CATIE-AD 1,2

The Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer’s Disease (AD)
National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease

TRIAL BACKGROUND 3,4,5,6

- > 90% of pts with dementia develop at least 1 behavioural or psychiatric symptoms. Non-drug approaches to management are recommended; however, antipsychotic drugs are also used despite uncertainty about overall efficacy and safety

TRIAL DESIGN: Double-blind, placebo-controlled, multicentre 42 U.S. sites trial; ITT analysis

- Assessed the use of antipsychotics in outpatients w/ AD including Lewy Body/Vascular and agitation, aggression, or psychosis
- Compared: olanzapine OLZ, quetiapine QUE, and risperidone RIS vs placebo PL physicians determined starting doses on clinical judgment & patient response
  - Superiority design for each atypical vs placebo; non-inferiority +/- superiority design between agents

POPULATION: 421 patients treated for up to 36 weeks

- “77 years, MMSE 15±6, ADAS-cog total score ~35; NPI: delusions 82%, hallucinations 49%, agitation or aggression 86%, depression 61%; on cholinesterase inhibitor 60%; received antipsychotic ≤2 wks prior 14%
- 73% reside at home, 10% assisted-living; 57% equivalent to assisted-living facilities care; 17% equivalent to nursing home care

Table I. Results: Primary endpoint: time to discontinuation of treatment for any reason

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Olanzapine n=99</th>
<th>Quetiapine n=94</th>
<th>Risperidone n=84</th>
<th>Placebo (PL) n=139</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose mg/day Mean(range)</td>
<td>3.2 [0-10]</td>
<td>34.1 [0-100]</td>
<td>0.7 [0.5-2.5]</td>
<td>-</td>
<td>There were no differences between any agent and PL in primary endpoint for time to DC for any reason. (*Time to DC based on 50th percentile)</td>
</tr>
<tr>
<td>Last Dose mg/day Mean(range)</td>
<td>5.5 [0-17.5]</td>
<td>56.5 [0-200]</td>
<td>1 [0-2]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time to DC: Any Reason HR vs PL (CI) (% of pts)</td>
<td>8.1 wks (5.1-11.6)</td>
<td>0.83 (0.62-1.11); 80%</td>
<td>5.3 wks (3.6-8.1)</td>
<td>1.01 (0.75-1.36); 82%</td>
<td>7.4 wks (5.0-12.0)</td>
</tr>
<tr>
<td>Time to DC: For Efficacy HR (CI) vs PL</td>
<td>22.1 wks (12.1-7)</td>
<td>0.51 (0.35-0.74)</td>
<td>9.1 wks (7.0-21.6)</td>
<td>0.81 NS (0.57-1.15)</td>
<td>26.7 wks (14.6-11.6)</td>
</tr>
<tr>
<td>D/C for AE, intolerability, or death. HR vs PL (CI)</td>
<td>4.32 (1.84-10.12)</td>
<td>3.58 (1.44-8.91)</td>
<td>3.62</td>
<td>(1.45-9.04)</td>
<td>1</td>
</tr>
<tr>
<td>25% D/C rate</td>
<td>16% D/C rate</td>
<td>18% D/C rate</td>
<td>5%</td>
<td>Overall D/C: 63% @ 12 wks</td>
<td></td>
</tr>
</tbody>
</table>

* Note: Greater efficacy w/ OLZ & RIS; offset by > AE s, especially for OLZ (see Table II) CI=confidence interval HR=harazard ratio

Table II. Significant Adverse Event, Safety Outcomes

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Olanzapine (n=100)</th>
<th>Quetiapine (n=94)</th>
<th>Risperidone (n=85)</th>
<th>Placebo (PL) (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious AE</td>
<td>14 (14)</td>
<td>17 (18)</td>
<td>9 (11)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Sedation</td>
<td>24 (24) NNH-6</td>
<td>21 (22) NNH-6</td>
<td>13 (15)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Parkinsonism or EPS</td>
<td>12 (12) NNH-9</td>
<td>2 (2)</td>
<td>10 (12) NNH-10</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Confusion / mental status △</td>
<td>18 (18) NNH-8</td>
<td>6 (6)</td>
<td>9 (11) NNH-18</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Weight ↑&gt;7% - # (%)</td>
<td>10/90 (11)</td>
<td>5/80 (6)</td>
<td>8/75 (11)</td>
<td>4/128 (3)</td>
</tr>
<tr>
<td>(Weight change lb/mo of tx)</td>
<td>(1.0 ± 0.4)</td>
<td>(0.4 ± 0.6)</td>
<td>(0.7 ± 0.4)</td>
<td>(-0.9 ± 0.3)</td>
</tr>
</tbody>
</table>

