Trends in Pharmacotherapy for Bladder Dysfunction Among Children in the United States, 2000-2013

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Abstract

Bladder-related issues such as nocturnal enuresis and incontinence have long been a part of general pediatric practice. Increasingly, clinicians are prescribing medications directed at a variety of types of bladder dysfunction, but no prior population-based data exist. We used MarketScan healthcare claims data on 32,074,638 insured children to estimate utilization patterns by age, sex, year, and geographic region in the United States from 2000-2013, and to assess related diagnosis codes. Approximately 1 in 500 children filled an antimuscarinic prescription. The most common prescriptions were for oxybutynin (78%) and tolterodine (17%). Rates were highest at ages 6-10 years (65/100,000 person-months), 31% higher for girls versus boys, peaked in 2011 (44/100,000 person-months), and were highest in the Midwest (59/100,000 person-months). 73% of children with prescriptions had diagnosis codes for genitourinary symptoms, and 13% had codes for congenital anomalies. Research is needed regarding the comparative effectiveness and safety of these drugs in children.

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INTRODUCTION

Bladder dysfunction, sometimes referred to as lower urinary tract dysfunction, is common in childhood[1] and characterized by abnormal filling and voiding of the bladder. It generally includes symptoms of urinary frequency, urgency and incontinence,[2] and often co-occurs with (nocturnal) enuresis or symptoms of bowel dysfunction including constipation.[3] For school-age children, daytime urinary incontinence can impair a child's quality of life and psychological development, and can negatively impact the family's quality of life as well.[4–7]

A large proportion of children with bladder dysfunction do not respond to conservative or behavioral therapy,[6,8] and may require further treatment to improve symptoms and avoid kidney injury. For them, first-line pharmacotherapy for bladder dysfunction includes antimuscarinic prescription medications, which decrease the frequency of smooth muscle contractions in the bladder.[9,10] Oxybutynin became the first antimuscarinic drug approved by the United States (U.S.) Food and Drug Administration (FDA) in 1975,[11] followed by tolterodine in 1998.[12] No antimuscarinic drugs have been FDA-approved for children under 5 years of age; however, immediate-release (IR) oxybutynin tablets and syrup are FDA-approved for children age 5 years and older,[13] and extended-release (ER) oxybutynin tablets are FDA-approved for children age 6 years and older[14] since they must be ingested whole.[15] At the time of this publication, no other antimuscarinics were FDA-approved for use under 18 years of age.

Currently, there are no population-based data published on antimuscarinic prescribing patterns among children. Especially amid concerns regarding potential adverse effects of antimuscarinics (e.g., new onset of constipation, dry mouth, dry eyes, flushing, cognitive impairment),[16–22] data to describe recent trends in children's utilization of these drugs are important for guiding future studies of pediatric comparative effectiveness and safety. We hypothesized that there would be differences in antimuscarinic utilization across age groups, between girls and boys, across years, and across geographic regions. Based on those hypotheses, the objective of this study was to estimate rates and trends of antimuscarinic prescription drug utilization among children in the U.S. from 2000-2013.

METHODS

Setting and participants

Data for this analysis were drawn from Truven Health Analytics' MarketScan databases (©2014 Truven Health Analytics Inc., all rights reserved), containing de-identified individual-level healthcare enrollment and claims data for inpatient, outpatient and prescription drug services in the U.S.[23] They are aggregated from >300 large employers across the U.S., are adjudicated and validated by Truven Health, and represent insured employees, their spouses, and dependents under age 65.[23,24] For this study, the study population included children under 18 years of age with prescription drug insurance coverage in the MarketScan data from 2000-2013.

We identified reimbursed prescription claims for six antimuscarinic drugs that are FDA-approved for treatment of overactive bladder in adults – oxybutynin, tolterodine, trospium,

solifenacin, darifenacin, and fesoterodine. Although oxybutynin is the only one approved for children age 5 and over, we included all six to allow for observation of potential off-label prescribing which is common in children.[25] We identified National Drug Codes for each drug by searching their generic names in National Drug Data File® Plus from First Databank (http://www.firstdatabank.com/). Appendix A contains further details on the release mechanisms (IR/ER), formulations (tablet/syrup/patch/gel), and year of FDA approval for each drug.

Measurements

We defined "claims" as individual administrative records of reimbursed prescription dispensation (i.e., fills) for any of the six antimuscarinic drugs. To standardize interpretation, we defined "prescriptions" as the days supply for each claim divided by 30, so that drug utilization could be considered on a monthly basis. For example, a claim for 90 days supply of oxybutynin was counted as three prescriptions. Finally, we defined the "utilization rate" as the number of prescriptions (i.e., 30 days supply) occurring per 100,000 months of prescription drug coverage.

