Neuropharmacologic Agents for Treatment of Cognitive Impairment After Brain Injury
Disclosures

• Most, it not all, of the medications discussed have not been tested in pediatric populations.

• Most, if not all, the medications discussed are being used off-label in pediatric populations.

• No financial disclosures
Neuropharmacology in Pediatric Brain Injury: A Review

Percival H. Pangilinan, MD, Angela Giacoletti-Argento, PhD, Renee Shellhaas, MD, Edward A. Hurvitz, MD, Joseph Edward Hornyak, MD, PhD

Efficacy and Safety of Dopamine Agonists in Traumatic Brain Injury: A Systematic Review of Randomized Controlled Trials

Anne Julie Frenette, Salmaan Kanji, Laura Rees, David R. Williamson, Marc M. Perreault, Alexis F. Turgeon, Francis Bernard, and Dean A. Fergusson

Impact of Pharmacological Treatments on Cognitive and Behavioral Outcome in the Postacute Stages of Adult Traumatic Brain Injury

A Meta-Analysis

Patricia Wheaton, PhD, Jane L. Mathias, BA, PhD, and Robert Vink, BSc, PhD
Cognitive Impairment after Pediatric TBI

- May not be apparent initially
- Deficits may become apparent later when child is at a developmental stage where a particular cognitive ability would be expected
- Those injured at a younger age show more cognitive impairment than those injured later in childhood
- Multiple factors impact recovery
Areas of Common Cognitive Impairments after TBI

• Arousal
• Attention/Impulsivity
• Memory
• Behavior
• Executive function
• Social Function
Attention

- Attention problems are common after TBI, estimates vary ~20% of all injuries
- Severity of TBI correlates with likelihood of developing attention problems
- Attention problems in children with TBI are different from ADHD
  - Children with TBI have slower response speeds
  - Attentional functions developed later are more preferentially affected in TBI (sustained and divided attention)
Executive Function

• The ability to manage and direct cognitive abilities to set, manage, and attain goals.
  – Working memory
    • Inhibition
    • Shifting focus
  – Problem solving
  – Metacognition
    • Self-monitoring
    • Self-regulation
    • Self-appraisal
    • Self-management
  – Social Cognition

• Develops throughout childhood and adolescence
  – Working Memory 7-12 months of age
  – Continued development of executive functioning, decision-making through 20’s

• Greater impairment if injury occurs earlier and injury more severe
Memory

- Often impaired after TBI
- Typically new memory formation impaired > long term memory
- Severity of impairment related to severity of injury
“Cognitive Rehabilitation”

- “systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient’s brain-behavioral deficits”
  - Adaptive, compensatory, and restorative approaches
- Online activity with subscription fees available and marketed to the public (at least on WKSU – NPR)
- 2013 Cochrane review
  - “We found no evidence that cognitive rehabilitation interventions were helpful for people with executive dysfunction”
  - Need more research?
  - Need other interventions?
Evidence for pharmacological intervention for cognitive impairment after TBI

• 2011 meta-analysis of adult TBI interventions
  – Included studies whose data could be combined, and from which effect sizes could be calculated
    • Excludes many that didn’t could not be combined
  – 3 treatments met their definition of clinical usefulness in adult TBI
    • 1. Methylphenidate reduced combativeness and improved psychosocial outcome
      – There were no improvements on any of the measures of attention that were used in a doubleblinded crossover design study that administered treatment from 12 days to more than a year after a moderate to severe TBI
    • 2. Donepezil improved memory and attention
    • 3. Amantadine improved arousal and global outcome
Dopamine Agonists

- Methylphenidate
- Dexmethylphenidate
- Bromocriptine
- Amantadine
- Methylphenidate
- Levodopa
- Ropinirole
- Pramipexole
- Pergolide
- Others . . .
Dopamine Agonists: Literature Review

• 2012 Systematic Review of RCTs of dopamine agonists in traumatic brain injury for any outcome measure
• 20 studies qualified
  – Methylphenidate (14)
  – Amantadine (4)
  – Bromocriptine (2)
• Heterogeneity of studies, outcome measures, and patient populations precluded meta-analysis
• Conclusions
  – “Our systematic review does not support the use of dopamine agonists as part of the treatment regimen for improving functional outcome measures in either the acute or sub-acute phases of care in TBI patients”
• However . . .
Attention

