diabetic: 146.9 (p<0.001 difference) Proportion of patients discontinued at 1 year: diabetic: 71.5% not diabetic: 76.2% (p<0.001 difference)	Mean MPR at 1 year; diabetic: 0.473 not diabetic: 0.424 (p<0.001 difference)	***Age and gender*** The odds of adherence generally increase with age, and females had higher odds of adherence than men ***Diabetes*** The diabetes cohort had greater odds of achieving an MPR ≥0.80 (OR 1.215, 95% CI 1.169–1.263, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period The diabetes cohort had greater odds of filling a second OAB medication prescription (OR 1.166, 95% CI 1.127–1.205, p<0.0001) vs non-diabetes cohort during the 12-month evaluation period

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kalder et al (2014)[10]	Proportion of patients discontinued at: 1 year: 74.8% 2 years: 77.6% 3 years: 87%	Not reported	***Gender*** At 3 years, there was a significantly higher risk of discontinuation in male than female patients (HR 1.14, 95% CI 1.11–1.18, p<0.001) ***Age*** Discontinuation was higher in younger patients than older patients: ≤60 years: 89.7% 61–70 years: 87.9% 71–80 years: 86.8% >80 years: 83.0% ***Prescriber's profession*** Discontinuation rate was higher in patients treated by gynecologists and general practitioners compared with urologists (HR 1.60 [95% CI 1.52–1.67] p<0.001; HR 1.24 [95% CI 1.20–1.29] p<0.001) ***Side effects*** A higher risk of discontinuation in patients experiencing side effects: headache: HR 1.27, 95% CI 1.12–1.43, p=0.002 stomach upset: HR 1.20, 95% CI 1.12–1.27, p<0.001 glaucoma: HR 1.46, 95% CI 1.16–1.84, p<0.001 ***Medication type*** Patients using propiverine (HR 0.94, 95% CI 0.88–0.99, p=0.022) or solifenacin (HR 0.93, 95% CI 0.87–0.98, p=0.003) had a significantly lower risk of treatment discontinuation compared with oxybutynin. However, the absolute difference was relatively small ***Comorbidities*** Diabetes, Parkinson's disease, epilepsy, dementia, and multiple sclerosis was associated with a lowered risk of treatment discontinuation A prior diagnosis of migraine was associated with a higher risk of treatment discontinuation

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Kleinman et al (2014)[11]	Median time until a ≥30-day medication gap: 64 days Proportion of patients persistent: beyond 1 month: 70% at 9 months: 10% at 1 year: 5%	Proportion of patients with PDC ≤10% at 1 year: 45.4% Proportion of patients with PDC ≥80% at 1 year: 12.7%	***Gender*** Compared to the group with PDC ≥80%, the group with PDC <80% contained a lower proportion of females (69.5% vs 76.3%, p=0.006) ***Age*** Compared to those with PDC ≥80%, patients with PDC <80% were younger (mean age: 46.18 years vs 49.79 years, p<0.001) ***Race*** Compared to the group with a PDC ≥80%, the group with PDC <80% contained a lower proportion of White patients (38.6% vs 50.0%, p<0.001) and higher proportion of Black and Hispanic patients (6.7% vs 3.7%, p=0.025; 11.6% vs 6.3%, p=0.002) ***Medication co-payment*** Compared to the group with a PDC ≥80%, those with PDC <80% paid a higher mean medication co-payment ($20.15 vs $14.68, p<0.001)
Krhut et al (2014)[12]	Median (SD) time to discontinuation: 6.53 (3.84) months Proportion of patients persistent at: 3 months: 59.7% 6 months: 39.3% 9 months: 33.6% 1 year: 27.2%	Not reported	***Medication type*** Persistence was significantly higher in patients treated with anticholinergic medication with an ER formulation than in patients treated with IR anticholinergics (ER: 7.10 [SD 3.90] months vs IR: 6.18 [SD 3.75] months, p=0.023)
Manack et al (2011)[13]	Mean (SD) duration of therapy: 201.9 (120.9) days Proportion of patients that: continued OAB medication ≥1 year: 28.9% discontinued OAB medication and did not restart[d]: 37.5% discontinued and restarted OAB medication[e]: 33.5%	Not reported	Not reported