*Safety data limited by short duration of treatment. * limited long-term role; “80% DC tx by 36 wks. ** NB: MMSE scores did not worsen in CATIE-AD; Ballard al. demonstrated clinically significant cognitive decline * is change >20 pt s with QUE vs. PL during longer follow-up period 6 & 26 wks

BOTTOM LINE:

- There were no significant differences between any atypical antipsychotics and placebo for overall rate of discontinuation.
- Atypical antipsychotics offer limited efficacy in the long term management of BPSD; non-drug therapies should be considered.
- Any benefit of atypical antipsychotics is largely offset by their adverse events. Therapy should be individualized & reassessed periodically. As 80% stopped therapy by 36 weeks, consider routine reassessment in 3-6 months for both efficacy & tolerability.
- [Note, although AE concerns with antipsychotics are significant, other psychotropic alternatives may even be worse.]
- At doses used, efficacy favored olanzapine ~1mg/day and risperidone 1mg/day. Quetiapine dose ~50mg/day may have been too low.
- Side effects profiles will differ depending on agent and dose. Olanzapine at dose used was associated with worse tolerability.
- The trial may offer some insight regarding potential advantages and disadvantages of each AP:
  - Efficacy longest Tx duration 1
  - Sedation: favours OLZ, RIS
  - Parkinsonism/EPS: most with OLZ, QUE
  - Confusion/mental status: most with OLZ, RIS
  - Cognitive disturabance: most with OLZ
  - Neurological composite: more with OLZ vs RIS
  - Weight gain: most with OLZ
  - RIS
  - QUE may be considered for patients with concurrent sleep disturbance or for patients at increased risk for falls, Parkinsonian symptoms & EPS (but some anticholinergic effects)

AD: Alzheimer’s disease
ADAS-cog score: Alzheimer’s Disease Assessment Scale – caregiver subscale
AP: antipsychotic
BPRS: Brief Psychiatric Rating Scale
CMIA: Cohen-Mansfield Agitation Inventory
Eps: extrapyramidal symptoms
MMSE: Mini-Mental Status Exam
QUE: Psychiatric Inventory
See pg 2 for back or online for supplementary information.

Ad Astra Carter, BSP PharmD Candidate & Julia Bareham, BSP
www.RxFiles.ca - Sep 2011
### RxFiles - CATIE-AD Trial Summary: Supplement Page

**Design: additional features**
- Patients eligible for 3 other Tx phases if physician deemed lack of efficacy or tolerability from assigned Tx: **Phase 2** from 2-12wks: randomized to different AP or citalopram; **Phase 3** from wk 4: randomized, open Tx; **Phase 4** “Open-Choice Phase” (anytime)
- **Primary endpoint:** time to D/C of Tx for any reason
- **Secondary endpoints:** time to D/C of Tx for lack of efficacy **Phase 1**; time to D/C of Tx for AE, intolerability, death **Phase 2**; Clinical Global Impression of Change (CGIC) **week 12**: continued Tx with original Phase 1 study drug & at least minimal improvement on scale

**RESULTS**

**Phase 3 Only: additional features**
- **Primary endpoint:**  [see Table 1]
  - NS among Tx groups; NS median time to D/C - range: 5.3wks QLE vs 8.wks QLE vs D/C in <50% by 8 wks
  - Only 19% completed entire study while taking their initially assigned medication
- **Efficacy** based on time to D/C of favoured OLZ; 21.7wks, RIS 20.7wks vs. QLE 23.1wks, PLS 20wks
  - OLZ and RIS Nt to each other; OLZ superior to QLE, D/C (6.1-9.6)
- **Tolerability** based on time to D/C due to AE, intolerability, or death of favoured PL
  - Discontinuation rates: PL 5% vs. OLZ 25% (two-sided p=.003), QLE 16% (two-sided p=.0071)
  - OLZ 18% vs. =D/C overall: 63% @12wks
- **CGIC:** NS among Tx groups
  - 17% did not receive an AP: randomization to PL, citalopram, or open-choice AP other than assigned study medications
  - 43 (12%) received OLZ & QLE, 42 (7%) received all 3 AP during trial follow-up

