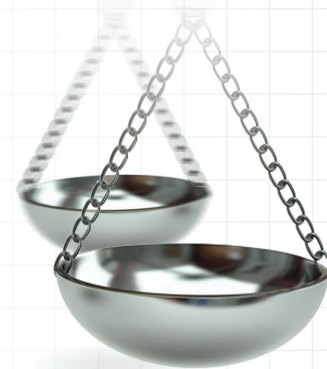




Healthcare and economic burden of anticholinergic use in adults with overactive bladder: a systematic literature review

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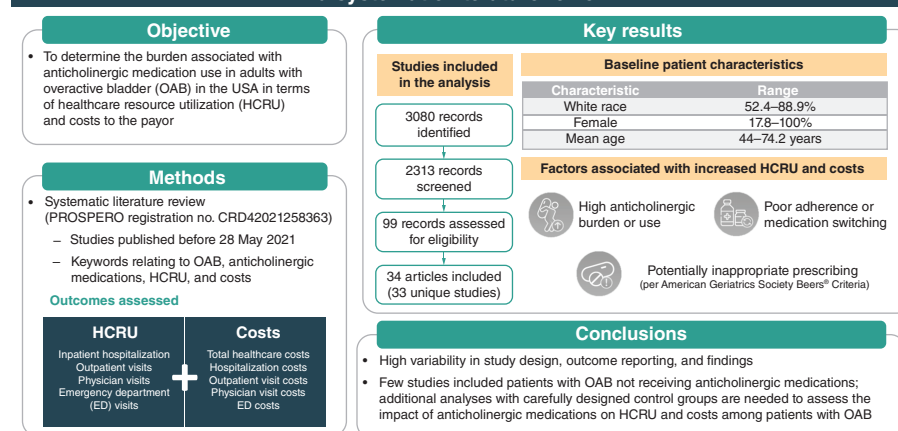
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Aim: To determine the economic burden associated with anticholinergic medication use in adults with overactive bladder (OAB) in the USA. **Methods:** A systematic literature review was conducted to identify articles assessing healthcare resource utilization (HCRU) and costs associated with anticholinergic use in adults with OAB. **Results:** From the 34 articles identified, increased anticholinergic burden, switching anticholinergic treatments and potentially inappropriate anticholinergic use were associated with increased HCRU and/or costs. However, studies comparing patients with OAB receiving anticholinergics to individuals with untreated OAB or without OAB reported a mix of increases and decreases in HCRU and costs. **Conclusion:** Additional controlled studies assessing the economic impact of anticholinergics in OAB are needed and may enable optimization of economic and potentially patient outcomes.

Graphical abstract:

Healthcare and economic burden of anticholinergic use in adults with overactive bladder: a systematic literature review



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Overactive bladder (OAB) is a urologic condition with symptoms including urinary urgency, with or without urge urinary incontinence (UUI); increased daytime urinary frequency; and nocturia [1]. It is estimated that at least 30 million individuals ≥ 40 years of age in the USA experience bothersome OAB symptoms [2]. OAB is



associated with increased incidence of comorbidities, including depression, anxiety and falls, as well as reduced health-related quality of life [3–5]. OAB is also associated with a high economic burden, including medical costs, lost productivity and healthcare resource utilization (HCRU); average healthcare costs (including inpatient, emergency room, outpatient, pharmacy and other costs) for patients with OAB have been estimated at \$3003 per patient per month versus \$1123 per patient per month for a matched control group without OAB [6,7].

Current American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) guidelines recommend behavioral therapy as first-line treatment and pharmacologic interventions with β_3 -adrenergic receptor agonists or anticholinergic medications as second-line treatment for patients with OAB [1]. Anticholinergic medications are the most prescribed OAB treatments in the USA [8–10].

Long-term use of anticholinergic medications is associated with side effects including dry mouth, constipation and potential for cognitive impairment [1,11–17]. Increasing anticholinergic burden is associated with increased risk of falls/fractures, all-cause mortality and major adverse cardiovascular events, as well as clinically relevant drug–drug interactions [1,18]. Furthermore, the use of anticholinergic medications is associated with an estimated 46% increase in the risk of developing dementia compared with nonuse [19]. Both using a single anticholinergic medication and switching anticholinergic medications have been reported to cumulatively increase the risk of incident dementia [17]. Furthermore, use of urologic anticholinergic medications has been associated with increased risk of dementia even when the drug exposure occurs 15–20 years before a dementia diagnosis [15]. Anticholinergic medication use has also been associated with increased brain atrophy, cognitive dysfunction and clinical decline [16]. Because of the increased risk of cognitive decline, the current American Geriatrics Society (AGS) Beers Criteria[®] for Potentially Inappropriate Medication Use in Older Adults recommend minimizing anticholinergic medication burden, and AUA/SUFU guidelines recommend that clinicians should exercise caution before recommending anticholinergic medications for patients with OAB who are frail or using other anticholinergic medications [1,20].

A retrospective claims analysis showed that 88% of patients taking an anticholinergic medication to treat OAB discontinued or switched medications within 12 months and only 31% of patients who had ≥ 2 prescription claims for an anticholinergic medication remained adherent (defined as $> 80\%$ of days covered by index medication) after 12 months [21]. Common patient-reported reasons for discontinuing an OAB medication include lack of efficacy, adverse effects and learning to manage their symptoms without medication [22,23].

The available evidence on the impact of anticholinergic medications on HCRU and associated healthcare costs has not been comprehensively reviewed among patients with OAB. Therefore, a systematic literature review was conducted to identify and summarize the burden associated with anticholinergic medication use in adult patients with OAB in the USA in terms of HCRU and costs to the payer.

Methods

Protocol & registration

The systematic literature review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [24] and reported in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. The protocol was registered in the PROSPERO database (registration no.: CRD42021258363) [26].

Search strategy

The search strategy was developed by an experienced information specialist and was peer reviewed by a second information specialist. Two reviewers (Corinne Duperrouzel [CD] and Coby Martin [CM]) independently reviewed studies for inclusion; data extraction and quality assessments were performed by a single reviewer and validated by a second. Any disagreements that could not be resolved by consensus were resolved by a third reviewer (Ari Mendell [AM] or Megan Bourque [MB]).

Studies published before 28 May 2021 were identified from MEDLINE, Embase and the Cochrane Database of Systematic Reviews using a combination of controlled vocabulary and keywords relating to OAB, anticholinergic medications, HCRU and costs. Published and validated economics and cost filters were applied, including both balanced and sensitive filters (see [Supplementary Table 1](#) for full search strategy). Opinion and animal studies were excluded in the search and no gray literature searches were conducted because it was assumed that clinical trial registries and health technology assessment bodies would be unlikely to report on the outcomes of interest. Conference abstracts older than 2 years before the date of the search were excluded, as it was expected that full-text publications of relevant studies would be available by the time the search was conducted.

Table 1. Summary of screening criteria.

Criteria	Inclusion criteria	Exclusion criteria
Primary considerations		
Population	- Adults (≥ 18 years) with a diagnosis of OAB - Adults without OAB were included as a control arm	- Patients <18 years - Patients without OAB, unless included as a control arm - Animals
Intervention	Anticholinergic medications approved for the treatment of OAB in the USA (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium)	- Other pharmacologic medications, including anticholinergics not approved for the treatment of OAB in the USA - Medical devices - Surgery - Nerve stimulation
Comparator	- A different anticholinergic medication approved for the treatment of OAB in the USA (see Intervention) - Placebo - No treatment	See Intervention
Outcomes	- HCRU (hospitalizations, inpatient stays, outpatient visits, emergency room/department visits, length of hospital and/or ICU stay) - Costs associated with HCRU outcomes from the payor perspective	Studies that do not report ≥ 1 of the outcomes of interest
Study design	- Prospective or retrospective (including database studies and chart reviews) single-arm or comparative observational studies - Economic analyses - RCTs - Conference abstracts published in 2019 or later	- Narrative reviews - Editorials - Letters - Case studies - Opinion pieces - Conference abstracts published before 2019 - Systematic reviews and meta-analyses[†]
Additional considerations		
Language	English	Non-English
Location	USA	Outside the USA
Date limit	- Conference abstracts and posters published in 2019 or later - No date restrictions were placed on full-text articles	Conference abstracts and posters published before 2019

[†]Systematic reviews and meta-analyses were not eligible for inclusion but were captured and used to identify additional studies meeting the eligibility criteria. HCRU: Healthcare resource use; ICU: Intensive care unit; OAB: Overactive bladder; RCT: Randomized controlled trial.

Eligibility criteria

The review focused on observational studies, randomized controlled trials and economic evaluations of healthcare use and costs to payors for adult patients (≥ 18 years) with OAB treated with anticholinergic medications. Eligibility criteria were established using the population, intervention, comparator, outcomes and study design (PICOS) framework (Table 1). Abstracts published >2 years before the date of the search were excluded, along with opinion articles, case studies, reviews and meta-analyses. However, the bibliographies of relevant meta-analyses and systematic literature reviews identified during the screening process were reviewed to identify any additional relevant references. Articles were also excluded if they were not in English or focused on populations exclusively outside the USA. Articles assessing OAB caused by neurogenic detrusor overactivity were included; this prevented the exclusion of articles that did not distinguish between patients with neurogenic and non-neurogenic OAB. No time horizon was specified in the database searches and manuscripts were not omitted based on publication date alone.