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Mauseth et al (2013)[14]	Proportion of patients persistent at 1 year: tolterodine: 39.0% solifenacin: 39.4% darifenacin: 34.3% fesoterodine: 29.1% overall: 38.0% Proportion of patients switched at 1 year: tolterodine: 12.0% overall: 10.3% Proportion of patients filled only one prescription: 31.9%	Mean MPR at 1 year: 0.62[f] Proportion of patients with MPR ≥0.80[f] at 1 year: tolterodine: 33.7% solifenacin: 35.7% darifenacin: 37.0% fesoterodine: 38.5% overall: 35.2%	***Age*** Persistence was lowest in the age group 18–39 years (20.9%), generally increased with age, and was highest in the age groups 70–79 years (43.5%) and ≥80 years (43.3%) ***Medication type*** At 1 year, persistence was highest for tolterodine (39.0%) and solifenacin (39.4%), both of which entered the market first. Persistence for darifenacin and fesoterodine, which were launched later, was 34.3% and 29.1%, respectively
Nitti et al (2016)[15]	Proportion of patients persistent at: 1 month; mirabegron: 68.4% tolterodine ER: 47.1% 3 months; mirabegron: 48.7% tolterodine ER: 28.6% 6 months; mirabegron: 34.7% tolterodine ER: 18.5% Median persistence (days): mirabegron: 170 tolterodine ER: 90	Not reported	***Age*** Compared with patients aged <65 years, patients aged ≥65 years were less likely to discontinue over 6 months with tolterodine (HR 0.88, 95% CI 0.80–0.96, p=0.0064) and mirabegron (HR 0.68, 95% CI 0.52–0.90, p=0.0068) ***Prior treatment*** Compared to patients without prior use of OAB medication, patients with prior OAB medication use were less likely to discontinue over 6 months with tolterodine (HR 0.76, 95% CI 0.68–0.85), p<0.0001) and mirabegron (HR 0.68, 95% CI 0.53–0.88, p=0.0025) ***Medication type*** The risk of discontinuation was lower with mirabegron compared with tolterodine (HR 0.72, 95% CI 0.61–0.85, p<0.0001)
Pelletier et al (2009)[16]	Not reported	Mean cohort PDC at 1 year: 0.32 Proportion of patients with PDC ≥0.80 at 1 year: 14.4%	***Demographics (gender, age, comorbidities)***[g] Female and older subjects were more likely to adhere. Those with a history of hypertension, diabetes, or multiple sclerosis were more adherent. Subjects with COPD were less adherent

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Perfetto et al (2005)[17]	Cumulative discontinuation rates at: 1 month; tolterodine ER: 6% oxybutynin ER: 11% 3 months; tolterodine ER: 55% oxybutynin ER: 62% 6 months; tolterodine ER: 69% oxybutynin ER: 76% 11 months; tolterodine ER: 79% oxybutynin ER: 85% Overall, at 11 months, 21% of patients remained on tolterodine ER and 15% of patients remained on oxybutynin ER	Not reported	Not reported
Sears et al (2010)[18]	Proportion of patients without prescription refills over 3 years: 35.1% Median persistence (days): overall: 273 patients with at least 1 refill: 582 Overall medication persistence duration was 273 days when all cases were analyzed and 582 days when those with at least 1 refill were analyzed	Median MPR at 3 years: oxybutynin 5 mg IR: 0.68 oxybutynin 5 mg ER: 0.83 oxybutynin 10 mg ER: 0.84 tolterodine 1 mg IR: 0.71 tolterodine 2 mg IR: 0.73 tolterodine 2 mg ER: 0.88 tolterodine 4 mg ER: 0.89 overall: 0.82 Proportion of patients with MPR ≥0.80 at 3 years: 34.0%	***Gender*** Male patients had a higher median MPR than female patients (0.86 vs 0.81, p<0.001) Medication adherence was higher in males than in females (0.370 vs 0.328, p<0.001) Of patients refilling their prescription at least once, the median number of days persisted was longer in females than in males (606.0 days vs 547.0 days, p=0.01) ***Medication type*** Of patients refilling their prescription at least once, median medication persistence was longest in 5 mg oxybutynin IR (634 days, 95% CI 596.1–671.9) and lowest with 10 mg oxybutynin ER (504 days, 95% CI 137.0–871.0)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2016)[19]	Proportion of patients persistent (without switching or experiencing a gap of >60 days) at: 6 months; fesoterodine: 71.4% solifenacin: 67.1% tolterodine: 64.8% 1 year; fesoterodine: 40.2% solifenacin: 34.7% tolterodine: 33.6%	Mean MPR at 1 year was: 0.880, 0.877 or 0.875, depending upon geographical location	***Medication type*** Persistence at 6 months and 1 year was statistically significantly higher with fesoterodine than solifenacin and tolterodine ($p<0.05$). Persistence at 1 year was significantly lower with solifenacin than fesoterodine ($p<0.01$)
Sicras-Mainar et al (2015)[f,20]	Proportion of patients persistent at: 3 months: 86.2% 6 months: 67.6% 9 months: 48.4% 1 year: 35.9% Mean (SD) treatment duration (without stopping, switching or a gap >30 days): fesoterodine: 8.1 solifenacin: 7.8 tolterodine: 7.7 overall: 7.9	Mean MPR at 1 year: fesoterodine: 0.900 solifenacin: 0.870 tolterodine: 0.861 overall: 0.877	Not reported
Sicras-Mainar et al (2014)[21]	Proportion of patients persistent (without switching or experiencing a gap of >30 days): 3 months; fesoterodine: 94.8% solifenacin: 76.2% tolterodine: 70.8% 6 months; fesoterodine: 70.7% solifenacin: 59.5% tolterodine: 57.1% 1 year; fesoterodine: 46.6% solifenacin: 36.5% tolterodine: 33.5%	Mean MPR at 1 year: fesoterodine: 0.907 solifenacin: 0.935 tolterodine: 0.936	***Medication type*** At 3 months, persistence was higher with fesoterodine than with tolterodine and solifenacin