Statistical methodology

We used stratified analysis methods[26] to estimate utilization rates with 99% confidence intervals (CI) for each antimuscarinic across individual years of age (0-17), sex (female/male), individual calendar years (2000-2013), and geographic region. We assessed geographic variation in utilization using two variable structures: (1) a 52-level variable for the 50 states, the District of Columbia, and Puerto Rico (henceforth, "state"); and (2) a 4-level variable for the Midwest, Northeast, South, and West Census Regions (henceforth, "region").

To contrast age groups and sexes, we estimated rate ratios (RR) with 99% CIs using negative binomial regression models, adjusted for calendar year, region, and either age or sex depending on the model. To estimate RRs, instead of Poisson models which imply strict assumptions about rate variability, we used negative binomial models which relax assumptions. To assess the relation between age and antimuscarinic utilization separately for boys and girls, we stratified by sex and then adjusted for calendar month and region. These adjusted regression models were sufficient because age and sex distributions did not vary across years or states.

To assess trends in utilization over time from 2000-2013, we again used stratified analysis[26] to estimate rates and RRs with 99% CIs. The geographic distribution of MarketScan data changed significantly over the years of the study; to examine time trends in utilization that were independent of those geographic shifts in the data, we weighted the state-specific rates based on each state's contribution of person-time to the nationwide Marketscan data from 2013. We standardized to 2013 because in that year, the state-level person-time distributions in MarketScan data were similar to the distributions of all U.S. children with employer-sponsored health insurance, according to the 2013 Current Population Survey (http://www.census.gov/cps/data/cpstablecreator.html) (Appendix B).

Last, we assessed diagnosis codes occurring proximal to children's first antimuscarinic prescription, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We retrieved diagnosis codes from the most recent inpatient or outpatient physician visit within 30 days before the date of a child's first antimuscarinic prescription reimbursement. We identified these first antimuscarinic prescriptions by including (1) claims that were not adjudicated in the database as a refill, and (2) claims for antimuscarinic drugs that were not preceded by any other antimuscarinic prescriptions in the child's available history. We grouped the diagnosis codes according to the U.S. Agency for Healthcare Research and Quality's Clinical Classifications Software (CCS) (Agency for Healthcare Research and Quality, Rockville, MD; https://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixCMultiDX.txt), and computed the percent of children in each diagnosis code group. Appendix C contains further information on diagnosis code groups.

Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). This study was reviewed by the institutional review board at the University of North Carolina at Chapel Hill (study # 10-0153) and found to be exempt.

RESULTS

From 2000-2013, we assessed 32,074,638 children over a total of 840,757,277 person-months (PM) of prescription drug coverage. Approximately 1 in 500 children filled an antimuscarinic prescription; 74,976 unique children filled a total of 347,159 prescriptions (i.e., equivalent to 30 days supply). From 2000-2013, 31.5% of these prescriptions were off-label, either because they were for an antimuscarinic other than oxybutynin (22.8%), or because they were for children under the minimum FDA-approved age for oxybutynin prescriptions (8.7%). Table 1 shows crude utilization rates for all antimuscarinics by calendar year, sex, age, and U.S. Census Region.

Age differences

Age-specific utilization rates are shown separately for girls and boys in Figure 1. Up to age 2, rates were stable for both girls and boys at 9.0 prescriptions per 100,000 PM (99% CI: 8.6–9.4). From age 2-5, rates for girls increased by 79% per year of age (RR=1.79; 99% CI: 1.75–1.82) and rates for boys increased by 59% per year of age (RR=1.59; 99% CI: 1.56–1.63).

At age 7, rates peaked for girls at 81.1 per 100,000 PM (99% CI: 79.6–82.7), which was higher than the peak for boys at age 8 (rate=63.0; 99% CI: 61.7–64.3). Boys' rates decreased from age 8 through 17. Girls' rates decreased from the peak at age 7 only until age 13; from age 14 through 17, girls' rates increased again by 5% per year of age (RR=1.05; 99% CI: 1.03–1.06).

Antimuscarinic types varied across age groups. For children age 4 years and older, the relative distribution of drug-specific utilization rates at each age was proportional to the overall distribution shown in Figure 2 (data not shown). Among children age 3 years and younger, however, 99% of antimuscarinic prescriptions were for oxybutynin syrup.

