Anticholinergic use in children: Persistence and patterns of therapy

Anne-Sophie Blais, MD; Michelle Bergeron, MD; Geneviève Nadeau, MD; Sophie Ramsay, MD; Stéphane Bolduc, MD

Université Laval, Quebec City, QC, Canada

Cite as: *Can Urol Assoc J* 2016;10(3-4):137-40. http://dx.doi.org/10.5489/cuaj.3527

Abstract

Introduction: Overactive bladder (OAB) symptoms are complex and generally require long-term therapy. Nevertheless, it has been demonstrated that persistence rates of antimuscarinic drug use are low in adults. Better understanding of the treatment patterns of children treated with antimuscarinics could help to improve drug management. Our objective was to evaluate persistence rates of patients under 20 years of age on antimuscarinic therapy over a four-year period.

Methods: Patients having received a first-ever antimuscarinic drug prescription between April 2007 and March 2008 were identified using IMS Brogan's Public and Private Drug Plans database. Canadian drug claims data from Private Drug Plans, Régie de l'Assurance Maladie du Québec, and Ontario Public Drug Plans were analyzed retrospectively. Patients were followed for four years to assess the prescribed drugs, the lines of treatment, and the duration of each treatment.

Results: Data were available for 374 patients. The most prescribed drug as a first-line therapy was oxybutynin (87.2%), followed by tolterodine LA (5.9%). Patients refilled their index prescriptions for an average of 429 days. Solifenacin had the highest mean duration of index therapy (765 days). The median number of antimuscarinics prescribed was one. At the end of the followup, 44 patients were still on therapy. Reasons for discontinuation of treatment were not available.

Conclusions: Overall discontinuation rate of antimuscarinic therapy in children is comparable to what has been reported in adult patients with OAB. However, children seem to persist on the medication for a longer duration before adherence rates start declining. The low rate of persistence highlights the need to identify the reasons for discontinuation of therapy in children in order to obtain better persistence rates.

Introduction

Overactive bladder (OAB) syndrome is the most common type of voiding dysfunction in children.[1] It is defined by the International Children's Continence Society as urinary urgency, with or without incontinence and increased voiding frequency.[2] These symptoms are especially troublesome for pediatric patients and their families. Indeed, it is well-established that OAB affects children's well-being, limits everyday activities, and impairs children's development.[3] Due to the prevalence of OAB and its severe repercussions on children's quality of life, novel options for the therapeutic management of pediatric patients with OAB have emerged in the last decade and are still a subject of great interest.

Improvement of quality of life and discomfort is the aim of OAB therapy. Antimuscarinic agents are currently the mainstay of therapy to achieve these goals.[1] It is well-known that OAB is a chronic condition that requires long-term treatment. Persistence of antimuscarinic therapy in the treatment of adults with OAB symptoms has been studied and the high rate of treatment discontinuation has been well-documented. A British study from Kelleher et al noted a persistence rate of 18.2% in women with OAB symptoms at six months after initial prescription.[4] Similarly, Wagg et al showed that 14–35% of patients remained on their initial therapy at 12 months.[5] These findings have led to the development of strategies to improve the persistence rates of antimuscarinic therapy.

To our knowledge, the persistence of antimuscarinic therapy in children has never been studied. Better understanding of the treatment patterns of children treated with antimuscarinics could potentially improve drug management and outcomes. Our objective was to evaluate treatment patterns of patients under 20 years of age on antimuscarinic therapy over a four-year period.

Methods

Patients under 20 years of age using a prescription for an anticholinergic drug for the first time ever between April 2007 and March 2008 were identified using IMS Brogan's Public and Private Drug Plans database. Canadian medical claims data from Private Drug Plans (PDP), Régie de l'Assurance Maladie du Québec (RAMQ), and Ontario Public Drug Plans (OPDP) were analyzed retrospectively. Target drugs were oxybutynin (Ditropan®), tolterodine (Detrol®, Detrol® long

acting (LA)), trospium (Trosec®), solifenacin (Vesicare®), and darifenacin (Enablex®). Prior to patients' inclusion in the study, any previous use of anticholinergic medications was determined by a 12-month look-back period; patients who were not identified as receiving the anticholinergic drug as a first-line treatment were excluded. Patients were then followed in the database for four years. During that time, the different antimuscarinic drugs they used, the lines of treatment, and the average number of days spent on each medication were recorded. The lines of therapy were reported by drug plan, product, age group, and gender. Verification was done three months after each patient's last claim to ensure each patient was still active in the database. Patients lost to followup were excluded from the database.

Discontinuation of drug treatment was defined as stopping the current line of therapy and not switching to another anticholinergic medication. At the end of the four-year followup period, patients were classified as "no change" if they had remained on the same line of therapy since the initiation of the study.