- 21 different tests used
- 10 of 21 (48%) showed benefit in at least 1 study
- Only 2 tests showed positive results in more than one study

| Study                  | Drug          | Detection task | Dual Task | Sustained Attention to Response task | Ruff 32 (all subtests) | Modified Posner Paradigm | Gordon Diagnostic System | Continuous Performance test | Digit span (WAIS-R) | Serial Digit Learning (alternative) | Letter-Cancellation test | Spatial Dissection-Response | Letter-Number Sequencing task | Two-back Working Memory | Selective Attention task | Reaction time | Sustained arousal and attention tasks (50,50 & 2000) |
|------------------------|---------------|----------------|-----------|--------------------------------------|------------------------|--------------------------|---------------------------|---------------------------|------------------------|---------------------------------|-----------------------------|--------------------------|-----------------------------|-----------------------------|--------------------------|--------------------------------|
| Wilfong and Lonsford 2009 | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Moen 2006              | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Kim 2006               | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Lee 2005               | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Wyntje 2004            | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Mahalick 1999          | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Williams 1998          | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Wyntje 1997            | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Plienger 1998          | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Speech 1993            | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Mooney 1993            | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Guillemin and Evans 1989 | Methylphenidate |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| McMahon 2000           | Amantadine     |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Beers 2005             | Amantadine     |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Meythaler 2002         | Amantadine     |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Schneider 2000         | Amantadine     |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Wyntje 2006            | Bromocriptine  |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |
| Medcalf 1993           | Bromocriptine  |               |           |                                      |                        |                          |                           |                           |                        |                                 |                             |                          |                  |                            |                            |                        |                             |

Legend
- Positive result
- Negative result
- Individual result not provided
- + Composite endpoint positive
- -- Composite endpoint negative

FIG. 3. Tests assessing attention (WAIS-R, revised Wechsler Adult Intelligence Scale).
Executive Functioning

- 2 studies showed benefit for sustained arousal or attention with methylphenidate

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<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Sustained Arousal and/or Attention task (80/50 &amp; 20/80)</th>
<th>Controlled Oral Word Association test</th>
<th>Tower of London</th>
<th>Porteus Maze</th>
<th>Stroop Interference task</th>
<th>Wisconsin Card Sorting test</th>
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**FIG. 2.** Tests assessing executive functioning.
Processing Speed and Reaction Time

- 50% of patients tested with choice reaction time task (8 studies) showed benefit

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<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Choice Reaction Time task</th>
<th>Selective Attention task</th>
<th>Symbol Digit Modalities Test</th>
<th>Stroop Word-Reading Interference Test</th>
<th>Stroop Color-Word Interference Test</th>
<th>Immediate Semantic Scanning test</th>
<th>Rapid Tapping task</th>
<th>Paced Auditory Serial Addition task</th>
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**FIG. 4.** Tests assessing processing speed and reaction time.
Memory

- No statistical significance found for any dopamine agonist medication

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<tr>
<th>Study</th>
<th>Drug</th>
<th>Serial Digit Learning (alternative)</th>
<th>Benton Visual Retention Test</th>
<th>Wechsler Memory Scale</th>
<th>Rivermead Behavioural Memory Test</th>
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**FIG. 5.** Tests assessing memory.
Methylphenidate

• Mechanism
  – upregulation of both dopamine and norepinephrine, primarily within the prefrontal cortex

• Research support is mixed
  – May be benefit for psychosocial outcome, mixed evidence for attention in adults
  – 2012 study of methylphenidate (double blind placebo crossover n=33 adults) (Kim and Whyte, 2012)
    • Visual sustained attention and reaction time improved
    • Attempts to localize fMRI changes in response to methylphenidate
Methylphenidate Side effects

- **Serious Reactions**
  - Dependency/abuse
  - Psychosis
  - Mania
  - Aggressive behavior
  - Tics
  - Hypertension/MI/stroke/arrhythmias
  - Growth suppression

- **Common**
  - Nervousness
  - Insomnia
  - Anorexia
  - Abdominal pain
  - Nausea
  - Headache
  - HR/BP changes
Donepezil

- Centrally acting acetylcholinesterase inhibitor
- Research supports benefit for memory and attention in adults
- Promotes changes in cortical metabolism measured by PET scanning after TBI
- 1 pediatric case series (n=3)
  - ABAB study design in 3 adolescents:
    - 2.5 mg daily for 1 week, then 5 mg daily then washout
    - Followed by 2.5 mg x 1 week, 5 mg x 1 week, then 10 mg
  - improvements in learning and immediate storage, but not delayed recall
Donepezil Side Effects

- **Serious**
  - AV block
  - Bradycardia
  - Syncope
  - Seizures
  - GI bleed
  - Hemolytic anemia
  - Urinary obstruction

- **Common**
  - Nausea/vomiting
  - Headache
  - Diarrhea
  - Pain
  - Insomnia
  - Dizziness
Summary

• Limited evidence for pharmacologic management of cognitive impairment after traumatic brain injury in children and adolescents
• Mixed/emerging research in adults for methylphenidate for attention/psychosocial outcome
• Adult research (+1 adolescent case series) suggests donepezil may help with memory
References

• Brink et al Recovery of motor and intellectual function in children sustaining severe head injuries. DMCN. 1970;12:565-71
• Arnsten AFT. Stimulants: therapeutic Actions in ADHD. Neuropsychopharmacology 2006;31:2376-2383.