Utilization of Amantadine in Traumatic Brain Injury

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Disclosure Statement

- *I have no disclosures concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation*.

- *Several medications will be discussed in regards to off-label use not approved by the FDA.*
Objectives

1. Recognize the role of amantadine in traumatic brain injury

2. Analyze the literature regarding the use of amantadine in traumatic brain injury

3. Identify the optimal dose and duration of amantadine in traumatic brain injury
Leading cause of death and disability amongst children and young adults

Falls cause 47% of all traumatic brain injuries

Almost half (43%) of all individuals hospitalized after TBI have a related disability one year after the event
Traumatic Brain Injury

**Cause**
- Bump, blow or jolt to the head
- Leads to disruption of normal brain function

**Mild**
- Brief change in mental status or consciousness
- Glasgow Coma Scale = 13 to 15

**Moderate**
- Loss of consciousness of several minutes to hours
- Glasgow Coma Scale = 9 to 12

**Severe**
- Extended period of unconsciousness or memory loss after the injury
- Glasgow Coma Scale = 3 to 8

Centers for Disease Control and Prevention. Severe TBI. 2018
Impact of Severe Traumatic Brain Injury

- **Cognitive function**
  - Decreased attention and concentration
  - Memory problems
  - Confusion and impulsiveness

- **Motor function**
  - Weakness
  - Impaired coordination and balance

- **Sensation**
  - Visual/hearing impairment
  - Impaired perception and touch

- **Emotion**
  - Irritability
  - Aggression
  - Depression

Centers for Disease Control and Prevention. Severe TBI. 2018
Acute Management of Traumatic Brain Injury

Primary Goal = Prevent secondary injury

Management

- Avoid hypotension (SBP<90 mm Hg)
- Avoid hypertension (SBP > 160 mm Hg)
- Avoid hypoxemia (SpO2 < 90%)
- Maintain cerebral perfusion pressure
- Management of elevated intracranial pressure (>20 mm Hg)

Prophylactic Medications

- Seizure prophylaxis
- Venous thromboembolism prophylaxis
- Stress ulcer prophylaxis

## Long Term Management of Traumatic Brain Injury

### Non-Pharmacologic

- Physical therapy
- Occupational therapy
- Cognitive-behavioral therapy
- Psychotherapy

### Pharmacologic

- Methylphenidate
- Antidepressants (SSRIs)
- Antiparkinsonian (amantadine, bromocriptine, levodopa)
- Anticonvulsants (valproic acid)

SSRI = selective serotonin reuptake inhibitor

Talsky A, et al. *BCMJ.* 2010
Amantadine

**Approved Indications**
- Parkinson’s disease
- Extrapyramidal symptoms
- Influenza A

**Mechanism**
- Enhance dopamine release
- Inhibit dopamine reuptake
- NMDA antagonist
- Antiviral

**Dosing Range**
- 100 – 200 mg PO BID at 0800 and 1200

**Adverse Effects**
- CNS: seizures, insomnia, confusion
- GI: GI upset

Aoki FY, Sitar DS. *Clin Pharmacokinet.* 1988
Amantadine for TBI

Diffuse axonal injury

Damage and death of neurons

Associated with a reduction in dopamine release

Amantadine ↑ dopamine

TBI = traumatic brain injury
Meythaler JM, et al. J Head Trauma Rehabil. 2002
How does amantadine affect neurotransmitters in the setting of TBI?

A. Increase dopamine release at the presynaptic neuron
B. Prevent reuptake of dopamine at the presynaptic neuron
C. Increase NMDA
D. A and B

TBI = traumatic brain injury
NMDA = N-methyl-D-aspartate
Literature Review
Disability Rating Scale

**DRS**
- Rating of 0-29
  - 0 = no disability
  - 25-29 = extreme vegetative state

**Criteria**
- Eye opening
- Communication ability
- Motor response
- Cognitive ability
- Level of functioning
- Employability

Giacino et al. (2012)

- Randomized, multi-center, placebo-controlled trial
  - Severe TBI
  - Enrolled 4-16 weeks post-TBI
  - Amantadine (n=87) vs placebo (n=97)

- Dosing

100 mg PO BID x 2 weeks
150 mg PO BID x 1-2 weeks
200 mg PO BID x 1 week (if DRS not improved ≥2 points)
Washout: 0 mg x 2 weeks

