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REVIEW

Patient and Clinician Challenges with Anticholinergic Step Therapy in the Treatment of Overactive Bladder: A Narrative Review

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ABSTRACT

Anticholinergics have been used in the treatment of overactive bladder (OAB), but their use is limited by poor tolerability and anticholinergic-related side effects. Increasingly, providers are discontinuing anticholinergic prescribing because of growing evidence of the association of anticholinergic use with increased risk of cognitive decline and other adverse effects. Newer medications for OAB, the β_3-adrenergic receptor agonists mirabegron and vibegron, do not have anticholinergic properties and are typically well tolerated; however, many insurance plans have limited patient access to these newer OAB medications by requiring step therapy, meaning less expensive anticholinergic medications must be trialed and/or failed before a β_3-agonist will be covered and dispensed. Thus, many patients are unable to easily access these medications. Step therapy and other drug utilization strategies (e.g., prior authorization) are often used to manage the growing costs of pharmaceuticals, but these policies do not always follow treatment guidelines and may harm patients as a result of treatment delays, discontinuations, or related increases in adverse events. Medical professionals have called for reform of drug utilization strategies through partnerships that include clinicians and policymakers. This narrative review discusses prescribing patterns for OAB treatment and the effect of switching between drugs, as well as the costs of step therapy and prior authorization on patients and prescribers.

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Key Summary Points

Many overactive bladder (OAB) medications have step therapy designations with insurance providers, meaning at least one less expensive anticholinergic medication must be trialed and/or failed before the initially prescribed medication can be covered and dispensed.

Currently, there are no clinical or pharmacologic data to support step therapy for OAB, and trialing anticholinergics goes against recommendations from multiple medical societies regarding limiting the use of anticholinergics, especially in older adults, owing to the potential relationship between their use and increased risk of impaired cognition and incident dementia.

β_3-adrenergic receptor agonists, including mirabegron and vibegron, do not have anticholinergic properties or any known association with risk of cognitive impairment, yet many patients are unable to easily access these medications because of step therapy protocols.

Because many patients do not return for next-step conversations with their healthcare provider after discontinuing a medication, all treatments that are safe, effective, and well tolerated should be available and provided to patients with OAB for whom pharmacotherapy is first being considered to ensure optimal patient outcomes and avoid unnecessary and potentially dangerous adverse effects.

INTRODUCTION

Overactive bladder (OAB) is a chronic condition characterized by the strong and sudden urge or need to urinate immediately (urgency); these episodes may occur frequently throughout the day and/or at night (known as nocturia) with or without urinary incontinence (UI) [1, 2]. These symptoms have a substantial impact on patient quality of life [3] and correlate with a high incidence of depression and anxiety, increased work impairment, and decreased enjoyment of intimacy in patients with bothersome symptoms of OAB [4, 5].

First-line treatment for reducing the symptom burden associated with OAB is behavioral therapy with or without use of pharmacotherapy, and oral pharmacologic agents are recommended as second-line treatment [2]. For decades, the pharmacologic armamentarium of OAB largely consisted of anticholinergic agents; oxybutynin, the oldest of these agents, was approved by the US Food and Drug Administration in 1975 and has been used for treatment of lower urinary tract disorders including OAB for nearly 50 years [6]. Though efficacious for many, anticholinergics have side effects associated with short- and long-term use, often necessitating alternative treatments. The chronic nature of OAB requires consistent and long-term therapy to manage symptoms. Long-term outcomes for patients with OAB are challenged by drug discontinuation [2] and loss of patients to follow-up. Patients may lack awareness of treatments goals needed for informed decision-making [7], further undermining the appropriate management of symptoms. The newer β_3-adrenergic receptor agonist class of medications, which include mirabegron and vibegron, offer an alternative to anticholinergics. β_3-adrenergic agonists are safe and efficacious for the treatment of OAB and are well tolerated [8, 9]. However, prescribing this class of medication is frequently undermined by drug utilization management strategies (e.g., formulary restrictions, prior authorization, step edits, quantity limits), which are used to manage expenditures.

Many US health plans have implemented step therapy for the treatment of OAB and other therapeutic areas [10], requiring treatment with at least one prerequisite drug (i.e., an anticholinergic medication in the case of OAB) prior to approval of a prescribed step therapy product. Although these strategies may save on initial pharmacy costs, the required use of anticholinergics and restriction of other drug classes may ultimately result in higher overall healthcare costs due to adverse events and increased healthcare resource utilization. Throughout the world, step therapy is relatively uncommon, with the US marketplace being one of only a few countries utilizing this cost-saving strategy. Whether step therapy treatment is best practice is under scrutiny by the medical community [11].

