OFF-LABEL USES OF DONEPEZIL:
A FOCUS ON SAFETY AND EFFICACY IN TRAUMATIC BRAIN INJURY AND POST STROKE APHASIA

Lindsay Shelledy, Pharm.D.
PGY1 Pharmacy Resident
Seton Healthcare Family
September 11th, 2015

OBJECTIVES

- Review the use of donepezil in traumatic brain injury and post stroke aphasia.
- Summarize the epidemiology, pathophysiology, and treatment recommendations.
- Analyze several clinical trials for the efficacy and safety of using donepezil for traumatic brain injury and post stroke aphasia.
- Identify potential areas for future research.
- Evaluate the clinical benefit versus risk.

DONEPEZIL

- Approved in December 1996
- Indications
  - Mild, moderate, and severe Alzheimer’s dementia
- Adverse effects
  - Insomnia (2-14%)
  - Nausea (3-19%)
  - Diarrhea (5-15%)

DONEPEZIL OFF-LABEL USES

- Traumatic Brain Injury (TBI)
- Post Stroke Aphasia
- Dementia associated with Parkinson’s Disease
- Lewy Body Dementia
- Mood Disorders
- Autism Spectrum Disorder

OFF-LABEL MEDICATIONS

- No approved medications for the specific populations
- Similar medication has been approved for the indication
- Pathologic or physiologic features of conditions are similar
- Health care professionals should weigh the risks and benefits of using an off-label medication
TRAUMATIC BRAIN INJURY

Approximately 2.5 million people sustained a TBI in 2010

Causes of TBI
- Falls: 40%
- Unintentional Blunt Trauma: 19%
- Motor Vehicle Accidents: 14%
- Assaults: 11%
- Other: 16%

EPIDEMIOLOGY

Injury Prevention & Control Traumatic Brain Injury, CDC.

Comparison of a normal brain, Alzheimer’s brain, and brain 4 years after TBI

ATROPHY IN THE BRAIN


http://www.nature.com/nrneurol/journal/v9/n4/fig_tab/nrneurol.2013.29_F1.html


TBI severity classification
- Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Severity</th>
<th>Glasgow Coma Scale Score</th>
<th>Post-traumatic amnesia</th>
<th>Loss of consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13-15</td>
<td>&lt; 1 hour</td>
<td>&lt; 30 minutes</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
<td>1-24 hours</td>
<td>1-24 hours</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 8</td>
<td>&gt; 24 hours</td>
<td>&gt; 24 hours</td>
</tr>
</tbody>
</table>

SEVERITY OF TRAUMATIC BRAIN INJURY

Up to 70% of TBI patients

COGNITIVE IMPAIRMENT

CURRENT RECOMMENDATIONS

- No approved medications to treat cognitive impairment associated with TBI
- Treatment should be symptom-based

<table>
<thead>
<tr>
<th>Impairment</th>
<th>First Line Medication</th>
<th>Side Effects</th>
<th>Other treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>Amantadine 200-400 mg/day</td>
<td>CNS depression, peripheral edema, hypotension, anorexia</td>
<td>Bromocriptine, pramipexole, carbidopa/levodopa</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Methylphenidate 0.3 mg/kg twice daily</td>
<td>Tachycardia, insomnia, decreased appetite, nausea, anxiety</td>
<td>Dextroamphetamine</td>
</tr>
<tr>
<td>Memory</td>
<td>Donepezil 5-10 mg/day</td>
<td>Nausea, insomnia, diarrhea, fatigue</td>
<td>Rivastigmine, galantamine, physostigmine</td>
</tr>
</tbody>
</table>

CURRENT RECOMMENDATIONS

EARLY LITERATURE

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whelen et al. 2000</td>
<td>Retrospective case series Cognitive dysfunction</td>
<td>N=53</td>
<td>5 mg daily titrated to 10 mg if tolerated</td>
<td>Improvement: daily functioning</td>
</tr>
<tr>
<td>Masanic et al. 2001</td>
<td>Open label retrospective study Memory, behavior, global function</td>
<td>N=4</td>
<td>5 mg daily x 8 wk 10 mg daily x 4 wk Washout x 4 wk</td>
<td>Improvements: verbal/visual memory, behavior</td>
</tr>
<tr>
<td>Morey et al. 2003</td>
<td>Single-subject retrospective study Memory</td>
<td>N=7</td>
<td>5 mg daily x 4 wk 10 mg daily x 5 mo Washout x 6 wk 5 mg daily x 6 mo</td>
<td>Improvement: visual memory Only seen with 10 mg</td>
</tr>
</tbody>
</table>

