### Darifenacin (ENABLE) vs Oxybutynin ER extended release (DITROPAN XL) vs Placebo: Effects On Memory / Cognitive Impairment

**STUDY DESIGN**

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin (D)</td>
<td>7.5mg/day</td>
<td>7.5mg/day</td>
<td>↑ 15mg daily</td>
</tr>
<tr>
<td>Oxybutynin ER (O)</td>
<td>10mg daily</td>
<td>↑ 15mg daily</td>
<td>↑ 20mg daily</td>
</tr>
<tr>
<td>Placebo (Pl)</td>
<td>daily</td>
<td>daily(↓ 1mg/day)</td>
<td>daily(↓ 1mg/day)</td>
</tr>
</tbody>
</table>

**CHARACTERISTICS OF SUBJECTS**

- **Inclusion**: healthy, age 60+; able to follow instructions – valid responses (did not have to have urinary incontinence)
- **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)

- **No difference between darifenacin 15mg/day & placebo; oxybutynin score declined at both 15mg & 20mg/day.**
- **Subjects did not notice any change in memory**

### Secondary (2°) End Points:

- **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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Any AE</th>
<th>Tx Related</th>
<th>Any Serious</th>
<th>Dry Mouth</th>
<th>Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>27/49</td>
<td>26/49*</td>
<td>0/49*</td>
<td>13/49*</td>
<td>10/49</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>26/50</td>
<td>22/50</td>
<td>1/50</td>
<td>20/50</td>
<td>2/50</td>
</tr>
<tr>
<td>Placebo</td>
<td>23/51</td>
<td>16/51</td>
<td>0/51</td>
<td>6/51</td>
<td>1/51</td>
</tr>
</tbody>
</table>

*Note: 9 of the darifenacin patients dropped out (early) compared to 6 and 1 drop-outs for oxybutynin and placebo.*

**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 oxybutynin 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.

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