This narrative review discusses evidence regarding the effect of switching between drugs for the treatment of OAB, as well as the effect of step therapy and prior authorization on patient and prescriber burden. This article is a review of previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PRESCRIBING PATTERNS FOR OAB

Anticholinergics are used commonly across therapeutic areas and have been the gold-standard treatment in OAB for almost 50 years [2]. In an analysis of claims from 2013 to 2017, oxybutynin made up the greatest proportion of prescriptions for patients with OAB enrolled in Medicare Part D [12]. In 2017, oxybutynin comprised 53.9% of OAB claims from all practitioners and 41.4% of claims from urologists. After its approval in 2012, the rate of mirabegron prescribing increased between 2013 and 2017; mirabegron was the second most prescribed drug for OAB by 2017, at 18.3% of all OAB medication claims and 28.8% of claims from urologists [12]. The rate of claims for solifenacin, an anticholinergic, fell during this time. As vibegron is a newer drug to the market (approved in 2020), real-world evidence of prescribing and use are unavailable.

ANTICHOLINERGICS AND SWITCHING BETWEEN OAB DRUGS: PERSISTENCE AND TREATMENT EFFECTS

Persistence with OAB medications is low, with a systematic literature review reporting a 12-month persistence rate ranging from approximately 5% to 40% [13]. Persistence rates decrease steadily over time for anticholinergic drugs, and the proportion of patients who add or switch medications at each time point is very low (approx. 1%) [14]. For patients with OAB who discontinue their first prescribed therapy, if they return for additional treatment, common clinical practice involves switching to another (often anticholinergic) medication [2]. Switching rates from first anticholinergic to another OAB medication range from 4.7% to 19.4% [15–18]. There are limited and conflicting data to suggest that switching from the first anticholinergic drug therapy to another anticholinergic drug for the treatment of OAB produces improvements in clinical benefits and patient-perceived improvement. Notable placebo responses to oral therapy have been reported [19], which may account for initial improvements reported by patients when switching medications. For example, switching (for any cause) from tolterodine extended release (ER) to fesoterodine within 3–4 months was shown to improve patient-reported scores on the Treatment Benefit Scale [20]. Switching from tolterodine ER to solifenacin after at least 4 weeks (for lack of patient-identified improvement in urgency) improved scores on the Patient Perception of Bladder Condition and Overactive Bladder Questionnaire [21]. However, in a study in which patients with OAB cycled through up to six anticholinergics, rates of UI remained similar regardless of the number of anticholinergics tried, suggesting that cycling on additional anticholinergics may not provide any additional therapeutic benefit [22]. One study (N = 103,250) reported that most (92%) patients with OAB treated with anticholinergic drugs failed to meet their treatment goals over a 24-month follow-up period; 6% of patients switched to another anticholinergic, and 51%

permanently discontinued all anticholinergic drugs [16]. In a study of patients with OAB treated with anticholinergics for at least 3 months who then switched to β_3-adrenergic receptor agonist mirabegron, there was generally no improvement in OAB symptoms after switching; however, the rate of adverse events decreased from 24.1% to 12.8%, and quality of life scores improved significantly [23].

ANTICHOLINERGICS AND RELATED BURDEN

Anticholinergics are associated with a number of well-established adverse effects, which include dry mouth, blurred vision, and constipation, and these side effects may limit treatment persistence [24–26]. The risk of falling among patients with OAB increases with age and level of anticholinergic burden [27]. Most concerning, however, is accumulating evidence from both long-term observational studies and randomized clinical trials, which suggests that long-term use of anticholinergics, and more specifically oxybutynin, increases the risk of developing cognitive impairment and dementia, although the measures of cognitive decline and respective study designs have varied greatly [28, 29]. For patients with OAB, high anticholinergic burden is a concern because first-line anticholinergic medications for OAB have some of the highest anticholinergic burden scores [30], and many patients with OAB have comorbidities for which they also take medications that may have anticholinergic properties, such as antidepressants, antihistamines, skeletal muscle relaxants, and antiparkinsonian agents. Clinicians therefore must manage issues of polypharmacy, cumulative anticholinergic burden, and the risk of drug–drug interactions [31] while considering tolerability issues to allow for patient persistence on a medication.

