



TITLE: Oxybutynin, Tolterodine, and Darifenacin: Review of Cognitive Adverse Events

DATE: 23 October 2009

CONTEXT AND POLICY ISSUES:

Overactive bladder (OAB) affects men and women of varying ages¹ and increases with age.² People with OAB experience a sudden and urgent need to pass urine, in the absence of other infections or other obvious pathologies.^{1,3,4} Involuntary urine leakage may or may not occur.² In people with OAB, the need to urinate usually occurs frequently during the day and also during the night.^{1,4} OAB affects the quality of life; it negatively impacts daily activities as well as emotional, physical, social, occupational, and domestic functions.^{1,2} One review estimated the economic burden of OAB to be approximately US\$12 billion per year.¹ The etiology of OAB is unknown.¹

Several treatments exist for OAB including lifestyle therapy (for example, weight loss), behavioural therapy (for example, bladder training), electrical stimulation therapy, magnetic stimulation therapy, and pharmacological therapy.⁵ Pharmacological therapy is a common treatment^{2,4,5} and antimuscarinic agents (a type of anticholinergic agent) are often the pharmacologic treatment of choice for OAB.^{1,4-6} OAB is usually associated with detrusor overactivity during the filling phase of the micturition cycle.¹ The underlying detrusor muscle contractions may be mediated by acetylcholine-induced stimulation of bladder muscarinic receptors¹ or through afferent pathways mitigating the sensation of urgency.² There are five subtypes of muscarinic receptors; M3 affects the bladder and bowel as well as salivary glands and eyes.¹ The other subtypes can affect areas like cognitive function and heart rate.¹ Adverse events associated with antimuscarinic agents can include dry mouth, drowsiness, blurred vision, and cognitive impairment.⁵

Three antimuscarinic agents used to treat OAB are oxybutynin,⁷ tolterodine,⁸ and darifenacin.³ While all three are antimuscarinic agents, their properties vary. For example, darifenacin is a M3 selective receptor antagonist which means that it is focused on selectively relaxing the bladder muscle, other areas of smooth muscle, salivary glands, and the eyes.¹ One result of this focused selectivity claims to be the reduction in adverse events associated with the other,

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untargeted receptors, such as cognitive impairment and tachycardia.¹ Oxybutynin and tolterodine are not as highly selective for the M3 receptor.¹

At least one health jurisdiction is interested in gathering further evidence in regard to cognitive adverse events associated with oxybutynin, tolterodine, and darifenacin. These antimuscarinic agents can be used to treat indications other than OAB.⁹ As such, this HTIS report will review evidence regarding cognitive adverse events in study participants taking oxybutynin, tolterodine, or darifenacin for OAB and other indications.

RESEARCH QUESTION:

What is the evidence of cognitive adverse events in patients who are taking oxybutynin, tolterodine, or darifenacin?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and September 2009. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), controlled clinical trials (CCTs), and observational studies.

To be included, studies had to report specifically on cognitive adverse events and patients could not be taking oxybutynin, tolterodine, or darifenacin concomitantly with medications associated with anticholinergic properties. For systematic reviews to be included, they had to contain evidence of systematic methodology such as having at least two reviewers select articles and perform data extraction.

SUMMARY OF FINDINGS:

Five relevant RCTs,¹⁰⁻¹⁴ two CCTs,^{15,16} and three advisories were identified.¹⁷⁻¹⁹

Of the included studies, four RCTs^{10,11,13,14} and one CCT¹⁵ concluded that oxybutynin, tolterodine, or darifenacin did not cause statistically significant deterioration in cognitive function. The patient population included children with urinary incontinence,^{10,15} female nursing home residents with urge urinary incontinence and varying levels of cognitive impairment,¹¹ healthy male adult volunteers,¹³ and elderly volunteers.¹⁴ Two of the RCTs^{10,11} and one CCT¹⁵ assessed oxybutynin, two RCTs^{13,14} assessed darifenacin, and one RCT¹⁰ assessed tolterodine.

