Anticholinergics for overactive bladder: Temporal trends in prescription and treatment persistence

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Abstract

Introduction: We sought to understand the contemporary pharmacologic management of overactive bladder (OAB) in a single-payer system. We examined temporal trends in the use of anticholinergic medications and assessed whether the likelihood of patients changing their anticholinergic therapy was predicted by their current therapy.

Methods: We conducted a retrospective, population-based analysis of prescription records from the PharmaNet database in BC, Canada. We identified patients treated with one or more anticholinergic prescriptions between 2001 and 2009. We characterized temporal trends in the use of anticholinergic medications. We used generalized estimating equations with a logit wing to assess the relationship between the type of anticholinergic medication and the change in prescription.

Results: The 114 325 included patients filled 1 140 296 anticholinergic prescriptions. The number of prescriptions each year increased over the study, both in aggregate and for each individual medication. While oxybutynin was the most commonly prescribed medication (68% of all prescriptions), the proportion of newer anticholinergics (solifenacin, darifenacin, and trospium) prescribed increased over time (p<0.0001). Patients taking tolterodine (odds ratio [OR] 1.03; p=0.01) and darifenacin (OR 1.12; p=0.0006) were significantly more likely to change their prescription than those taking oxybutynin. There was no association seen for patients taking solifenacin (p=0.6) and trospium (p=0.9).

Conclusions: There are an increasing number of anticholinergic prescriptions being filled annually. Patients taking newer anticholinergics are at least as likely to change therapy as those taking oxybutynin. The reimbursement environment in BC likely affects these results. Restrictions in the available data limit assessment of other relevant predictors.

Introduction

Overactive bladder (OAB) is common, affecting an estimated 10–31% of the population.[1] It results in significant quality of life impairment due to urinary urgency, frequency, and nocturia.[2] Anticholingeric medications have been the mainstay in pharmacologic management of OAB.[3] However, due to the well-known side effect profile of these medications, persistence rates at one year are <40%.[4] Oxybutynin is the original anticholinergic used in the management of OAB, introduced in Canada over 30 years ago. Since that time, a number of additional medications have been introduced. Currently, the Canadian Urological Association[5] and American Urological Association[3] guidelines recommend six agents: oxybutynin, tolterodine, fesoterodine, solifenacin, darifenacin, and trospium. While many of these newer agents are reported to have fewer side effects, the effect of this on medication adherence remains to be addressed.

Using population-based pharmacy records, we sought to assess (1) temporal trends in the management of OAB in the province of BC; and (2) persistence on anticholinergic medications.

Population and data sources

In BC, a single-payer, government-operated health insurance system provides coverage for prescription medications (PharmaCare) for eligible residents. The PharmaCare formulary provides coverage for certain medication within each therapeutic category. For anticholinergic medications, oxybutynin is covered within the general auspices of the program. Other medications must be covered out-of-pocket or through third-party insurance programs.

In this study, we used PharmaNet, a network that links pharmacies throughout the province. All prescription medications dispensed in community pharmacies throughout BC are recorded in this system, regardless of the payer. Using this dataset, we identified all patients who filled one or more prescriptions for an anticholinergic medication between January 1, 2001 and December 31, 2009. Due to limitations in the dataset, we were unable to obtain personal information, including demographics for patients receiving these

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prescriptions. Research ethics approval was obtained from the Island Health Research Ethics Board (H2014-063).

Analysis

We assessed the absolute number of anticholinergic prescriptions, in aggregate and for each medication, as well as the relative proportion of prescriptions for each anticholinergic medication. We estimated the proportion of the population of BC receiving anticholinergic therapy for OAB annually by dividing the number of individual patients prescribed a medication each year by the general adult (age ≥20 years) population estimate, as provided by BCStats.[6]

We assessed the association between the proportion of each anticholinergic medication and the passage of time using Somer's D.