Sex differences

Overall age-, state-, and month-adjusted utilization rates were 31% higher for girls compared to boys (RR=1.31; 99% CI: 1.29–1.33; Figure 1). Comparing adjusted RRs for sex across years, the RR was stable from 2000-2003 (average RR=1.52, average 99% CI: 1.29–1.73), but sex differences in utilization rates decreased over time through 2013 (RR=1.12; 99% CI: 1.04–1.21). Drug-specific utilization rates were similar between girls and boys with respect to increasing age and changes over calendar time. The distributions of prescriptions and claims per child were similar for boys and girls (data not shown), indicating that sex differences in rates were driven primarily by a larger number of girls filling prescriptions compared to the number of boys, rather than by girls filling multiple prescriptions more than boys doing so.

Calendar time trends

For all antimuscarinic types combined, utilization rates increased during the early 2000s but remained largely stable after the mid-2000s. Taken separately, each antimuscarinic type exhibited a distinct time trend. Figure 2 shows state-standardized utilization rates by month for all antimuscarinics (top curve), and separately by each antimuscarinic type (lower curves).

Over the entire study period, oxybutynin IR syrup (22%), IR tablets (22%), and ER tablets, patches and gels (34%) were the most commonly prescribed antimuscarinics; tolterodine IR tablets (3%) and ER tablets (14%) were less common. Of note, in the mid-2000s, the FDA approved four new antimuscarinics (trospium, solifenacin, darifenacin and fesoterodine) for use in adults.[12] After 2005, oxybutynin's share of overall prescribing increased monotonically from 75% to 82%, while tolterodine's share decreased monotonically from 24% to 10%.

From 2000-2004, as prescribing shifted from IR oxybutynin to ER oxybutynin and ER tolterodine, state-standardized utilization rates for all antimuscarinics combined increased by 7% per year (average RR=1.07; 99% CI: 1.03–1.12). From 2004-2011, rates were stable but drug-specific trends varied. From 2011-2013, overall prescribing decreased by 3% per year (average RR=0.97; 99% CI: 0.95–0.99), driven by decreasing rates for ER tolterodine.

Geographical differences

The map in Figure 3 shows rates across the U.S., averaged over all years of the study. Rates were lowest in the West Census Region and highest in the Midwest, which comprised the five highest state-level rates: Minnesota (73 per 100,000 PM), Indiana (69), Ohio (68), Kansas (66), and Iowa (61). Forty-one states had rates between 20 and 53 prescriptions per 100,000 PM. Although average rates varied across geographic regions, time trends for all antimuscarinics combined (depicted by black curve in Figure 2) were similar across most states (data not shown).

Diagnosis codes

Eighty-five percent of children who filled an antimuscarinic prescription had at least one diagnosis code from within 30 days before their first observed prescription fill. Among

children with available diagnosis codes, across all ages, 73% had codes for genitourinary diseases, including urinary incontinence/urgency (20%), urinary frequency (14%), urinary tract infection (13%), and nocturnal enuresis (10%); 13% had diagnosis of congenital anomalies. Compared to school-age children whose diagnosis codes often reflected genitourinary disease, children under 4 years of age more often had codes related to congenital anomalies, acute postoperative pain, and vesicoureteral reflux. Table 2 shows the percent of children in each group of ICD-9-CM diagnosis codes, stratified by age group (0-3 years versus 4-17 years). In a *post hoc* sensitivity analysis of diagnosis codes within 7 days of prescription (instead of 30 days), results were similar to those shown in Table 2 (data not shown).

DISCUSSION

Our analysis provides novel information regarding trends in pediatric utilization of antimuscarinic prescription drugs from 2000-2013. These drugs are being prescribed to children for a wide variety of indications, with widely variable prescribing rates across the U.S. Prescribing is frequently off-label and there is not a strong evidence-base of effectiveness in pediatric populations.[27] IR oxybutynin was most commonly prescribed, followed closely by ER oxybutynin.

From 2000-2013, we found that state-standardized prescribing rates of all antimuscarinics increased by 7% annually from 2000-2004, remained stable from 2004-2011, and decreased slightly over the last two years of the study. Drug-specific trends over calendar time were all unique, but most variation occurred prior to 2005. During the 14-year study period, several new antimuscarinics were approved for adults, but prescribing in children did not seem to accelerate for those medications. It is unclear why these prescribing trends have fluctuated.

Rates of prescriptions were higher for girls than boys, though the size of the difference between girls and boys varied across age groups. Rates were highest among children 6-10 years of age, and likely reflect higher prevalence of symptomatic bladder dysfunction in this age range, which corresponds to the hypothesized peak for overactive bladder incidence between 5-7 years of age.[1] This age range is also where social expectation is for complete continence, so incontinence or other bladder symptoms are potentially more likely to be brought to the attention of a physician. The concentration of prescribing ("peakedness") was highest for girls in this age range, and was also shifted toward younger ages for girls compared to boys.