One RCT¹² concluded that healthy elderly volunteers taking darifenacin experienced statistically significant cognitive decline whereas patients on oxybutynin did not. The authors of the remaining CCT¹⁶ concluded that patients with Alzheimer's Disease (AD) performed statistically better on cognitive function tests when they stopped taking oxybutynin or tolterodine.

Three advisories¹⁷⁻¹⁹ were identified from the Food and Drug Administration (FDA) that stated there were post-market surveillance reports of memory impairment with oxybutynin,¹⁷ tolterodine,¹⁹ and darifenacin.¹⁸

No relevant health technology assessments, systematic reviews, meta-analyses, or observational studies were identified. Appendix 1 contains an additional reference that may be of interest.

Randomized controlled trials

In 2008, Giramonti *et al.*¹⁰ published a double-blind RCT that examined the effects of oxybutynin and tolterodine on attention span and short-term memory in children with urinary incontinence.

The children were recruited from an outpatient office and agreed to stop taking anticholinergic medication for a minimum of one week before starting the study. Fourteen children were enrolled in the study. The mean age was 7.7 years [standard deviation (SD) =2.0 years, range 5 years to 12 years]. Children were randomized to receive long-acting tolterodine, long-acting oxybutynin, or placebo. Dosing for tolterodine was calculated as 0.1 mg per kg per day and for oxybutynin it was calculated as 0.3 mg per kg per day. The children randomly assigned to the tolterodine or oxybutynin group were crossed over after two weeks and received placebo for an additional two weeks. The children randomly assigned to the placebo group at the start of the study were crossed over after two weeks to receive either tolterodine or oxybutynin for an additional two weeks. No statistically significant differences between the three groups in regard to age or gender were seen at baseline (no statistics reported). Overall, six children received tolterodine and eight received oxybutynin. One child initially randomized to the oxybutynin group did not complete the study.

Attention span and short-term memory were assessed by six sub-tests of the NEPSY, a standardized neuropsychological test used in children ages three to 12 years. The children were assessed at baseline, two weeks after the first treatment, and after the second two weeks of cross-over treatment. For all children, the scores for attention span and memory both statistically significantly increased over time [for attention $F(2, 22)=6.35$, $p=0.007$; for memory $F(2, 22)=12.45$, $p<0.001$]. There were no statistically significant differences between medication groups for attention or memory [for attention $F(2, 22)=0.837$, $p=0.446$; for memory, $F(2, 22)=0.55$, $p=0.582$]. A reliable change index was computed for the medication groups for attention and memory and the authors reported that that medication type did not produce a clinically significant change in attention or memory (based on scores that were less than 1.96).

The authors stated that attention and memory were not statistically significantly affected, as measured by the NEPSY, by long-acting oxybutynin or tolterodine.

The authors clearly identified the objective, used a standardized measure for children to assess attention and memory, and the authors stated that the RCT was double blinded. While the drop out rate was one child, it was unclear whether that child's data was used in the analyses. While the authors stated that the study was double blind, no further details were provided. Nor were details regarding randomization or allocation concealment provided. No rationale was provided for the sample size, thus the power of detecting a statistically significant difference is unknown. Compliance rates were not reported. The authors stated that most children with urinary incontinence would be taking these drugs longer than four weeks, thus a four week study may

not be long enough to adequately study the effects on tolterodine and oxybutynin on attention and memory in children. The authors also reported that other cognitive functions that were not assessed may be affected. The study did not appear to be industry funded.

Lackner *et al.*¹¹ published a double-blinded RCT in 2008 that assessed the impact of oxybutynin on female nursing home residents with urge urinary incontinence and impaired cognition.