Study selection

The study records and corresponding full-text articles were reviewed for inclusion using DistillerSR software.

Data extraction

Studies meeting the inclusion criteria were extracted into a standardized form; the extraction data included publication characteristics, study design characteristics, study participant and baseline characteristics, model methods, HCRU outcomes, cost outcomes and study conclusions. All HCRU and cost outcomes related to the population and comparators of interest were extracted. For HCRU outcomes, mean values were prioritized and median values were extracted if means were not reported.

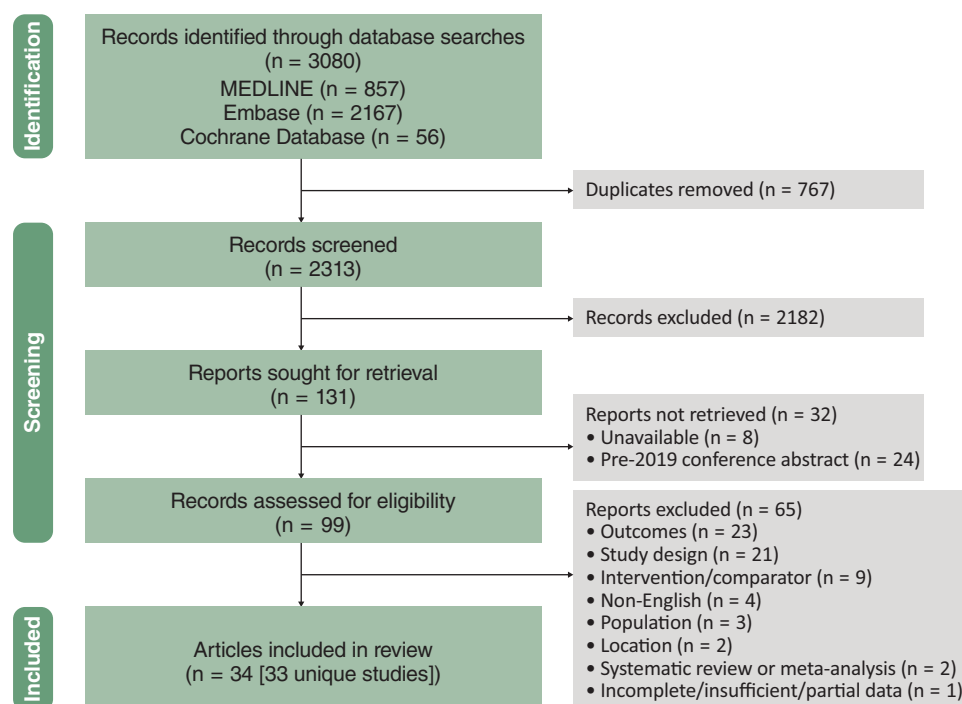


Figure 1. PRISMA flow diagram.

Risk of bias assessment

Bias was assessed using the established Downs and Black checklist for observational studies [27] and the Drummond and Jefferson checklist for economic analyses [28].

Results

Overview of search results

The electronic search returned 3080 citations. A total of 2313 records were screened after removing duplicates and 2182 were excluded because they did not meet the prespecified inclusion criteria. Of the remaining 131 records, 24 were conference citations published before 2019, 8 did not have available full-text articles and 99 were retrieved for full-text review. After assessing full-text articles, 65 were excluded and 34 were included in the review (Figure 1, Table 2).

Characteristics & quality of included studies

The 34 publications included 33 unique studies; 18 were observational studies, 2 reported results from a single prospective trial and 14 were economic evaluations or economic models. The observational studies were of overall fair to poor quality (scoring ≤ 19 on the Downs and Black checklist; Supplementary Table 2) and were predominantly retrospective cohort/database analyses assessing HCRU and collective costs of anticholinergic medications, often focusing on comorbidities including dementia and falls/fractures. Eleven studies did not clearly define the interventions of interest; in general, these studies stated that patients had a prescription for an anticholinergic medication without listing the medications included. Most articles did not describe the characteristics of patients lost to follow-up. Studies generally recruited patients from a single population (i.e., from the same database) over the same period of time and adjusted for confounders; common sources of bias included not accounting for compliance or different lengths of follow-up between comparator arms.

The economic studies included cost-effectiveness analyses, cost-minimization analyses, a budget impact model, a decision analytic model and a cost analysis. The studies generally reported on most applicable items on the Drummond and Jefferson checklist (Supplementary Table 3). All studies answered their posed research question and all but 2 articles provided limitations for their conclusions. Articles varied in whether they justified the variables and ranges in sensitivity analyses; some studies did not clearly define the source of model inputs, currency, price

Table 2. Summary of included studies.

Study (year)	Study design	Cost year	n	Treatments [†]	Patients	Ref.
Economic evaluations						
Arikian <i>et al.</i> (2000)	Cost-effectiveness analysis	NR	1363	Oxybutynin ER, oxybutynin IR, tolterodine	Patients with OAB	[29]
Armstrong <i>et al.</i> (2012)	Cost-effectiveness analysis	2011	NA	Solifenacin, trospium IR, trospium ER, darifenacin, fesoterodine, oxybutynin IR, oxybutynin ER, oxybutynin TD, oxybutynin gel, tolterodine IR, tolterodine ER	Patients with OAB	[30]
Chen <i>et al.</i> (2012)	Cost-effectiveness analysis	2010	100	Tolterodine ER, PTNS	Female patients with OAB	[31] [‡]
Ko <i>et al.</i> (2006)	Cost-effectiveness analysis	2005	NA	Oxybutynin IR, oxybutynin ER, oxybutynin TD, tolterodine IR, tolterodine ER, trospium, solifenacin, darifenacin	Patients with OAB	[32]
Murray <i>et al.</i> (2019)	Cost-effectiveness analysis	2014	NA	Tolterodine ER, solifenacin, BSC	Patients with refractory OAB	[33]
Murray <i>et al.</i> (2021)	Cost-effectiveness analysis	NR	NR	BSC, solifenacin, tolterodine ER	Patients with OAB	[34]
Noe <i>et al.</i> (2002)	Cost-minimization analysis	2000	NA	Tolterodine ER, oxybutynin CR	Patients aged 20–89 years with OAB, currently using behavioral therapy and drug treatment	[35]
Perfetto <i>et al.</i> (2005)	Cost-minimization analysis	NR	59,984	Tolterodine ER, oxybutynin ER	Patients with new diagnosis of OAB or new use of a treatment of interest	[36]
Perk <i>et al.</i> (2016)	Budget impact model	2015	1-M-member plan	Fesoterodine, darifenacin, solifenacin, tolterodine IR, tolterodine ER, oxybutynin, trospium	Hypothetical patients in a commercial plan or Medicare Advantage plan; patients aged 24–64 years with OAB	[37]
Qin <i>et al.</i> (2016)	Decision analytic cost model	2013	7096	Fesoterodine, no OAB treatment	Patients aged ≥65 years with OAB wet; 2–15 UUI episodes per day, at risk of deteriorating health (score of ≥3 on Vulnerable Elders Survey)	[38]
Shepherd <i>et al.</i> (2018)	Cost-effectiveness analysis	2016	NA	Tolterodine, solifenacin	Patients with OAB	[39]
St Martin <i>et al.</i> (2020)	Cost-effectiveness analysis	NR	NA	Oxybutynin	Medicare-eligible women with OAB refractory to conservative management	[40]
Wielage <i>et al.</i> (2016)	Cost-effectiveness analysis	2015	NR	Solifenacin, tolterodine ER, fesoterodine, trospium, tolterodine IR, oxybutynin	Commercial plan: 2% of patients aged ≥65 years; Medicare plan: ≥83.2% of patients aged ≥65 years	[41]
Yehoshua <i>et al.</i> (2018)	Cost analysis	NR	NA	Darifenacin, fesoterodine, oxybutynin IR, oxybutynin ER, oxybutynin gel, solifenacin, tolterodine IR, tolterodine LA, trospium IR, trospium ER, SNS, PTNS	Patients with OAB	[42]
Observational studies						
Balkrishnan <i>et al.</i> (2006)	Longitudinal cohort	NR	275	ACHs	Patients with OAB aged ≥65 years; enrolled in an HMO; treated with ACHs	[43]
Campbell <i>et al.</i> (2021)	Retrospective cohort	2017	226,712	Concurrent use of ≥2 unique ACHs for ≥30 days	Older adults with OAB with Medicare coverage from 2006–2017	[44]
Hall <i>et al.</i> (2001)	Retrospective database analysis	NR	8661	Oxybutynin, flavoxate, tolterodine IR, hyoscyamine sulfate, propantheline	Patients aged 18–64 years with OAB diagnosis or ACH claim	[45]

[†]All treatments analyzed in the study are listed in the table; however, only outcomes relating to anticholinergic medications were extracted. Individual anticholinergic medications are listed for studies that provided this information. In studies that assessed anticholinergic medications collectively, the treatment is described as “ACHs”.

