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Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes

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Abstract

OBJECTIVES—To determine the cognitive and functional consequences of dual use of cholinesterase inhibitors (ChIs) and the bladder anticholinergics oxybutynin or tolterodine.

DESIGN—Prospective cohort study.

SETTING—Nursing homes (NHs) in the state of Indiana.

PARTICIPANTS—Three thousand five hundred thirty-six Medicaid-eligible NH residents aged 65 and older taking a ChI between January 1, 2003, and December 31, 2004. Residents were excluded if they were taking an anticholinergic other than oxybutynin or tolterodine.

MEASUREMENTS—Indiana Medicaid claims data were merged with data from the Minimum Data Set (MDS). Repeated-measures analyses were performed to assess the effects of dual therapy on change in cognitive function measured using the MDS Cognition Scale (MDS-COGS; scored 0–10) and change in activity of daily living (ADL) function using the seven ADL items in the MDS (scored 0–28). Potential covariates included age, sex, race, number of medications, and Charlson Comorbidity Index score.

RESULTS—Three hundred seventy-six (10.6%) residents were prescribed oxybutynin or tolterodine concomitantly with a ChI. In residents in the top quartile of ADL function, ADL function declined an average of 1.08 points per quarter when not taking bladder anticholinergics (ChI alone), compared with 1.62 points per quarter when taking dual therapy, a 50% greater rate in

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quarterly decline in ADL function (P =.01). There was no excess decline attributable to dual therapy in MDS-COGS scores or in ADL function for residents who started out with lower functioning.

CONCLUSION—In higher-functioning NH residents, dual use of ChIs and bladder anticholinergics may result in greater rates of functional decline than use of ChIs alone. The MDS-COGS may not be sensitive enough to detect differences in cognition due to dual use.

Keywords

dementia; incontinence; pharmacotherapy; anticholinergics; cholinesterase inhibitors

Older adults, particularly those in nursing homes (NHs), are likely to have multiple medical conditions requiring complex medical management that can lead to therapeutic dilemmas. For example, two of the most common medical conditions in NH residents are dementia and urinary incontinence (UI), and they often coexist.[1,2] Cholinesterase inhibitors (ChIs) are commonly prescribed to persons with dementia to reduce rates of cognitive and functional decline by increasing acetylcholine levels at brain synapses, but therapeutic agents that are used to treat conditions that frequently coexist with dementia, such as UI, may reduce potential beneficial effects of ChIs. The agents typically used to treat UI have anticholinergic properties, acting on muscarinic receptors to decrease acetylcholine. Thus, anticholinergics and ChIs are in pharmacological opposition, and the simultaneous pharmacological treatment of dementia and UI could lead to reduced effectiveness of one or both drugs.

Although dual use of ChI and anticholinergics occurs for as many as one-third of persons with dementia,[3,4] the extent to which dual use of these drugs is associated with excess cognitive and functional deterioration has not been determined. Prior studies have demonstrated that use of anticholinergics, including bladder anticholinergics, is associated with cognitive impairment in persons with dementia,[5–7] but data documenting outcomes in patients concomitantly taking ChIs and anticholinergics are limited to case reports and small observational studies.[8–10] In addition, prior studies have typically been conducted over short intervals and have not determined whether long-term use of anticholinergics is associated with greater rates of cognitive and functional decline over time.[11]

The goals of this study were, therefore, to examine changes in function in activities of daily living (ADLs) and cognition over time in NH residents taking ChIs while receiving concomitant therapy with a bladder anticholinergic (dual use) and in those taking ChIs without a bladder anticholinergic. It was hypothesized that the bladder anticholinergics oxybutynin and tolterodine would decrease the efficacy of ChIs with respect to cognitive and functional outcomes. Loss of functioning in persons with dementia is costly to consumers and the government.[12] Information is needed regarding prescribing practices that may accelerate rates of cognitive and functional decline in persons with dementia.