The inclusion and exclusion criteria were provided. Examples of inclusion criteria were that patients had to be at least 65 years of age, be residents of a long-stay nursing home unit for at least three months, score between five and 23 on the Mini-Mental State Examination (MMSE), score three to six on the Global Deterioration Scale, and be diagnosed with urinary incontinence. The MMSE is a common tool used to evaluate cognitive impairment by assessing orientation, immediate and short-term memory, and language functioning.²⁰ The test takes approximately 10 minutes to administer and has been validated in several populations.²⁰ A score of less than 17 is indicative of severe impairment, a score of 18 to 24 is indicative of mild-to-moderate impairment, and a score of 25 to 30 is indicative of normal cognitive function.²⁰

Patients were first stratified into two groups by MMSE score. One group was comprised of patients who scored five to 10 on the MMSE and the second group was comprised of patients who scored 11 to 23 on the MMSE. Participants were then randomized to receive either four weeks of extended-release oxybutynin 5 mg tablets once daily or placebo. Randomization was performed by a computer randomization program by the investigational pharmacy. Twelve nursing facilities participated in the study.

The primary outcome measured was cognitive decline, as measured by the Confusion Assessment Method (CAM). The CAM was administered at baseline and at one, three, seven, 14, 21, and 28 days on treatment. If treatment was discontinued, then cognitive function tests were administered at one, three, and seven days post discontinuation. The authors reported that the CAM had been validated on elderly outpatients and used in previous research involving nursing home residents. Secondary outcome measures of cognition were the MMSE and the Severe Impairment Battery (SIB). Adverse event data was also collected. The authors calculated that 21 patients per group would provide 80% power to detect equivalence between the two groups in mean change CAM scores from baseline.

Of the 50 patients randomized, 26 received oxybutynin and 24 received placebo. Thirty-seven patients were in the group with MMSE scores between 11 and 23 (19 of whom were receiving oxybutynin) and 13 patients had MMSE scores between five and 10 (of whom seven received oxybutynin). No statistically significant ($p < 0.05$) differences in the baseline characteristics occurred. The authors measured age, BMI, neuropsychiatric measures, predisposing or precipitating factors for delirium, and urological parameters. The mean age of the oxybutynin group was 88.2 years ($SD = \pm 1.0$ years) and the mean age for the placebo group was 88 years ($SD = \pm 1.5$ years). Compliance rates were approximately 97% for each group ($p = 0.54$). Of the 50 patients who started the study, 47 completed the study (25 in the oxybutynin group and 22 in the placebo group).

Compared to placebo, patients taking oxybutynin scored statistically significantly lower on the CAM at each post-treatment time point. However, at each time point, the upper and lower limits of each confidence interval were within the range ± 2 points which the authors reported as clinical equivalence. No statistically significant differences between the oxybutynin and placebo

groups for median MMSE and SIB scores occurred. The p values for the MMSE ranged between 0.24 and 0.93 and for the SIB ranged between 0.38 and 0.85. No further statistics were reported. Approximately 30% of patients taking oxybutynin and 37% of patients taking placebo experienced at least one adverse event ($p=0.53$), with the majority of events classified as mild. The most common adverse event reported for both groups was cough. The second most common adverse event for oxybutynin was constipation (7.7% for oxybutynin compared to 0.0% for placebo) and for placebo it was falls (3.8% for oxybutynin and 8.3% for placebo). One patient in the oxybutynin group withdrew due to an adverse event (elevated postvoid residual volume).

The authors concluded that the study provided evidence that extended-release oxybutynin (5 mg daily) was well tolerated and resulted in little risk for short-term cognitive decline in elderly female nursing home residents with urge urinary incontinence and mild to severe cognitive impairment.

The authors clearly reported their objective and primary outcomes for the study. Randomization was carried out, however, it was unclear as to whether the allocation to groups was concealed. The authors stated that the RCT was double blinded but did not report who was blinded. The dropout rate was reported and the analyses were intention to treat. Additional statistical information on the scores may have provided additional useful information to the reader. The group sizes were calculated based on a power calculation. The use of a standardized instrument to assess cognition is another potential strength of the design. The research was industry funded although it was declared that they did not have a role in design, methods, patient recruitment, data collection, analysis, or preparation of the manuscript.

