Does Treatment With Amantadine Increase the Rate of Improvement of Cognitive Function in Patients Suffering From Traumatic Brain Injury?

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Does Treatment with Amantadine Increase the Rate of Improvement of Cognitive Function in Patients Suffering from Traumatic Brain Injury?

Matthew Voit, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013
ABSTRACT

Objective: To determine, “Does treatment with amantadine improve the rate of cognitive function in patients with Traumatic Brain Injury?”

Study Design: Review of three English language randomized controlled trials from 1999-2012

Data Sources: Three randomized, placebo-controlled, double blind crossover trials comparing amantadine to placebo were found using Pub-Med and Cochrane Databases.

Outcomes Measured: The trials measured the effects of amantadine on command-following, object recognition, functional object use, intelligible verbalization, reliable yes-or-no communication, sustained attention, orientation, attention, memory, executive flexibility, and behavior and used the following assessment tools: Neurobehavioral Rating Scale and DRS (Disability Rating Scale).

Results: Two studies demonstrated an improvement in eye opening, verbalization, motor response, cognitive understanding of feeding, dressing, and grooming; degree of assistance and supervision required; and employability at higher rates than the placebo. One study did not indicate an increase of rate in improvement of cognitive function when comparing amantadine to placebo.

Conclusion: Based on two of the trials, treatment with amantadine does increase the rate of improvement of cognitive function in patients suffering from Traumatic Brain Injury. One trial did not show an increase in rate of improvement, but small sample size discounted its validity.

Key Words: Traumatic Brain Injury, Cognitive Function, Amantadine
Introduction

Each year, severe traumatic brain injury contributes to a significant number of deaths and cases of permanent disability, as well as economic and familial consequences. TBI is the most common cause of death and disability in persons aged 15-30 and accounts for approximately one-third of all injury related deaths in the United States. The direct and indirect costs of TBI in the US have been estimated to be $48.3 billion annually. Survival costs account for $31.7 billion and fatal brain injuries cost another $16.6 billion.

Physical effects of traumatic brain injury can range from minimal symptoms like headaches, nausea, and dizziness to more severe consequences, such as decreased consciousness and cognitive function, vegetative states, and death. The severity of internal or external brain damage correlates to the amount of cognitive dysfunction. The higher the severity of trauma to the skull/brain, the more severe the dysfunction will be, thereafter. High-speed motor vehicle collisions cause 50% of traumatic brain injuries in the United States and tend to have the most detrimental effects.

For severe TBIs, it is not known for sure how long a particular patient will take to regain lost cognitive function or to what degree that patient will heal. A majority of healing occurs spontaneously and shortly after injury. There are off-label neuropharmacological therapies that attempt to increase consciousness and arrousability by tampering with dopaminergic and noradrenergic receptors, but the exact mechanism by which these medications work is not fully understood and effects are generally temporary.

There is no current cure for Traumatic Brain Injury. Methods of pharmacological treatment are aimed at control of systemic physiological effects of TBI. Diuretics are used to decrease the amount of third-spacing as well as intracranial pressures. Beta-blockers, ACEi and
ARBS are used to regulate blood pressure. Medications to prevent seizures and control pain are also utilized, but stabilizing a TBI patient with these pharmacological agents does not improve the amount of cognitive damage initially sustained. Currently the main methods of treatment of long-term cognitive damage are physical, speech, and occupational therapies.  

Typically in the case of severe traumatic brain injury, such as those sustained in a motor vehicle collision, the mechanism is diffuse axonal injury (DAI). DAI involves a widespread damage to axons in the brain and is highly associated with a reduction of dopamine availability. Amantadine is a medication that causes increased release of dopamine from neurons in the brain and delay of cellular uptake. It is known for its use as an antiparkinsonian agent and as an antiviral in treatment of influenza. Currently it is a topic for research in the area of traumatic brain injury, and is the focus of this systematic review.

Objective

The objective of this selective EBM review is to determine “Does treatment with Amantadine increase the rate of improvement of cognitive function in patients suffering TBI?” Previous studies have showed the benefits of using dopamine agonists in treatment of cognitive dysfunction; therefore, it is suggested that amantadine will have a positive impact on the rate of cognitive recovery in patients with TBI.

Methods

An online search was done to locate randomized control trials evaluating the use of amantadine in patients suffering TBI. Articles used included male and female patients above the age of 16 with TBI and excluded those with previous chronic disease or cognitive disability. 50 – 200 mg BID of Amantadine was compared with placebo in its affects on cognitive dysfunction and DRS and Neurobehavioral Rating Scale were used to evaluate that dysfunction.
Key words used in the search engine Pub-Med included were “cognitive function”, “amantadine”, and “Traumatic Brain Injury”. All articles used were English language randomized, double-blind, controlled cross-over studies from 1999 to 2012. The articles were selected based on the importance of the outcomes to the patient.