[‡]Chen *et al.* reported a model input based on a personal communication for number of physician visits and reported total cost from a societal perspective, which did not meet the PICOS criteria. Because the study did not meet PICOS criteria and only included model inputs, Chen *et al.* is included with identified studies, but results are not cited nor discussed in the main text.

[§]Ju *et al.* report conflicting numbers for the total number of outpatient office visits made by women in 2009 between the abstract and full text. The abstract indicates that 516.8 million adult women made outpatient office visits, whereas the full text notes that this is the number of women who had a visit not associated with active use of an anticholinergic medication for OAB. The number from the abstract is provided herein as this value was used for the calculation of the proportion of total outpatients visits where a patient reported active use of an anticholinergic medication.

ACH: Anticholinergic medication; BSC: Best supportive care; CR: Controlled release; ER: Extended release; HMO: Health Maintenance Organization; IR: Immediate release; LA: Long acting; M: Million; NA: Not applicable; NR: Not reported; OAB: Overactive bladder; PICOS: Population, Intervention, Comparator, Outcomes and Study design; PTNS: Percutaneous tibial nerve stimulation; SNS: Sacral nerve stimulation; TD: Transdermal; UI: Urinary incontinence; UUI: Urge urinary incontinence.

Table 2. Summary of included studies (cont.).

Observational studies						
Ivanova <i>et al.</i> (2014)	Database analysis	2012	10,318	ACHs	Patients aged 18–64 years with OAB and ACH claim; enrolled in non-HMO plan	[46]
Ju <i>et al.</i> (2014)	Cross-sectional	NA	516.8 M [§] visits; 8.1 M ACH visits	ACHs	Women aged ≥18 years who had an ambulatory visit in 2009	[47]
Jumadilova <i>et al.</i> (2006)	Retrospective cohort	2003	26,386	Tolterodine ER, oxybutynin ER, oxybutynin IR	Patients with OAB and ACH claim	[48]
Kachru <i>et al.</i> (2021)	Retrospective cohort	NA	18,075	Nonselective or selective ACHs	Older Medicare patients with OAB and dementia; treated with ACHs after dementia diagnosis	[49]
Lozano-Ortega <i>et al.</i> (2021)	Retrospective cohort	2019	154,432 with OAB; 9939 with falls/fractures	ACHs	Patients aged ≥18 years with OAB-related claim	[50]
Nitz <i>et al.</i> (2005)	Retrospective database analysis	NR	14,582	Oxybutynin IR, oxybutynin ER, tolterodine ER	Patients aged ≥18 years with OAB with OAB-related claim; commercial or Medicare insurance with prescription drug benefit	[51]
Pelletier <i>et al.</i> (2009)	Retrospective cohort	2007	86,734	ACHs, nonpharmacologic management	Patients aged ≥18 years with OAB diagnosis or ACH claim; enrolled in a health plan	[52]
Rogula <i>et al.</i> (2019)	Retrospective cohort	2017	154,432	ACHs	Patients with OAB	[53]
Suehs <i>et al.</i> (2016)	Retrospective cohort	2013	46,140	ACHs	Patients aged 65–89 years with ACH prescription; enrolled in Medicare Advantage prescription drug plan	[54]
Suehs <i>et al.</i> (2017)	Retrospective database analysis	NR	10,220	ACHs	Patients aged 65–89 years with OAB taking ACHs; Medicare Advantage prescription drug plan	[55]
Tang <i>et al.</i> (2014a)	Retrospective cross-sectional	NA	1730 overall; 411 from the USA	ACHs	Outpatients aged >18 years with OAB treated with ACHs	[56]
Tang <i>et al.</i> (2014b)	Retrospective database analysis	NA	313 overall; 89 from the USA	ACHs	Outpatients aged >18 years with OAB and underlying neurologic conditions treated with ACHs	[57]
Varadharajan <i>et al.</i> (2005)	Retrospective cohort	2004	26,386	Tolterodine ER, oxybutynin ER, oxybutynin IR	Patients with OAB and ACH claim	[58]
Walker <i>et al.</i> (2021)	Database analysis	NR	1548	ACHs	Patients aged ≥65 years with ACH dispensation	[59]
Yehoshua <i>et al.</i> (2016)	Retrospective claims analysis, real-world observational	2013	2480	ACHs	Patients covered by HealthCare Partners; patients with OAB and UI and ACH claim; patients without OAB or an ACH claim	[60]
Zinner <i>et al.</i> (2008)	Prospective open-label trial	NA	440	Solifenacin 5 or 10 mg	Ambulatory patients aged ≥18 years with OAB; treated with tolterodine 4 mg/d for ≥4 weeks immediately preceding study entry without sufficient improvement in urgency episodes	[61]
Zinner <i>et al.</i> (2009)	Prospective open-label trial	NA	440	Tolterodine ER 4 mg/d followed by solifenacin 5/10 mg/d	Patients with OAB aged ≥18 years; treated with tolterodine 4 mg/d for ≥4 weeks immediately preceding study entry without sufficient improvement in urgency episodes	[62]

[†] All treatments analyzed in the study are listed in the table; however, only outcomes relating to anticholinergic medications were extracted. Individual anticholinergic medications are listed for studies that provided this information. In studies that assessed anticholinergic medications collectively, the treatment is described as “ACHs”.

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date or inflation adjustments. Many of the economic evaluations compared the costs of anticholinergic medications over a period of 3 months to 10 years.

Baseline patient characteristics

Patients were predominantly white (range: 52.4–88.9%) and female (range: 17.8–100%) with differing mean ages (range: 44–74.2 years). Reported geographic locations were predominantly in the midwestern and southern USA. Most studies did not report baseline comorbidities; among the studies that did, the most frequently reported baseline comorbidities were falls/fractures and urinary tract infections (UTIs).

Overview of findings

The included studies primarily reported on HCRU and cost outcomes associated with the use of anticholinergic medications in patients with OAB. HCRU outcomes generally fell into 4 groups: inpatient hospitalizations, outpatient visits, physician visits and emergency department visits. Cost outcomes generally fell into 6 groups: total healthcare costs, inpatient hospitalization costs, outpatient visit costs, physician visit costs, emergency department costs and cost of individual OAB-related conditions (UTI, depression, falls/fractures and skin irritation/infection). The remainder of the review is structured according to these categories.

HCRU

Inpatient hospitalizations

Overall, 11 of the 34 articles reported data on inpatient hospitalizations (Table 3 & Supplementary Table 4). Across all studies, the proportion of patients requiring hospitalization ranged from 0 to 5% for OAB-related hospitalizations [46,56,57] and 9.9 to 49.0% for all-cause hospitalizations [43,46,49,60].

Three studies included a comparator arm with patients who were not treated with anticholinergic medications; however, comparators differed between studies [45,59,60]. A claims analysis by Yehoshua *et al.* reported that patients who experienced OAB with incontinence (i.e., OAB wet) and received anticholinergic medications experienced significantly more yearly all-cause hospitalizations (0.301) compared with patients without OAB (0.235; $p = 0.001$) [60]. A claims analysis by Hall *et al.* reported no differences in monthly hospitalizations in patients receiving tolterodine or oxybutynin versus patients with OAB who did not receive pharmacotherapy [45]. In a 2021 claims analysis by Walker *et al.*, no significant difference in inpatient visits was shown among frail patients with OAB receiving anticholinergic medications or a β_3 -receptor agonist (both groups had a median of 0 monthly inpatient visits) [59].

The remaining 8 studies did not include nonanticholinergic comparators but instead assessed anticholinergic medication burden [50], medication persistence [46] and anticholinergic medication [48,49,58] or patient [43,56,57] characteristics. Anticholinergic burden was assessed by one study, a claims analysis by Lozano-Ortega *et al.* [50], which estimated the impact of falls/fractures on HCRU and costs according to levels of anticholinergic burden among individuals with OAB. HCRU and costs were compared before and after a fracture and the anticholinergic burden measure [64] was used to calculate anticholinergic burden as a unitless score, accounting for dose and potency. It showed that medium to high anticholinergic burden (score ≥ 90 on the cumulative anticholinergic burden measure) was associated with a greater mean number of hospitalizations per 100 person-years than no to low anticholinergic burden (score < 90) [50]. Persistence with anticholinergic medications was also assessed by one study, a claims analysis by Ivanova *et al.*, which found that patients with OAB who switched from one anticholinergic medication to another had significantly higher rates of hospitalization in the following 6 months than those who persisted with or discontinued an anticholinergic medication [46].