Kay *et al.*¹² published a multi-center, double-blind, double-dummy, placebo-controlled RCT in 2006. The objective was to study the effects of darifenacin and oxybutynin on memory in healthy participants 60 years of age or older.

The 150 participants who entered the three-week study had to successfully complete a cognition test and not take medication with anticholinergic properties two weeks prior to the start of the study. Of the 150 participants, 49 were randomized to receive darifenacin, 50 received extended-release oxybutynin, and 51 received placebo. The authors calculated that a sample size of 35 participants per group was required to detect an effect size of 0.867 for active treatment versus placebo. Patients in the darifenacin group received 7.5 mg in the first and second week and 15 mg in the third week. The oxybutynin group received 10 mg in the first week, 15 mg in the second week, and 20 mg in the third week. The treatment was once per day. Participants either received an actual or sham titration every week.

Participants were excluded if they had contraindications to anticholinergic use, dementia, depression (as evidenced by \geq nine on Geriatric Depression Scale), or scored \leq 27 on the MMSE. The mean age was 66.4 years (range 60 years to 82 years) for the darifenacin group, 68.0 years (range 60 years to 81 years) for the oxybutynin group, and 67.4 years (range 61 years to 83 years) for the placebo group. Females made up more than half of each group; 59% in the darifenacin, 68% in the oxybutynin group, and 65% in the placebo group.

A modified intention-to-treat was used for the primary analysis, comprised of 134 participants. In the darifenacin, nine participants withdrew, six of whom had partial data and were included in the secondary analyses. In the oxybutynin group, six discontinued treatment, five of whom had partial data and were included in the secondary analyses. In the placebo group, one participant

discontinued treatment and no partial data was available and was not included in any secondary analyses.

Cognitive function was measured through cognitive function tests at baseline and following each week of treatment, prior to the dose or sham dose titration. Immediate memory recall, delayed memory recall, visual attention and memory, and reaction time and information processing were assessed by nine tests overall. The primary end point was the accuracy on the delayed recall Name-Face Association Test.

The mean baseline scores for the delayed recall Name-Face Association Test was 5.2 for the darifenacin group, 5.8 for the oxybutynin group, and 5.4 for the placebo group. At week three, the mean score difference between the darifenacin and placebo group on Name-Face Association Test was not statistically significantly different (mean difference -0.06, $p=0.908$). However, participants in the oxybutynin group at week three had a statistically significantly lower mean difference than the placebo group (mean difference -1.30, $p=0.011$) and the darifenacin group (mean difference -1.24, $p=0.022$). The difference was also seen at week two but not at week one. Repeated testing effects were seen in the darifenacin and placebo groups as the participants improved their scores from practice; this was not seen in the oxybutynin group.

The most commonly reported adverse event was dry mouth (13 participants in darifenacin group, 20 participants in oxybutynin group, six participants in placebo group) followed by constipation (10 participants in the darifenacin group, two participants in the oxybutynin group, one participant in the placebo group). The authors reported that there was a low incidence of all causality nervous system events (five participants from the darifenacin group, four participants in the oxybutynin group, and three participants in the placebo group). No statistics on adverse events were reported.

The authors stated that the results of the memory tests (both primary and secondary) indicated that memory deterioration occurred in the participants taking oxybutynin and that the memory deterioration in performance on the Name-Face Association Test at week three was comparable to a decline that would be expected to be seen over the course of 10 years of normal aging. The authors also stated that darifenacin had no significant effect on memory in older participants.

Strengths of the study included a double-blinded randomized design, clear objectives with stated primary analysis, sample size that corresponded with power calculations, and a primary end point that used a standardized instrument to assess a relevant and common memory exercise for participants. Weaknesses of the study included a lack of information on how the study was double-blinded, whether allocation was concealed, the lack of a true intention-to-treat analysis, and a three-week study length that may not be representative of the longer-term effects of darifenacin and oxybutynin on memory. The conclusions of the authors may be too generalized as the primary end point consisted of one test that assessed a very specific aspect of memory. The study was industry funded.