Some anticholinergics may have greater cognitive effects than others. Oxybutynin and solifenacin were associated with a dose-dependent increased risk of dementia in a nested case–control study [32]. In a crossover study, a single dose of oxybutynin 10 mg immediate release (IR), but not solifenacin 10 mg, was associated with statistically significant impairments in multiple measures of cognitive function vs placebo in healthy older adults [33]. Post hoc analyses of a crossover trial of older adults with mild cognitive impairment showed that oxybutynin use was associated with significant decreases in attention vs placebo at 1 to 2 h post dose whereas solifenacin was not [34]. In six observational studies examining risk of mortality with anticholinergic use for the treatment of OAB [35–40, reviewed in 41], oxybutynin was associated with a higher risk of all-cause mortality compared with other OAB medications. Oxybutynin—a small, nonselective, lipophilic agent that can accumulate in the central nervous system—and other highly lipophilic tertiary amines may have more of an effect on older patients in particular because of their less favorable neuropharmacologic profile. Neutral charge and low molecular weight of tertiary amines facilitates penetration of the blood–brain barrier, whereas drugs that are quaternary amines, such as trospium chloride, do not cross the blood–brain barrier as readily [reviewed in 42].

There are differences in selectivity of the various anticholinergic drugs to muscarinic receptors that may also cause the differences between these drugs. Oxybutynin, fesoterodine, tolterodine, and trospium are nonselective, with affinity for all five muscarinic receptors (M1–M5 affinity); darifenacin and solifenacin are selective, with higher affinity for the M3 receptor, the primary muscarinic receptor involved in bladder contractility [43]. Of all anticholinergic OAB medications, higher persistence has been seen for selective (i.e., solifenacin and darifenacin) over nonselective (i.e., trospium and tolterodine) anticholinergics [44]. Nonselective anticholinergics were associated with a 50% higher risk of 180-day mortality than selective anticholinergics in patients with dementia [38], potentially due to the increased risk of adverse events from the nonselective binding to M1 receptors in the brain and M2 receptors in cardiac tissue [45]. However, a claims analysis evaluating the comparative risk of falls/fractures and cognitive decline associated with selective and nonselective anti-

cholinergic use among older adults with dementia and OAB found no difference based on anticholinergic selectivity [46]. More research is needed as to whether differences in selectivity drive differences in clinical outcomes.

MOVING AWAY FROM ANTICHOLINERGIC PRESCRIBING

Multiple organizations recommend reducing anticholinergic burden and/or avoiding anticholinergic use in certain patient populations. The American Geriatrics Society (AGS) provides guidance for medication selection in the Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults [47]. Avoidance of anticholinergics is recommended because of the risk of anticholinergic effects including confusion, dry mouth, and constipation, and the Beers Criteria® further recommends minimizing the number of anticholinergics taken by a patient owing to increased risk of cognitive decline, as well as delirium and falls or fractures, that increases with cumulative burden. A consensus statement from the American Urogynecologic Society (AUGS) states that for patients with OAB for whom behavioral therapies have failed, healthcare professionals should provide counseling on the risk of cognitive impairment, dementia, and Alzheimer disease associated with anticholinergic medications [48]. Similar to AGS Beers Criteria®, AUGS recommends using the lowest effective dose of all anticholinergic medications to lower overall anticholinergic burden. Furthermore, medications that do not add to the cumulative burden should be considered, especially for patients at high risk. A Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) committee report stated that the sum of available research indicates an increased risk of new-onset dementia is likely associated with use of anticholinergic OAB medications for 3 months or more [49]. The committee recommended that cognitive risks be considered in all patient populations and that β_3-adrenergic receptor agonists be trialed before anticholinergics. If necessary to proceed to an anticholinergic, oxybutynin should be avoided.

DRUG UTILIZATION MANAGEMENT OF OAB THERAPIES

There are no clinical data to suggest that step therapy is beneficial to patient care, yet anticholinergics are generally preferred agents and/or required by insurance payers as initial treatment for the management of OAB. Utilization protocols for OAB drugs vary across US private health plans (Table 1) and Medicare prescription plans (managed through healthcare insurers that create treatment formularies; Table 2). In many formularies, exceptions to step therapy protocols may be made for patients with documented difficulties in swallowing, allowing for the prescribing of granules or other formulations that are not otherwise preferred products. β_3-adrenergic receptor agonists (mirabegron and vibegron) have been given preferred status in older adults (65 years of age or older) in some plans (Table 1). Considering the mounting evidence of an increased risk of cognitive decline with increased anticholinergic burden and the cumulative burden of anticholinergics, formularies that require patients of any age to be treated with anticholinergics before receiving approval for the prescribed step therapy may be problematic.