METHODS

Subjects and Study Design

Medicaid eligibility and claims data from the Indiana Family and Social Services Administration were merged with Minimum Data Set (MDS) data from the Social Services Administration to create a data set with detailed drug prescription claims data (Medicaid) and clinical data (MDS). Identifying information was replaced with unique identifiers to protect the privacy of patients' health information. The institutional review board at Purdue University approved the study.

Subjects were included if, between January 1, 2003, and December 31, 2004, they were eligible for Indiana Medicaid benefits, were aged 65 and older, had at least two consecutive prescriptions for a ChI (donepezil, galantamine, rivastigmine, or tacrine), and had at least two consecutive NH MDS assessments while continuously taking a ChI. Subjects were excluded if they were taking an anticholinergic other than oxybutynin or tolterodine during the period in which they contributed data to the analyses.[3,4,13] Derivation of the cohort of 3,536 residents who met the inclusion criteria is diagrammed in Figure 1.

The starting date of each subject's study interval was defined as the date of the first nonadmission MDS assessment after the resident's first prescription for a ChI between January 1, 2003, and December 31, 2004. The admission assessment was not included, because functioning at the admission assessment may be temporarily depressed because of the acute illness or event that precipitated the NH placement. The end date of the study interval was the last MDS assessment before discontinuation of the ChI, initiation of an anticholinergic other than the bladder anticholinergics oxybutynin or tolterodine, or December 31, 2004, whichever came first. Only assessments that occurred while the subject was continuously taking a ChI were included in the analyses. Based on the dates of claims for prescriptions and the number of tablets dispensed, the assumption was made that the ChI use was continuous if a refill of the ChI was obtained within 60 days after exhausting the supply from the previous prescription.[14] If subjects were continuously taking a ChI between January 1, 2003, and December 31, 2004, they could contribute as many as 2 years of assessment data to the analyses.

Measures

Predictors—The two predictor variables were the number of days of continuous ChI use without dual use of a bladder anticholinergic and the number of days of continuous ChI use with dual use of oxybutynin or tolterodine. Because change in function between adjacent MDS assessments was modeled, the number of days the subject was continuously taking a ChI was computed as the number of days between two consecutive MDS assessments during which the subject was continuously taking a ChI. Similarly, the number of bladder anticholinergic days was computed as the number of days between consecutive MDS assessments in which the subject was simultaneously taking oxybutynin or tolterodine and a ChI. When computing the number of days of bladder anticholinergic use, it was assumed that the subject was continuously taking the drug between the first day the prescription was filled until the prescription was exhausted.

The coefficients for the predictor variables represent the daily changes in the outcome when taking or not taking dual therapy. The difference between the coefficients represents the additional change in the outcome associated with dual therapy. Because the MDS assessments were generally made quarterly, the coefficients were multiplied by 90 to present the amount of change per quarter rather than per day.

Outcomes—This study had two primary outcomes. First, level of functioning in ADLs was determined using the MDS ADL-Long Form,[15] which included assessments of dressing, personal hygiene, toileting, transferring, bed mobility, eating, and locomotion on the unit. Each ADL item was scored from 0 to 4, with 0 reflecting complete independence and 4 reflecting complete dependence. The scores were summed to create a scale score that ranged from 0 to 28, with higher scores indicating greater dependence. The ADL-Long Form has been shown to be reliable ($\alpha = 0.94$) and sensitive to change over time.[15] ADL assessments occurred quarterly and when there was significant change in the patient's health status.

The second primary outcome was change in cognitive functioning as measured with the MDS-Cognition Scale (MDS-COGS).[16] The MDS-COGS score was generated from seven items that assessed short- and long-term memory, orientation, communication, and dressing. Those items were scored 0 to indicate no disability in that area of functioning or 1 to indicate disability in that area of functioning. The scale score also included a 3-point item that reflected the subject's ability to make decisions, with 0 reflecting the ability to make decisions, 1 reflecting mild disability, and 2 reflecting inability to make decisions. Scores were summed and ranged from 0 to 10, with higher scores indicating worse cognition. The instrument has good internal consistency ($\alpha = 0.85$)[17] and has been validated against the Mini-Mental State Examination (MMSE).[16,17] The MDS-COGS was also obtained quarterly and whenever there was significant change in the patient's health status.