We then assessed medication adherence. A change in prescription was defined as either (1) initiation of a different medication or (2) cessation of anticholinergic therapy. This was operationalized as a binary outcome. Prescriptions that extended past the study end date (n=9395) were censored for this portion of the analysis. We descriptively characterized the proportion of patients changing their prescription, as a function of their current medication. We then assessed whether the medication prescribed was predictive of the chance that there would be a change in the prescription once it expired. We used a generalized estimating equation with a logit wing to assess the relationship between type of anticholinergic medication and change in prescription, while accounting for clustering at the level of the patient.

Results

Between January 1, 2000 and December 31, 2009, we identified a total of 1 140 296 anticholinergic prescriptions dispensed to 114 325 patients. This represented 3.21% of all prescriptions for these patients. The number of individual patients receiving anticholinergic annually ranged from 17 710–28 309 over the study interval (Table 1). This represents 0.58–0.89% of the population of BC aged 20 years and older.

Over the study interval, there was an increase in the absolute number of anticholinergic prescriptions, both in aggregate and for each individual medication (Fig. 1). Oxybutynin was the most commonly prescribed anticholinergic over the study interval (68.2%), followed by tolterodine (28.2%), solifenacin (2.1%), darifenacin (1.5%), and trospium (0.1%). From 2006–2009, following the introduction of solifenacin, darifenacin, and trospium, oxybutynin remained the most commonly prescribed medication (66.2%), followed by tolterodine (26.8%), solifenacin (4.0%), darifenacin (2.8%), and trospium (0.1%).

Table 1. Proportion of population of BC who filled a prescription for anticholinergic medication, 2000–2009

Year	Number of patients prescribed anticholinergics*	Population of BC	Proportion of population prescribed anticholinergics
2000	17 710	3 030 749	0.58%
2001	19 305	3 071 665	0.63%
2002	21 420	3 105 325	0.69%
2003	26 184	3 139 804	0.83%
2004	28 309	3 178 987	0.89%
2005	27 080	3 224 315	0.84%
2006	25 184	3 271 570	0.77%
2007	25 918	3 322 647	0.78%
2008	26 486	3 381 874	0.78%
2009	27 909	3 443 759	0.81%

*Number of patients exceeds total study sample size as patients may contribute to multiple years.

After the introduction of solifenacin, darifenacin, and trospium in 2006, there was a statistically significant increase in prescriptions of these medications year over year, with a corresponding decrease in prescriptions of oxybutynin (Fig. 2; Somers' D(R|C)=0.0522, 95% confidence interval [CI] 0.0510–0.0533; p<0.0001), despite not being covered by PharmaCare.

Of the 1 130 901 prescriptions that expired prior to the study end date, 137 977 (12.2%) were followed by either a switch to a different anticholinergic medication or cessation of anticholinergic therapy. Based on a logistic regression model accounting for clustering at the level of the individual patient, prescriptions of tolterodine and darifenacin were significantly

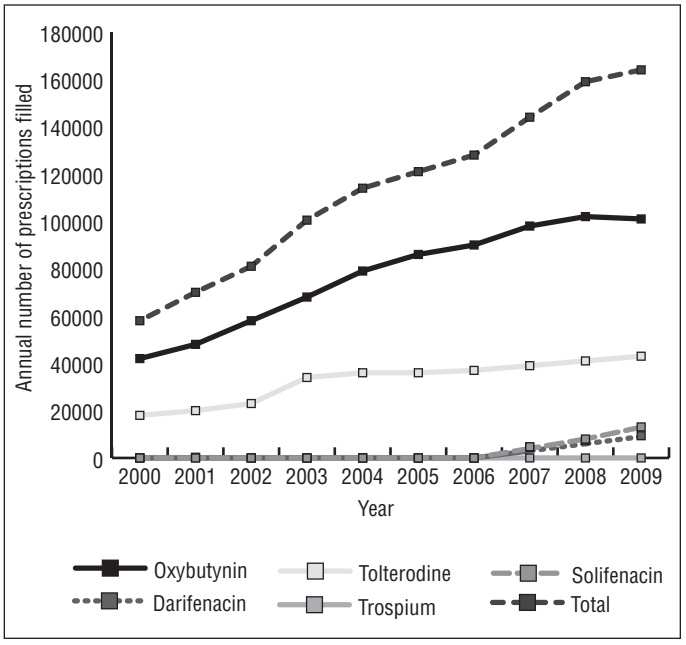

Fig. 1. Total anticholinergic prescriptions in BC, 2000–2009.