DRS = disability rating scale
TBI = traumatic brain injury
Outcomes

Primary Outcome

• Rate of improvement in DRS during 4 weeks of active treatment

Secondary Outcomes

• Sustainability of treatment effect
  • Compared DRS between weeks 4 and 6
• Adverse drug events

DRS = disability rating score
Results: Weeks 1-4

Disability Rating Scale

<table>
<thead>
<tr>
<th>Drug</th>
<th>Improvement of DRS from baseline</th>
<th>Rate of recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>P&lt;0.05</td>
<td>P=0.007</td>
</tr>
<tr>
<td>Placebo</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

DRS = disability rating score
NS = non-significant
Results: Weeks 5-6

- **Disability Rating Scale**

- **Washout Period**

<table>
<thead>
<tr>
<th>baseline</th>
<th>week 1</th>
<th>week 2</th>
<th>week 3</th>
<th>week 4</th>
<th>week 5</th>
<th>week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td><img src="image" alt="Graph showing improvement in DRS from week 4" /></td>
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</thead>
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<tr>
<td>Amantadine</td>
<td>NS</td>
</tr>
<tr>
<td>Placebo</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**DRS = disability rating score**

**NS = non-significant**

Outcome Category at Week 6

Amantadine
- DRS=22-29: 18.60%
- DRS=14-21: 55.80%
- DRS=7-13: 25.60%

Placebo
- DRS=22-29: 31.60%
- DRS=14-21: 51.60%
- DRS=7-13: 16.80%

DRS = disability rating scale

Safety Outcomes

Adverse events

- No statistically significant difference found
- Seizures
- Agitation
- Insomnia
- Spasticity

\( P > 0.20 \)

Meythaler et al. (2002)

- Randomized, single center, double blind, placebo-controlled, crossover study
  - Various severity TBI
  - Enrolled within 6 weeks of TBI
- Dosing
  - Group 1 (n=15)
    - Amantadine 200 mg daily (Weeks 1-6)
    - Crossover
    - Placebo (Weeks 7-12)
  - Group 2 (n=20)
    - Placebo (Weeks 1-6)
    - Crossover
    - Amantadine 200 mg daily (Weeks 7-12)

Meythaler JM, et al. J Head Trauma Rehabil. 2002
Efficacy

Disability Rating Scale

Baseline Week 6 Week 12

Placebo
P=0.0022

Amantadine
P=0.006

Amantadine
P=0.0099

Placebo
P>0.05

Crossover

Meythaler JM, et al. J Head Trauma Rehabil. 2002
Amantadine Effects on DRS

• Similar timeframe post-injury
  • Giacino et al.
    • Enrolled within 4-16 weeks post-injury
    • Amantadine x 4 weeks (4-20 weeks post-injury)
  • Meythaler et al.
    • Enrolled within 0-6 weeks post-injury
    • Amantadine x 6 weeks (0-18 weeks post-injury)

• Results
  • Accelerated rate of improvement with amantadine at least 4 weeks post-injury
  • Ongoing benefit at least 6 weeks post-injury
  • No differences in adverse events

Meythaler JM, et al. J Head Trauma Rehabil. 2002
Neuropsychiatric Inventory

- Developed for use in dementia but frequently used in TBI
- Assess each domain
  - Frequency
  - Severity
  - Distressing
  - Problematic

12 Behavioral Domains
- Irritability
- Aggression
- Memory

2 Assessors
- Observer (primary caregiver)
- Reporter (patient)

40 Item Tool

Hammond et al. (2014)

- Randomized, single center, placebo-controlled, parallel trial
  - Chronic TBI
  - Enrolled ≥6 months post-TBI
  - Amantadine (n=38) vs placebo (n=38)
- Dosing: 100 mg PO BID x 4 weeks at 0800 and 1200

Outcomes

Primary Outcome

• Irritability domain of NPI (observer)

Secondary Outcomes

• Aggression domain of NPI (observer)
• Adverse events

NPI = neuropsychiatric inventory
## Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amantadine (n=38)</th>
<th>Placebo (n=38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in Irritability Domain of NPI</td>
<td>-4.3</td>
<td>-2.6</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Mean change in Aggression Domain of NPI</td>
<td>-4.65</td>
<td>-2.46</td>
<td>P=0.046</td>
</tr>
<tr>
<td>Adverse Events, n (%)</td>
<td>19 (50%)</td>
<td>17 (45%)</td>
<td>P=0.637</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>P=1.000</td>
</tr>
</tbody>
</table>