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sicras-Mainar et al (2014)[g,22]	Proportion of patients persistent at 1 year: fesoterodine: 35.8% solifenacin: 31.9% tolterodine: 30.9%	Mean MPR at 1 year: fesoterodine: 0.937 solifenacin: 0.948 tolterodine: 0.935	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found. However, adjusted HRs for remaining on treatment at 1 year significantly favored fesoterodine compared with solifenacin (HR 1.24 [95% CI 1.05–1.47]; p=0.011) and tolterodine (HR 1.28 [95% CI 1.07–1.52]; p=0.006)
Sicras-Mainar et al (2013)[g,23]		Mean MPR at 1 year: fesoterodine: 0.945 solifenacin: 0.954 tolterodine: 0.946	***Medication type*** The mean duration of treatment was numerically higher with fesoterodine compared to solifenacin and tolterodine, but no statistical between-medication differences were found
Suehs et al (2016)[24]	Proportion of patients not refilling their index medication: PIM: 41.4% Non-PIM: 47.8% (p<0.01) Mean number of days persistent (before discontinuation or experiencing a gap >15 days): PIM: 87.6 Non-PIM: 80.9 (p<0.001) Proportion of patients persistent at: 3 months; PIM: 23.9% Non-PIM: 20.3% 6 months; PIM: 13.2% Non-PIM: 11.4% 1 year; PIM: 5.1% Non-PIM: 4.5% (all p<0.001 differences)	Mean PDC at: 3 months; PIM: 0.62 Non-PIM: 0.59 6 months; PIM: 0.45 Non-PIM: 0.42 1 year; PIM: 0.32 Non-PIM: 0.30 (all p<0.001 differences) Proportion of patients with PDC ≥0.80: 3 months; PIM: 37.0% Non-PIM: 35.0% 6 months; PIM: 23.3% Non-PIM: 19.7% 1 year; PIM: 12.7% Non-PIM: 10.7% (all p<0.001 differences)	***Medication use appropriateness*** At 1 year, there was no statistical difference between PIM status and OAB treatment discontinuation in the multivariable adjusted model based on the primary analysis definition (15-day definition OR 0.977, 95% CI 0.891–1.072, p=0.63; 30-day definition OR 0.939, 95% CI 0.871–1.013, p=0.10)

