Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

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ABSTRACT

BACKGROUND

Amantadine hydrochloride is one of the most commonly prescribed medications for patients with prolonged disorders of consciousness after traumatic brain injury. Preliminary studies have suggested that amantadine may promote functional recovery.

METHODS

We enrolled 184 patients who were in a vegetative or minimally conscious state 4 to 16 weeks after traumatic brain injury and who were receiving inpatient rehabilitation. Patients were randomly assigned to receive amantadine or placebo for 4 weeks and were followed for 2 weeks after the treatment was discontinued. The rate of functional recovery on the Disability Rating Scale (DRS; range, 0 to 29, with higher scores indicating greater disability) was compared over the 4 weeks of treatment (primary outcome) and during the 2-week washout period with the use of mixed-effects regression models.

RESULTS

During the 4-week treatment period, recovery was significantly faster in the amantadine group than in the placebo group, as measured by the DRS score (difference in slope, 0.24 points per week; P=0.007), indicating a benefit with respect to the primary outcome measure. In a prespecified subgroup analysis, the treatment effect was similar for patients in a vegetative state and those in a minimally conscious state. The rate of improvement in the amantadine group slowed during the 2 weeks after treatment (weeks 5 and 6) and was significantly slower than the rate in the placebo group (difference in slope, 0.30 points per week; P=0.02). The overall improvement in DRS scores between baseline and week 6 (2 weeks after treatment was discontinued) was similar in the two groups. There were no significant differences in the incidence of serious adverse events.

CONCLUSIONS

Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness. (Funded by the National Institute on Disability and Rehabilitation Research; ClinicalTrials.gov number, NCT00970944.)
EVERE TRAUMATIC BRAIN INJURY IS A CAT-
astrophic event that frequently has devastat-
ing familial, economic, and societal conse-
quences. Traumatic brain injury is the most
common cause of death and disability in persons
between 15 and 30 years of age. The most severe
injuries can result in prolonged disorders of con-
sciousness. Approximately 10 to 15% of patients
with severe traumatic brain injury are discharged
sciousness. Approximately 10 to 15% of patients
injuries can result in prolonged disorders of con-
sciousness. Approximately 10 to 15% of patients
is distinguished from a vegetative state by the pres-
ence of at least one clearly discernible behavioral
sign of consciousness, is 8 times as high as the
prevalence of a vegetative state. Of patients who
are in a vegetative state for at least 4 weeks, ap-
proximately 50% will regain consciousness by
1 year.

No intervention has been shown in rigorous
studies to alter the pace of recovery or improve
the functional outcome. Neuropharmacologic
therapies are commonly used off label to enhance
arousal and behavioral responsiveness, on the
premise that injury induced derangements in
dopaminergic and noradrenergic neurotransmit-
ter systems can be improved through supplemen-
tation.

Amantadine hydrochloride is one of the most
commonly prescribed medications for patients
with disorders of consciousness who are under-
going inpatient neurorehabilitation. The mech-
nanism of action is unclear, although amantadine
appears to act as an N-methyl-D-aspartate antago-
nist and indirect dopamine agonist. The results
of two randomized trials involving patients with
traumatic disorders of consciousness suggested
that amantadine was effective, although method-
ologic limitations, including small samples and
unbalanced groups, precluded definitive conclu-
sions.

In 1998, a consortium of brain-injury rehabili-
tation centers conducted an observational pilot
study designed to establish the rate of spontane-
ous recovery from vegetative and minimally
conscious states and provide the basis for a mul-
ticenter clinical trial. A multiple-regression anal-
ysis exploring the effect of cognition-enhancing
medications at 16 weeks after injury on scores
on the Disability Rating Scale (DRS), a mea-
sure of functional outcome that is specific to
traumatic brain injury, showed better scores at
16 weeks after injury in patients who received
amantadine than in those who did not.

On the basis of these findings, we designed the
current multicenter, prospective, double-blind, ran-
domized, placebo-controlled trial to determine
the effectiveness of amantadine in promoting re-
covery from a post-traumatic vegetative or mini-
mally conscious state. We hypothesized that
4 weeks of treatment with amantadine adminis-
tered between 4 and 16 weeks after injury in pa-

METHODS

PATIENTS AND SITES
We conducted this study at 11 clinical sites in
three countries. Eligible patients were 16 to 65
years of age, had sustained a nonpenetrating trau-
matic brain injury 4 to 16 weeks before enroll-
ment, and were receiving usual inpatient rehabili-
tation at each site. Additional eligibility criteria
were a vegetative state or a minimally conscious
state, as indicated by a DRS score greater than 11,
and an inability both to follow commands consist-
tently and to engage in functional communication,
as assessed by the score on the Coma Recovery
Scale–Revised (CRS-R).