Compared to children age 4 years and over, children under age 4 had higher prevalence of diagnosis codes for congenital anomalies (e.g., hypospadias, congenital chordee, spina bifida), and 99% of their antimuscarinic prescriptions were for oxybutynin syrup. Future studies of safety and effectiveness of antimuscarinic drugs should consider children age 3 years and under a unique subgroup in the pediatric population.

Rates of antimuscarinic utilization varied considerably by geographic region, with highest rates in the Midwest. Although no prior data on regional variation exist for antimuscarinic drugs, nationwide studies of psychotropic prescriptions in the U.S. have described

geographic variation among commercially-insured children[28,29] and children in Medicaid,[30] with highest rates in the Midwest and South; however, data from the National Ambulatory Medical Care Survey demonstrated highest pediatric psychotropic rates in the South and Northeast.[31] It is unclear why rates would vary by region. Future research of antimuscarinics should consider potential geographic variation in use, including differences between urban and rural settings.

There is mixed evidence in the literature on the effectiveness of oxybutynin therapy for treatment of bladder dysfunction in children,[27] and the efficacy of tolterodine has not been demonstrated.[22] Additionally, there is mounting concern regarding potential adverse effects of antimuscarinics (e.g., new onset of constipation, dry mouth, dry eyes, flushing, cognitive impairment, urinary tract infection) in children[16–18,22] and adults.[19–22] Constipation in particular is a concerning side effect in this population since it can lead to rectal distension and alteration of pelvic floor dynamics which can then lead to or exacerbate bladder dysfunction.[3] Given our data on changes in prescribing patterns of antimuscarinics in recent years, and differences between population subgroups, these safety concerns can be assessed more effectively in future studies.

Several limitations should be considered when interpreting results from this analysis. First, these data reflect reimbursed prescription claims. This study was therefore not designed to address the actual consumption, discontinuation rates of antimuscarinic medications, or prescriptions written by healthcare providers, as some prescriptions may not be filled (an issue[32] that has previously been described). Second, we evaluated claims for medications that have been FDA-approved for treatment of bladder dysfunction in adults. However, since a significant amount of pediatric prescribing is off-label, there may be other antimuscarinic medications that clinicians try for bladder symptoms in children that are not included in our analysis. Potential examples of those drugs could include antihistamines, which also have antimuscarinic properties, or dicyclomine, another anticholinergic. Additionally, other non-antimuscarinic medications are sometimes prescribed for bladder-related symptoms such as tricyclic antidepressants (imipramine) or desmopressin for nocturnal enuresis. Third, this study assessed a special segment of the child population, specifically those who have prescription drug coverage under a parent's employer-provided insurance. Therefore these rates and trends are likely not generalizable to populations with Medicaid or no insurance. Fourth, our data cannot elucidate the severity of symptoms or the point in the continuum of care when children were prescribed drugs because (1) diagnosis code data could represent potential indications for treatment as well as comorbidities and rule-out diagnoses, and (2) claims data are unlikely to reflect conservative treatments which were likely tried prior to prescribing.[33] These include voiding behavior modification or treatment of comorbid constipation[33,34] which, if necessary for children with combined bowel and bladder dysfunction, often involve laxative medications available over-the-counter. While social stress[4–7,35,36] or parents' frustration[27,37–40] may result in initiation of antimuscarinic drugs, the limitations of these data preclude us from speculating on these reasons.

The strengths of this study include the comprehensive data on prescription claims and insurance enrollment data for a large portion of the U.S. pediatric population, providing population-based estimates of antimuscarinic drug utilization for the dependents of insured

employees in the U.S. The trends presented in this analysis describe 14 years of prescribing changes during a period when prescribing practices for children's bladder dysfunction were in flux. Differences in prescribing by age, sex, time period, and geographic region are reported using rates estimated in a well-defined pediatric population.