The move toward reducing anticholinergic prescribing has started to become common practice for specialty providers. Results of a 2020 survey of AUGS members revealed nearly all respondents were aware of the literature concerning anticholinergic burden and cognitive decline, and encouragingly, nearly the same amount responded that their prescribing practices have changed in response to the data [50]. However, 62% of respondents reported that a trial of anticholinergics was required by insurance payers for most of their patients prior to authorizing the β_3-adrenergic receptor agonist mirabegron [50]. Although specialty providers (i.e., urologists and urogynecologists) may be well versed in the high anticholinergic burden of many first-line OAB treatments, most OAB medications are prescribed by

Table 1 Examples of OAB medication coverage among major US plans

Insurance plan	Preferred	Nonpreferred	Utilization management (ST, PA)
Aetna (2022)	Bethanechol chloride, flavoxate, Myrbetriq® (oral suspension), oxybutynin (ER, syrup, tablet), solifenacin, tolterodine, trospium	Darifenacin ER, tolterodine ER, Toviaz® oral ER, trospium ER	ST: Toviaz® oral ER
Blue Cross Blue Shield (2022)	Step 1: Darifenacin ER, oxybutynin, oxybutynin ER, solifenacin, tolterodine, tolterodine ER, trospium, trospium XR	Step 2: Gemtesa®, Myrbetriq® (tablets and granules) Step 3: Detrol®, Detrol LA®, Ditropan®, Ditropan® XL, Enablex®, Gelnique®, Oxytrol, Toviaz®, Vesicare®	For all patients prescribed a step 2: prior use of step 1 required For all patients prescribed a step 3: prior use of step 1 and step 2 required
Cigna (2021)	Darifenacin ER, oxybutynin IR (tablets and syrup), oxybutynin ER, solifenacin, tolterodine, tolterodine ER, trospium, trospium ER	Detrol®, Detrol® LA, Ditropan® XL, Enablex®, Gelnique®, Gemtesa®, Myrbetriq® (tablets and granules), Oxytrol®, Toviaz®, Vesicare®, Vesicare LS™	For all patients prescribed nonpreferred: ST (fail 1 preferred treatment), unless: Patient ≥ 65 years of age: approve Myrbetriq®, Gemtesa® Patient < 5 years of age: approve Vesicare LS™, Myrbetriq® (tablets or granules) Patient with difficulty swallowing: approve Gelnique®, Myrbetriq® granules, Oxytrol®
Humana (2022)	Detrol®, Detrol® LA ER, Ditropan® XL ER, flavoxate, Gemtesa®, oxybutynin IR (tablet and syrup), oxybutynin ER, solifenacin, tolterodine, tolterodine ER, trospium, trospium ER	Darifenacin, Gelnique®, Myrbetriq®, ER (tablet and suspension), Oxytrol®, Toviaz® ER, Vesicare® (tablet and suspension)	PA: Myrbetriq® ER (tablet and suspension) ST: darifenacin ER, Gelnique®, Oxytrol®, Toviaz® ER, Vesicare® (tablet and suspension)

Table 1 continued

Insurance plan	Preferred	Nonpreferred	Utilization management (ST, PA)
UnitedHealthcare (2021)	Oxybutynin (syrup and tablet), oxybutynin ER, Oxytrol® for Women (OTC)	Ditropan® XL ER, Detrol® LA ER, Enablex® ER, flavoxate, Gelnique®, Myrbetriq® ER, Oxytrol®, Toviaz ER, trospium ER, Vesicare®	Tolterodine, trospium: approved ≥ 65 years of age; otherwise: ST Nonpreferred drugs: ST: fail 3, 1 must be oxybutynin ER
Medical Mutual (2021)	Darifenacin ER, Gelnique®, Myrbetriq® (tablets, granules), oxybutynin (IR tablets, IR syrup, ER tablets), solifenacin, tolterodine, tolterodine ER, Toviaz®, trospium, trospium ER	Detrol®, Detrol® LA, Ditropan® XL, Enablex®, Oxytrol®, Oxytrol® for Women (OTC), Vesicare®, Vesicare LS™	For patients prescribed nonpreferred drugs: ST (try 1 preferred), unless: Patient ≥ 65 years of age: approve Myrbetriq®, Gemtesa®

Formulary details were pulled from publicly available information. Formularies vary by region and may change during the service year. Coverage of preferred and nonpreferred medications are specific to each plan