Covariates—Variables that might explain the relationship between dual use of ChIs and anticholinergics and cognitive or functional decline were considered. They were sex, age (65–74, 75–79, 80–84, 85–89, and ≥90), race (white or other), and the number of medications used in the 7 days before the first assessment. These variables were obtained from the MDS data. A modified Charlson Comorbidity Index[18] was calculated based on claims data from the 12 months before the start of each subject's study interval. This modified Charlson index was computed using an algorithm validated with administrative claims data.[19] Scores were categorized as 0, 1, or 2 or greater, with higher scores indicating greater number and severity of comorbidities.

Statistical Analysis

To assess the effects of dual therapy on change in ADL function over time, repeated-measures analyses were performed. Piecewise linear regression was used to model the change between each adjacent pair of observations of ADL functioning. Predictors were the number of days taking and not taking dual therapy between the adjacent observations. To allow rates of change to vary for different levels of functioning at the beginning of the interval, the interactions between time taking dual therapy and ADL category at the start of

each interval and between time not taking dual therapy and ADL category at the start of the interval were included. ADL category was categorized according to quartiles (0–5 was considered to reflect little or no dependence, 6–12 moderate dependence, 13–19 severe dependence, and 20–28 complete or nearly complete dependence). Results are reported for the TOEP(2) correlation structure, because it produced the best-fitting model, although results did not vary significantly when other correlation structures were employed. Adjusted estimates of change in functioning were computed by including covariates in the repeated-measures model. Although age, race, sex, number of medications, and Charlson comorbidity scores were initially included as potential covariates, only age was retained in the model, because it was the only covariate that significantly contributed to the prediction of change in ADL scale scores.

A similar model was run in which the dependent variable was the MDS-COGS score. The interaction was modeled as the time taking and not taking dual therapy, with a categorical variable that described the subjects' MDS-COGS level of functioning at the start of the interval. The MDS-COGS categories were defined as: intact (0–1), moderate impairment (2–4), severe impairment (5–8), and very severe impairment (9–10).[16] Residents with scores of 10 were not excluded to allow for the possibility that they might improve. Adjusted estimates of change in MDS-COGS score were computed by including covariates in the repeated-measures model. Age, race, sex, number of medications, and Charlson comorbidity score were included as potential covariates in the model but were not retained, because they did not significantly contribute to the prediction of MDS-COGS change.

Because tolterodine is less lipophilic and therefore thought to be less likely to cross the blood–brain barrier,[20] additional analyses were conducted to compare rates of decline in ADL function and cognition for the two bladder anticholinergics by differentiating time taking oxybutynin and time taking tolterodine. The statistical model was similar to those described above except that three predictor variables were included: number of days not taking dual therapy, number of days taking oxybutynin, and number of days taking tolterodine. The difference between the coefficients associated with the days not taking dual therapy and taking oxybutynin represents the additional change in functioning associated with dual use of a ChI and oxybutynin. Similarly, the difference between the coefficients associated with the days not taking dual therapy and taking tolterodine represents the additional change in functioning associated with dual use of a ChI and tolterodine. Age, race, sex, number of medications, and Charlson comorbidity score were included as potential covariates in the model but were not retained, because they did not significantly contribute to the prediction of ADL or cognitive change. As shown in Figure 1, 13 residents had exposure to oxybutynin and tolterodine at separate times during the study. For these secondary analyses, the time they were taking oxybutynin contributed to the oxybutynin results, and the time they were taking tolterodine contributed to the tolterodine results. Nineteen residents were taking both drugs simultaneously. Because it was not possible to separate the effect of one drug from the other, these 19 residents were excluded from this drug-specific secondary analysis.

Finally, because side effects, including central nervous system side effects, are reported to be more common with immediate-release preparations,[21,22] additional analyses were

performed to determine whether there was a difference in rates of decline in ADL function and cognition for immediate- versus extended-release formulations. In similar models to those described above, the predictors were time not taking bladder anticholinergic, time taking and immediate-release formulation of oxybutynin or tolterodine, and time taking and extended-release formulation of oxybutynin or tolterodine.

Analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the 3,536 residents enrolled in this study and followed for a median of 183 days are presented in Table 1. Briefly, 44% were among the oldest old (aged ≥85), 75% were women, and 90% were white. More than half of the sample had severe or very severe cognitive impairment, and 47% had severe or complete dependence in ADL functioning. Forty-six percent were incontinent at least once daily. Incontinence is reported in the MDS on a scale ranging from 0 (continent) to 4 (multiple daily episodes of urinary incontinence). Residents in the highest two categories of the variable (incontinent daily (but with some control) and multiple daily episodes of incontinence) were considered to be incontinent at least daily. All residents were taking a ChI; the most common was donepezil (70.5%), followed by rivastigmine (19.9%), galantamine (16.5%), and tacrine (0.1%). (Percentages sum to >100% because some residents changed cholinesterase inhibitors during the study period.) The mean number of total prescription medications ± standard deviation was 9.6 ± 4.1.

Of the 3,536 residents included in this study, 376 (10.6%) were prescribed bladder anticholinergics with a ChI (oxybutynin (n = 164), tolterodine (n = 199), both at separate times (n = 13), or both simultaneously (n = 19)) (Figure 1). Of the residents taking bladder anticholinergics, 197 were taking immediate-release formulations, and 268 were taking extended-release formulations over the course of the study. Some residents used both at different times. Of residents who took a bladder anticholinergic during the study, 75.5% continued using them for more than half of their study interval. The median (25th–75th percentile) duration of dual use was 141 (77–262) days.

ADL Function

In unadjusted analyses, residents in the top quartile of ADL function who were not taking bladder anticholinergics (taking ChIs alone) declined in ADL function by an average of 1.08 points per quarter. Dual therapy with bladder anticholinergics was associated with an additional worsening of 0.54 ADL points per quarter (P =.01). For residents who started out with lower functioning, dual use was not associated with additional worsening in ADL scores. Results did not vary significantly after accounting for autocorrelation and adjusting for age. Adjusted results are presented in Table 2.

To compare rates of change in function specific to type of bladder anticholinergic, subjects taking oxybutynin were compared with those taking no bladder anticholinergic. Similarly, subjects taking tolterodine were compared with those not taking a bladder anticholinergic.

Regardless of level of functioning at the beginning of the interval, rates of decline in ADL function for those taking oxybutynin or tolterodine were not statistically different from rates of decline for those not taking a bladder anticholinergic (Table 3). Nevertheless, for the highest functioning, the magnitude of the difference for oxybutynin was the same as for the combined analysis (−0.54 points/quarter), although this trend was not statistically significant (P =.10). There were no significant differences in rates of ADL decline for immediate- and extended-release formulations.

Cognitive Function

Rates of worsening in MDS-COGS scores did not differ significantly for residents taking a ChI, but not taking a bladder anticholinergic, and those who received bladder anticholinergics in addition to a ChI (Table 2). Similarly, regardless of level of cognitive impairment at the beginning of the interval, rates of decline in cognitive functioning did not differ for those taking oxybutynin or tolterodine and those not taking a bladder anticholinergic (Table 3). Residents whose cognitive functioning was classified as very severely impaired were not included in this analysis, because too few residents in the very severely impaired group were taking each of the bladder anticholinergics. There were no significant differences in rates of decline in MDS-COGS scores when comparing immediate- and extended-release formulations.

DISCUSSION

Even though dual use of anticholinergics and ChIs is common, prior studies have not documented the long-term detrimental effects of dual therapy on patients' functioning. This study revealed that, for NH residents with higher levels of functioning, the rate of functional decline was 50% faster when bladder anticholinergics were used in combination with ChIs than when ChIs were used without anticholinergics. To the authors' knowledge, this is the first study to provide objective evidence that simultaneous use of bladder anticholinergics and a ChI is associated with excess decline in patients' functioning. Additional loss of functioning in NH patients reduces patients' quality of life and is costly to NHs. Although the findings from this study cannot describe whether the therapeutic benefits of the bladder anticholinergic outweigh the additional decline in functioning associated with their use, it reveals that pharmacological management of dementia and UI poses a clinical dilemma.