**Table 3: Adverse Event, Safety Outcomes**

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Olanzapine (n=100)</th>
<th>Quetiapine (n=94)</th>
<th>Risperidone (n=85)</th>
<th>Placebo (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious AE</td>
<td>14 (14)</td>
<td>17 (18)</td>
<td>9 (11)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Sedation</td>
<td>24 (24)</td>
<td>21 (22)</td>
<td>13 (15)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Parkinsonism or EPS</td>
<td>12 (12)</td>
<td>2 (2)</td>
<td>10 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>% D/C due to EPS</td>
<td>6 (6)</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Falls, fractures, injuries</td>
<td>17 (17)</td>
<td>7 (7)</td>
<td>10 (12)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Cerebrovascular event/TIA</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cognitive Disturbance</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Confusion/mental status Δ</td>
<td>18 (18)</td>
<td>6 (6)</td>
<td>9 (11)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Psychotic Symptoms</td>
<td>7 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Weight↑ -7% ~ -10%</td>
<td>10/90 (11)</td>
<td>5/60 (8)</td>
<td>8/75 (11)</td>
<td>4/128 (3)</td>
</tr>
<tr>
<td>[Weight change lb/mo of Tx]</td>
<td>[1.0 + 0.4] vs. 0.12 ± 0.05</td>
<td>[0.4 + 0.6] vs. 0.12 ± 0.05</td>
<td>[0.7 + 0.4] vs. 0.12 ± 0.05</td>
<td>[-0.9 + 0.3]</td>
</tr>
</tbody>
</table>
| Magnitude of gain/loss (lb)
| 1.7 | 1.2 | 1.4 | 1.4 |
| Glucose A1c baseline (mmol/L) | 0.62 ± 0.32 | 0.14 ± 0.36 | 0.14 ± 0.33 | -0.07 ± 0.28 |
| TC A1c baseline (mmol/L) | 0.29 ± 0.12 | 0.05 ± 0.13 | -0.19 ± 0.13 | -0.19 ± 0.11 |
| TG A1c baseline (mmol/L) | 0.23 ± 0.12 | 0.18 ± 0.13 | 0.11 ± 0.12 | 0.13 ± 0.11 |

**COMMENTS**

- Quetiapine dose may have been too low; lack of efficacy versus other AP secondary to suboptimal dose?
  - Some argue that optimal dose may be ~100mg/day based on an open-label study (n=10, 76 years, significant improvement in agitation subscale of NPI at 6 & 12 wks w/ mean QLE 100mg/day)
  - However, more recent RCT of quetiapine 100mg/day vs. placebo N=29 did not find benefit for agitation CMR at 6 or 26 wks using this suggested “optimal dose”

- Rate of AE w/ QLE likely underestimated with dose used; negative benefit of QLE vs. PL also observed in more recent trial: median dose: 200mg/day

- Lack of washout period was of concern to some
- Safety measures limited by short duration of Tx
  - High rate of discontinuation limits assessment of metabolic changes and incidence of stroke, mortality, and cognitive decline observed in other trials
  - NB: MMSE scores did not worsen in the present trial however Ballard, et al. demonstrated clinically significant cognitive decline
  - Knowledge of possible randomization to placebo may have influenced early D/C rates by study physicians by accelerating select patients into definitive active treatment
  - Primary outcome beneficial in assessing efficacy, safety, & tolerability into single global measure, however does not agree with Tx guidelines supporting reassessment & D/C after period of behavioural stability
  - Endpoint suggested to be more clinically relevant in comparison to previous studies using behavioural rating scales
  - NS findings may be secondary to small sample size and Tx duration too short to determine benefit
  - Findings not generalizable to patients with DLB neuropathic sensitivity or OD excluded from trial may not be generalizable to nursing home patients with more severe AD/BD or to -earlier trial did not find benefit for QLE vs. P for agitation in severe AD pts & was associated with significant cognitive decline
  - Recent antipsychotic meta-analysis for off-label uses

**References:**