ER extended release, *IR* immediate release, *LS* lower strength, *OAB* overactive bladder, *OTC* over the counter, *PA* prior authorization, *ST* step therapy

nonspecialists [12]. A small survey (conducted from February 27 to May 11, 2020; $N = 71$ respondents) of directors of nursing in long-term care settings indicated that oxybutynin was the most prescribed treatment for residents with UI, and 75% of respondents were unaware of the literature concerning anticholinergics and cognitive risks [51]. These data indicate a need for broader education of healthcare providers concerning these risks; consultant pharmacists for patients in long-term care as well as pharmacists involved in the dispensing of prescribed treatments also have important roles in recognizing when changes need to be made to a patient's treatment plan. Nevertheless, the high prescription rate of oxybutynin and other anticholinergics also results from drug management protocols restricting access to newer drugs, such as β_3-adrenergic receptor agonists. When step therapy designation for fesoterodine and mirabegron was removed in May 2013 and July 2013, respectively, across Humana Medicare plans, use by Medicare patients with OAB increased from 0.6% to 1.9% for fesoterodine and 0.1–2.6% for mirabegron by the end of the year [52]. Among Nordic countries, which do not impose step therapy restrictions, prescriptions for mirabegron accounted for 73–95% of all OAB medications for treatment-naive patients in the 6 to 8 months after the introduction of mirabegron [53].

DRUG UTILIZATION PROTOCOL REQUIREMENTS AND HEALTHCARE RESOURCE UTILIZATION

By requiring the selection of a less expensive drug before a more expensive treatment, step therapy and other utilization management strategies are intended to save pharmacy costs. Between 2008 and 2016, branded prescriptions across therapeutic areas increased in cost by 208% [54]. The median out-of-pocket cost for the top 100 drugs in Medicare Part D increased 32% between 2011 and 2015 [54]. A savings of $253 billion in 2016 for the US healthcare system is attributed to the use of generics, which are less frequently subject to significant price increases [54]. By having designated preferred

Table 2 Examples of OAB medication coverage among medicare prescription plans

Insurance plan	Preferred (tier 1–3)	Nonpreferred (tier 4+)	Utilization management (ST, PA)
Aetna (2022)	–	Darifenacin (4), fesoterodine ER (4)	–
Blue Cross Blue Shield (2022)	Fesoterodine ER (3), Myrbetriq® granules and tablet (3), oxybutynin (2), oxybutynin ER (3), trospium (3)	Oxybutynin syrup (4), tolterodine (4)	–
Cigna (2021)	Fesoterodine (3), flavoxate (2), Myrbetriq® ER (3), oxybutynin oral tablet and syrup (2), oxybutynin ER (2), solifenacin (2), Toviaz® (3)	Darifenacin (4), Gemtesa® (4), tolterodine (4), tolterodine ER (4)	Tolterodine ER (ST)
Humana (2022)	Fesoterodine ER (3), Myrbetriq® ER (3), oxybutynin ER (2), solifenacin (2)	Gemtesa® (4), tolterodine (4), tolterodine ER (4)	–
UnitedHealthcare	Fesoterodine ER (3), Myrbetriq® ER oral suspension (3) and oral tablet (3), oxybutynin ER (3), oxybutynin syrup (3), oxybutynin IR (2), Toviaz® ER (3)	Tolterodine ER (4)	Oxybutynin ER (ST)
Medical Mutual (2022)	Myrbetriq® ER oral suspension and tablet (3), oxybutynin (2), trospium (2)	Tolterodine (4)	–

Medicare plans are owned by private companies. Formulary details were pulled from publicly available information. Formularies vary by region and may change during the service year. Coverage of preferred and nonpreferred medications are specific to each plan

ER extended release, *IR* immediate release, *OAB* overactive bladder, *PA* prior authorization, *QL* quantity limit, *ST* step therapy

Tier 1: Preferred generic drug
Tier 2: Generic drug
Tier 3: Preferred brand and generic drugs
Tier 4: Nonpreferred drug
Tier 5: Specialty drug
Tier 6: Select care

drugs in treatment formularies, insurers are able to better negotiate drug pricing, which should lower costs for patients. In a review of 14 publications of step therapies for commonly prescribed medications (antidepressants, antihypertensives, antipsychotics, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors) [55], all step therapy protocols except for those for antipsychotics led to significant pharmacy costs savings. However, these savings were in part due to reduced drug dispensing, and in some studies, savings may have only been short term. A more recent study assessed the impact of step therapy protocols on costs for angiotensin-converting enzyme/angiotensin receptor blockers (ACE/ARBs) in the treatment of hypertension [56]. Some plans required patients to try preferred ACE/ARBs (sometimes for up to 130 days) before nonpreferred ACE/ARBs. With implementation of step therapy protocols, prescription drug costs initially decreased 3.1% but were followed by increased emergency department visits, leading to higher long-term costs for patients with hypertension on step therapy in comparison to patients not subjected to step therapy [56]. Thus, although drug utilization management strategies may initially decrease pharmacy costs,

long-term medical benefit costs may later surpass these savings.