Results

Data were available for 191 males and 183 females for a total of 374 patients. All patients were under 20 years of age, with a majority being under 18 years old. The most prescribed drug as a first-line therapy was oxybutynin, followed by tolterodine LA, tolterodine, and solifenacin (Table 1). None of the study patients used trospium or darifenacin as a first-line therapy and both medications were, in fact, very rarely used. Patients refilled their first prescriptions of antimuscarinics (or index therapy) for an average of 429 days. Solifenacin had the highest mean duration of index therapy with 765 days (Table 1). Differences were noted in duration of index therapy based on gender and drug used. However, when looking at the pooled data from all drugs, no significant differences were noted in mean duration of index therapy (421 vs. 437 days for males and females, respectively; p=ns). The mean time for which a patient was prescribed a second- or third-line therapy was 637 and 566 days, respectively.

The median number of antimuscarinics prescribed was one. During the four-year followup, 324 (86.6%), 35 (9.4%), 14 (3.7%), and 1 (0.3%) patients had one, two, three, or four different drugs prescribed, respectively. Interestingly, the drug initially prescribed affected the number of antimuscarinics used during the four-year period. For example, the majority of patients (55.6%) whose initial prescription was for tolterodine had a second-line therapy. Table 2 summarizes the total number of drugs used by patients during the followup according to their index therapy. The most prescribed drug as a second- or a third-line therapy was tolterodine LA.

Three hundred sixteen patients (84.4%) discontinued their first-line therapy and did not switch to another medication during the followup. At the end of the four-year period, only 44 patients (11.8%) were still using an antimuscarinic agent, eight of which were still on their index therapy.

Table 1. Mean time on index therapy

	n	Mean time (days)
Oxybutynin		
M	172	444
F	154	428
Total	326	436
Tolterodine		
M	11	109
F	7	539
Total	18	276
Tolterodine LA		
M	6	264
F	16	342
Total	22	321
Solifenacin		
M	—	630
F	—	810
Total	8	765
All anticholinergic drugs		
M	191	421
F	183	437
Total	374	429

F: female; M: male.

Discussion

OAB symptoms are complex and generally require long-term therapy. Despite the impact of these symptoms on patients' well-being and quality of life, persistence rate of antimuscarinic treatment was shown to be very low. Many studies have assessed the persistence rate of antimuscarinic therapy for lower urinary tract symptoms in adults. Brostrom Hallas have noted a persistence rate of <50% at six months, >25% at one year, and <10% at two years and longer.[6] Similarly, Wagg et al have shown that only 14–35% of patients remain on their initial therapy at 12 months.[5] To our knowledge, our study is the first to evaluate persistence rate of antimuscarinic therapy in the pediatric population. Our results showed a

Table 2. Percentage of patients in regards to number of drugs prescribed over four years and initial prescription

Number of drugs	Oxybutynin n (%)	Tolterodine n (%)	Tolterodine LA n (%)	Solifenacin n (%)
1	293 (89.9)	8 (44.4)	17 (77.3)	6 (75.0)
2	19 (5.8)	10 (55.6)	4 (18.2)	2 (25.0)
3	13 (4.0)	–	1 (4.5)	–
4	1 (0.3)	–	–	–

persistence rate of 11.8% at four years. Comparison with existing adult studies is quite difficult, as our followup is longer than what has been reported in literature to date. However, we can advance that younger patients appear more likely to persist on antimuscarinic therapy than older patients because our persistence rate at four years is similar to the reported rates at one or two years of followup in the adult population. Nonetheless, discontinuation rate still remains high in children.

An interesting fact that can be drawn from our results is that only 13% of all patients assessed in the study were prescribed a second line of therapy. Since 87% of our population received oxybutynin as their index therapy, we can assume that most children were exposed exclusively to oxybutynin in accordance to the fact that it is the only antimuscarinic drug currently approved for the pediatric population. Up-to-date literature on other antimuscarinics, such as tolterodine, solifenacin, propiverine, and trospium, and on novel therapies for OAB, such as the β-3 agonist mirabegron, might encourage physicians and parents to consider other lines of therapy in children presenting with OAB symptoms.[7-17] As a result, changes could eventually be seen in the patterns of therapy and persistence of OAB drugs.