In 2005, Kay *et al.*¹³ published a double-blind, four-way cross-over RCT that gave darifenacin to healthy male volunteers. The authors wanted to study the pharmacodynamic effects which included cognitive function.

The study consisted of 27 healthy males with a mean age of 28 years (range 19 years to 44 years). Participants were randomized to one of four treatment sequences. These were:

darifenacin controlled release tablets 7.5 mg once daily, darifenacin controlled-release tablets 15 mg tablets once daily, dicyclomine 20 mg capsules four times daily, and matching placebo. The four different treatment sequences were established using a balanced Latin square design. The treatment sequences administered were not reported. A pseudorandom code using permuted blocks was used to allocate patients to one of the four treatment sequences. Each treatment lasted seven days and the washout period was seven days.

The authors believed that six participants per group (six participants in each of the four groups for a total of 24) would be sufficient to detect a difference in cognitive function tests. This was with the assumption of 80% power testing with a 5% level of significance. Of the 27 participants who started the study, 23 completed the study and were included in the cognitive function tests. Two withdrew their consent and two were excluded because drugs of abuse were detected.

The participants were given a computer-based cognitive function test, along with other cardiac and salivary tests before each dose and at the end of each seven-day treatment period. On the seventh day of treatment, the cognitive function tests were done seven times; once prior to the medication dose and again at two, four, six, eight, 10, and 12 hours after the dosing.

To assess cognitive function, participants were given twelve different cognitive tests including immediate word recall, visual tracking, spatial working memory, numeric working memory, and delayed word recognition. Performance on the cognitive function tests on the seventh day were subtracted from performance at baseline to give a difference from baseline score. There were no statistically significant differences in the change from baseline scores between darifenacin (of either dose) and placebo. No further statistical information was provided. When the difference from baseline scores was compared between dicyclomine and placebo, statistically significant impairment was detected for five of the twelve cognitive function measures (p values <0.05). These p values represent the differences at the two hour mark on the seventh day, which was when the most impaired performance occurred. No further information on cognitive performance was provided.

For the three drugs, the reported adverse events were generally mild or moderate. The most commonly reported adverse event for all four groups was dry mouth.

The authors concluded that they did not find any evidence that darifenacin, at therapeutic doses of 7.5 mg once daily and 15 mg once daily, caused cognitive impairment on tests of short-term memory, concentration, or speed of response when compared to placebo.

The authors provided clear research questions and tasks that addressed the research question. The authors stated it was a double-blind trial but details were not provided thus it was unclear who was blinded. The treatment duration of the medication may not have been adequate for darifenacin to show impairment to cognitive function; perhaps a treatment period longer than seven days would be more appropriate as patients are typically receiving chronic treatment. More statistics regarding the cognitive function tests, such as confidence intervals, would help inform the reader about the precision of the estimates of effect. The one week washout period may have affected the results. The study was funded by industry.

Lipton *et al.*¹⁴ published a double-blind cross-over RCT in 2005 that assessed the cognitive effects of darifenacin on elderly volunteers.

To be eligible, the volunteers had to be at least 65 years of age, have a score of 10 or less on the Short Orientation Memory and Concentration Test, a short version of the Blessed Information-Memory Concentration test (shown to have sensitivity to muscarinic blockade by scopolamine in young and elderly volunteers), not have a condition that would impair participation in the study, and not be on medication known to affect cognitive function. The participants were randomized to receive three of five oral treatments. These treatments were darifenacin controlled release tablets once a day in a dose of 3.75 mg, 7.5 mg, or 15 mg, darifenacin immediate release tablets three times a day in a dose of 5 mg, or placebo. Investigators and patients were both blinded to the treatment.