LIMITATIONS

- Very few patients
- Adverse effects not reported in detail
- Placebo effect

Zhang, et al. 2004

- 24-week randomized, placebo-controlled, double-blind crossover trial
- Short-term memory and sustained attention
- Inclusion criteria:
  - Short-term memory impairment
  - Participants were 2-24 months post TBI

ASSESSMENT TOOLS

- Wechsler Memory Scale (WMS-III)
  - Auditory Immediate Index (All)
  - Visual Immediate Index (VII)
  - Indexes have a mean of 100 and a standard deviation of 15
- Paced Auditory Serial Addition Test (PASAT)
  - Sustained attention, working memory, and information-processing speed
  - Maximum of 60
Auditory Immediate Index

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>63.7 ± 2.5</td>
<td>62.3 ± 2.0</td>
<td>0.611</td>
</tr>
<tr>
<td>Week 10</td>
<td>95.4 ± 4.5</td>
<td>73.6 ± 4.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 24</td>
<td>105.9 ± 4.5</td>
<td>102.4 ± 4.5</td>
<td>0.588</td>
</tr>
</tbody>
</table>

Visual Immediate Index

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>65.9 ± 2.6</td>
<td>63.3 ± 3.2</td>
<td>0.116</td>
</tr>
<tr>
<td>Week 10</td>
<td>93.5 ± 3.0</td>
<td>64.9 ± 3.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 24</td>
<td>91.3 ± 3.0</td>
<td>94.9 ± 3.0</td>
<td>0.397</td>
</tr>
</tbody>
</table>

Score of 100 defines average performance in a healthy population

WHAT ABOUT THE OTHER ACETYLCHOLINESTERASE INHIBITORS (AI)?

Retrospective, open cohort study with 3 arms

Treatment response between donepezil, galantamine, and rivastigmine

111 patients

1 year post injury, with symptoms of fatigue, poor memory, diminished attention, or initiation problems

CONCLUSION

Auditory and visual immediate memory and attention

Improvement continued after washout

Limitations

- Spontaneous recovery
- Small number of patients
- 1 patient dropped out due to adverse effects

TENOVUO, ET AL. 2004

Retrospective, open cohort study with 3 arms

Treatment response between donepezil, galantamine, and rivastigmine

111 patients

1 year post injury, with symptoms of fatigue, poor memory, diminished attention, or initiation problems
**ASSESSMENT TOOLS**

**TENOVUO, 2004**

- Response based on **subjective** assessment
  - Graded as none, modest, good, or excellent
- Glasgow Outcome Scale, extended (GOS-E) form was also determined
  - Functional outcome scale that rates patient status from 1-8

**RESULTS**

**TENOVUO, 2004**

- No difference between groups
- Increase in general functioning
- No wearing off of response
- Extra benefit with dose increase
- Response to one acetylcholinesterase inhibitor and not another
- Adverse effects were persisting in 26% of patients

**LIMITATIONS**

**TENOVUO, 2004**

- 39% of patients had a modest or no response
- Improvement was based on subjective assessment
- Difference in the number of patients in each arm
- Placebo effect

**KHATEB, ET AL. 2005**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Dose</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khat et al.</td>
<td>N=10</td>
<td>5 mg daily + 1 mg daily</td>
<td>Behavior</td>
<td>Improved</td>
</tr>
<tr>
<td>Prospective</td>
<td>Mod/severe, &gt; 6 months post injury</td>
<td>10 mg daily + 2 months</td>
<td>Executive functioning</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Learning/Memory</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Attention</td>
<td>Improved</td>
</tr>
</tbody>
</table>

**SAFETY**

**KHATEB, 2005**

- Side effects:
  - Nausea, sleep disorders, anxiety, excitability, cramps, dizziness
  - 4/15 patients stopped the drug
  - Side effects subsided in 2-3 weeks for some patients
**Acute and late phases of memory and attention improved**