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Sussman et al (2017)[25]	Proportion of patients discontinued at 1 year (gap of ≥30 days): mirabegron: 67.1% anticholinergic: 84.1% Median time to discontinuation (days): mirabegron: 131 anticholinergic: 30	Mean PDC: mirabegron: 0.66 anticholinergic: 0.55 Proportion of patients with PDC ≥0.80 at 1 year: mirabegron: 43.6% anticholinergic: 30.9%	***Medication type*** Users of mirabegron appeared to achieve greater persistence and adherence at 1 year than users of anticholinergics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2012)[26]	Time (days) to discontinuation (or a gap >1.5 times the length of the previous prescription without a refill): darifenacin: 135.9 flavoxate: 77.4 oxybutynin ER: 146.7 oxybutynin IR: 119.3 propiverine: 141.1 solifenacin: 158.7 (5 mg); 216.0 (10 mg) tolterodine ER: 156.7 tolterodine IR: 151.7 trospium: 138.5 Proportion of patients persistent at 3 months: darifenacin: 52% flavoxate: 28% oxybutynin ER: 44% oxybutynin IR: 40% propiverine: 47% solifenacin: 58% tolterodine ER: 47% tolterodine IR: 46% trospium: 42% Proportion of patients persistent at 6 months: darifenacin: 30% flavoxate: 16% oxybutynin ER: 35% oxybutynin IR: 29% propiverine: 36% solifenacin: 46% tolterodine ER: 36% tolterodine IR: 33% trospium: 33% Proportion of patients persistent at 1 year: darifenacin: 17.4% flavoxate: 13.5% oxybutynin ER: 26.1% oxybutynin IR: 21.7% propiverine: 26.8% solifenacin: 35% tolterodine ER: 28.2% tolterodine IR: 24.1% trospium: 25.9%	Not reported	***Age*** Over 1 year, the majority of patients aged ≥60 years were more likely to persist than younger patients. Graphical results only ***Medication type*** Patients receiving solifenacin spent the longest mean duration on therapy compared with other OAB medications

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[27]	Proportion of patients persistent at 1 year (without switching or experiencing a gap ≥30 days): mirabegron: 31.7% fesoterodine: 21.0% oxybutynin ER: 18.9% oxybutynin IR: 13.8% solifenacin: 22.0% tolterodine ER: 19.7% Median duration of treatment (days): mirabegron: 221 solifenacin: 108 fesoterodine: 100 tolterodine ER: 100 oxybutynin ER: 100 oxybutynin IR: 75 Proportion of patients persistent at 1 year: treatment-naïve:19.0% treatment-experienced: 30.0% Median days on therapy: treatment-naïve: 90 treatment-experienced: 205	Median MPR at 1 year: mirabegron: 0.645 fesoterodine: 0.492 oxybutynin ER: 0.328 oxybutynin IR: 0.186 solifenacin: 0.459 tolterodine ER: 0.454	***Age*** As age increased, median MPR increased for OAB medications: <46 years: 0.273 45–64 years: 0.372 ≥65 years: 0.492 (p<0.001 difference compared to ≥65 years) ***Treatment status*** Patients with prior experience of OAB medication use achieved a higher MPR than treatment-naïve patients (0.546 vs 0.328, p<0.001) ***Medication type*** Compared with antimuscarinics, patients taking mirabegron demonstrated greater persistence and statistically significantly greater adherence (64.5% vs 18.6%–49.2%, p<0.001) than those taking antimuscarinics

Author (year)	Persistence*	Adherence*	Determinants of persistence and adherence
Wagg et al (2015)[28]	Proportion of patients persistent at 6 months: <40% Proportion of patients discontinued at 4 years: oxybutynin: 93% tolterodine IR: 90% tolterodine ER: 90% solifenacin: 90% darifenacin: 91% trospium: 94% flavoxate: 98% overall: 91.4% Median duration of first-line treatment (days): oxybutynin: 60 tolterodine IR: 90 tolterodine ER: 100 solifenacin: 106 darifenacin: 91 trospium: 90 flavoxate: 10	Not reported	***Medication type*** Initial treatment with solifenacin, darifenacin, tolterodine ER and tolterodine was associated with a significantly lower risk of discontinuation compared with oxybutynin as the first medication (HRs 0.68, 0.72, 0.77 and 0.84, respectively; p<0.001 vs oxybutynin for each) Patients receiving flavoxate as initial treatment had a significantly higher risk of discontinuation compared with those who received oxybutynin (HR 2.48, p<0.0001) There was no statistically significant difference in the risk of discontinuation with trospium as first-line compared with oxybutynin (p=0.1074) ***Age*** Compared with patients aged 40–64 years, patients aged <20, 20–39, 65–74 and ≥75 years had a higher risk of discontinuation (HRs 1.08–1.19, all p≤0.0022) ***Gender*** Males had a slightly higher risk of discontinuation than females (HR 1.03, 95% CI 1.00–1.06, p=0.0341)
Yeaw et al (2009)[29]	Proportion of patients remaining on therapy (without a refill gap >60 days) at: 6 months: 28% 1 year: 18%	Proportion of patients with mean MPR at 1 year: 35%	Not reported
Yu et al (2005)[30]	Proportion of patients without index prescription refill within the first 6 months: 36.9% Proportion of patients discontinued at: 1 month: 42.7% 2 months: 66.8% 5 months days: 77.6% 9 months: 86.3% At a 1-year follow-up, the rate of discontinuation was increased to 88.6%	Mean MPR at: 6 months: 0.34 1 year: 0.22 Proportion of patients with MPR ≥0.80 at: 6 months: 4.9% 1 year: 0.7%	***Medication type*** Compared with oxybutynin, patients receiving tolterodine were less likely to have discontinued at 6 months (HR 0.74, 95% CI 0.67–0.81, p<0.01) ***Polypharmacy*** The use of multiple drugs was associated with a higher risk of discontinuation by the 6-month follow up (HR 1.26, 95% CI 1.09–1.46, p<0.01) Other significant predictors of higher persistence included: White ethnicity, previous hospitalization length, and starting treatment with tolterodine