Bladder antimuscarinic utilization for children varied considerably during the study period, was higher for girls than boys, and occurred most commonly among children age 6-10 years. The data presented in this paper can be used to guide needed research on the comparative effectiveness and safety of antimuscarinic drugs in children, compared to other pharmacologic and behavioral treatments for bladder dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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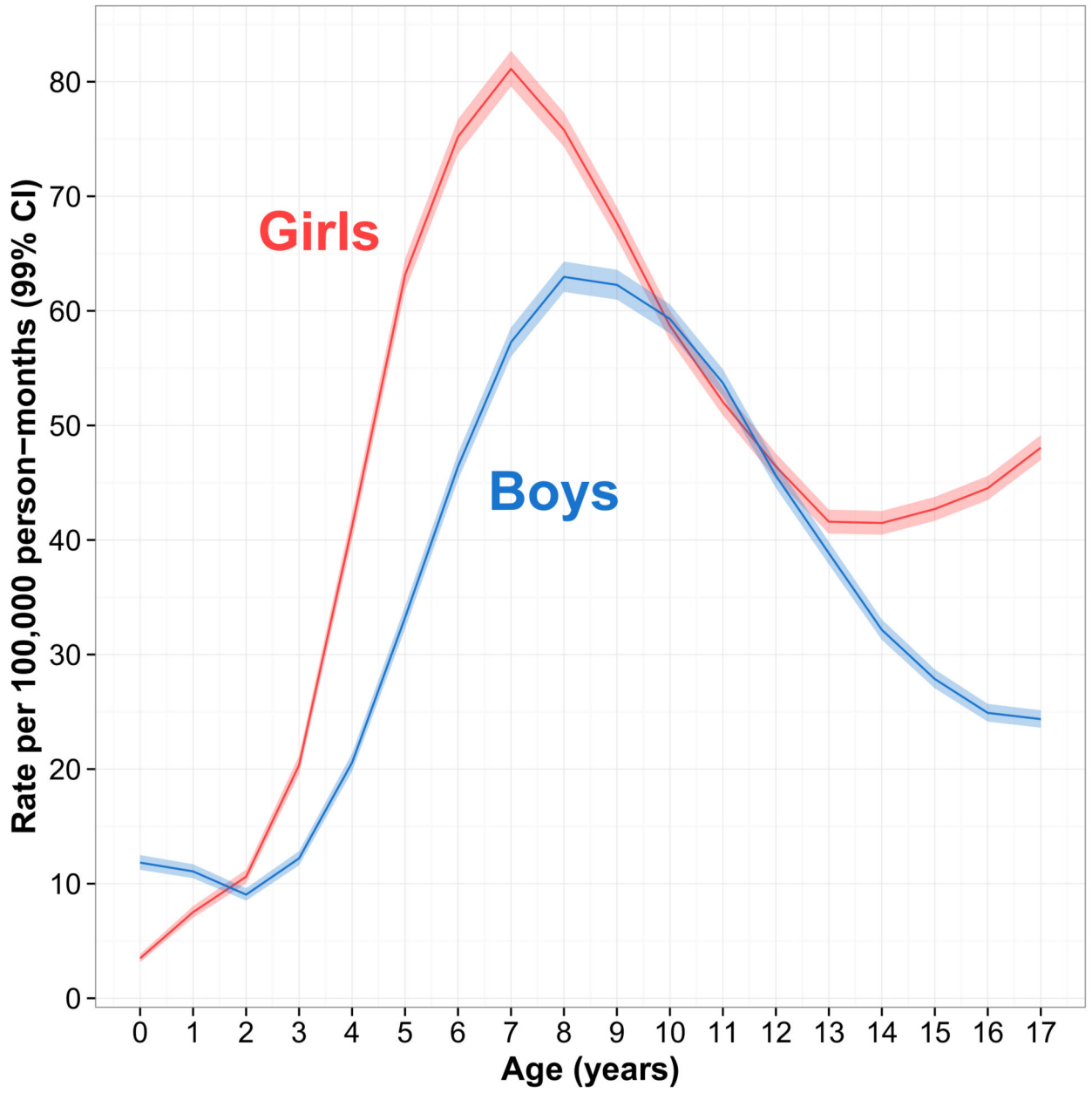
Figure 1.
Antimuscarinic drug utilization rates (per 100,000 PM) and 99% CI for children, stratified by age and sex, all antimuscarinic drugs combined, U.S. 2000-2013.