The DRS includes measures of eye opening,
verbalization, and motor response (derived from
the Glasgow Coma Scale); cognitive understand-
ing of feeding, dressing, and grooming; degree of
assistance and supervision required; and employ-
ability. Scores range from 0 to 29, with higher
values indicating greater disability (see the Supple-
mentary Appendix, available with the full text of
this article at NEJM.org, for details). The CRS-R is
a standardized neurobehavioral assessment tool
comprising six hierarchically organized subscales
(i.e., auditory, visual, motor, oromotor–verbal,
communication, and arousal); scores range from
0 to 23, with higher scores indicating a higher
level of neurobehavioral function.

Exclusion criteria were any disability related to
the central nervous system that predated the trau-
Amantadine for Severe Traumatic Brain Injury

AMANTADINE FOR SEVERE TRAUMATIC BRAIN INJURY

Table 1. Demographic and Clinical Characteristics at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amantadine (N = 87)</th>
<th>Placebo (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>35.5±15.3</td>
<td>37.2±15.4</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>64 (74)</td>
<td>69 (71)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (11)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>White</td>
<td>73 (84)</td>
<td>87 (90)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Yes</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>82 (94)</td>
</tr>
<tr>
<td>Education — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>57 (66)</td>
<td>57 (59)</td>
</tr>
<tr>
<td>At least some college</td>
<td>29 (33)</td>
<td>34 (35)</td>
</tr>
<tr>
<td>At least some graduate school</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Time from injury to randomization — days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>IQR</td>
<td>38–66</td>
<td>37–65</td>
</tr>
<tr>
<td>Time from rehabilitation admission to ran-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>domination — days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>IQR</td>
<td>6–20</td>
<td>6–19</td>
</tr>
<tr>
<td>Score on Disability Rating Scale‡</td>
<td>21.8±2.0</td>
<td>22.2±2.1</td>
</tr>
<tr>
<td>Score on Coma Recovery Scale–Revised§</td>
<td>9.6±3.8</td>
<td>9.2±4.4</td>
</tr>
<tr>
<td>Minimally conscious state — no. (%)</td>
<td>56 (64)</td>
<td>64 (66)</td>
</tr>
<tr>
<td>Vegetative state — no. (%)</td>
<td>31 (36)</td>
<td>33 (34)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences between the study groups (P≥0.05). IQR denotes interquartile range.
† Race and ethnic group were reported by legal surrogates or next of kin.
‡ Scores on the Disability Rating Scale (DRS) range from 0 to 29, with higher scores indicating more severe disability. The actual DRS ranges were 18 to 26 in the amantadine group and 17 to 28 in the placebo group.
§ Scores on the Coma Recovery Scale–Revised (CRS-R) range from 0 to 23, with higher scores indicating a higher level of neurobehavioral function. The actual CRS-R ranges were 3 to 20 in the amantadine group and 2 to 19 in the placebo group.

STUDY PROCEDURES

Amantadine and a visually identical placebo were supplied by four compounding pharmacies serving the different study regions. On randomization, the data coordinating center assigned coded medication bottles to patients enrolled at each clinical site. The patients began receiving treatment at a dose of 100 mg twice daily on the day after randomization, with this dose continued for 14 days. The dose was increased to 150 mg twice daily at week 3 and to 200 mg twice daily at week 4 if the DRS score had not improved by at least 2 points from baseline (see Table S1 in the Supplementary Appendix for a breakdown of the drug doses received by patients in each study group). After the week 4 assessment, the study drug was tapered over a period of 2 to 3 days, with assessment of the patients continued through week 6. Additional procedural details are provided in the study protocol.

To minimize exposure to confounding psychoactive medications during the treatment phase,
a list of suggested treatments for commonly observed medical problems was compiled. This list was ordered roughly from the least to the most potentially confounding treatment. Treating physicians were requested to follow the order in this list, when possible, in choosing treatments.

OUTCOMES
The primary outcome was the rate of improvement in the DRS score during the 4 weeks of treatment. DRS scores were collected at baseline and weekly through week 6 on the basis of consensus ratings compiled by the interdisciplinary treatment team.