Of the 239 volunteers that were screened, 129 were randomized to a treatment or placebo group. Most of the volunteers were screened out of the study because of concomitant medical conditions (hypertension most prevalent) or were receiving certain concomitant medications known to affect cognitive function. The patients were seen at two visits before randomization occurred. At the first visit, physical examination, blood work, and the Blessed Information-Memory Concentration test were completed. The participants who were still eligible attended a second visit one week later where they completed two additional training sessions of the cognitive test. The intent was for the participants to have maximized performance for the study. Each participant was randomized to an initial treatment group and then cross-over to a different treatment group twice after a seven-day washout period.

Of the 129 volunteers randomized, 22 discontinued the study. The authors reported that 10 of these drop outs were treatment related. The range of participants eligible for primary analyses in each of the five groups ranged between 61 and 70. Appendix 2 contains more information. The mean age was 71.2 years (range 65 years to 84 years). No statistically significant differences emerged on the three primary cognitive function tests (memory scanning sensitivity, choice reaction time speed, or delayed word recognition sensitivity) at any dose or formulation. When compared to placebo, participants taking darifenacin had no statistically significant difference in cognitive function scores at two weeks for the primary or secondary end points (e.g., memory scanning sensitivity, speed of choice reaction time, digit vigilance speed or accuracy, word recognition speed). The one statistically significant difference occurred in memory scanning speed. The level of memory scanning speed improved more in participants taking placebo than for participants in the 3.75 mg darifenacin group.

There were no statistically significant differences in the rates of adverse events reported across the five groups. The most commonly reported adverse events in each group were dry mouth and constipation.

The authors concluded that darifenacin did not impair attention, vigilance, memory, and reaction time in people 65 years or older.

Randomization was performed using a balanced incomplete block design. Allocation concealment was not reported but investigators, along with patients, were reported to have been blinded to the medication or placebo. The authors stated that the study was powered to detect a beneficial effect of darifenacin compared to placebo. No further information was provided. The authors did not attempt to substitute values for missing data, thus, it is assumed that the authors did not perform an intention-to-treat analysis. No adjustments were made for multiple testing, however, the authors did expose the participants to the test four times prior to

the test to attempt to get the participants performing at their best for the study. The seven day washout periods may have affected the results. The study was funded by industry.

Controlled clinical trials

In 2005, Sommer *et al.*¹⁵ published a study that examined the effects of oxybutynin and behaviour therapy compared to behaviour therapy alone for children with daytime urinary incontinence. The parents determined the treatment group for their children.

The children in the study were recruited from an outpatient pediatric urology clinic and were being treated for incontinence. Children were excluded if they experienced nocturnal enuresis or were diagnosed with a neurological or psychiatric disorder. Children had been diagnosed with dysfunctional voiding with signs of detrusor instability. All 25 children received four weeks of behaviour modification. The treatment for the 10 children in the control group was an additional four weeks of behaviour modification. The 15 children who received the oxybutynin treatment for four weeks also received behaviour modification. The mean age of the children in the control group was 7.6 years (SD=±2.31) and the mean age for the children in the treatment group was 7.0 years (SD=±1.36). These ages were not statistically significantly different.

Cognitive function was assessed at baseline and revealed that children who were in the treatment group had statistically significantly lower scores than the control group for immediate memory [$t(1, 24)=2.09, p<0.04$], for delayed memory [$t(1, 24)=2.21, p<0.03$], and for learning [$t(1, 24)=2.70, p<0.01$]. The mean follow-up testing interval was 50 days (SD=±15.5 days). At follow-up, and controlling for baseline cognitive function, the authors stated the regression analysis revealed oxybutynin did not statistically significantly affect the cognition scores. The statistical analysis testing results were not reported.

The authors concluded that patients receiving oxybutynin did not display a difference in cognitive performance.