A portion of increases in adverse events with step therapy may occur because patients are placed on medications without consideration of comorbidities, concomitant medications, or previous medication history. However, as discussed above, although there are exceptions to step therapy protocols in place (e.g., for older adults and patients with documented swallowing difficulties), many exceptions may not be categorized as medically necessary. This lack of provider discretion can lead to nonmedical switching: changing medications for reasons unrelated to patient health and safety. Step therapy and nonmedical switching ostensibly require the selection of medications that are considered therapeutically equivalent in terms of efficacy and safety before more expensive treatments. Although many less expensive generic prescriptions can be just as effective as branded medications [57], therapeutic equivalence may not be the critical concern in the treatment of OAB. While most systematic reviews have been unable to show efficacy differences among various OAB medications [58, 59], step therapy should not be required if harmful to the patient. Potential increases in adverse events, or cognitive impairment in the case of long-term anticholinergic use [28], raise questions about the ethics of "fail-first" therapy policies.

STEP THERAPY EVALUATIONS: EVIDENCE IN OTHER DISEASE STATES

Utilization protocols should be evidence-based to provide better outcomes for patients. An analysis of the consistency of step therapy protocols with clinical guidelines across therapeutic areas found that only 17.5% of protocols were consistent with US Food and Drug Administration indications, and the majority (82%) were more stringent [10]. A systematic review of 38 studies reporting outcomes of nonmedical switching in any disease state showed negative or neutral effects on patient outcomes, healthcare resource utilization, and medication-taking behavior in the majority of evaluated studies [60]. A separate systematic literature review ($N = 59$ studies) of outcomes associated with formulary restrictions (i.e., step therapy or prior authorizations) showed a positive effect on pharmacy costs in 83% of the studies but a negative or neutral effect on patient clinical outcomes and healthcare resource utilization in 83% and 65% of the studies, respectively [61]. Interpretation of these results, however, is limited by the potential for reporting bias, as studies showing limited benefit may be less likely to be published, and by low internal validity in studies with shorter follow-up periods [60].

Although as yet there are no studies investigating step therapy in OAB, studies in other therapeutic areas have evaluated the effect of different treatment restrictions. In patients with rheumatoid or psoriatic arthritis, those on insurance plans requiring step therapy had a lower likelihood of achieving treatment effectiveness within 12 months compared with patients without restrictions; adherence was also higher in patients on plans with no access restrictions than in patients with step therapy requirements [62]. The STAR*D trial for major depressive disorder was carried out to provide evidence-based suggestions for treatment regimens, especially for patients who experience treatment failure [63]. The study evaluated switching from a range of first- to fifth-line therapies and demonstrated that patients were more likely to respond in the first two treatments (remission rate, 20–30%) than in subsequent switches (remission rate, 10–20%) [63]. Similarly, monotherapy, step treatment, and combination treatment of hypertension therapy have also been investigated, and both American and European societies have stated that combination treatment is the most preferable initial treatment for hypertension, except in certain cases such as frail older adults [64]. Thus, the benefits of varying treatment regimens can be investigated, and such studies could be used to inform both treatment guidelines and insurance requirements.

BURDEN OF STEP THERAPY

Patient Experience

OAB is a prevalent condition, affecting one in six adults in the USA [65]. However, surveys sent to women indicate that although many identify as having UI or OAB, approximately 30–76% of women who report having UI do not discuss their symptoms with clinicians, with rates varying on the basis of type of UI, age, and demographics [66, 67]. Feelings of embarrassment were reported to be a major barrier in initiating discussions [67]. Many patients will attempt self-management strategies, such as locating restrooms in new locations in advance, voiding preemptively, and limiting water intake, before seeking medical care for their symptoms of OAB [68, 69]. A quantitative patient survey reports a gap of 3.5 years between the appearance of symptoms to the time of receiving diagnosis [70].