To gauge the clinical significance of the effects of amantadine, clinically relevant behavioral benchmarks were assessed by study personnel using the CRS-R. We used the CRS-R as a qualitative measure to better understand the effects of the study drug on key behaviors associated with a vegetative state, a minimally conscious state, and emergence from a minimally conscious state. We also assessed whether the rate of recovery was altered in the amantadine group during the 2-week washout period. All DRS and CRS-R assessments were conducted by study personnel who were unaware of the group assignments. Adverse events were documented throughout the 6-week assessment period and were coded with respect to their severity, whether they were expected, and whether they were thought by the investigator to be related or possibly related to the study drug. Exposure to other psychoactive drugs was recorded for all patients throughout the 6-week period. All outcome assessments and the final data analysis were conducted without knowledge of group assignments.

STATISTICAL ANALYSIS
The planned sample size of 184 was estimated, on the basis of our previously described pilot study, to provide 80% power to detect a difference in the rate of change in the DRS score of 0.3 points per week, or 1.2 points by the end of the 4-week treatment interval. This sample size also provided 90% power to detect an unforeseen adverse event with an incidence of at least 2.5% and allowed estimation of the incidence of adverse events to an accuracy of ±10%. Two blinded interim analyses were conducted after the enrollment of 60 and 120 participants, with the use of the O’Brien–Fleming boundaries and with alpha levels set at 0.0005 and 0.014, respectively. An alpha level of 0.045 was set for the final analysis.

We used t-tests for continuous variables and a chi-square analysis for categorical variables for comparison of the study groups at baseline. We used mixed-effect regression models with random intercepts to test the primary and secondary hypotheses of a difference in the rate of change in the DRS score between the amantadine and placebo groups overall and in stratified subgroups.

The first hypothesis (primary outcome) was assessed by comparing the slope of change in the DRS score over the 4-week treatment period between the two groups, with a negative slope reflecting functional improvement. We conducted a post hoc descriptive analysis of behavioral recovery as defined by the six CRS-R behavioral benchmarks associated with the highest level of cognitive processing on each subscale. Because this analysis was not prespecified in the protocol and was conducted for descriptive purposes only, a statistical comparison of the percentage of patients within each group who were able to engage in these behaviors was not conducted.

The second hypothesis (durability of the treatment effect) was assessed by comparing the slope of change in the DRS score between weeks 4 and 6 in the two groups. Preplanned subgroup analy-
ses were conducted to determine the consistency of the results across the strata of diagnosis (vegetative state vs. minimally conscious state) and interval between injury and enrollment (28 to 70 days vs. 71 to 112 days). An analysis of residuals was conducted to determine model fit. Fisher’s exact test was used to compare the proportions of patients who had adverse events in the two groups. The Wilcoxon signed-rank test was used to compare non-normally distributed variables. All analyses were conducted according to the intention-to-treat principle.

RESULTS

STUDY PARTICIPANTS

Of 1170 patients who were screened for eligibility, 350 met all eligibility criteria and 184 were enrolled (Fig. S2 in the Supplementary Appendix). Of these 184 patients, all but 3 (2 assigned to the placebo group and 1 to the amantadine group) completed the study. The amantadine and placebo groups were well matched with respect to major demographic variables and prognostic factors, including the DRS score at baseline, interval between injury and enrollment, and diagnosis at enrollment (Table 1). Of the 184 patients, 154 (84%) missed no more than 4 of the 56 total doses of study medication. The remaining 30 patients (16%) missed between 5 and 52 doses, in most cases owing to transfer to an acute care facility where it was not feasible or was medically inadvisable to continue the study treatment. Approximately one third of the patients received potentially confounding medications (Table S3 in the Supplementary Appendix). Exposure to stimulants and open-label amantadine was uncommon. Antiepileptic drug use was more frequent in the amantadine group (P = 0.04), whereas use of narcotic analgesic agents was more frequent in the placebo group (P = 0.08).

OUTCOMES

Both groups had significant improvement in the DRS score over the 4-week treatment interval, but the amantadine group had significantly faster recovery (difference in slope, −0.24 points per week; P = 0.007) (Fig. 1) and had fewer dose increases at weeks 2 and 3. Although in both study groups, patients who were enrolled earlier after injury versus later (i.e., 28 to 70 days vs. 71 to 112 days) and those who were in a minimally conscious state rather than a vegetative state at enrollment had faster recovery rates, the treatment effect was consistent across subgroups. The advantage of exposure to amantadine was most pronounced for patients who were enrolled later as compared with those who were enrolled earlier (effect size, −0.40 points vs. −0.19 points). The effect size was similar between diagnostic subgroups (vegetative state, −0.25 points; minimally conscious state, −0.24 points). However, all subgroup effect sizes fell within the 95% confidence interval for the overall effect (95% confidence interval, −0.41 to −0.07 points) (Fig. S4 and S5 in the Supplementary Appendix).