The study provided a clear objective and children appeared to be similar in condition. The instruments used to assess immediate memory, delayed memory, and learning were not reported. No blinding or randomization occurred in the study which means there may have been a higher chance for selection bias or outcome assessor bias that may have affected the results. The rationale for the sample size was not reported, thus it was not clear whether the group sizes allowed for a statistically significant difference to be confidently detected. The precision of the estimates are unclear as confidence intervals and p values were not provided for the follow-up test scores. Study length was four weeks which provides information on short-term use of oxybutynin on children's cognitive performances but not on the longer-term effects of oxybutynin on cognition.

Jewart *et al.*¹⁶ published a study with the primary objective to assess whether patients with AD would experience worsened disease-related deficits when taking oxybutynin or tolterodine.

To be included, the participants had to have been diagnosed with AD, have a MMSE score between 10 and 26, have a caregiver to accompany them to the evaluations, and could not be on antipsychotics, narcotic analgesics, or sedatives. The patients were recruited from a university clinic. Patients were tested both off and on the medication and paired-sample t-tests were used to compare the test results. If the patient was on oxybutynin or tolterodine at the start

of the study, the assessments were administered and then the patients discontinued the medication for three weeks. At the end of three weeks, the patients were tested once again. If the patient was not on oxybutynin or tolterodine at the start of the study, they were assessed and then asked to start treatment for three weeks where at the end, they were assessed once again.

Patients were tested on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the MMSE. Other tests to measure neuropsychiatric status and behaviour were also administered. Blood tests were also performed. The psychometrist who administered the cognition tests was blinded to the treatment status of the patients. No statistically significant differences occurred on the ADAS-Cog test for patients when they were on medication (mean=28.0, SD=±16.89) compared to when the same patients were off medication (mean=29.0, SD=±17.12). For the MMSE, patients off medication scored statistically significantly higher (mean=17.44, SD=±8.16) than when the same patients were on the medication (mean=16.44, SD=±7.83; $p=0.017$).

Of the 12 patients that met the inclusion criteria, nine were assessed. This was due to technical difficulties with three patients' serum assay tests. Each patient's performance on and off medication was assessed through paired t-tests. Analysis was not performed by type of medication. No further details were reported on the medication (dose, drug formulation, number of patients taking the drug, adverse events).

The authors reported that the study provided preliminary evidence that patients with AD perform better on tests of mental status when taken off tolterodine or oxybutynin.

The study had several limitations including the fact that the important methodological details were not reported (for example, how was choice of medication allotted) and the study had a sample size of nine which the authors stated as being small. As the risk of bias is unclear, the reliability of the results and conclusions is uncertain. The authors did not state how many patients were on the medication at the start of the study, information regarding the dose of medication, and length of time of which these patients were on the medication. A lack of statistical reporting also created difficulty in interpreting the results of the study.

Advisories

Recent reports (2008 and 2009) from the FDA safety information and adverse event reporting program noted that post-market surveillance has had reports of memory impairment for oxybutynin;¹⁷ memory impairment, confusion, and disorientation for tolterodine;¹⁹ and confusion for darifenacin.¹⁸ The reports stated that these cognitive adverse events were world-wide and spontaneously reported and that the frequency and role of the specific drug could not be determined.