Figure 2.
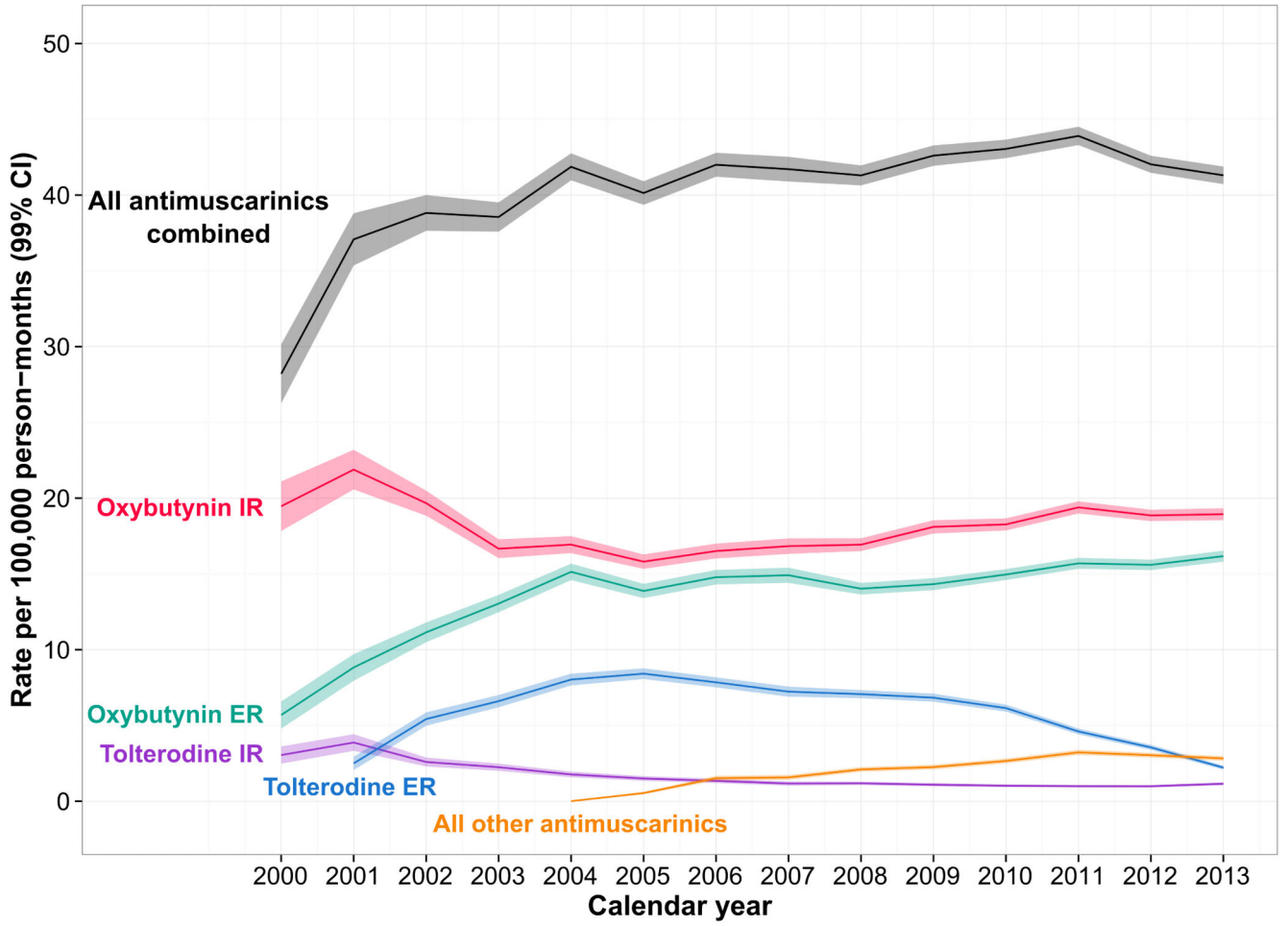Antimuscarinic drug utilization rates (per 100,000 PM) and 99% CI for children aged 0-17 years, by calendar year and drug type, standardized to the state-level geographic distribution of pediatric person-time in MarketScan data in 2013, U.S. 2000-2013.
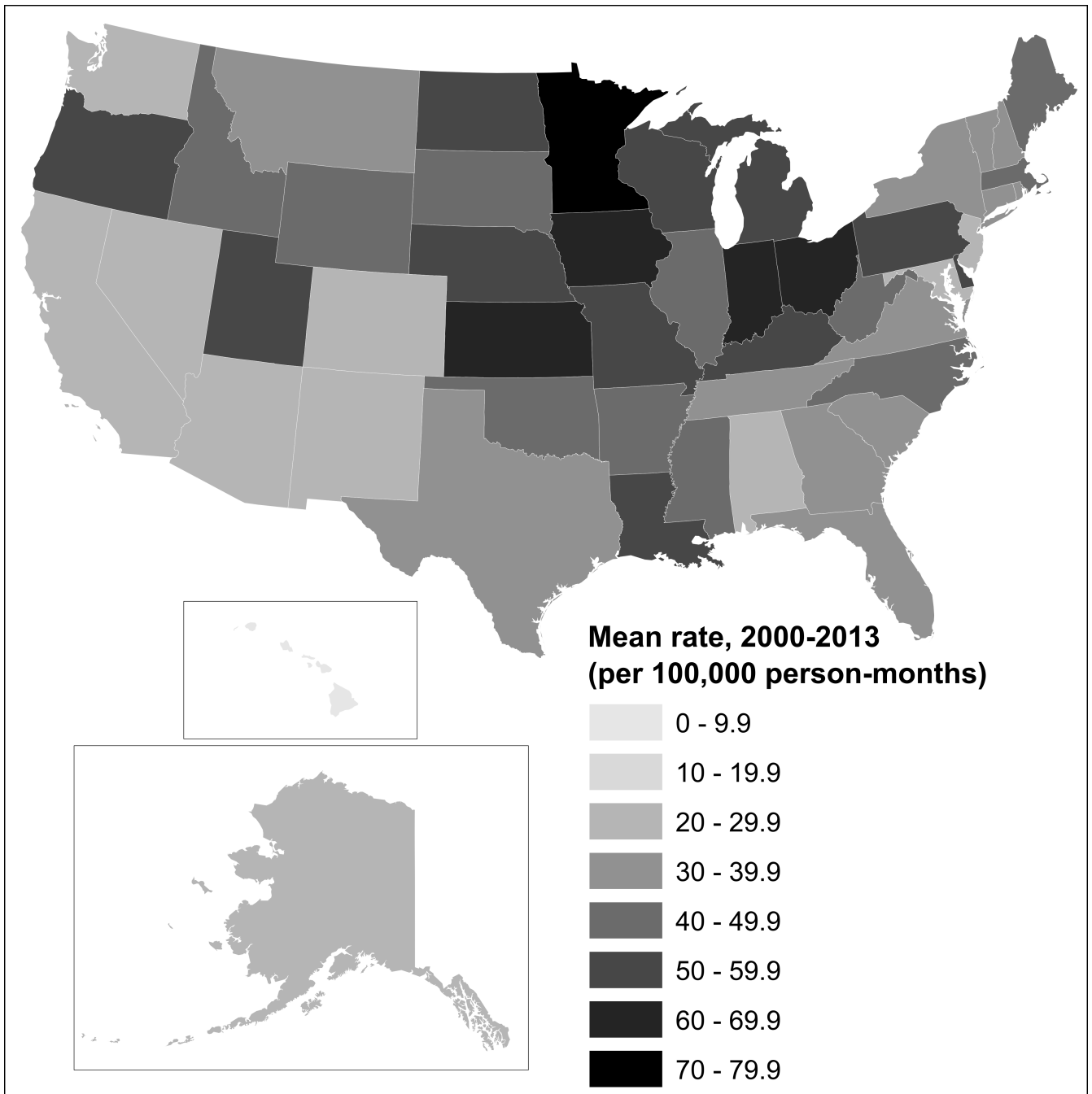
Figure 3.
Antimuscarinic drug utilization rates (per 100,000 PM) by state, for children aged 0-17 years, all antimuscarinic drugs combined, U.S. 2000-2013.