Three studies assessed hospitalizations according to anticholinergic medication characteristics. A claims analysis by Kachru *et al.* found that patients using nonselective anticholinergic medications, which have an affinity for muscarinic receptors M1–M5 (oxybutynin, fesoterodine, tolterodine, trospium), experienced a higher all-cause hospitalization rate over the 6 months after initiation than patients using selective anticholinergic medications, which have a high affinity for the M3 muscarinic receptors that are responsible for bladder contraction (solifenacin, darifenacin; 24.14 vs 21.58%, respectively; $p = 0.0007$) [49]. Jumadilova *et al.* assessed inpatient hospitalizations, categorized as those related to UTI or depression or unrelated to OAB, among patients with OAB taking tolterodine extended release (ER), oxybutynin ER or oxybutynin immediate release (IR) [48]. It was found that patients taking tolterodine ER experienced fewer yearly UTI-related hospitalizations than patients taking oxybutynin ER or IR, fewer yearly depression-related hospitalizations versus oxybutynin ER but not versus oxybutynin IR and fewer

Table 3. Summary of studies reporting healthcare resource utilization.

Study (year)	Outcome [†]			Ref.
	Inpatient hospitalization	Outpatient visits	Physician visits	
Balkrishnan et al. (2006)	Patients with hospitalization (%): ≥ 1 , 23%; ≥ 2 , ≥ 1 , 1.48; ≥ 2 , ≥ 3 , 1.12 24%; ≥ 3 : 28%		NR	[43] Mean ED visits (n): ≥ 1 , 1.61; ≥ 2 , 1.26; ≥ 3 , 1.61
Chen et al. (2012)	NR	NR	Model input: mean 5 visits per 3 months	[31] NR
Hall et al. (2001)	0.2 hospitalizations per patient per month	Tolterodine/oxybutynin/no OAB drug: 0.23/0.21/0.18 visits per patient per month	Tolterodine/oxybutynin/no OAB drug: 1.51/1.26/1.17 visits per patient per month	[45] 0.03 visits per patient per month
Ivanova et al. (2014)	Persisters/switchers/discontinuers with hospitalization (%): All cause, 9.9%/14.9%/14.9%; OAB related, 0.4%/1.0%/0.5%	Persisters/switchers/discontinuers with visit (%): All cause, 95.1%/96.6%/93.4%; OAB related, 29.4%/43.0%/22.2%	NR	[46] Persisters/switchers/discontinuers with ED visit (%): All cause, 15.9%/16.4%/17.6%; OAB related, 0.2%/0.4%/0.3%
Ju et al. (2014)	NR	1.6% of all patients had an outpatient visit; annual rate of outpatient visits, 6.8%	NR	[47] NR
Jumadilova et al. (2006)	Hospitalizations, n (range): UTI related, 0.01–0.03; depression related, 0.01–0.02; OAB unrelated, 0.19–0.25	Management visits, n (range): UTI related, 0.16–0.26; depression related, 0.55–0.68; OAB unrelated, 12.25–12.86	NR	[48] ED visits, n (range): UTI related, 0.04–0.09; depression related, 0.01–0.03; OAB unrelated, 0.91–1.36
Kachru et al. (2021)	Hospitalization within 6 months of ACH medication use (%): Nonselective, 24.1%; selective, 21.6%	NR	NR	[49] NR
Lozano-Ortega et al. (2021)	Hospitalizations per 100 person-year, n (no-low/medium-high ACB [‡]): Pre-fall/fracture, 17.1%/31.6%; post-fall/fracture, 22.5%/39.8%	Visits, n (no-low/medium-high ACB [‡]) Total outpatient: Pre-fall/fracture, 22.6/28.5; post-fall/fracture, 27.6/33.6 Other outpatient service: Pre-fall/fracture, 8.1/10; post-fall/fracture, 10.6/12.8	Visits, n (no-low/medium-high ACB [‡]) General practitioner: Pre-fall/fracture, 3.6/5; post-fall/fracture, 4.2/5.7 Specialist: Pre-fall/fracture, 11/13.5; post-fall/fracture, 12.7/15.2	[50] Visits, n (no-low/medium-high ACB [‡]) ED visits: Pre-fall/fracture, 7.9/15.4; post-fall/fracture, 12.6/22 ICU visits: Pre-fall/fracture, 2.6/5.2; post-fall/fracture, 3.8/7.1
Perk et al. (2016)	NR	Mean 1.135 outpatient visits per increase in ACB score	NR	[37] 0.114 additional visits/year per increase in ACB score
Tang et al. (2014a)	Patients with OAB-related hospitalizations (%): Continent, 0%; incontinent, 1.4%	NR	OAB-related visits in past 3 months (n): Continent, 1.3; incontinent, 1.2	[56] NR
Tang et al. (2014b)	Patients with OAB-related hospitalizations (%): Continent, 5%; incontinent, 4.6%	NR	OAB-related visits in past 3 months (n): Continent, 1.3; incontinent, 1.5	[57] NR
Varadharajan et al. (2005)	Hospitalizations (n): OAB related, 0.01; all other, 0.21–0.29	Management visits (n): OAB related, 0.46–0.53; all other, 12.99–13.8	NR	[58] ED visits (n): OAB related, 0.01–0.02; all other, 0.96–1.47
Walker et al. (2021)	Median 0 hospitalizations/month in each treatment group	NR	NR	[59] NR
Yehoshua et al. (2016)	Patients with hospitalization (%): OAB, 49.0%; no OAB, 37.6%	Patients with visit (%): OAB, 100%; no OAB, 98.7%	NR	[60] ED visits (n): OAB, 1.92; no OAB: 1.41
Zinner et al. (2008)	NR	NR	Nonprotocol-related visits/12 weeks (n): Prewashout, 1.24; end of study, 0.24	[61] NR
Zinner et al. (2009)	NR	NR	Nonprotocol-related visits/12 weeks (n): Prewashout/end of study, for aged <65 years, 1.32/0.20; for aged 65–74 years, 1.20/0.25; for aged ≥ 75 years, 1.07/0.34	[62] NR

[†]Reported as per patient per year unless otherwise noted.

[‡]ACB is a unitless, cumulative score that considers daily dose of anticholinergic medications, the Anticholinergic Burden Scale and the duration of anticholinergic exposure. No ACB is defined as 0, low is 0–89, medium is 90–499 and high is ≥ 500 [63].

ACB: Anticholinergic burden; ACH: Anticholinergic medication; ED: Emergency department; ICU: Intensive care unit; NR: Not reported; OAB: Overactive bladder; UTI: Urinary tract infection.

yearly OAB-unrelated hospitalizations versus oxybutynin IR but not versus oxybutynin ER [48]. In contrast, a 2005 claims analysis by Varadharajan *et al.* found no significant differences in total OAB-related inpatient hospitalizations among patients taking tolterodine ER versus oxybutynin ER or IR [58].

Three studies assessed hospitalizations in patients with OAB taking anticholinergic medications according to patient characteristics. A claims analysis by Balkrishnan *et al.* found that patients who were enrolled in a Health Maintenance Organization (HMO) health plan for 1 to 3 years and continuously on anticholinergic medications experienced a numeric increase in the rate of hospitalizations over time, with 23, 24 and 28% of patients in years 1, 2 and 3, respectively, having experienced a hospitalization in the previous year [43]. Two analyses by Tang *et al.* compared hospitalizations between patients with OAB [56] or neurogenic detrusor overactivity [57] with or without incontinence; no significant difference was found in the 12-month rate of OAB-related hospitalizations between patients in the USA with OAB or neurogenic detrusor overactivity, with or without urinary incontinence.

Outpatient visits

Nine studies reported data on outpatient visits, with variation between studies on the type of outpatient visits (i.e., physician visits and emergency department visits). Across all studies, the percentage of patients with ≥ 1 OAB-related outpatient visit ranged from 20.3 to 100%; however, observation periods varied from 1 month to 1 year. An analysis by Ju *et al.* used the National Ambulatory Medical Care Survey database to estimate the prevalence of outpatient visits associated with an anticholinergic medication to treat OAB among adult female patients in the USA and found that women actively taking anticholinergic medications for OAB had 8.1 million outpatient visits in 2009, accounting for 1.6% of all outpatient visits in the USA [47].

Two studies included a comparator arm with patients who were not treated with anticholinergic medications; however, comparators differed between studies. Yehoshua *et al.* reported that patients with OAB wet and receiving an anticholinergic medication had more yearly outpatient visits per patient than those without OAB (16.96 vs 11.25, respectively) [60]. Similarly, Hall *et al.* reported 0.21 to 0.23 monthly outpatient hospitalizations in patients with OAB taking an anticholinergic medication compared with 0.18 monthly outpatient hospitalizations in patients not receiving any drug treatment for OAB; however, no statistical comparisons were made [45].

The remaining studies did not include nonanticholinergic comparators. They instead stratified by medication persistence [46], anticholinergic medication burden [37,50] and reason for outpatient visit [48,58].

Ivanova *et al.* was the only study to assess the effect of anticholinergic medication persistence on outpatient visits. Patients with OAB who switched from 1 anticholinergic medication to another had a greater mean number of all-cause and OAB-related outpatient visits in the 6 months following switching than patients who persisted with an anticholinergic medication and had more outpatient visits than patients who discontinued an anticholinergic medication [46].