Prior studies have shown that anticholinergics are associated with cognitive decline[11,23,24] and that persons with dementia are especially sensitive to the cognitive side effects of anticholinergics,[5–7] but few studies have considered the cognitive and functional consequences of concurrent use of anticholinergics and ChI. To the authors' knowledge, the only published data on outcomes with the combination of anticholinergics and a ChI have been in case reports[8,9] and one small longitudinal study.[10] In that longitudinal study, two groups of patients were studied for 2 years. One group consisted of 16 patients who were taking one or more anticholinergics in combination with donepezil. The other group consisted of 53 patients who were taking donepezil but not an anticholinergic. Those taking dual therapy declined by 7 points on the MMSE over 2 years, compared with a 3-point decline seen in those taking donepezil but no anticholinergic. Unlike the above study that

compared rates of decline between two groups of patients with varying drug treatments (and potentially different characteristics that led to different treatment patterns), the current study assessed whether patients experienced greater decline while taking or not taking dual therapy.

It is likely that the oppositional pharmacological effects of anticholinergics and ChI contribute to the accelerated rates of decline in ADL function seen for subjects on dual therapy. Oxybutynin and tolterodine block muscarinic receptors in the brain, resulting in lower acetylcholine levels, whereas ChIs act to increase acetylcholine levels in brain synapses by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine in the synaptic cleft. ChIs have been shown in randomized, controlled trials to delay onset of ADL disability.[25] In addition, there is mounting evidence that anticholinergics blocking muscarinic receptors in the brain are associated with greater Alzheimer's neuropathology in animals[26] and humans.[27] Therefore, the bladder anticholinergics could be accelerating the dementing process. Although significantly worsening MDS-COGS scores were not found with dual use, additional ADL decline was found. Because cognitive decline is strongly associated with subsequent loss of ADL function,[28–30] it is likely that the nonsignificant findings for the MDS-COGS were because the MDS-COGS was created to stage dementia severity rather than to quantify change in neuropsychological functioning over time. Scores on the MDS-COGS are based on reports by facility staff about the residents' ability to do things such as find their way back to their room, make themselves understood and understand others, and remember things after 5 minutes and in the distant past. Although the possibility that there is no effect of dual use of bladder anticholinergics and ChI on cognition cannot be excluded, a more plausible explanation is that the measure is not sensitive to detecting change in specific areas of cognitive functioning such as memory or concentration.

Although this study provides evidence to support the hypothesis that dual therapy with ChIs and bladder anticholinergics results in worse functional outcomes than management with ChI alone, there are several additional limitations to the study. First, given the observational nature of the study, the reasons patients may take bladder anticholinergic therapy could not be controlled for, which may contribute to the reason patients are declining at a faster rate while taking dual therapy. It was attempted to limit potential confounding by indication through a study design that used subjects as their own controls, comparing rates of decline while taking and not taking bladder anticholinergics. In addition, only bladder anticholinergics were considered. Thus, subjects who were taking anticholinergics for other indications (such as depression) that may be associated with functional decline were excluded. This study revealed a significant association between dual therapy and ADL decline only for those with the highest level of ADL functioning. These subjects were also the least likely to have UI, which suggests that UI status, rather than use of a bladder anticholinergic, is unlikely to explain the findings. A randomized, controlled trial is needed to more precisely determine the magnitude of excess ADL decline that can be attributed to dual therapy. Second, the measures used in this study were not sensitive for detecting change in functioning for those at the lowest levels of functioning. It is possible that the lack of significant findings for those at the lowest levels of functioning was due to a floor effect in the outcome measures. Future assessment of adverse effects of dual therapy in persons with severe dementia must include measures that are sensitive to changes in those with very

