Traumatic Brain Injury in Children — A Review of Pharmacological Approaches to Acquired ADHD

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BACKGROUND

- Traumatic brain injury (TBI), a common condition seen in both adults and children, can lead to cognitive, social, and physical complications.
- Attention Deficit/Hyperactivity Disorder (ADHD) induced by TBI (secondary ADHD or ADHD/TBI) in children is one consequence that has limited discussion in the literature.

OBJECTIVE

This poster reviews the psychopharmacologic treatment options available, their effectiveness, and what is currently under study.

METHODS

- A literature search was conducted using the following databases: Medline, Cochrane/EBM and PubMed from 1988-2011.
- Stimulants TBI, TBI, ADHD TBI, Bromocriptine, Guanfacine, Donepazil and Atomoxetine were the key search terms used.
- Limits include clinical trial publication, human subjects, English language, adults and children age 0-18 years.
- Information was extracted on study characteristics, interventions and outcomes.
- Data extracted included subjective and objective tests and baseline measures. (see details in Tables)

RESULTS

- Eleven clinical trials evaluating the efficacy and safety of Methylphenidate (MPH) in pediatric and adult patients with TBI match the search criteria. (see details in Table 1)
- Methylphenidate administration resulted in a statistically significant increase in pulse of 12.3 beats/min (95% confidence interval (CI) 9.25–15.36), diastolic blood pressure of 4.1 mmHg (95% CI 2.11–6.10), and mean arterial pressure of 3.75 mmHg (95% CI 1.79–5.72). These changes did not, however, appear to be symptomatic, as no participants were withdrawn due to adverse events, and there was no significant self-report of increased heart rate with methylphenidate. (Catherine Wilmott et al 2009)

- Methylphenidate was safely used in brain injured patients, even those at high risk for seizures, as it was associated with a trend toward reduction (rather than increase) in seizure frequency in this population. (Wrobleski et al. 1992)

- Many drugs showed encouraging pre-clinical results with neuroprotective, neurorestorative, neurogenetic and synaptogenetic properties but all phase II and III clinical trials have failed so far. They include Progesterone, Dexamabolin, Dexamethasone, Magnesium, Cyclosporin A, Erythropoietin (and its carboxylated form), Statins, and Bone marrow stromal cells. (Robert Vink et al. ’04), (Ye-Xione et al. ’09)

CONCLUSION

- There are a limited number of randomized double blind placebo controlled multicenter trials studying the effects of methylphenidate in ADHD/TBI.
- No randomized controlled studies in ADHD/TBI using stimulants other than MPH were found.
- Statistical analyses of the limited data demonstrate the efficacy of short term treatment with MPH in the pediatric population.
- There is very scant literature available on the use of non stimulant treatment options in Secondary ADHD.

RECOMMENDATIONS

- More studies are required to see the effects of amphetamine group of stimulants and non-stimulant treatment options for secondary ADHD.
- Based on our review, additional multicenter, randomized, double blind, placebo controlled studies with larger sample sizes, longer length of treatment and wider dose ranges would be helpful in guiding clinical practice.

Table 1: Published Clinical Studies for Methylphenidate in TBI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Total Pts.</th>
<th>TITRATION</th>
<th>CROSSED-OUT</th>
<th>Blind</th>
<th>TBI</th>
<th>ADHD</th>
<th>MPH</th>
<th>Duration</th>
<th>Outcomes Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whyte et al. (1996)</td>
<td>R, DB, PC, crossover</td>
<td>10</td>
<td>6 mg</td>
<td>4 to 8 mg</td>
<td>R, DB, PC</td>
<td>crossover</td>
<td>54</td>
<td>4 mg</td>
<td>4 wks</td>
<td>Attention, behavior, processing speed</td>
<td>Significant improvement in all measures of attention with MPH vs placebo</td>
</tr>
<tr>
<td>Mahalick et al. (1998)</td>
<td>DB, PC, crossover</td>
<td>12</td>
<td>5 mg</td>
<td>4 to 8 mg</td>
<td>R, DB, PC</td>
<td>crossover</td>
<td>74</td>
<td>4 mg</td>
<td>4 wks</td>
<td>Attention, behavior, processing speed</td>
<td>Significant improvement in all measures of attention with MPH vs placebo</td>
</tr>
<tr>
<td>Weizman et al. (1999)</td>
<td>DB, PC, crossover</td>
<td>8</td>
<td>2 mg</td>
<td>4 to 8 mg</td>
<td>R, DB, PC</td>
<td>crossover</td>
<td>28</td>
<td>4 mg</td>
<td>4 wks</td>
<td>Attention, behavior, processing speed</td>
<td>Significant improvement in all measures of attention with MPH vs placebo</td>
</tr>
<tr>
<td>Xiono et al. (2009)</td>
<td>DB, PC, crossover</td>
<td>9</td>
<td>2 mg</td>
<td>4 to 8 mg</td>
<td>R, DB, PC</td>
<td>crossover</td>
<td>45</td>
<td>4 mg</td>
<td>4 wks</td>
<td>Attention, behavior, processing speed</td>
<td>Significant improvement in all measures of attention with MPH vs placebo</td>
</tr>
<tr>
<td>Holsen et al. (2011)</td>
<td>DB, PC, crossover</td>
<td>19</td>
<td>2 mg</td>
<td>4 to 8 mg</td>
<td>R, DB, PC</td>
<td>crossover</td>
<td>45</td>
<td>4 mg</td>
<td>4 wks</td>
<td>Attention, behavior, processing speed</td>
<td>Significant improvement in all measures of attention with MPH vs placebo</td>
</tr>
</tbody>
</table>

Table 2: Published Clinical Studies on Non-Stimulant Medication in Secondary ADHD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medication</th>
<th>Design</th>
<th>Total Pts.</th>
<th>Duration</th>
<th>Dose Used</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holsen et al. (2008)</td>
<td>Donepazil</td>
<td>DB, PC, crossover</td>
<td>18</td>
<td>24 wks</td>
<td>5-10 mg daily</td>
<td>Short term memory, sustained attention</td>
<td>Donepazil increased neuropsychologic testing scores in short-term memory and sustained attention</td>
</tr>
<tr>
<td>Xiono et al. (2009)</td>
<td>Bromocriptine</td>
<td>DB, PC, crossover</td>
<td>12</td>
<td>6 wks</td>
<td>5 mg BD</td>
<td>Attention and work productivity</td>
<td>Bromocriptine (5 mg BD) did not seem to enhance attentional abilities, and it may be associated with an excess of adverse events. It is not clear whether intermediate dosing or lower dose might confer benefit</td>
</tr>
<tr>
<td>Whyte et al. (2009)</td>
<td>Alpha adrenergic agonist (Guanfacine)</td>
<td>PC, DL, PC, crossover</td>
<td>12</td>
<td>17 days</td>
<td>2 mg daily</td>
<td>Working memory/ability to hold info in mind for an attentional component</td>
<td>TBR associated with increased working memory performance</td>
</tr>
<tr>
<td>Xiono et al. (2011)</td>
<td>Aconitum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved cognition following experimental TBI in animals. No study on human subjects</td>
<td></td>
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