Two studies assessed the effect of anticholinergic burden on outpatient visits. Lozano-Ortega *et al.* found that medium to high anticholinergic burden was associated with a greater mean number of outpatient visits per 100 person-years than no to low anticholinergic burden [50]. In the course of developing a budget impact model, Perk *et al.* [37] performed a retrospective medical record analysis to assess the relationship between the 6-point anticholinergic cognitive burden (ACB) scale score [65] and outpatient visits in adults ≥ 65 years. Consistent with results from Lozano-Ortega *et al.*, Perk *et al.* estimated a mean increase of 1.14 annual outpatient visits per unit increase in ACB score.

Two studies reported annual outpatient visits by reason for visit among patients with OAB and an anticholinergic medication claim. Jumadilova *et al.* found that, depending on the specific anticholinergic agent used, patients had 0.16 to 0.26 outpatient management visits related to UTIs, 0.55 to 0.59 outpatient management visits related to depression and 12.25 to 12.86 outpatient management visits related to non-OAB causes per year [48]. Varadharajan *et al.* found that patients with OAB and an anticholinergic medication claim had 0.46 to 0.53 outpatient management visits related to OAB and 12.99 to 13.8 outpatient management visits related to other causes per year [58].

Physician visits

Six studies reported data on physician visits; however, only 1 study included a comparator arm with patients who were not treated with an anticholinergic medication. Hall *et al.* found that patients with OAB and taking anticholinergic medications experienced a numerically greater mean number of physician visits per month than patients with OAB who were not receiving pharmacologic treatment (1.26–1.51 with treatment vs 1.17 without treatment) [45]. A

single study assessed the relationship between physician visits and anticholinergic burden; Lozano-Ortega *et al.* found that patients with OAB with medium to high anticholinergic burden had a greater mean number of general practitioner visits than patients with no to low anticholinergic burden [50]. Two studies by Tang *et al.* assessed the relationship between continence and physician visits, finding similar numbers of physician visits related to OAB or neurogenic detrusor overactivity in patients with versus without urinary incontinence taking anticholinergic medications [56,57]. Two studies by Zinner *et al.* assessed the relationship between anticholinergic medication and physician visits, finding that patients in the VESicare Efficacy and Research Study US (VERSUS) trial had fewer nonprotocol-related office visits after switching from tolterodine to solifenacin [61,62].

Emergency department visits

Eight studies reported data on emergency department visits. Across all studies reporting emergency department visits, 15.9 to 46.9% of anticholinergic-treated patients with OAB required ≥ 1 emergency department visit per year, with a yearly average of 0.96 to 1.92 emergency department visits per patient. Two studies included a comparator arm with patients with OAB not treated with anticholinergic medications [45,60]; the remainder stratified by anticholinergic burden [37,50], medication persistence [46] and medication [48,58] or patient characteristics [43].

Two studies included a comparator arm of patients not treated with anticholinergic medications, but comparators differed between studies. Yehoshua *et al.* found that patients with OAB wet taking anticholinergic medications had more annual emergency department visits than those without OAB (1.92 vs 1.41, respectively) [60]. In contrast, Hall *et al.* found no difference in annual emergency department visits among patients taking tolterodine IR, taking oxybutynin or receiving no pharmacologic treatment (0.03 unadjusted emergency department encounters per patient per month in all groups) [45].

Ivanova *et al.* was the only study to assess the effect of anticholinergic medication persistence on emergency department visits and reported no differences in OAB-related emergency department visits in the 6 months after switching anticholinergic medications [46].

Two studies assessed the relationship between anticholinergic burden and emergency department visits. Lozano-Ortega *et al.* reported that patients with OAB and medium to high anticholinergic burden had increased mean emergency department visits compared with those with no to low anticholinergic burden [50]. Similarly, the previously described analysis reported by Perk *et al.* found that the number of annual emergency department visits increased by 0.114 per unit increase in anticholinergic burden score [37].

The relationship between specific anticholinergic medications and emergency department visits was evaluated in two studies. Jumadilova *et al.* found that patients receiving tolterodine ER experienced a decrease in frequency of UTI-related emergency department visits and no changes in frequency of depression-related or other OAB-unrelated emergency department visits versus oxybutynin ER or IR [48]. However, Varadharajan *et al.* found no significant differences between anticholinergic types in OAB-related and non-OAB-related emergency department visits [58].

Balkrishnan *et al.* assessed the relationship between emergency department visits and patient characteristics. Patients who were enrolled in an HMO health plan for 1 to 3 years and continuously on anticholinergic medications experienced a numeric increase in the rate of emergency department visits over time, with 26, 29 and 30% of patients in years 1, 2 and 3, respectively, having experienced an emergency department visit in the previous year [43].

Healthcare costs

Total healthcare costs

Total cost estimates were reported in 26 of the 34 studies; metrics included total healthcare (23 studies), total medical (10 studies), total pharmacy (13 studies) and OAB-related condition (2 studies) costs (Table 4 & Supplementary Table 5). Some articles compared patients with and without pharmacologically managed OAB [37,45,52,60], whereas others stratified by adherence [35,36,46], anticholinergic burden or potentially inappropriate anticholinergic prescribing [44,50,53,54,64] or type of OAB medication [29,33,34,37,39–42,51,59].

An analysis conducted by Yehoshua *et al.* found that patients with OAB wet treated with anticholinergic medications had higher annual healthcare costs (\$7562) than those without OAB (\$5293) [60]. In a study by Hall *et al.*, patients with OAB who were treated with tolterodine IR or oxybutynin had higher monthly total healthcare costs (\$585–\$593) than patients with OAB who received no OAB drug treatment (\$420) [45]. A study by Pelletier *et al.* also compared total healthcare costs between patients with OAB receiving anticholinergic medications and patients who received no OAB drug treatment, reporting costs of \$9917 and \$9657, respectively [52].

Table 4. Healthcare cost outcomes.

Study (year)	Outcome [†]					Ref.
	Total healthcare costs	Hospitalization costs	Outpatient visit costs	Physician visit costs	ED and ICU costs	
Arikian <i>et al.</i> (2000)	6-month per patient total healthcare costs, \$1,530; net cost to HMO per patient per month, \$0.29–\$0.32	NR	NR	NR	NR	[29]
Armstrong <i>et al.</i> (2012)	Mean healthcare cost lowest for oxybutynin IR, \$754; range: \$952–\$1243 for other medications	NR	NR	NR	NR	[30]
Balkrishnan <i>et al.</i> (2006)	Total: ≥ 1 , \$5692; ≥ 2 , \$6099; ≥ 3 , \$5447; Lower during year 1 and 3 among patients with high vs low adherence	NR	NR	NR	NR	[43]
Campbell <i>et al.</i> (2021)	Total medical: 0 years, \$8645; ≥ 1 year, \$9762	NR	NR	NR	NR	[44]
Hall <i>et al.</i> (2001)	Increased medical/pharmacy costs per patient per month for all patients and those receiving OAB drugs vs untreated; at follow-up: medical, \$361–\$430; pharmacy, \$60–\$155	NR	NR	NR	NR	[45]
Ivanova <i>et al.</i> (2014)	Increased all-cause and OAB-related medical and pharmacy for all treatment groups; lowest OAB-related medical for persisters and highest for switchers	Higher for switchers (all-cause, \$2505; OAB related, \$68) vs persisters (\$1462; \$22) or discontinuers (\$1744; \$22)	Higher for switchers (all cause: \$4063; OAB related: \$394) vs persisters (\$2972; \$116) or discontinuers (\$2977; \$139)	NR	OAB related, \$1–\$5; lower all-cause for persisters (\$185) and highest for switchers (\$229) vs discontinuers (\$231)	[46]
Ko <i>et al.</i> (2006)	Range per patient per 3 months: \$3373–\$3769	NR	NR	NR	NR	[32]
Lozano-Ortega <i>et al.</i> (2021)	Higher mean all-cause in patients with higher vs lower ACB [‡] (\$24,428–\$18,930 vs \$15,439–\$19,463)	Higher in patients with higher vs lower ACB [‡] (\$6684–\$7943 vs \$3931–\$5343)	Higher in patients with higher vs lower ACB [‡] (\$11,526–\$14,758 vs \$8638–\$11,079)	NR	NR	[50]
Murray <i>et al.</i> (2019)	Lower per 10 years for tolterodine ER (\$12,776) vs solifenacin 5 and 10 mg (\$13,342 and \$13,335)	NR	NR	NR	NR	[33]
Murray <i>et al.</i> (2021)	Lower per 10 years for tolterodine (\$13,193) vs solifenacin 5 and 10 mg (\$14,822 and \$14,830)	NR	NR	NR	NR	[34]
Nitz <i>et al.</i> (2005)	Increased total medical for all patients; lower for tolterodine ER (\$5074); highest for oxybutynin ER (\$14,766)	NR	NR	NR	NR	[51]
Noe <i>et al.</i> (2002)	Mean total 3-month treatment cost per patient (tolterodine/oxybutynin): \$1207/\$1283	NR	NR	No difference in cost per visit (\$40 PCP follow-up; \$144 specialist follow-up)	NR	[35]
Pelletier <i>et al.</i> (2009)	Total: \$9917 (healthcare), \$2796 (pharmacy) for ACH medications; \$9657 (healthcare), \$2150 (pharmacy) for no pharmacotherapy	Lower for ACH medications (all cause: \$2164; OAB related, \$47) vs no pharmacotherapy (\$2325; \$93)	Lower total ACH medications (OAB unrelated, \$4734; OAB related, \$176) vs no pharmacotherapy (\$4812; \$277)	Lower for ACH medications (all cause: \$803; OAB related, \$42) vs no pharmacotherapy (\$892; \$70)	OAB related: \$1 for ACH medications vs \$9 for no pharmacotherapy; all cause: \$240 vs \$235	[52]
Perfetto <i>et al.</i> (2005)	Similar medical costs regardless of time on therapy, increased pharmacy costs with length of therapy	NR	NR	NR	NR	[36]
Perk <i>et al.</i> (2016)	Lowest total pharmacy for oxybutynin (\$638), highest for darifenacin (\$3405)	NR	\$551 (commercial); \$595 (Medicare Advantage)	\$354–\$536 (commercial); \$232–\$350 (Medicare Advantage)	\$166 (commercial); \$217 (Medicare Advantage)	[37]

[†] Reported as per patient per year unless otherwise noted.