Table 2. Odds ratio of a patient changing anticholinergic medication or stopping anticholinergic therapy as a factor of the current anticholinergic medication

Anticholinergic	Odds ratio	95% confidence interval	p value
Oxybutynin	Referent	Referent	Referent
Tolterodine	1.033	1.01–1.06	0.01
Solafenacin	1.034	0.93–1.16	0.55
Darifenacin	1.107	1.04–1.17	0.0006
Trospium	1.017	0.75–1.38	0.91

more likely to result in a change of prescription when compared to oxybutynin. There was no association observed for prescriptions of solifenacin and trospium (Table 2).

Discussion

The worldwide prevalence of OAB is estimated to increase by over 20% from 2008 to 2018.[7] This trend is likely due to the aging population combined with a rising awareness of OAB as a clinical entity. This will have a significant impact on demand for anticholinergic medications. We found that the total number of anticholinergic prescriptions has increased steadily in BC since 2000. Despite barriers to their use, the newer medications, including solifenacin and darifenacin, have seen steady growth in their respective share of the anticholinergic market. In contrast, oxybutynin has seen a steady decline in its proportion of anticholinergic prescriptions.

The EPIC study investigators conducted a cross-sectional survey on patients in five countries, including Canada, and found that 11.8% of patients aged 18 years and older reported symptoms consistent with OAB.[1] In this study, the proportion of the adult population (aged 20 years and older) who filled a prescription for an anticholinergic medication was much lower than would be anticipated given the prevalence of lower urinary tract symptoms. Our findings are, however, in keeping with Mauseth et al, who found that 0.94% of the Norwegian population filled a prescription for an anticholinergic to treat OAB in 2010.[8] Therefore, while many patients with OAB are likely adequately managed with first-line behavioural therapy, our data suggest that many patients may be undertreated.

While the use of anticholinergic medications has increased in BC, they accounted for only a small proportion (3%) of the total prescriptions filled by patients with OAB. This suggests that OAB patients have many other health concerns and that risks of medication interaction due to polypharmacy must be considered in their management. Furthermore, a recent report on seniors' health in BC found that 21% of seniors receiving home care support have urinary incontinence and 44% are taking nine or more medications.[9] With this in mind, finding OAB treatments with tolerable side effect profiles is crucial in this vulnerable population.

Persistence for patients on anticholinergic medication is an ongoing concern in the treatment of OAB. The high discontinuation rates are thought to be due to both the lack of efficacy and the side effects of anticholinergic medications.[10] As newer generation anticholinergics selectively target muscarinic M3 receptors in the bladder, an improvement in the side effect profile is expected. This would lead to the hypothesis that discontinuation rates would be lower for patients taking newer medications. One study found a slight decrease in discontinuation with solifenacin and propiverine when compared to oxybutynin with no significant difference between the other medications.[11] Similarly, considering the influence of side effects, a systematic review from 2012 indicated discontinuation rates due to adverse events of 13 per 1000 for solifenacin compared to 63 per 1000 for oxybutynin.[12] This data was extracted from studies with a maximum duration of three months and likely underestimates true long-term discontinuation rates. In recent years, a number of papers have been published looking at discontinuation rates over a prolonged period.[4,8,11,13] These papers report discontinuation rates at one year between 51.7 and 88%. Our data demonstrate no difference in discontinuation between oxybutynin and solifenacin and increased discontinuation for patients taking tolterodine or darifenacin; however, factors beyond clinical efficacy and tolerability may explain these results. In particular, a significant confounding factor is that oxybutynin is much more accessible economically, as it is covered by PharmaCare, while the other medications require out-of-pocket or third-party payment. This fact alone may influence patients' decisions to persist or change therapy. It has long been known that drug prices