Limitations

- The methodology of the HTIS reports facilitates an efficient and timely report; thus limitations on the search strategy were employed.
- The identified RCTs focused on short-term (four weeks or less) use of oxybutynin, tolterodine, or darifenacin. The lack of longer-term studies limits the generalizability of the findings to patients taking these medications for chronic conditions.
- The cross-over periods in the RCTs may have affected the results (i.e., carry-over effect) as the washout periods may not have been sufficient.
- Four of the five RCTs had industry funding which raises the issue of potential bias favouring the drugs.
- No study that used more than one dose of a drug analyzed the relationship between dose and cognitive function scores.
- No comparative trials designed to study the adverse events of oxybutynin, tolterodine, and darifenacin were identified. Without such evidence, it is not possible to reliably compare the effects on cognition between the three medications.
- Several different measures of cognitive function were used in the identified RCTs and CCTs. This complicates the comparison between studies and their respective findings.
- The included studies were limited to those studies that excluded patients taking medications with anticholinergic properties. The cumulative effect of taking more than one medication with anticholinergic properties was beyond the scope of this HTIS report.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Most of the studies concluded that cognitive function was not affected by taking oxybutynin, tolterodine, or darifenacin.¹⁰⁻¹⁵ The patient population of the studies varied widely, from children to elderly nursing home patients and from patients with normal cognitive function to patients with cognitive impairment. All of the studies, however, were short-term which may not reflect the typical patient on these medications. Three FDA advisories have been issued which stated that there have been reports of cognitive adverse events like confusion in the post-market use of oxybutynin,¹⁷ tolterodine,¹⁹ and darifenacin.¹⁸ These reports do not contain enough data to determine meaningful information such as cognitive adverse event rates.

It has been postulated that certain populations, such as older adults, may be less suitable candidates for oxybutynin, tolterodine, or darifenacin. This is because normal aging contributes to a deterioration of the central cholinergic system which may contribute to cognitive decline associated with aging.⁹ Elderly patients are often taking multiple prescriptions which can increase the possibility of experiencing a drug to drug interaction and if those drugs have anticholinergic properties then the probability of cognitive impairment and other anticholinergic-associated adverse events may be higher.^{2,4,9} This was not evidenced in the short-term trials of

oxybutynin, tolterodine, and darifenacin that were included in this HTIS report. However, biases may have been introduced into these studies from issues such as industry funding.

Given the lack of longer-term trials of oxybutynin, tolterodine, and darifenacin, it is unknown whether the longer-term use of these medications for chronic issues such as OAB negatively affects the cognitive function of patients. In addition, trials designed specifically to compare the cognitive adverse events of oxybutynin, tolterodine, and darifenacin were not identified. Without comparative evidence between these medications, the argument that a drug designed to have enhanced receptor binding selectivity that relieves cognitive adverse events remains theoretical.

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APPENDIX 1: ADDITIONAL REFERENCES

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This report provides the Canadian Expert Drug Advisory Committee recommendation for listing darifenacin on Canadian formularies. The report stated that darifenacin may theoretically have less effect on cognition than other muscarinics but that no studies have examined the effects of darifenacin on cognition in elderly patients with OAB.

APPENDIX 2: ADDITIONAL INFORMATION FOR LIPTON *ET AL.*¹⁴ STUDY

Table1. Lipton *et al.*¹⁴ Study Groups and Outcomes

	3.75 mg controlled-release once daily	7.5 mg controlled-release once daily	15 mg controlled-release once daily	5 mg immediate release three times a day	Placebo
Number of Participants	65	70	61	65	66
Memory scanning sensitivity, treatment versus placebo (95% CI)	-0.006 (-0.049, 0.036)	0.007 (-0.034, 0.049)	0.023 (-0.020, 0.067)	0.006 (-0.037, 0.048)	
Choice reaction time speed (msecs), treatment versus placebo (95% CI)	3.29 (-9.3, 15.9)	2.61 (-9.8, 15.0)	-6.59 (-19.7, 6.5)	-3.56 (-16.3, 9.1)	
Delayed word recognition sensitivity, treatment versus placebo (95% CI)	-0.001 (-0.058, 0.056)	0.010 (-0.046, 0.066)	-0.019 (-0.078, 0.041)	-0.002 (-0.059, 0.056)	
Memory scanning speed (msecs), treatment vs. placebo (95% CI)	42.3 (2.9, 81.7), p=0.04	19.1 (-19.5, 57.8)	8.7 (-32.0, 49.4)	10.3 (-29.3, 49.9)	
Adverse events (%)	20.8	14.9	18.5	22.5	14.5

CI=confidence interval; mg=milligrams; msecs=milliseconds