Table 1

Demographic Characteristics and Crude Utilization Rates of Antimuscarinic Drugs among Children Aged 0-17 Years, U.S. 2000-2013.

Characteristic	Person-months[a] (%) (total = 840,757,277 PM)		Utilization rate[b] (99% CI)[c]	
Calendar year				
2000	8,563,392	(1.0%)	31.1	(29.6–32.7)
2001	13,386,132	(1.6%)	36.6	(35.3–38.0)
2002	25,297,074	(3.0%)	39.3	(38.3–40.4)
2003	38,413,700	(4.6%)	36.2	(35.5–37.0)
2004	47,944,256	(5.7%)	39.0	(38.3–39.8)
2005	55,008,082	(6.5%)	38.9	(38.3–39.6)
2006	54,459,625	(6.5%)	41.9	(41.2–42.6)
2007	54,800,274	(6.5%)	40.8	(40.1–41.5)
2008	85,119,109	(10.1%)	41.6	(41.0–42.2)
2009	84,117,998	(10.0%)	42.9	(42.3–43.5)
2010	90,032,506	(10.7%)	43.0	(42.4–43.5)
2011	98,600,946	(11.7%)	43.9	(43.3–44.4)
2012	101,490,509	(12.1%)	41.9	(41.4–42.4)
2013	83,523,674	(9.9%)	41.2	(40.7–41.8)
Sex				
Female	411,161,868	(48.9%)	46.8	(46.5–47.1)
Male	429,595,410	(51.1%)	36.0	(35.8–36.2)
Age (years)				
0-1	75,246,594	(8.9%)	8.6	(8.3–8.9)
2-3	81,072,523	(9.6%)	13.0	(12.7–13.4)
4-5	85,973,556	(10.2%)	39.3	(38.8–39.9)
6-7	89,973,676	(10.7%)	64.8	(64.1–65.4)
8-9	93,972,718	(11.2%)	67.1	(66.4–67.7)
10-11	97,881,287	(11.6%)	55.9	(55.3–56.5)
12-13	102,070,080	(12.1%)	43.1	(42.5–43.6)
14-15	105,665,013	(12.6%)	35.9	(35.4–36.4)
16-17	108,901,832	(13.0%)	35.2	(34.8–35.7)
Census Region				
Midwest[d]	214,024,126	(25.5%)	59.4	(59.0–59.9)
Northeast[e]	110,520,931	(13.1%)	38.8	(38.3–39.3)
South[f]	334,555,957	(39.8%)	37.5	(37.2–37.8)
West[g]	171,393,532	(20.4%)	27.8	(27.5–28.1)
Not specified	10,262,731	(1.2%)	38.4	(36.8–40.0)

