

SENIOR: Solifenacin (VESICARE) vs Oxybutynin (DITROPAN) vs Placebo Use in Elderly People with Mild Cognitive Impairment (MCI) ¹

BOTTOM LINE

At first glance this trial appears to support the use of solifenacin over oxybutynin because of their differing effects on cognition in elderly people with MCI. However, this is somewhat misleading as there was no difference in the primary end-point studied. There is some potential for differences between the two agents based on secondary endpoints. Possible changes in cognition were reported with oxybutynin vs placebo at various time points in the secondary endpoints, but the clinical significance of these findings is uncertain. There was no overall difference in cognitive function between the two antimuscarinic agents reported. The primary conclusion that can be drawn from this study is that neither solifenacin nor oxybutynin was associated with significant changes from baseline in any of the five standard, composite outcomes of cognitive function. Given the limited potential for any differences between the agents, and the substantially higher cost, an initial trial of oxybutynin is preferred.

BACKGROUND

- Overactive Bladder (OAB) is a common condition in the elderly population
- Common non-drug approaches to OAB treatment: bladder training, habit training, pelvic floor muscle exercises, prompted voiding, scheduled voiding, and lifestyle changes (i.e. avoiding excess fluid intake, limiting caffeine/carbonated beverages)
- Antimuscarinic agents (i.e. oxybutynin and solifenacin) are the drugs of choice for treatment, but have potential for cognitive impairment (for which the elderly are at higher risk)

STUDY PURPOSE: to investigate the cognitive safety of antimuscarinics in older people with existing cognitive impairment

TRIAL BACKGROUND

DESIGN: RCT, double-blind, multicentred, placebo-controlled, triple-crossover trial, 15 week trial (+2 week screening)

INTERVENTION: Three different treatment periods were used (3 weeks) with a 21-day washout period between each

Funded by Astellas (involved in study) and Pfizer

- Solifenacin 5mg po daily
 - Oxybutynin 5mg po BID
 - Placebo
- Were the study doses comparative? Oxybutynin 2.5mg BID may have been a more suitable starting dose for these elderly patients.

INCLUSION: age ≥ 75 yrs with MCI; BMI between 18-30kg/m²; and avoiding stimulants i.e. caffeine, tobacco 1hr before cognitive function tests

EXCLUSION: Mini-Mental State Examination (MMSE) score ≤ 23 , Geriatric Depression Scale (GDS) score ≥ 5 , history or risk of urinary retention, or on current medications for OAB

POPULATION: Caucasian males n=14 (54%) and Caucasian females n=12 (46%); mean age=78.8 yrs; baseline mean MMSE score=27.5 (normal cognition); baseline mean GDS=1.2; no cholinesterase inhibitors used

RESULTS

PRIMARY END POINT:

Change in cognitive function with solifenacin at 6hr postdose and oxybutynin 2hr postdose – (assessed using five standard, composite measures: power of attention, continuity of attention, quality of working memory, quality of episodic memory, and speed of memory).

- No statistically significant changes in cognitive function for solifenacin or oxybutynin versus placebo.

SECONDARY END POINTS:

Change from baseline in cognitive function at time points other than predicted t_{max} (predose and 1, 2, 4, and 6hr postdose)

- No significant differences between solifenacin and placebo at any time points.
- Oxybutynin decreased continuity of attention vs placebo at 1-2hr postdose (p=0.008) vs 1hr postdose (-2.35; 95% CI, -4.06 to -0.64; p=0.0084).
- At the pooled 1+2hr time point, oxybutynin had decreased power of attention (LSM: 26.01; 95% CI, 1.65 to 50.36; p=0.037) and continuity of attention (LSM: -1.66; 95% CI, -2.70 to -0.62, p=0.002) vs placebo.
- At the pooled 4+6hr time point, oxybutynin had a statistically significant increase in power of attention (LSM: -24.75; 95% CI, -49.17 to -0.30; p=0.047) vs placebo.
- Statistically significant decrease in self-rated alertness for oxybutynin vs placebo at pooled 1+2hr time point (LSM: -8.31; 95% CI, -16.01 to -0.61; p=0.035).

Safety and Tolerability Outcomes

- Agents well tolerated
- Most common AE: mild or moderate dry mouth (see next page)

ADVERSE EVENTS (AE):

	<u>Tx Related</u> n (%)	<u>Dry Mouth</u> n (%)	<u>Dyspepsia</u> n (%)	<u>Constipation</u> n (%)	<u>Nervous System Disorders</u> n (%)
Solifenacin (n=23)	14 (60.9%)	4 (17.4%)	0	1 (4.3%)	2 (8.7%)
Oxybutynin (n=25)	21 (84%)	13 (52%)	4 (16%)	0	3
Placebo (n=22)	11 (50%)	2 (9.1%)	0	1 (4.5%)	1 (4.5%)

* Note: All drug-related events were considered mild or moderate severity. P-values not reported.

Two subjects discontinued the study due to AE. No significant differences in vital signs and ECG between treatment groups.

COST COMPARISON: Oxybutynin ▼ 5mg BID \$19/month vs Solifenacin 5mg daily \$57/month

LIMITATIONS & UNCERTAINTIES

- Concern about generalizability of the results:
 - Small sample size (n=23), all of Causasian ethnicity, excluded patients who required therapy for overactive bladder (i.e. the indication for the study drugs), mild changes in cognitive impairment may not have been captured in study time span.
 - The majority of patients with mild cognitive impairment (i.e. MMSE scores 20-24) were excluded from the study with the exclusion criteria of MMSE ≤23. Instead, the study group captured patients with normal cognition (average baseline MMSE score was 27.5).
- Triple-crossover trial design, but only the active drug and placebo were compared. There was no direct comparison of oxybutynin to solifenacin.
- Analysis was not by ITT.
- The lowest dose of solifenacin (5mg daily) was used, but a moderate-high dose of oxybutynin (5mg BID) was used for this age group. Both of these medications have dose-dependent effects and AE, so this may have impacted the study results.
- Solifenacin and oxybutynin are renally eliminated, but no baseline SCr values were reported. Dialysis patients were not listed in the exclusion criteria, but these medications are contraindicated in this population.
- Change in cognitive function scales reports statistically significant change, but the variation required for clinically significant changes is unclear.

RxFILES RELATED LINKS

- Drugs with Anticholinergic Effects <http://www.rxfiles.ca/rxfiles/uploads/documents/members/psyc-anticholinergic-Ref%20List%20SPDP-complete.pdf>
- Anticholinergics for Overactive Bladder http://www.rxfiles.ca/rxfiles/uploads/documents/OveractiveBladder_OAB_-HEADER.pdf
- Trial Summary- Darifenacin (ENABLEX) vs Oxybutynin ER extended release (DITROPAN XL) vs Placebo: Effects On Memory / Cognitive Impairment <http://www.rxfiles.ca/rxfiles/uploads/documents/UI-Darifenacin-Kay-Trial-QandA.pdf>
- Urinary Incontinence Chart <http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-urinary-incontinence.pdf>

AE=adverse events; BID=twice daily; BMI=body mass index; CI=confidence interval; GDS=Geriatric Depression Scale; hr=hour; i.e.=example; ITT=intention to treat; LSM=least-squares mean; MCI=mild cognitive impairment; mg=milligrams; mL/min=milliliters per minute; MMSE=Mini-Mental State Examination; n=number; RCT=randomised control trial; SCr= serum creatinine; t=time; Tx=treatment; vs=versus; ▼=covered by NIHB; ⚠=Exception Drug Status SK; Ⓞ=prior approval NIHB

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