When patients do present for treatment of their OAB symptoms, they may face a confusing process for treatment options and decisions. Patient focus groups, mostly made up of older women, have shown that there are misunderstandings and knowledge gaps common to patients with OAB [7]. The reasons for and results of diagnostic tests, the goals of treatment, and the physiology underlying OAB are not well understood by patients [71]. If treatment goals are not made clear to patients, they may not know to return for next-step conversations with their provider. Decision aids are tools to explain diagnosis and treatment options, typically provided to patients in print, video, or mobile applications to explain their diagnosis and treatment options [72]. Unfortunately, few decision aids are available for patients with OAB, and most have readability scores that are higher than recommended by the US National Institutes of Health [73].

Such lack of patient tools, particularly outside of specialist offices, may lead to the persistence of knowledge gaps. This may leave patients without a clear understanding of options for treatment and, when medications are prescribed, the expected outcomes, possible side effects, and planned duration of treatment. When patients do not have a clear understanding of the goals of medical therapy, any difficulties encountered in acquiring the medications—due to step therapy restrictions, cost, or lack of coverage—may lead to abandonment of therapy altogether.

In some cases, the treatment prescribed by the healthcare provider may require prior authorization, a lengthy process that can lead to treatment delays. If the authorization request is accepted, the patient can have the prescription filled but only if they can cover the cost-sharing price. If it is not affordable, the prescription may be abandoned by the patient if they have not already lost hope that their condition can be managed [71]. Here, the patient would need to inform their healthcare provider about the issue and discuss alternatives, a step that often does not occur. In some cases, financial support from the drug manufacturer may be available, but again many patients and providers are unaware of these programs or may find them challenging to understand and use.

In other cases, step therapy requirements may lead to the prescribed drug being replaced with a less expensive drug at the pharmacy. Across therapeutic areas, the average step therapy protocol includes trialing 1.5 drugs before receiving the prescribed/nonpreferred drug [10]. It is difficult to ascertain whether patients receive adequate counseling on the reason for the change to another medication, possible side effects, and next steps if the treatment is found to be suboptimal. For anticholinergic medications used in OAB, tolerability issues with the required drug are a common reason leading a patient to discontinue the medication [24]. Many patients may not realize, however, that medication options without those side effects exist and may have been what was originally prescribed. Again, this course of events places the burden on the patient to know that alternatives exist and requires them to inform their healthcare provider of the switch and request assistance so that the originally prescribed drug can be obtained.

If the treatment is not performing as expected, the burden is on the patient to follow up with their healthcare provider for additional

options. Guidelines from the American Urological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction recommend the trialing of new medications for 4–8 weeks to allow for a clear picture of the efficacy and adverse events [2], but many patients may often instead discontinue treatment. In a 2018 online survey sent to 800 patients who experienced switching of their prescribed medication for nonmedical reasons, 40% of patients reported the new medication was not as effective as the previous one [74]. Complications from the new drug were reported by 60% of respondents, and 9% were hospitalized. Up to 39% of respondents found the switching of their medication frustrating and discontinued treatment [74]. Thus, delayed or inhibited access to effective treatments may put patient safety at risk.

In a 2022 study of insurance coverage and patient-incurred costs for lower urinary tract symptoms, oxybutynin was the only OAB medication (of oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine, and mirabegron) covered in the plans of five large insurers (Aetna, Blue Cross Blue Shield, Cigna, Humana, and UnitedHealthcare) at a monthly average cost of less than $10 [75]. Mirabegron was offered by only one plan for less than $40 per month, with median cost across plans of $349 per month (interquartile range, $47–450/month) [75]. Drug utilization management annual spending is estimated at $93.3 billion, adjusted for 2019 US dollars [76]. Though this figure includes costs incurred by healthcare providers working with payers over prior authorizations ($26.7 billion annually)—as well as manufacturer costs pertaining to financial payments to assist with cost-sharing, payments to patient assistance programs, and administrative support for navigating utilization management requirements ($24.8 billion)—the brunt of costs associated with prior authorizations went to patients by cost-sharing ($35.8 billion) [76].

Provider Experience

If a preferred prescribed drug requires prior authorization, the healthcare provider must begin a time-consuming process of sending the prescription for approval to the insurer or pharmacy benefit manager supplemented with medical records to inform the need to prescribe this medication [76]. The submitted application is reviewed by the insurance provider, and the prescription request can be rejected if the prior authorization criteria are not met or if the application or documentation is incomplete. In 2020, 18% of in-network claims from non-group qualified health plans across www.healthcare.gov users were denied [77]. The provider can appeal the decision; however, this requires more time and paperwork, which may lead instead to abandoning the prescription and prescribing another treatment that is more readily attained. In a 2021 American Medical Association physician survey, physicians responded that when prior authorization was required for necessary treatments, treatment delays were experienced in 93% of cases [78]. In a study of outcomes of prior authorizations from an outpatient urology center, the median time to initial decision on a prior authorization request was 2 days [79]. However, if an initial request was denied, the median time to decision on an appeal was 10 days. Though most prior authorization requests for medications were approved, only approximately 32% of medication denials were appealed. In most denials, new prescriptions were ordered instead. In some cases, clinicians may select initial treatments on the basis of whether prior authorization is required because they do not have the resources for time-consuming prior authorization processes. Thus, the prior authorization process may lead to healthcare providers prescribing medications other than what they would initially have selected.