**Positive effects after treatment discontinuation**

**Possible improvement in processing speed and learning**

**No significant difference between donepezil and other acetylcholinesterase inhibitors**

**Adverse effects were often transient**

---

**Large scale randomized placebo-controlled trial**

**Effectiveness based on time since TBI, severity of TBI, and location of injury**

**Clinical observation**

---

**Loss or impairment of language due to brain damage**

**Affects about 20-40% of all stroke patients**

**Aphasia recovery tends to plateau by 1 year after onset**

---

**Nonfluent aphasia**
- Speech production is halting

**Fluent aphasia**
- Comprehension is poor

**Severe impairment of both expressive and receptive skills**
**PHARMACOLOGIC THERAPY**

- Bromocriptine – no significant impact on aphasia
- Amphetamines – improved aphasia recovery when combined with language therapy
- Donepezil – positive effect on global language function during active treatment

**MECHANISM OF EFFECT**

- Vascular lesions interrupt cholinergic pathways
- Cerebral circulation is influenced by cholinergic mechanisms

**ASSESSMENT TOOLS**

- Tests used to assess aphasia
  - Communication, linguistic ability, comprehension
- Western Aphasia Battery (WAB)
- Psycholinguistic Assessment of Language Processing in Aphasia (PALPA)

**BERTHIER, ET AL. 2006**

- 20 week double-blind, randomized, placebo-controlled study
- Primary endpoint: aphasia severity
- Inclusion criteria:
  - < 70 years
  - Chronic aphasia (1 year since onset)
  - Unilateral stroke lesion

**METHODS**

<table>
<thead>
<tr>
<th>Baseline Assessment (N=26)</th>
<th>Placebo x 4 weeks (N=13)</th>
<th>Placebo x 12 weeks</th>
<th>Washout period x 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil 5 mg/day x 4 weeks (N=13)</td>
<td>Placebo x 4 weeks (N=13)</td>
<td>Placebo x 12 weeks</td>
<td>Washout period x 4 weeks</td>
</tr>
<tr>
<td>Donepezil 10 mg/day x 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS**

- Significant improvement
  - Aphasia severity (p = 0.037)
  - Picture naming subtest of PALPA (p = 0.025)
- Adverse events not significant
CONCLUSION
BERTHIER, 2006

- Between group differences no longer significant after washout period
- Only enhances language and communication performance during treatment

CHEN, ET AL. 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Dose</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, et al. 2010</td>
<td>N=60</td>
<td>5 mg daily x 12 wks</td>
<td>Western Aphasia Battery measured at baseline and 12 weeks</td>
</tr>
</tbody>
</table>

RESULTS
CHEN, 2010

- Aphasia Quotient was significantly greater (p = 0.004)
- Significant recovery in spontaneous speech, comprehension, repetition, and naming functions (p = 0.05)

FINAL CONCLUSION

- Speech and language therapy is the mainstay of treatment
- Recovery in spontaneous speech, comprehension, repetition, and naming functions
- Presents a good option for patients that require augmentation to speech and language therapy

FUTURE STUDIES

- Large scale randomized placebo-controlled trial
- Determine if aphasia type or severity is linked to effectiveness of donepezil to better target certain patient populations
- Compare donepezil with the other acetylcholinesterase inhibitors

DISCUSSION: TRAUMATIC BRAIN INJURY

- Use is controversial
- Available trials are limited by design
- Improvement in memory and attention for many patients
- Positive effects remained after discontinuation
- Adverse events may limit use
- Donepezil should be used to treat memory impairment following traumatic brain injury
  • 10 mg daily
DISCUSSION: POST STROKE APHASIA

- No pharmacological treatment for post stroke aphasia
- Few clinical trials
- Significant recovery in speech and comprehension
- Positive effects did not remain after discontinuation
- Donepezil should be used to treat post stroke aphasia
  - 5-10 mg both showed improvement

ACKNOWLEDGEMENTS

- Special thanks to:
  - Tamara Knight, Pharm.D., BCPS
  - Lyndsi Meyenburg, Pharm.D., BCPS

OFF-LABEL USES OF DONEPEZIL:
A FOCUS ON SAFETY AND EFFICACY IN TRAUMATIC BRAIN INJURY AND POST STROKE APHASIA

Lindsay Shelledy, Pharm.D.
Pgy1 Pharmacy Resident
Seton Healthcare Family
September 11th, 2015