Outcomes Measured

The outcomes evaluated were POEMS (Patient Oriented Evidence that Matters). For example, DRS and Neurobehavioral Rating scores were measured by rating improvements in several types of cognitive functioning. The DRS (Disability Rating Scale) measured consistent command-following, object recognition, functional object use, intelligible verbalization, reliable yes-or-no communication, and sustained attention scores. Scores were measured as a function of time, where disability was scored using a number scale; 7-13 being moderate-severe-to-severe, 14-21 severe-to-extremely-severe, and 22-29 vegetative-state-to-extreme-vegetative-state. The Neurobehavioral Rating scale involved tests in orientation, attention, memory, executive flexibility, and behavior as a function of time. Functioning tests included consistent command-following, reliable yes-or-no communication, and sustained attention.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W.D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giacano (2012)</td>
<td>Double-Blind, RCT, Placebo-controlled</td>
<td>184</td>
<td>16-65</td>
<td>Patients who sustained a nonpenetrating traumatic brain injury who are currently in a vegetative state or a minimally conscious state</td>
<td>Any patient with a CNS disability that predated the TBI</td>
<td>3</td>
<td>Amantadine</td>
</tr>
<tr>
<td>Meythaler (2002)</td>
<td>Double-Blind, RCT, Placebo-</td>
<td>35</td>
<td>16-75</td>
<td>Patients with a GCS of less than 11, loss of consciousness</td>
<td>Patients with penetrating TBI, prior experimental</td>
<td>5</td>
<td>Amantadine</td>
</tr>
</tbody>
</table>
Results

Three randomized controlled trials are presented in this review, using cognitive grading scales to track progress over time, with study participants being clinically diagnosed with Traumatic Brain Injury. One trial was analyzed with intention to treat while the others as change in mean cognitive scores from baseline.

In the Galiano et al study, participants were given BID doses of 100 mg Amantadine for 14 days, 150 mg at week three, and 200 mg at week four. A visually matched BID dose placebo was given to the control group.

181 patients completed the trial. At the end of the 4-week treatment interval, both the amantadine and control group had significant improvements in DRS scores, but the amantadine group had a faster rate of recovery. Also, more patients in the amantadine group had positive DRS score outcomes and greater percentage of recovery at the end of the trial, as shown in Table 1.

Table 2. Distribution of DRS scores after 4-week trial

<table>
<thead>
<tr>
<th>Method Used</th>
<th>Percentage of mod-severe-to-severe disability (95% CI)</th>
<th>Percentage of severe-to-extremely-severe (95% CI)</th>
<th>Percentage of vegetative state to extreme vegetative state (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>25.6</td>
<td>55.8</td>
<td>18.6</td>
</tr>
</tbody>
</table>
To analyze treatment effects, absolute benefit increase (ABI), relative benefit increase (RBI), and numbers needed to treat (NNT) values were used, shown below in Table 3. RBI and ABI were calculated as 0.52% and 0.09%, respectively, while the number of patients needed to treat was 12.²

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>16.8</th>
<th>51.6</th>
<th>31.6</th>
</tr>
</thead>
</table>

**Table 3. Treatment effects of randomized, placebo-controlled, double-blind crossover trial**

<table>
<thead>
<tr>
<th>CER</th>
<th>EER</th>
<th>EER- CER (RBI)</th>
<th>EER – CER (ABI)</th>
<th>1/ABI (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.168</td>
<td>0.256</td>
<td>0.523</td>
<td>0.09</td>
<td>12</td>
</tr>
</tbody>
</table>

The Methayler et al trial included a study sample of 35 patients with diagnosed Traumatic Brain Injury. Amantadine 200 mg QD was given to group one for 6 weeks, while group two was given a visually matched placebo. For weeks 6-12 group one was given placebo and group two was given amantadine.

All patients’ baseline DRS scores were taken and averaged as a whole in their respective groups. After 6-week treatment with either placebo or amantadine, mean DRS scores were again taken, producing a new average for both groups. New means were analyzed, using statistical procedures Wilcoxon signed-rank test and Mann-Whitney U test, shown below in Table 4. After the initial 6 weeks, group one showed an improvement in DRS scores of 9.8 point (15.5 ± SD 4.5 to 5.7 ± SD 4.2) improvement in DRS score, while showing a 0.15 point (5.7 ± SD 4.12 to 5.5 ± SD 4.6) during the second 6 weeks.³

Group two had a 9.4 point (21.7 ± 7.8 to 12.3 ± 9.9) improvement in DRS score and a 3.8 point (12.3 ± 9.9 to 8.5 ± 9.0) improvement during weeks 6-12, while taking amantadine. The Mann-Whitney U test showed a statistically different DRS point score at week zero, as
evidenced by P score of .0455 shown below, but there was still a statistically significant amount of change in favor of the amantadine group 2 at weeks 6 thru 12 (P=.2269).  