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ER = extended release; HR = hazard ratio; IR = immediate release; MPR = medication possession ratio; OAB = overactive bladder; OR = odds ratio; PIM = potentially inappropriate medication; PDC = proportion of days covered; RR = risk ratio; SD = standard deviation; UTIs = urinary tract infections

*In cases where reported values differ from published values, they were derived from the published data; [a]cohort discontinuation percentages are also quoted for 3, 6, 12 and 18 months. However, these figures included some non-oral OAB medications. Therefore, these have not been included; [b]within 1.5x the duration of the initial prescription; [c]over a 4-year period; [d]stopped receiving an OAB medication for ≥6 months between end of therapy and end of the study's eligibility period; [e]stopped receiving an OAB medication for <6 months before restarting an OAB medication; [f]patients who filled only one prescription were given an MPR of zero; [g]no exact figures were quoted within the article text

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Supplemental Information

Literature Search Strategies

The following databases were searched;

- Allied and Complementary Database [AMED] (via OVID)
- Cumulative Index to Nursing and Allied Health Literature [CINAHL] (via EBSCOhost)
- MEDLINE (via EBSCOhost)
- Database of Reviews of Effects [DARE] (via CRD, University of York)
- Health Technology Assessment [HTA] (via CRD, University of York)
- Centre for Reviews and Dissemination [CRD] (via CRD, University of York)

The searches were conducted on the 24th April 2017

The date span of the searches;

- AMED – 1985 to April 2017
- CINAHL – 1937 to April 2017
- MEDLINE – 1946 to April 2017
- DARE / HTA / CRD – 1994 to April 2017

	Searches (AMED)*	
1	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
2	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
3	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
4	(#1 AND #2 OR #3)	18
	Searches (CINAHL & MEDLINE)*	
5	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
6	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
7	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–

8	(#5 AND #6 OR #7)	3,855
	Searches (DARE / HTA / CRD)*	
9	persisten* OR adheren* OR complian* OR discont* OR tolera* OR utili* OR database [In Article Title]	–
10	Bladder" OR "Overactive Bladder" OR "OAB" OR urin* OR incontinen* [In Article Title]	–
11	Oxybutynin OR Tolterodine OR Fesoterodine OR Trospium OR Darifenacin OR Solifenacin OR Propiverine OR Imidafenacin OR Mirabegron OR Flavoxate OR Hyoscyamin* OR Anticholinerg* OR Antimuscarin* [In Article Title]	–
12	(#9 AND #10 OR #11)	24
13	Total from #4, #8 and #12	3,897
14	Remove duplicates from 13 using EndNoteWeb	**3,614**

* Boolean operators were used. No other limits or filters were applied to each database.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3–5
2	Hypothesis statement	N/A
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	6–8
5	Type of study designs used	6
6	Study population	6–7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	6-7, Figure 1, Supplemental Information
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	5–6, Supplemental Information
11	Search software used, name and version, including special features used (eg, explosion)	Supplemental Information
12	Use of hand searching (eg, reference lists of obtained articles)	6–7
13	List of citations located and those excluded, including justification	6–7, Supplemental Tables 1 and 2
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6–7
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6–7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6–7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6–7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Not performed – see response to reviewers
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
24	Provision of appropriate tables and graphics	Figures 1 and 2 and Supplemental Tables

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2 and Supplemental Tables 1 and 2
26	Table giving descriptive information for each study included	Supplemental Tables 1 and 2
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	N/A

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	N/A
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1 legend
31	Assessment of quality of included studies	Not performed – see response to reviewers
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12–14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	13-15
34	Guidelines for future research	15
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.