low levels of functioning. Third, cases of dementia were identified using *International Classification of Diseases, Ninth Revision*, codes rather than established clinical diagnostic criteria. This prevents determination of whether the findings were similar for all types of dementia. Although the Food and Drug Administration (FDA) has not approved ChIs for non-Alzheimer's dementias, they are prescribed for vascular dementia and Lewy Body dementia,[31,32] and mechanistically, the pharmacological opposition between ChIs and bladder anticholinergics occurs irrespective of type of dementia. If ChIs were less effective in subjects with non-Alzheimer's dementia, inclusion of cases of non-Alzheimer's dementia might have attenuated the reported effect of dual therapy. Fourth, the findings may not be generalizable to all bladder anticholinergics or doses. Although there are newer bladder anticholinergics on the market that are reported to be more selective for bladder muscarinic receptors (e.g., darifenacin) or less likely to cross the blood–brain barrier (e.g., trospium), oxybutynin and tolterodine were examined, because the newer agents were not FDA approved until late 2004, the end of the study period. Nevertheless, oxybutynin and tolterodine continue to be the most widely prescribed bladder anticholinergics. In addition, a recent review highlights that all bladder anticholinergics should be considered to have the capacity to cross the blood–brain barrier, especially in older adults, because the blood–brain barrier becomes leaky with age and comorbidities.[33] Studies of the cognitive side effects of the newer agents are needed, particularly in people with dementia.

These results have significant public health implications. The additional decline of 0.5 points per quarter in this study translates to 2 points per year on the MDS ADL scale. A 2-point decline would represent a change from requiring only limited assistance in an ADL to being completely dependent in an ADL or from requiring only supervision in any particular ADL to requiring extensive assistance. One study estimates that, for every additional ADL dependency, there is an increase of $1,958 (1998 dollars) in healthcare costs per year.[12] In addition, bladder anticholinergics and ChIs are costly and only modestly effective.[34–36] The combined monthly consumer cost for a ChI and oxybutynin or tolterodine is approximately $200. If using these medicines together reduces the desired effect of the ChI or the incontinence drug, then it is adding significant cost with reduced benefit and potentially adding risk of harm.

Until now, the clinical dilemma for the pharmacological management of dementia and UI has been largely theoretical. The findings reported in this study suggest that the dual use of ChIs and bladder anticholinergics may lead to worse functional outcomes, which is the opposite intention of ChI therapy. Because the negative functional effect of dual therapy was found only for NH residents with the highest function, additional studies should be conducted in a population of community-dwelling older adults with dementia. In addition, studies using more-sensitive measures of cognition are needed, as well as studies of newer, presumably more selective bladder anticholinergics. To truly determine whether the risks of dual therapy to cognition or function outweigh benefits for UI, changes in continence status also need to be included as outcomes. Clinicians should continue to implement nonpharmacological management strategies for incontinence before beginning drug therapy,[37] especially because the etiology of incontinence in many patients with dementia is functional rather than urge.[38]

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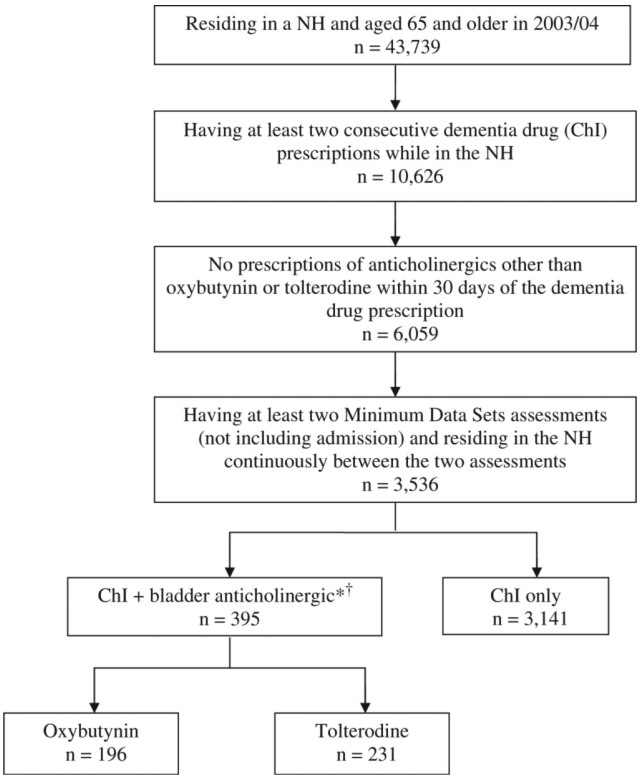