Table 4. Wilcoxon Matched-Pair, Signed-Rank test results + Mann-Whitney U test.  

<table>
<thead>
<tr>
<th></th>
<th>P-Values (Weeks 0-6)</th>
<th>P-Values (Weeks 6-12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS Cognitive Function Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>0.0022</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.0006</td>
<td>0.0099</td>
</tr>
<tr>
<td>Mann-Whitney U test</td>
<td>0.045</td>
<td>0.2269</td>
</tr>
</tbody>
</table>

In the review by Schneider et al, 10 participants diagnosed with TBI were separated into two groups. Group one was started on 50 mg BID of amantadine and dose was increased every 3 days to 150 mg. After 2 weeks, patients were subjected to 2 weeks withdrawal, followed by 2 weeks placebo. Group two was given placebo for two weeks, followed by two weeks withdrawal, and then amantadine 50 mg BID with dose increased every 3 days up to 150 mg.  

Although only 2 subjects followed the trial to completion, the results were reported and analyzed. Information was examined using repeated measures analysis of variance, which looked at test score results of five cognitive function variables: orientation, attention, memory, executive flexibility, behavior, and composite variable. Scores in these areas were recorded over time and repeatedly compared to baseline scores. This allowed researchers to compare results before and after testing. Time by group interactions tests compared those scores over time with scores of the other group, indicating whether or not changes over time were different from amantadine group than placebo. Results are shown below in Table 5.
Table 5. Results of repeated measures of variance for effects of time

<table>
<thead>
<tr>
<th></th>
<th>Orientation</th>
<th>Attention</th>
<th>Memory</th>
<th>Executive flexibility</th>
<th>Behavior</th>
<th>Composite variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>p = 0.032</td>
<td>p = 0.047</td>
<td>p = 0.012</td>
<td>p = 0.001</td>
<td>p = 0.017</td>
<td>p = 0.003</td>
</tr>
<tr>
<td><strong>Time by group</strong></td>
<td>p = 0.849</td>
<td>p = 0.548</td>
<td>p = 0.425</td>
<td>p = 0.261</td>
<td>p = 0.852</td>
<td>p = 0.722</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td>p = 0.062</td>
<td>p = 0.325</td>
<td>p = 0.341</td>
<td>p = 0.732</td>
<td>p = 0.737</td>
<td>p = 0.405</td>
</tr>
</tbody>
</table>

All scores improved over time between both groups one and two and there was no difference in rates of improvement. This suggests that although cognitive function improved over time, the improvement was equal with and without amantadine.4

Discussion

The Methayler and Giacano randomized control trials showed benefit in the use of amantadine following Traumatic Brain Injury. These two trials showed an increased rate in cognitive function improvement, as measured by DRS, when compared to placebo. The Schneider trial did not show a difference between the use of amantadine and placebo.

The Schneider trial offered conflicting information. Although there were only two subjects who followed the trial to completion, initially only 10 subjects signed on, which is already too small a number to find significant effects. Also, the rate of spontaneous recovery following a TBI is known to be high, which could have masked the positive effects of amantadine.4

The Methayler and Giacino studies both showed results consistent with acceleration of cognitive recovery in patients with acute losses of cognitive function following TBI. Neither study demonstrated a benefit with early treatment compared to later and both seem to showed an
eventual “leveling-off” of DRS scores between amantadine and placebo groups. However, both studies did demonstrate that patients improved more rapidly while on amantadine and improvement was sustained after follow-up.2,3

Conclusion

Based on two of the trials addressed in this review, treatment with amantadine increases the rate of cognitive function improvement in patients with traumatic brain injury. One study showed no benefit in the use of amantadine for TBI, but a small sample size hindered its validity. Overall, it can be inferred that amantadine does have a positive impact on the rate of cognitive recovery following TBI.

Although the Schneider study did not agree with the Methayler or Giacino, it provides an example of the importance of a large sample size. It also demonstrates the difficulty in finding subjects for studies involving TBI. Since decreased consciousness and cognitive function are central side effects of severe TBI, healthcare decision making for victims is often left in the hands of family members. One can expect that some family members would be hesitant to subject their loved one to a pharmaceutical study of any kind during such a critical time.

Usage of amantadine in the realm of traumatic brain injury will likely continue to be explored and studied. With proper education regarding its potential benefits and decreased side effects, more subjects for research will come. This review provides significant patient-oriented evidence as well as incentive for further investigation.
REFERENCES


