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COMPARATIVE SAFETY OF ANTIMUSCARINICS AMONG ADULTS IN THE UNITED STATES, 2000–2011

Hypothesis / aims of study
Antimuscarinics are first-line pharmacotherapy for overactive bladder. There are limited population-based comparative safety data for antimuscarinics, particularly among older adults who are at increased risk of adverse effects. Our aim was to compare rates of diagnosis codes for cognitive decline and constipation among new users of antimuscarinics.

Study design, materials and methods
Using longitudinal healthcare claims in Truven Health Analytics' MarketScan and Medicare Supplemental Commercial Claims and Encounters healthcare databases from 2000 to 2011, we identified new users of antimuscarinics among women and men age 50 years and over. We defined new users as individuals receiving an antimuscarinic prescription with no prior prescriptions for an antimuscarinic in the previous year. Antimuscarinics assessed included oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine.
We excluded individuals with a diagnosis during the prior year for either cognitive decline or constipation, as these were the outcomes of interest. Additionally, we excluded those with a diagnosis in the prior year for dry mouth because it is a known side effect of antimuscarinics. We also excluded those with a diagnosis of the following conditions which may potentially cause constipation: malignant neoplasm of the colon (ICD-9 code 153) or the rectum, rectosigmoid junction or anus (154) or other intestinal malabsorption (579.8, 579.9).
Because cognitive decline and constipation were not competing risks, we assessed these as separate outcomes of interest. ICD-9 codes for cognitive decline included Alzheimer's disease (331.0), frontotemporal dementia (331.1), unspecified cerebral degeneration (331.9), senility (797), dementia (290, 294.1), other mental disorders (294.8, 294.9), cognitive deficits (438.0), cognitive communication deficit (799.52), and reactive confusion (298.2). The ICD-9 code for constipation was 564.0.
We followed each individual from initial antimuscarinic prescription for up to one year. During the year of follow-up, we considered an individual to have the outcome of interest if there were two occurrences of a diagnosis code for the same outcome of interest (i.e., either cognitive decline or constipation). We used the date of the first diagnosis as the date of outcome occurrence.
We used Kaplan-Meier curves to estimate cumulative risks for each outcome at one year. Individuals were censored if they changed insurance provider or were no longer insured. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), stratified by sex and adjusted for age. For our analysis, we compared extended release (ER) formulations with ER oxybutynin as the referent drug group. We also compared immediate release (IR) to ER formulations with ER as the referent group. To compute our power to detect clinically relevant associations, we estimated our power to detect hazard ratios of ≥ 1.30. For both cognitive decline and constipation, we had > 95% power to detect a HR ≥ 1.30 when comparing ER formulations of tolterodine, solifenacin and darifenacin to ER oxybutynin for both men and women. Due to fewer individuals receiving prescriptions for trospium and fesoterodine, power for comparisons of those drugs compared to ER oxybutynin ranged from 38-74% for cognitive decline and 21-55% for constipation. We had > 99% power to detect a HR ≥ 1.30 comparing IR and ER formulations.

Results
There were 590,500 eligible, new users of antimuscarinics: 69% were female, with a median age of 67 years (interquartile range: 59–78). Approximately 69% had uninterrupted healthcare coverage for the full year of follow-up after antimuscarinic prescription; the other 31% were followed for an average of 179 days. The majority of formulations were extended-release (ER, 78%) compared to immediate-release (IR, 22%) antimuscarinics. Tolterodine (43%) and oxybutynin (33%) were the most common medications, compared to solifenacin (15%), darifenacin (7%), trospium (3%), and fesoterodine (1%).
The 1-year cumulative risks for cognitive decline and constipation were 2.1% and 1.3%, respectively, based on diagnosis codes. Incidence of cognitive decline was similar among ER drugs compared to ER oxybutynin (Table 1) Compared to ER drugs, IRs had similar rates for cognitive decline (females: HR 0.96, 95% CI 0.90–1.01; males: HR 0.96, 95% CI 0.89–1.03).
Compared to ER oxybutynin, incidence of constipation was higher for solifenacin, darifenacin, and trospium, but similar for tolterodine (Table 2). Compared to ER drugs, IRs had similar rates for constipation (females: HR 0.95, 95% CI 0.88–1.03; males: HR 0.96, 95% CI 0.87–1.06).

Table 1. Hazard ratios (HR) and 95% confidence intervals (CI) of codes for cognitive decline among extended release formulations, stratified by sex

	Females		Males	
Formulation	HR	95% CI	HR	95% CI
Oxybutynin	1.00 (ref)	–	1.00 (ref)	–
Tolterodine	1.04	0.97–1.12	1.00	0.91–1.10
Trospium	1.14	0.89–1.46	1.10	0.86–1.41
Solifenacin	1.04	0.95–1.14	1.04	0.92–1.16
Darifenacin	1.06	0.95–1.18	1.06	0.92–1.22
Fesoterodine	1.48	0.76–2.86	0.70	0.22–2.18

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) of codes for constipation among extended release formulations, stratified by sex

	Females		Males	
Formulation	HR	95% CI	HR	95% CI
Oxybutynin	1.00 (ref)	–	1.00 (ref)	–
Tolterodine	1.01	0.92–1.10	0.96	0.84–1.09
Trospium	2.02	1.61–2.54	1.71	1.28–2.29
Solifenacin	1.17	1.05–1.30	1.18	1.01–1.37
Darifenacin	1.34	1.18–1.52	1.37	1.14–1.64
Fesoterodine	1.22	0.81–1.84	1.19	0.59–2.41

Interpretation of results

With respect to drug-specific antimuscarinic associations with cognitive decline and constipation, there were negligible differences by sex. Differential antimuscarinic treatment was not associated with meaningful change in rates of diagnosis for cognitive decline. Estimates for the association between fesoterodine and cognitive decline were imprecise and subject to small sample bias. Regarding constipation, trospium and darifenacin had elevated rates of constipation diagnosis. This apparent association may be due to selective prescribing of these medications to individuals based on concurrent anticholinergic medication use or their underlying health status, and may not be indicative of a causal association between these drugs and constipation outcomes.

Given the large study size for this investigation, we were specifically interested in hazard ratios denoting differences in outcome occurrence of 30% or more between treatment groups. We felt that this effect size was clinically relevant, whereas more modest effects may be statistically significant but not necessarily be clinically relevant in this large dataset.

Concluding message

There were similarities in rates of diagnosis codes for cognitive decline among different antimuscarinic drugs. There were meaningful differences in rates of codes for constipation between different extended-release medications with lowest levels for oxybutynin and tolterodine. Further research is needed to determine whether these differences are the result of differences in the patients to whom these medications are prescribed, or to differences in the effects of the medications themselves.

Disclosures

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