Figure 1.

Sample source. *Thirteen people were taking oxybutynin and tolterodine at separate times. †Nineteen people taking oxybutynin and tolterodine simultaneously were excluded from analyses assessing change in cognition and functioning associated with specific bladder drug use. NH = nursing home; ChI = cholinesterase inhibitor.

Table 1

Resident Characteristics at the Index Assessment (N = 3,536)

Resident Characteristic	Value
Age, %	
65–74	10.7
75–79	16.9
80–84	28.1
85–89	26.0
≥90	18.3
Female, %	75.3
White, %	89.5
Charlson Comorbidity Index score, %	
0	43.6
1	32.8
≥2	23.6
Activity of daily living score, (range 0–28)	
Mean ± SD	12.2 ± 8.1
None to little dependence (0–5), %	27.6
Moderate dependence (6–12), %	25.2
Severe dependence (13–19), %	25.3
Complete or nearly complete dependence (20–28), %	21.9
Minimum Data Set Cognitive Subscale score (range 0–10), %	
Intact (0–1)	10.0
Moderate impairment (2–4)	37.8
Severe impairment (5–8)	45.7
Very severe impairment (9–10)	6.5
Number of medications, mean ± SD	9.6 ± 4.1
Bladder incontinence (at least once daily), %	45.9
Dependent in transfers (extensive assistance or totally dependent), %	36.5

SD = standard deviation.

Table 2

Difference in Change in Function While Taking and Not Taking Bladder Anticholinergics Concomitantly with Cholinesterase Inhibitors

Outcome	Change (Points per Quarter)	*P*-Value
Activity of daily living scale score (range 0–28)*		
None to little dependence	–0.53	.02
Moderate dependence	0.27	.21
Severe dependence	0.14	.52
Complete or nearly complete dependence	–0.03	.92
Minimum Data Set Cognitive Subscale (range 0–10)†		
Intact	0.08	.36
Moderate impairment	0.05	.50
Severe impairment	0.05	.47
Very severe impairment	0.25	.86

Note: Negative estimates refer to greater decline in functioning while taking versus not taking a bladder anticholinergic.

*Analyses were adjusted for age. Race, sex, number of medications, and Charlson Score were not independently associated with the rate of decline.

†Age, race, sex, number of medications, and Charlson score were not independently associated with the rate of decline.

Table 3

Difference in Change in Function According to Specific Drug

Outcome	Oxybutynin (Points per Quarter)	*P*-Value	Tolterodine (Points per Quarter)	*P*-Value
Activity of daily living scale score (range 0–28)*				
No to little dependence	–0.53	.10	–0.38	.23
Moderate dependence	0.35	.24	–0.13	.70
Severe dependence	–0.18	.56	0.43	.16
Complete or nearly complete dependence	0.01	.99	–0.17	.71
Minimum Data Set Cognitive Subscale (range 0–10)†				
Intact	–0.06	.60	–0.23	.06
Moderate impairment	0.13	.06	–0.10	.22
Severe impairment	–0.02	.77	0.04	.60

Note: Negative estimates refer to greater decline in functioning while taking versus not taking the bladder anticholinergic.

*Analyses were adjusted for age. Race, sex, number of medications, and Charlson score were not independently associated with the rate of decline.

†Residents in the very severe impairment category were excluded from this analysis' because too few of them were taking each of the respective drugs. Age, race, sex, number of medications, and Charlson score were not independently associated with the rate of decline.