NPI = Neuropsychiatric Inventory

Hammond et al. (2017)

- Randomized, multi-center, placebo-controlled, parallel trial
  - Chronic TBI with moderate-severe aggression
  - Enrolled ≥ 6 months post TBI
  - Amantadine (n=61) vs placebo (n=57)
- Dosing: 100 mg PO BID x 60 days at 0800 and 1200
Outcomes

Primary Outcome

- Aggression Domain of NPI per **Observer**
- Distress
- Problematic
- Aggression Domain of NPI per **Reporter**
- Distress
- Problematic

Secondary Outcomes

- Adverse events

NPI = Neuropsychiatric Inventory
## Aggression Domain of NPI at Day 28

<table>
<thead>
<tr>
<th>Observer</th>
<th>Amantadine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, problematic</td>
<td>-3.33</td>
<td>-2.70</td>
<td>P=0.72</td>
</tr>
<tr>
<td>Mean change, distress</td>
<td>-1.09</td>
<td>-1.15</td>
<td>P=0.94</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Reporter</th>
<th>Amantadine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, problematic</td>
<td>-4.15</td>
<td>-3.38</td>
<td>P=0.47</td>
</tr>
<tr>
<td>Mean change, distress</td>
<td>-1.97</td>
<td>-1.18</td>
<td>P=0.22</td>
</tr>
</tbody>
</table>

NPI = Neuropsychiatric Inventory
Hammond FM, et al. *J Head Trauma Rehabil.* 2017
### Aggression Domain of NPI at Day 60

<table>
<thead>
<tr>
<th>Observer</th>
<th>Amantadine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, problematic</td>
<td>-3.91</td>
<td>-3.04</td>
<td>P=0.41</td>
</tr>
<tr>
<td>Mean change, distress</td>
<td>-1.54</td>
<td>-1.26</td>
<td>P=0.41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporter</th>
<th>Amantadine</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, problematic</td>
<td>-5.27</td>
<td>-2.89</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Mean change, distress</td>
<td>-2.56</td>
<td>-1.44</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>
Amantadine Effects on NPI

• NPI score is subjective
  • Potential for bias
• Two studies by Hammond et al. discuss two different patient populations
  • 2014 (general)
  • 2017 (aggression)
Amantadine has shown improvements in which of the following when used for traumatic brain injury?

A. Accelerated rate of recovery  
B. Decreased irritability  
C. Decreased aggression  
D. All of the above
Amantadine Dosing in TBI

- 100 - 200 mg PO BID at 0800 and 1200

- Titrate up to 200 mg PO BID
  - If not seeing adequate response
  - Reasonable to titrate weekly
  - Reduce dose if experience side effects

TBI = traumatic brain injury

Ahlskog JE. The New Parkinson’s Disease Treatment Book. 2005
Amantadine Timing in TBI

• No clear benefits over placebo immediately post-injury (0-4 weeks post-TBI)

• Benefits seen in the acute setting (4-20 weeks post-TBI) to enhance recovery

• Benefits seen in the chronic setting (≥6 months post-TBI) to reduce neurobehavioral symptoms

TBI = traumatic brain injury
Amantadine Duration in TBI

• Clinical Trial Duration
  • Used for maximum of 60 days
  • Limited adverse events

• Tapering
  • Reduce dose by 1 tablet (100 mg) per week until off
  • Lowest dose 100 mg daily before discontinuation
  • Re-escalate dose if symptoms worsen

TBI = traumatic brain injury
Ahlskog JE. *The New Parkinson’s Disease Treatment Book*. 2005
Based on the current literature, what is an ideal dosing regimen for amantadine in TBI?

A. 50 mg PO BID; 4 weeks
B. 100 mg PO BID; 26 weeks
C. 100-200 mg PO BID; 4-8 weeks
D. 500 mg PO BID; 4 weeks

TBI = traumatic brain injury
Conclusion

• Treatment options for TBI are currently limited
• Promising data to support amantadine in TBI
  • Improved DRS
  • Improved behavioral symptoms
  • No current standard of care
  • Limited adverse events
• Further studies
  • Dose initiation
  • Duration

DRS = disability rating scale
TBI = traumatic brain injury
References


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