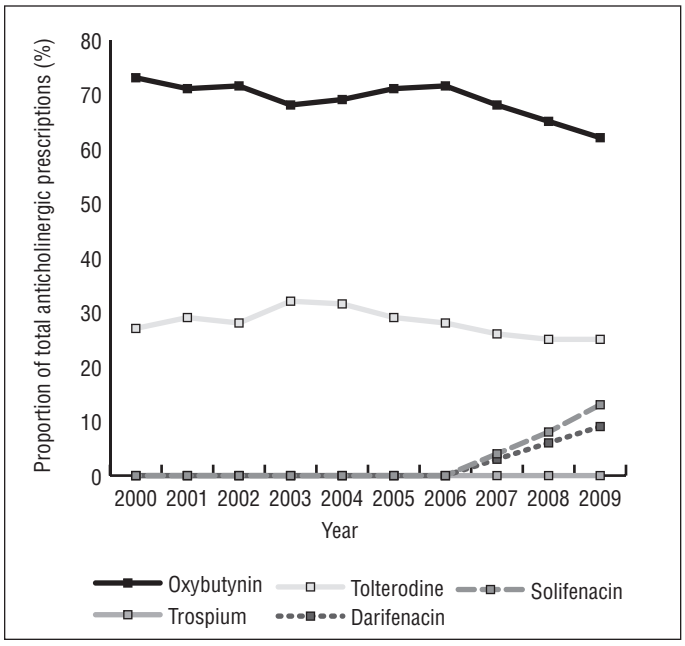

Fig. 2. Relative proportion of anticholinergic prescriptions in BC, 2000–2009.

affect compliance regimes and that patients frequently report delaying or abstaining from purchasing medications due to cost considerations.[14] Therefore, cost may play a significant role in why patients persist on oxybutynin, as well as why they discontinue treatment with more expensive medications. Thus, the reimbursement environment for the present study does not allow for a truly fair comparison between the medications. It is possible though, that the presumed benefits of newer anticholinergics are not sufficient enough to continue treatment given the increased cost. This is borne out by a recent systematic review that found insufficient high-quality evidence to recommend one anticholinergic agent over another in terms of efficacy or side effects.[15]

Due to the nature and security of the provincial PharmaNet system from which data was obtained, very limited information was granted for the purposes of this study. This restricted the analysis of data and, as a result, our findings. We were unable to determine age of patients, third-party insurance coverage and other associated patient demographics. Whether patient age or gender affects their likelihood of being prescribed a newer anticholingeric or their likelihood of persisting on therapy remains a question to be addressed in future studies.

Conclusion

Using population-level data, we identified an increasing number of anticholinergic prescriptions year over year. However, we did not demonstrate a significant increase in the proportion of the population receiving treatment for OAB over time. This suggests a potential for significant undertreatment of OAB at the population level. Further, we identified that patients taking newer anticholinergics are at least as likely to change medication as those taking oxybutynin. The reimbursement environment in BC is postulated to significantly affect this observation.

Competing interests: Dr. Wallis has received an investigator-initiated, peer-reviewed grant from Astellas Pharma Canada during the conduct of the study. Dr. Pommerville has received personal fees (advisory boards) from Allergan, Amgen, Astellas, Ferring, and Mylan, all outside of the submitted work. Dr. Carr has received personal fees (advisory board and lectures) from Allergan, Astellas, and Pfizer; and has received research funding from Allergan and Astellas, all outside of the submitted work. The remaining authors report no competing personal or financial interests.

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