Children who took a second or third line of therapy stayed on those drugs for a mean time of 637 and 566 days, respectively. Furthermore, 36 of the 50 patients who switched to another line of therapy were still on antimuscarinics at the end of the four-year followup period. This could indicate that children and their physicians are willing to persist on therapy as long as they find a drug that suits their needs and expectations. Interestingly, our patients' second-, third-, or fourth-line therapy was commonly a long-acting antimuscarinic. In the literature, many studies have assessed the efficacy and tolerability of immediate- vs. extended-release formulas. It is easy to assume that the convenience of once-daily dosing should enhance the patients' compliance and persistence to the selected drug treatment. In fact, a preponderance of studies showed an improvement in efficacy and tolerability with extended-release formulations, especially with regard to dry mouth, a common adverse effect of antimuscarinics.[18-23] Likewise, some studies reported a greater adherence and persistence rate with the once-daily formulas.[5,24-25] Reinberg et al reported great tolerability and better efficacy with the extended-release forms of oxybutynin and tolterodine in children with diurnal urinary incontinence due to OAB.[10]Although the majority of the previously mentioned studies concerned adult patients, they represent the only possible point of comparison to our study due to the current lack of data on the pediatric population.

Limitations of this study include the lack of healthcare data, such as adherence to treatment, severity of symptoms, and reason for treatment discontinuation. In fact, a significant proportion of pediatric patients might have discontinued their treatment because symptoms have resolved during the four-year period, and not because of side effects or lack of efficacy. The lack of healthcare data can be explained by the fact that data were originally collected for a post-marketing analysis of persistence. Furthermore, the database made it impossible to differentiate whether the patients had OAB symptoms, neurological disorder, enuresia, or other conditions. Nevertheless, the patients assessed in the study were children with a first-ever prescription of antimuscarinics. It is reasonable to believe that our study included a majority of patients with OAB, which is a common voiding dysfunction and indication for antimuscarinics in children. Regarding patients with neurogenic bladder, they would most likely represent a very small proportion of our population, as there can only be a limited number of newly diagnosed children with a neurological condition per year.

Another limitation is the small number of patients in the tolterodine, tolterodine LA, and solifenacin groups compared to the oxybutynin group. Therefore, although this study tells us more about the persistence rate of oxybutynin in the pediatric population, the data might not be generalizable to other antimuscarinic medications. Indeed, it is hard to draw conclusions on persistence rates of tolterodine or solifenacin considering the minimal number of patients having used these drugs during the course of our study. Moreover, it is important to remember that solifenacin was listed on the OPDP formulary for the first time in 2011 and that the initial reports on its use in children were only published in 2009 and 2010,[15,17] which can explain the smaller number of patients in this cohort.[26]

Conclusion

The overall discontinuation rate of antimuscarinic therapy in children (88% at four years) seems comparable to what has been reported in adult patients with OAB. However, children appear to persist on the medication for a longer duration before adherence rates start declining. These observations were mainly based on oxybutynin as a first-line therapy. The impact of long-acting formula will need validation when pediatric usage is approved by federal agencies. The low rate of persistence highlights the need to identify the reasons for discontinuation of therapy in children in order to obtain better persistence rates.

Competing interests: Dr. Nadeau has been an Advisory Board member for Allergan, Astellas, AMS, Ferring, Pfizer, and Red Leaf Medical; has been a member of the Speakers Bureau for Allergan, Astellas, Ferring, Laborie, and Pfizer; and has participated in clinical trials for Astellas and Ipsen. Dr. Bolduc has received Investigator Initiated Research funds from Astellas and Pfizer. The remaining authors declare no competing financial or personal interests.

Acknowledgement: This study was funded by Astellas Pharma Canada, Inc. Retrospective prescription claims data and statistical analyses were provided by IMS Brogan (IMS Health Canada Inc,

Kirkland, QC, Canada), Brad Millson (Engagement manager). The statement, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from IMS Brogan information services. All rights reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Brogan or any affiliated or subsidiary entities.

This paper has been peer-reviewed.

