Darifenacin (ENABLEX) vs Oxybutynin ER extended release (DITROPAN XL) vs Placebo: Effects On Memory / Cognitive Impairment [1]

STUDY DESIGN - RCT, blinded, placebo controlled & parallel group, 3 week (+2 week initial screening period)

Doses used bias the results

Drug	Week 1	Week 2	Week 3	
Darifenacin (D)	7.5mg daily	7.5mg daily	↑ 15mg daily	{note only 1 dose ↑ in 3 weeks}
Oxybutynin ER (O)	10mg daily	↑15mg daily	↑ 20mg daily	{note, a high dose for elderly}
Placebo (Pl)	daily	daily (sham ↑dose)	daily (sham ↑dose)	

CHARACTERISTICS OF SUBJECTS (n=150 for initial and safety analysis; n=136 for modified ITT cognitive function analysis)

- **Inclusion**: healthy, age 60+; able to follow instructions – valid responses (did not have to have urinary incontinence)
  - Baseline: **Score** on *Name-Face* test: **D**:5.2; **O**:5.8; **Pl**:5.4; **♀%:** D:59%; O:62%; Pl:64.7%; **Ave Age:** D:66.4; O:68; Pl:67.4
- **Exclusion**: on drugs affecting cognition (e.g. other anticholinergics); dementia, low score on MMSE, depression

RESULTS

- **Primary (1°) End Point**: **Delayed Recall - *Name-Face Association Test* score** (test for memory)

Positive outcome on 1 test

  - No difference between darifenacin 15mg/day & placebo; oxybutynin score declined at both 15mg & 20mg/day.
    - Score @week 3: Darfenacin$^{15mg/day}$ vs pl: -0.06 $_{p=0.9}$; {Oxybutynin$^{20mg/day}$: vs pl: -1.30 $_{p=0.011;}$ vs Darifenacin$^{15mg/day}$ -1.24 $_{p=0.022}$.}
  - Subjects did not notice any change in memory {may question clinical significance of 1° result in light of 2° results}
- **Secondary (2°) End Points**:

No difference on 15 other tests

  - **15 other (2°) endpoints evaluated weekly x3** {memory, attention, information processing, reaction time}
  - **Week 1**: none of the 15 endpoints showed any statistical difference between darifenacin and oxybutynin
  - **Week 2**: only 1/15 endpoints found a statistical difference favoring oxybutynin over darifenacin (divided attention – premature hits)
  - **Week 3**: 0/15 endpoints showed any statistical difference for darifenacin vs oxybutynin (trends heterogeneous)
- **Adverse Events (AE)**:
  - One would expect more adverse events in oxybutynin group given more aggressive titration to higher doses in subjects whose average age was 68 years.

Potential for more of some & less of other adverse events

	Any AE	Tx Related	Any Serious	Dry Mouth	Constipation
Darifenacin	27/49*	26/49*	0/49*	13/49*	10/49*
Oxybutynin ER	26/50	22/50	1/50	20/50	2/50
Placebo	23/51	16/51	0/51	6/51	1/51

* Note: 9 of the darifenacin patients dropped out (early) compared to 6 and 1 drop-outs for oxybutynin and placebo. Unfortunately we do not know when drop-outs occurred, a point of interest since darifenacin patients had 2 initial weeks of the lowest dose, whereas oxybutynin patients had only 1 week at a moderately low dose.

LIMITATIONS & DIFFICULTIES IN INTERPRETING RESULTS

- Of 150 subjects randomized, only 134 completed study; however rather than conduct an ITT analysis, investigators did a "modified ITT" analysis, excluding those who discontinued (9 in the darifenacin group, 6 in the oxybutynin group, and 1 in placebo group). Excluding those who stopped early could bias the results.
- Oxybutynin ER dose higher than necessary. For many patients age >65, a dose of 5 to 10mg/day is common. There were no significant differences at week 1 with lower treatment doses. (1° score declined only at 15 & 20mg/day.)
- Increasing the oxybutynin dose at week 2 without increasing darifenacin dose biases this study in favor of darifenacin for CNS effects. The "learning effect" or improvement seen from administering same tests for 3 consecutive weeks may also be impacted by this dosing titration design as subjects in darifenacin arm had 2 weeks to practice at same low dose before being tested at higher dose.
- Of all the 2° endpoint direct comparisons for darifenacin vs oxybutynin over 1, 2 & 3 weeks, only **1/45** was statistically significant (& actually favored oxybutynin); however write-up draws on trends & indirect placebo comparisons to reflect positively on darifenacin suggesting a reporting bias. {Head-to-head 2° comparisons did not favor darifenacin.}
- Group differences at baseline: slightly lower age, less females, lower *name-face* score; potential bias
- Frail elderly not represented as not able to complete entry tests and more likely to be on excluded medications

BOTTOM LINE: Darifenacin has theoretical cognitive advantages. Some preliminary placebo controlled trials have results supporting this claim. At first glance this trial by Kay et al. appears to support these advantages based on the *name-face association test.* However when trial design issues (e.g. high oxybutinin dose for elderly, early drop outs), discussion bias, adverse event rates and overall limitations are considered, this study does not prove a definite advantage for darifenacin over oxybutynin. Further study is needed (especially with a more rational dose comparator) in elderly with urinary incontinence and at high risk for cognitive impairment. Darifenacin may offer a relative advantage or disadvantage to other anticholinergics depending on dose used and individual patient response. Currently, darifenacin offers a cost advantage over some comparators. {Cost/month^{SK}: Enablex 7.5-15mg/day= $64; Ditropan XL 5-10mg/day= $84,15-20mg/day=$159; Uromax10-15mg/day=$52-55; Detrol LA 2-4mg/day= $74.}

[1] Kay G, Crook T, Rekeda L, Lima R, Ebinger U, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. EurUrol 2006;50(2):317-26.