The process involved with handling prior authorizations places a burden on healthcare professionals [78, 80]. In the 2021 American Medical Association physician survey, respondents reported that physicians and their staff spend an average of almost 2 workdays a week completing prior authorizations; 88%

responded that the burden associated with prior authorizations is high to extremely high [78]. About 93% of survey respondents reported that some patients experienced treatment delays [78]. Most (82%) physicians responded that prior authorization can lead to treatment abandonment; 34% replied that the prior authorization process was a factor that led to a serious adverse event. In a study of outcomes of prior authorizations from an outpatient urology center with 20 healthcare providers, 267 prior authorization urology treatments were requested over a 4-month period [79]. Of medications for voiding issues that required prior authorizations, 77% were approved at the initial request. Each initial request was reported to take 23 min to complete, amounting to more than 14 h of staff time attributed to prior authorizations per month [79]. Because of the significant resources needed for implementation, prior authorization may dictate the care patients receive.

STEP THERAPY REGULATION

Actions are being taken in the USA to curb step therapy protocol requirements [81]. The Safe Step Act endeavors to require evidence-based criteria for step therapy protocols and exclusions, a clearer appeal process, and expedited responses to requests and appeals. Currently, 15 US states have passed legislation to regulate step therapy, and several more have bills under consideration [82]. A federal bill to standardize and add transparency to the prior authorization process in Medicare Advantage plans is also under consideration [83].

The American College of Physicians (ACP) has come out with a series of recommendations regarding step therapy and medication switching policies [11]. The first recommendation is to minimize disruptions in care and risks to the patient. This means that a patient should never be switched from a medication on which they are stable; should not have to go back onto a medication that previously proved ineffective, caused adverse effects, or was poorly tolerated; and should not be required to fail more than two medications before approval of the originally prescribed medication. Furthermore, what constitutes treatment failure should be defined, and if a patient experiences treatment failure, they should be able to switch medications quickly (i.e., within 24 h). Step therapy should not be applied to treatments for patients classified as high risk. Before switching, medical history, cognitive state, comorbidities, concomitant and previous medications, and other pertinent factors should be considered. The ACP recommends that policies be based upon evidence that the preferred drug is equally effective and safe as the nonpreferred step therapy drug, evidence of which should be publicly provided.

To aid in the regulation of drug utilization management/step therapy, the ACP recommends greater involvement of the medical community in designing the protocols, especially clinicians who regularly prescribe the medications. They further recommend that support is needed for research into and creation of decision aids; further, physician training in informed decision-making, as well as lower copay options, rebates, and in-kind medical services need to be made more readily available.

CONCLUSION

OAB is a chronic condition requiring consistent therapy to improve symptoms and positively impact activities of daily living and quality of life. Many insurance providers, however, have step therapy designations for OAB medications, meaning less expensive anticholinergic medications must be trialed and/or failed before the prescribed medication can be covered and dispensed. There are no studies to support that step therapy protocols are effective or improve care for the treatment of OAB. There is, however, growing evidence of the risks associated with anticholinergic use. Trialing anticholinergics goes against recommendations from multiple professional medical associations because of the associated increased risk of incident dementia and low persistence due to side effects, especially in older or at-risk populations. Thus, utilization strategies implemented by insurance companies may not be evidence-based or in accordance with available guidance,

especially when considering the increased risk of cognitive impairment and other adverse effects in a population with high rates of comorbidities and other risk factors, such as older age. Although there may be initial cost-savings for payers, the overall burden is greater on patients, providers, and the healthcare system. β_3-adrenergic receptor agonists mirabegron and vibegron do not have anticholinergic properties, yet many patients are unable to easily access these medications because of step therapy protocols. Removing step therapy protocols and designating preferred agent status of β_3-adrenergic receptor agonists for older adults with OAB would be steps in the right direction. More research is needed for strategies that can keep medical expenditure spending in check while providing the best possible care for patients.

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Declarations

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