References

1. Franco I. Pediatric overactive bladder syndrome: Pathophysiology and management. *Pediatric Drugs* 2007;9:379-90. http://dx.doi.org/10.2165/00148581-200709060-00005
2. Nevéus T, Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Report from the standardization committee of the International Children's Continence Society. *J Urol* 2006;176:314-24. http://dx.doi.org/10.1016/S0022-5347(06)00305-3
3. Caldweel HY P, Hodson, E, Craig J, et al. Bedwetting and toileting problems in children. *Med J Aust* 2005;182:190-5.
4. Kelleher CJ, Cardozo LD, Khukkar V, et al. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol* 1997;104:988-93. http://dx.doi.org/10.1111/j.1471-0528.1997.tb12054.x
5. Wagg A, Compion G, Fahey A, et al. Persistence with prescribed antimuscarinic therapy for overactive bladder: A UK experience. *BJU Int* 2012;11:1767-74. http://dx.doi.org/10.1111/j.1464-410X.2012.11023.x
6. Brostrom S, Hallas J. Persitence of antimuscarinic drug use. *Eur J Clin Pharmacol* 2009;65:309-14. http://dx.doi.org/10.1007/s00228-008-0600-9
7. Bolduc S, Upadhyay J, Payton, J et al. The use of tolterodine in children after oxybutinine failure. *BJU Int* 2003;91:398-401. http://dx.doi.org/10.1046/j.1464-410X.2003.04085.x
8. Hjälmås K, Hellström AL, Mogren K, et al. The overactive bladder in children: A potential future indication for tolterodine. *BJU Int* 2001;87:569-74. http://dx.doi.org/10.1046/j.1464-410X.2001.00084.x
9. Munding M, Wessells H, Thornberry B, et al. Use of tolterodine in children with dysfunctional voiding: An initial report. *J Urol* 2001;165:926-8. http://dx.doi.org/10.1016/S0022-5347(05)66576-7
10. Reinberg Y, Crocker J, Wolpert J, et al. Therapeutic efficacy of extended release oxybutynin chloride, and immediate release and long-acting tolterodine tartrate in children with diurnal urinary incontinence. *J Urol* 2003;169:317-9. http://dx.doi.org/10.1016/S0022-5347(05)64115-8
11. Nijman RJ, Borgstein NG, Ellsworth P, et al. Long-term tolerability of tolterodine extended release in children 5–11 years of age: Results from a 12-month, open-label study. *Eur Urol* 2007;52:1511-6. http://dx.doi.org/10.1016/j.eururo.2007.05.002
12. Lopez Pereira P, Miguelez C, Caffarati J, et al. Trospium chloride for the treatment of detrusor instability in children. *J Urol* 2003;170:1978-81. http://dx.doi.org/10.1097/01.ju.0000085667.05190.ad
13. Marschall-Kehrel D, Feustel C, Persson de Geeter C, et al. Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: Results of a randomized, placebo-controlled, phase 3 clinical trial. *Eur Urol* 2009;55:729-36. http://dx.doi.org/10.1016/j.eururo.2008.04.062
14. Kim WJ, Lee DG, Lee SW, et al. Efficacy and safety of propiverine in children with overactive bladder. *Korean J Urol* 2012;53:275-9. http://dx.doi.org/10.4111/kju.2012.53.4.275
15. Bolduc S, Moore K, Nadeau G, et al. Prospective, open-label study of solifenacin for overactive bladder in children. *J Urol* 2010;184:1668-73. http://dx.doi.org/10.1016/j.juro.2010.03.124
16. Nadeau G, Schröder A, Moore K, et al. Long-term use of solifenacin in pediatric patients with overactive bladder: Extension of a prospective, open-label study. *Can Urol Assoc J* 2014;8:118-23. http://dx.doi.org/10.5489/cuaj.1356
17. Hoebeke P, De Pooter J, De Caestecker K, et al. Solifenacin for therapy-resistant overactive bladder. *J Urol* 2009;182:2040-4. http://dx.doi.org/10.1016/j.juro.2009.05.100
18. Versi E, Apell R, Mobley D, et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. The Ditropan XL Study Group. *Obstet Gynecol* 2000;95:718-21. http://dx.doi.org/10.1016/S0029-7844(99)00661-4
19. Van Arendonk KJ, Knudson MJ, Austin C, et al. Improved efficacy of extended-release oxybutynin in children with persistent daytime urinary incontinence converted from regular oxybutynin. *Urology* 2006;68:862-5. http://dx.doi.org/10.1016/j.urology.2006.04.034
20. Rovner ES, Wein AJ. Once-daily, extended-release formulations of antimuscarinic agents in the treatment of overactive bladder: A review. *Eur Urol* 2002;41:6-14. http://dx.doi.org/10.1016/S0302-2838(01)00009-4
21. Van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: Superior efficacy and tolerability in the treatment of the overactive bladder. *Urology* 2001;57:414-21. http://dx.doi.org/10.1016/S0090-4295(00)01113-4
22. Homma Y, Paick JS, Lee JG, et al. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: A randomized, placebo-controlled trial. *BJU Int* 2003;92:741-7. http://dx.doi.org/10.1046/j.1464-410X.2003.04468.x
23. Omotosho T, Chen CCG. Update on tolterodine extended-release for treatment of overactive bladder. *Open Access J Urol* 2010;2:185-91. http://dx.doi.org/10.2147/OAJU.S7232
24. D'Souza AO, Smith MJ, Miller LA, et al. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. *J Manag Care Spec Pharm* 2008;14:291-301. http://dx.doi.org/10.18553/jmcp.2008.14.3.291
25. Shaya FT, Blume S, Gu A, et al. Persistence with overactive bladder pharmacotherapy in a Medicaid population. *Am J Manag Care* 2005;11:121-9.
26. Ontario Ministry of Health and Long-term Care, Update AC: Ontario Drug Benefit, December 2011, No 41, http://www.health.gov.on.ca/en/public/programs/drugs/. Accessed August 2013.

Correspondence: Dr. Stéphane Bolduc, Université Laval, Quebec City, QC, Canada; stephane.bolduc@fmed.ulaval.ca