[‡] ACB is a unitless, cumulative score that considers daily dose of anticholinergic medications, the Anticholinergic Burden Scale and the duration of anticholinergic exposure. No ACB is defined as 0, low is 0–89, medium is 90–499 and high is ≥ 500 [63].

ACB: Anticholinergic burden; ACH: Anticholinergic medication; ED: Emergency department; ER: Extended release; HMO: Health Maintenance Organization; ICU: Intensive care unit; IR: Immediate release; NR: Not reported; OAB: Overactive bladder; PCP: Primary care physician; PIM: Potentially inappropriate medication.

Table 4. Healthcare cost outcomes (cont.).

Study (year)	Outcome [†]					Ref.
	Total healthcare costs	Hospitalization costs	Outpatient visit costs	Physician visit costs	ED and ICU costs	
Qin <i>et al.</i> (2016)	Costs per cohort for fesoterodine vs no treatment: \$92,889,606 vs \$100,162,050 (total medical); \$7,832,919 vs \$0 (total pharmacy)	Lower for fesoterodine (\$41,407,439 per cohort/year) vs no treatment (\$44,111,891)	Lower for fesoterodine (\$15,242,498 per cohort/year) vs no treatment (\$17,019,337)	Lower for fesoterodine (\$36,239,668 per cohort/year) vs no treatment (\$39,030,822)	NR	[38]
Rogula <i>et al.</i> (2019)	Lowest for patients with no ACB or fall/fracture, highest with ACB and fall/fracture	NR	NR	NR	NR	[53]
Shepherd <i>et al.</i> (2018)	Lower cost per 2 years including/excluding refractory untreated OAB for tolterodine (\$6122/\$1457) vs solifenacin (\$9166/\$5108)	NR	NR	NR	NR	[39]
St Martin <i>et al.</i> (2020)	Total 10-year healthcare cost per patient: \$28,497	NR	NR	Input cost per appointment: \$112	NR	[40]
Suehs <i>et al.</i> (2016)	OAB related (no PIM vs PIM): \$83 vs \$104 (medical), \$478 vs \$560 (pharmacy); all-cause: \$6515 vs \$13,380 (medical), \$2415 vs \$3888 (pharmacy)	NR	NR	NR	NR	[54]
Suehs <i>et al.</i> (2017)	Total medical (2015 vs 2012 Beers Criteria [®]): \$13,555 vs \$11,484; pharmacy: \$3142 vs \$3532	NR	NR	NR	NR	[55]
Varadharajan <i>et al.</i> (2005)	Total: \$188–\$279 for OAB-related medical, \$5575–\$8045 for all other medical, \$2204–\$2791 for total pharmacy	\$78–\$160 for OAB related, \$2328–\$3720 for all other	Total outpatient management: \$32–\$40 for OAB related, \$782–\$923 for all other; total outpatient/ancillary: \$72–\$109 for OAB related, \$2197–\$3076 for all other	NR	OAB related, \$1; all other, \$98–\$137	[58]
Walker <i>et al.</i> (2021)	Median total cost per patient per month: \$1197 (healthcare), \$255 (pharmacy)	Median cost per patient per month: \$0	Median cost per patient per month: \$498	NR	NR	[59]
Wielage <i>et al.</i> (2016)	Similar total 3-year medical costs across treatment groups (commercial, \$2416–\$2431; Medicare: \$2573–\$2612); varied pharmacy costs (commercial: \$1392–\$4077; Medicare: \$1239–\$3847)	NR	Input cost per patient per 3 years: \$214.83	Input cost per patient per 3 years: \$112.38	Input cost per patient per 3 years: \$800.05	[41]
Yehoshua <i>et al.</i> (2016)	Higher for patients with OAB wet receiving ACH medications (healthcare, \$7562; pharmacy, \$1697) vs without OAB (healthcare, \$5293; pharmacy, \$1046)	Higher for patients with OAB wet receiving ACH medications (\$2239) vs without OAB (\$1719)	Higher for patients with OAB wet receiving ACH medications (\$2326) vs those without OAB receiving no treatment (\$1609)	NR	Higher for patients with OAB wet receiving ACH medications (\$330) vs without OAB (\$193)	[60]
Yehoshua <i>et al.</i> (2018)	Increased total healthcare cost with duration of therapy; higher with tolterodine (\$3472) vs oxybutynin (\$500)	NR	NR	NR	NR	[42]

[†] Reported as per patient per year unless otherwise noted.

[‡] ACB is a unitless, cumulative score that considers daily dose of anticholinergic medications, the Anticholinergic Burden Scale and the duration of anticholinergic exposure. No ACB is defined as 0, low is 0–89, medium is 90–499 and high is ≥ 500 [63].

ACB: Anticholinergic burden; ACH: Anticholinergic medication; ED: Emergency department; ER: Extended release; HMO: Health Maintenance Organization; ICU: Intensive care unit; IR: Immediate release; NR: Not reported; OAB: Overactive bladder; PCP: Primary care physician; PIM: Potentially inappropriate medication.

Several studies showed that low adherence or persistence led to higher costs among patients taking anticholinergic medications. Ivanova *et al.* found that patients who switched anticholinergic medications had higher total adjusted all-cause and OAB-related healthcare costs 6 months after index (all cause: \$8806; OAB related: \$797) than patients who persisted with the original anticholinergic medication (all cause: \$7017; OAB related: \$642) [46]. A pharmacoeconomic model by Noe *et al.* also predicted that patients who continued with either tolterodine ER or oxybutynin ER monotherapy would have lower total healthcare costs (\$963 and \$1040, respectively) than those

who discontinued (\$1545 and \$1539), switched (\$1482 or \$1491) or added a new anticholinergic medication (\$1668 or \$1649) [35].

A cost-minimization analysis by Perfetto *et al.* showed that annual costs for patients taking tolterodine ER or oxybutynin ER increased with greater persistence (\$8714–\$8766 for patients who discontinued in the first month vs \$9136–\$9761 for patients who remained on therapy for a year) [36]. The increase in costs was driven by higher pharmacy costs among patients who persisted versus those who discontinued therapy in the first month (\$1192–\$1217 vs \$99–\$101, respectively). However, medical costs were lower over time among patients who persisted than among those who discontinued (\$7944–\$8544 vs \$8615–\$8665, respectively) [36].

Potentially inappropriate medication (PIM) use of anticholinergics (according to AGS Beers Criteria) and increased anticholinergic medication burden were associated with increased costs. A study by Lozano-Ortega *et al.* examined the impact of falls/fractures on HCRU and costs according to the level of cumulative anticholinergic burden. Compared with patients who had medium to high anticholinergic burden, patients with no to low anticholinergic medication burden had lower total annual healthcare costs (before fall/fracture, \$15,439 vs \$24,428; after fall/fracture, \$19,463 vs \$28,930) and pharmacy costs (before fall/fracture, \$2870 vs \$6217; after fall/fracture, \$3041 vs \$6229) [50]. Two studies by Suehs *et al.* showed that PIM use of anticholinergic medications increased costs among patients with OAB [54,55]. Patients with PIM use of anticholinergic medications according to the 2012 Beers Criteria had total adjusted all-cause healthcare costs of \$12,001 per patient per year compared with \$9373 for those with non-PIM use [54]. In a follow-up study comparing the 2012 and 2015 Beers Criteria, the 2015 Criteria identified increased PIM use of anticholinergic medications; however, this was found in a younger population with a lower comorbidity burden, resulting in lower total healthcare costs versus the 2012 Criteria (all-cause total healthcare costs: \$16,698 based on 2012 Beers Criteria vs \$15,016 based on 2015 Beers Criteria; prevalence of PIM use: 20.6 vs 25.0%, respectively) [55].

Pharmacy costs accounted for most OAB-related costs, whereas medical costs – including outpatient and physician visits, hospitalizations and emergency department or intensive care visits – usually accounted for most total healthcare costs [36,38,54,58]. One exception was from a cost-effectiveness model of mirabegron by Wielage *et al.*, which reported that costs were differentially driven by pharmacy costs or medical costs depending on the type of anticholinergic medication and/or the health plan (commercial or Medicare Advantage) [41].