Abbreviations: PM, person-months; CI, confidence interval.

[a] Demographic characteristics weighted by total PM for each characteristic rather than the number of children, because children contributed varying amounts of follow-up time.

[b]Number of 30-day prescriptions per 100,000 PM of prescription drug coverage.

[c]99% CI = $e^{\ln(\text{prescriptions/PM}) \pm 2.576 \times (1/\text{prescriptions})} \times 100{,}000$

[d]Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI.

[e]Northeast: CT, ME, MA, NH, NJ, NY, PA, RI, VT.

[f]South: AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV.

[g]West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.

Table 2

Percent of Children in Each Diagnosis Category, Stratified by Age, U.S. 2000-2013.

Diagnosis code category[b] -Selected specific sub-categories[c]	Percent of children[a] (%)	
	Age 0-3 years (n=9,376)	Age 4-17 years (n=54,494)
Diseases of the genitourinary system	60.9	75.2
-Urinary incontinence/urgency	4.2	22.6
-Urinary frequency	6.4	15.7
-Urinary tract infection	10.4	13.3
-Nocturnal enuresis	0.9	11.0
-Dysuria	4.9	6.2
-Vesicoureteral reflux	14.1	4.4
-Calculus of urinary tract	0.6	2.5
-Nocturia	0.1	0.6
-Other diseases of bladder and urethra	10.8	13.7
-Other diseases of kidney and ureters	6.6	3.1
Congenital anomalies	56.5	6.0
-Hypospadias	41.1	0.9
-Congenital chordee	14.7	0.2
-Spina bifida	3.3	1.6
Symptoms, signs, ill-defined conditions and factors influencing health	9.8	11.4
-Routine child health exam	1.3	4.5
-Abdominal pain	3.3	2.7
Diseases of the nervous system and sense organs	16.6	5.3
-Acute postoperative pain	12.5	0.7
Diseases of the digestive system	5.3	6.3
-Constipation	1.5	4.4
Diseases of the respiratory system	4.3	6.4
Mental illness	1.0	6.7
-Enuresis/encopresis	0.4	2.3
-Attention-deficit disorder	0.0	2.0
11 other categories combined[d]	11.1	13.9

Abbreviation: CCS, Clinical Classification Software.

[a] Among 74,976 children with an antimuscarinic prescription, 63,870 had an inpatient or outpatient visit   30 days before their first antimuscarinic prescription. Column percents do not sum to 100 because children could have multiple diagnosis codes from their physician visit.

[b] Based on Level 1 from Multi-level Diagnosis Categories in CCS.

[c] Based on Levels 2 and 3 of Multi-level Diagnosis Categories in CCS (see eMethods).

[d] Includes: infectious and parasitic diseases (3.3%); injury and poisoning (2.1%); diseases of the musculoskeletal system and connective tissue (1.9%); diseases of the skin and subcutaneous tissue (1.6%); endocrine, nutritional, and metabolic diseases and immunity disorders (1.6%); residual codes, unclassified codes, and external causes of injury (1.3%); neoplasms (0.7%); diseases of the circulatory system (0.6%); diseases of the blood

and blood-forming organs (0.2%); certain conditions originating in the perinatal period (0.2%); and complications of pregnancy, childbirth, and the puerperium (0.1%). Percentages are pooled because age-stratified percentages did not differ by more than 2% for any of these categories.