A budget impact model by Perk *et al.* reported comorbidity costs for patients receiving anticholinergic medications [37]. The model predicted that comorbidity costs (per patient per year) would be higher for patients who did not receive treatment (commercial: \$229.78 for prescriptions, \$172.95 for medical fees; Medicare Advantage: \$150.19 and \$113.04, respectively) than for patients receiving anticholinergic medications (commercial: \$69.13 for prescriptions, \$60.01 for medical fees; Medicare Advantage, \$45.18 and \$39.22, respectively) [37].

Several studies assessed the costs of anticholinergic medications relative to other approved treatments for OAB, including botulinumtoxin derivatives [33,34,39,42] and a β_3 -adrenergic receptor agonist [40,59]. These analyses generally found that anticholinergic medications were not cost-effective compared with other treatments for OAB. One study, a claims analysis by Walker *et al.*, found that frail older adults taking a β_3 -adrenergic receptor agonist (mirabegron) had higher total costs than patients taking anticholinergic medications, potentially driven by improved adherence [59].

Hospitalization costs

Seven studies reported on the hospitalization costs of patients taking anticholinergic medications for OAB. However, this included 1 abstract, a claims analysis by Walker *et al.* that did not identify any inpatient visits in their cohort and thus reported median hospitalization costs of \$0 [59]. Of the remaining 6 studies, 3 included a comparator arm comprising patients without pharmacologically managed OAB [38,52,60] and 3 stratified by anticholinergic burden [63], medication adherence [46] or medication type [58].

A claims analysis by Yehoshua *et al.* reported hospitalization costs of patients with OAB wet relative to a matched cohort of patients without OAB, finding that patients with OAB wet who were treated with anticholinergic medications had significantly higher annual hospitalization costs (\$2239) than those without OAB (\$1719) [60]. A claims analysis by Pelletier *et al.* found significantly lower hospitalization costs among patients with OAB who received an anticholinergic medication versus those who were not pharmacologically managed [52]. Similarly, an economic impact model by Qin *et al.* predicted that patients with OAB treated with fesoterodine would have lower 1-year hospitalization costs than untreated patients [38].

Ivanova *et al.* was the only study to assess the relationship between adherence to anticholinergic medications and hospitalization costs in patients with OAB, reporting that patients who switched anticholinergic medications had higher all-cause (\$2505) and OAB-related (\$68) hospitalization costs in the 6 months after switching than patients who persisted with an anticholinergic medication (all cause: \$1462; OAB related: \$22) or discontinued (all cause: \$1744; OAB related: \$22) [46].

Lozano-Ortega *et al.* was the only study to assess the relationship between anticholinergic burden and hospitalization costs in patients with OAB. It showed that patients who experienced falls/fractures and had medium to high anticholinergic burden had higher mean hospitalization costs (prefalls/fractures, \$6684; post-falls/fractures, \$7943) than patients who experienced falls/fractures and had no to low anticholinergic burden (prefalls/fractures, \$3931; post-falls/fractures, \$5343) [50].

A claims analysis by Varadharajan *et al.* assessed hospitalization costs in 2 cohorts of patients with OAB receiving tolterodine ER to matched cohorts receiving either oxybutynin ER or oxybutynin IR; OAB-related hospitalization costs ranged from \$78 to \$160 per patient per year, whereas non-OAB-related hospitalizations ranged from \$2328 to \$3720 per patient per year [58]. It found no significant differences in OAB-related hospitalization costs when patients received tolterodine ER versus oxybutynin ER or IR; non-OAB-related related hospitalization costs were significantly lower with tolterodine ER versus oxybutynin IR ($p = 0.0148$) but not versus oxybutynin ER [58].

Outpatient visit costs

Eight studies reported on outpatient visit costs of patients taking anticholinergic medications for OAB. Four studies compared patients with OAB taking anticholinergic medications to patients without pharmacologically managed OAB [37,38,52,60]. The remaining studies focused on anticholinergic burden [50], medication adherence [46] or comparing patients taking different OAB medications [58,59].

A claims analysis by Yehoshua *et al.* reported outpatient visit costs of patients with OAB wet relative to a matched cohort of patients without OAB, finding that patients with OAB wet who were treated with anticholinergic medications had significantly higher average annual outpatient visit costs (\$2326) than those without OAB (\$1609) [60]. Pelletier *et al.* found significantly lower outpatient costs among patients with OAB who were on an anticholinergic medication versus those who were not pharmacologically managed [52]. Similarly, an economic impact model by Qin *et al.* predicted that patients treated with fesoterodine would have lower 1-year outpatient costs than those with no pharmacologic management [38]. However, a budget impact model by Perk *et al.* predicted that patients taking anticholinergic medications would have higher anticholinergic medication-related outpatient costs than patients not receiving pharmacologic treatment from both the Medicare Advantage and commercial perspectives, with higher costs for patients on Medicare Advantage versus commercial plans [37].

The claims analysis by Ivanova *et al.* was the only study to assess the relationship between adherence to anticholinergic medications and hospitalization costs in patients with OAB, reporting that patients who switched anticholinergic medications had higher all-cause and OAB-related outpatient visit costs in the 6 months after switching than patients who persisted with or discontinued an anticholinergic medication [46].

The claims analysis by Lozano-Ortega *et al.* was the only study to assess the relationship between anticholinergic burden and outpatient visit costs in patients with OAB. It reported that patients with medium to high anticholinergic medication burden who had experienced falls/fractures had higher outpatient visit costs (mean all-cause cost per patient: pre-fall/fracture, \$11,526; post-fall/fracture, \$14,758) than those with no to low anticholinergic burden (pre-fall/fracture, \$8638; post-fall/fracture, \$11,079) [50].

The claims analysis by Varadharajan *et al.* compared mean annual per patient outpatient costs of 2 cohorts of patients receiving tolterodine ER with matched cohorts of patients receiving oxybutynin ER or oxybutynin IR [58]. It reported that patients on tolterodine ER had significantly lower outpatient management costs (OAB related, \$33; all other, \$782) than patients on oxybutynin ER (OAB related, \$40; all other, \$829) [58]. There was no significant difference in OAB-related outpatient management costs between patients treated with tolterodine ER (\$34) and oxybutynin IR (\$32); however, all other outpatient management costs were lower in the tolterodine ER-treated group (\$816) than the oxybutynin-treated group (\$923) [58]. OAB-related and all other outpatient ancillary costs were lower for tolterodine ER (OAB related, \$72; all other, \$2197) than oxybutynin ER (OAB related, \$109; all other, \$2372) and lower in a second tolterodine ER cohort (OAB related, \$82; all other, \$2558) than for oxybutynin IR (OAB related, \$74; all other, \$3076) [58].

Two articles compared outpatient visit costs between patients with OAB receiving anticholinergic medications and a β_3 -adrenergic receptor agonist (mirabegron). A 2021 claims analyses by Walker *et al.* included patients with

OAB who were aged ≥ 65 years, frail (claims-based frailty index [66] score ≥ 0.25) and taking either anticholinergic medications or mirabegron [59]. It found that patients taking anticholinergic medications had slightly lower monthly outpatient visit costs than patients taking the β_3 -adrenergic receptor agonist (\$498 vs \$549, respectively) [59]. In contrast, the 2016 budget impact model by Perk *et al.* compared patients with OAB taking anticholinergic medications to patients taking mirabegron and predicted that patients taking anticholinergics would have higher outpatient costs than patients taking mirabegron owing to increased anticholinergic burden–related outpatient visits; the cost of anticholinergic burden related to outpatient visits was estimated at \$594.50 (vs \$138.90 for mirabegron) for Medicare Advantage and \$551.40 (vs \$5.58 for mirabegron) for a commercial insurance plan [37].

Physician visit costs

Three articles reported data or model results on physician visit costs of patients taking anticholinergic medications for OAB. The 2009 claims analysis by Pelletier *et al.* found that annual physician visit costs were lower among patients with OAB who received an anticholinergic medication (OAB related, \$42; all other, \$803) than among those who were not pharmacologically managed (OAB related, \$70; all other, \$892) [52]. Similarly, the 2016 economic impact model by Qin *et al.* predicted that older adult patients with OAB treated with fesoterodine would have lower annual physician visit costs (\$36,239,668 for a cohort of 7096 patients) than those with no pharmacologic management (\$39,030,822) [38]. The 2016 budget impact model by Perk *et al.* assumed that differences in physician visit costs between OAB medications would be most influenced by persistence, with lower persistence (and therefore increased medication switching) driving increased physician visits [37]. The lowest annual physician visit costs per patient were predicted in patients treated with mirabegron (commercial, \$248.59; Medicare Advantage, \$162.48). Among anticholinergic medications fesoterodine had the lowest physician visit costs (commercial, \$456.77; Medicare Advantage, \$298.54) and trospium had the highest (commercial, \$536.10; Medicare Advantage, \$350.39) [37].

Emergency department costs

Five articles reported data or model results on the emergency department costs of patients taking anticholinergic medications for OAB. Three articles compared patients with OAB taking anticholinergic medications to patients without pharmacologically managed OAB [37,52,60], whereas other articles assessed medication adherence [46] or compared anticholinergic medications [58].

The 2016 claims analysis by Yehoshua *et al.* reported that patients with OAB who were treated with anticholinergic medications had higher average annual emergency department visit costs (\$330) than those without OAB (\$193) [60]. Similarly, Pelletier *et al.* found slightly lower OAB-related emergency department costs among patients with OAB who were on an anticholinergic medication (\$1) versus those who were not pharmacologically managed (\$9; $p < 0.001$) [52]. A 2016 budget impact model by Perk *et al.* predicted that patients with OAB taking anticholinergic medications would have higher anticholinergic medication–related emergency department costs than patients not receiving pharmacologic treatment from both the commercial and Medicare Advantage perspectives (commercial, \$166.42 vs \$1.17, respectively; Medicare Advantage, \$216.77 vs \$48.98) [37].

The 2014 claims analysis by Ivanova *et al.* examined the relationship between persistence with OAB medication and emergency department costs in patients with OAB. All-cause emergency department costs were highest among patients who discontinued an anticholinergic medication (\$231), followed by those who switched anticholinergic medications (\$229) or who persisted with the original anticholinergic medication (\$185) [46].

The 2005 claims analysis by Varadharajan *et al.* compared mean annual per-patient emergency department costs of 2 cohorts of patients receiving tolterodine ER with matched cohorts of patients receiving oxybutynin ER or oxybutynin IR [58]. In each group, the average cost of emergency department visits was \$1 for OAB-related visits; average cost of emergency department visits related to other causes ranged from \$98–\$137 [58].

Cost of individual OAB-related conditions

Two articles reported data or model results on the costs of OAB-related conditions in patients taking anticholinergic medications. A 2016 economic analysis by Qin *et al.* predicted that a cohort of 7096 patients who were treated with fesoterodine would have lower 1-year costs than nonpharmacologically managed patients for falls/fractures (fesoterodine, \$62,308,176 vs no treatment, \$66,983,236), UTIs (\$8,759,786 vs \$10,763,598) and depression (\$31,982,765 vs \$36,551,387) [38]. A 2006 model by Ko *et al.* calculated the average cost of falls/fractures over

3 months for patients taking an anticholinergic medication and found that costs ranged from \$3373 with solifenacin to \$3769 with oxybutynin IR [32].

Discussion

The objective of this analysis was to determine the healthcare and economic burden associated with use of anticholinergic medications in adults with OAB in the USA. Among the 34 captured articles, relatively few studies included a comparator group of patients with OAB who were not receiving anticholinergic medications. Many articles compared patients with OAB who were managed by different anticholinergic medications or assessed the effects of medication adherence/persistence or anticholinergic medication burden on HCRU and costs.

The observational studies that did include control groups of patients without pharmacologically managed OAB reported mixed results. Findings from retrospective claims analyses showed that anticholinergic use was associated with increases in hospitalizations, emergency department visits, outpatient visits and their associated costs, as well as total healthcare costs, relative to individuals without OAB [60] or with OAB who did not receive pharmacologic therapy [45]. However, one retrospective analysis showed that treatment of OAB with anticholinergic medications was associated with reduced total costs, OAB-related outpatient and inpatient costs and non-OAB-related total outpatient and inpatient costs relative to patients with nonpharmacologically managed OAB [52].

Economic modeling studies that included patients without pharmacologically managed OAB also reported mixed results. A model by Qin *et al.* predicted that patients with OAB treated with fesoterodine would have lower yearly hospitalization, outpatient visit and physician visit costs, as well as fewer comorbidity-related costs, than patients receiving no pharmacologic management [38]. However, a budget impact model by Perk *et al.* predicted that anticholinergic burden would drive increased physician, outpatient and emergency visit costs in anticholinergic-treated patients relative to untreated controls [37].

A few studies examined the effects of increasing anticholinergic medication burden on HCRU and costs; these generally found that increased exposure to anticholinergic medications was associated with increased HCRU and costs [50,53]. Similarly, concurrent use of ≥ 2 anticholinergic medications for ≥ 1 year was associated with greater rates of falls, fractures, altered mental states and increased annual medical care spending [44]. Furthermore, patients with OAB and potentially inappropriate anticholinergic use (according to 2012 or 2015 Beers Criteria) had increased healthcare, medical and pharmacy costs relative to patients without potentially inappropriate anticholinergic use [54].

A claims analysis found that 88% of patients taking anticholinergic medications discontinue or switch therapies within 12 months [21]. Switching anticholinergic medications [46] and lower adherence to anticholinergic medications [43] were associated with increased HCRU and healthcare costs in patients with OAB, suggesting that low adherence to anticholinergic medications may contribute to healthcare costs in this population. OAB treatments with reduced side effects and improved efficacy may result in improved medication adherence and persistence, leading to reduced HCRU and costs. For example, a systematic literature review has reported that a greater proportion of patients persist with mirabegron for 1 year (range: 32–38%) compared with anticholinergic medications (range: 8–25%) [67].

Anticholinergic medications are the most commonly prescribed OAB treatments in the USA [8–10], despite associations with debilitating and costly adverse outcomes including cognitive impairment and dementia [1,19,68]. Surprisingly, this analysis identified multiple key data gaps in the literature reporting the HCRU and economic burden of anticholinergic medication use in patients with OAB. There are relatively few reports comparing HCRU and healthcare costs between patients with OAB taking anticholinergic medications and those taking other pharmacotherapy (i.e., β_3 -adrenergic receptor agonists) or untreated controls; in the studies that were available, heterogeneous methodologies may have contributed to variable conclusions. No studies specifically compared HCRU or costs associated with OAB-related comorbidities between patients with OAB taking anticholinergic medications and untreated controls; thus, the economic impact of anticholinergic-related comorbidities, particularly cognitive impairment and dementia, remains incompletely understood. Further, well-controlled studies are needed to assess the impact of anticholinergic medications on HCRU and costs associated with OAB, relative to other treatment alternatives.

The observational studies were of poor to fair quality and heterogeneity in study design and outcome definitions made it difficult to directly compare results between studies. Furthermore, comparisons between studies must be made with caution because costs were analyzed over different time periods and reported in various cost years from the perspective of different payors. Only studies in English were included; however, because this analysis focused on burden in the USA, this filter is unlikely to bias results.

Conclusion

Among the articles included in this systematic literature review of the burden of anticholinergic medications for treatment of OAB in the USA, there was high variability in study design, outcome reporting and findings across available studies. Higher anticholinergic medication use or burden, potentially inappropriate anticholinergic use (as defined by Beers Criteria) and low adherence and persistence with anticholinergic medications were associated with increased HCRU and costs. Additional studies assessing the impact of anticholinergic medications on HCRU and costs among patients with OAB in comparison with appropriate control groups are needed and may enable optimization of economic and potentially patient outcomes.

Summary points

- Overactive bladder (OAB) is associated with a high healthcare and economic burden.
- Anticholinergic medications are the most frequently prescribed OAB treatments in the USA; long-term use is associated with dry mouth, constipation, potential for cognitive impairment and increased risk of dementia, and increasing anticholinergic burden is associated with increased risk of falls/fractures, all-cause mortality, major adverse cardiovascular events and clinically relevant drug–drug interactions.
- A systematic literature review was conducted to identify and summarize the burden associated with anticholinergic medication use in adult patients with OAB in terms of healthcare resource utilization (HCRU) and costs to the payor.
- MEDLINE, Embase and the Cochrane Database were searched on 28 May 2021 for articles (observational studies, randomized controlled trials and economic evaluations) assessing HCRU and costs associated with use of anticholinergic medications in adult patients with OAB in the USA.
- 3080 articles were identified and 34 met the inclusion criteria including 18 articles reporting observational studies, 2 articles reporting results from a single clinical trial and 14 articles reporting economic evaluations or economic models.
- The observational studies were of overall fair to poor quality, scoring ≤ 19 on the Downs and Black checklist; the economic studies generally reported on most applicable items on the Drummond and Jefferson checklist.
- In general, greater anticholinergic medication use or burden, potentially inappropriate anticholinergic medication use (according to American Geriatrics Society Beers Criteria®) and poor persistence with anticholinergic medications were associated with greater HCRU and costs.
- Among the 34 captured articles, relatively few included a comparator group of patients with OAB who were not receiving anticholinergic medications, limiting assessment of anticholinergic impact on HCRU and costs.
- The observational studies that did include control groups of patients without pharmacologically managed OAB reported mixed results.
- Real-world studies assessing the impact of oral pharmacologic therapy on HCRU and costs among patients with OAB using proper control groups, along with practical provider and patient experience, are needed and may enable optimization of economic and potentially patient outcomes and health equity.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2022-0160

Author contributions

C Duperrouzel, C Martin, A Mendell, M Bourque, A Carrera, A Mack and J Nesheim were involved in the study design. C Duperrouzel, C Martin, A Mendell and M Bourque were responsible for executing the systematic searches and data extraction. All authors were involved in data analysis, contributed to the development and critical revision of the manuscript for intellectual content and approved the final version for submission.

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relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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