More patients in the amantadine group than in the placebo group had favorable outcomes on the DRS, fewer remained in a vegetative state (Fig. 2), and a greater percentage had recovery of key behavioral benchmarks on the CRS-R at the end of the 4-week treatment period. Statistical comparison of the behavioral benchmarks was not prespecified and therefore was not performed (Fig. 3).
During the 2-week washout period, only the placebo group had significant improvement in the DRS score (slope, −0.44 points per week; P<0.001 for the change from the beginning of week 5 to the end of week 6). Although behavioral improvements were generally maintained in the amantadine group, the pace of recovery was significantly slower in the amantadine group (slope, −0.14 points per week; between-group difference in slope, 0.30 points; P = 0.02) (Fig. 1). The percentage of patients who were able to engage in each of the six clinically relevant behaviors was higher in the amantadine group than in the placebo group at 4 weeks, but the difference was smaller at the 6-week follow-up assessment (Fig. 3).

**ADVERSE EVENTS**

As expected, medical complications were common (median number of adverse events per patient, 2), with no significant difference in the incidence of adverse events between groups (P>0.20) (Table 2). During the course of the trial, one patient in the amantadine group died from cardiac arrest (see Table S6 in the Supplementary Appendix for a list of all serious adverse events).

**DISCUSSION**

In this international, multicenter, randomized, controlled trial involving patients with post-traumatic disorders of consciousness, we found that the administration of amantadine between 4 and 16 weeks after injury significantly improved the rate of functional recovery over the 4-week period of treatment, as compared with placebo. In keeping with evidence on the rate of change during inpatient rehabilitation,10,18 both groups had improvement during the 4-week period. However, the rate of recovery was more rapid in the amantadine group, affecting functionally meaningful behaviors such as consistent responses to commands, intelligible speech, reliable yes-or-no communication, and functional-object use.

The benefit of amantadine appeared to be con-
AMANTADINE FOR SEVERE TRAUMATIC BRAIN INJURY

Our findings are consistent with observational reports suggesting the acceleration of recovery in patients who are receiving amantadine and the deceleration or loss of function after treatment is discontinued. The acute phase of recovery from severe traumatic brain injury is characterized by a brief period of neuronal excitability followed by a longer period of hypoexcitability, involving depletion of multiple neurotransmitters, including dopamine. Amantadine may promote dopaminergic activity by facilitating presynaptic release and blocking reuptake postsynaptically. The favorable neurobehavioral effects of amantadine may reflect enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, and frontostrital circuits that are responsible for mediating arousal, drive, and attentional functions.

Two case studies that used serial F-fluoro-deoxyglucose–positron-emission tomography to evaluate the effects of amantadine showed significant increases in prefrontal cortical metabolism and a nonsignificant increase in striatal D2 dopamine–receptor availability, supporting this proposed mechanism of action. The extent to which the treatment effect was mediated by general improvements in arousal cannot be discerned from this study because arousal functions generally recover in parallel with cognition.

Our study has some limitations. The sample comprised patients admitted to inpatient rehabilitation centers, raising the possibility of selection bias because decisions about admission to a rehabilitation center may be influenced by the probability of further improvement. In addition, nonwhites were underrepresented, potentially limiting the generalizability of the results to nonwhite populations. Second, practical and ethical constraints required the use of a brief treatment interval and a short-term assessment of the outcome, because we anticipated that caregivers would withdraw patients who were not making gains in order to try other treatments. Thus, our findings do not address the effects of prolonged treatment on long-term outcomes. Third, we did not restrict standard rehabilitation interventions, so we cannot determine the degree to which the benefits of amantadine are independent of or synergistic with such standard treatments. Fourth, despite attempts to limit the use of potentially confounding psychoactive drugs, such drugs were used frequently. However, exposure to other psychoactive drugs would be expected either to block the benefits of amantadine in treated patients or to provide alternative mechanisms for similar benefits in the placebo group, thereby reducing rather than exaggerating the magnitude of the difference between the groups. Finally, we did not use continuous electroencephalographic monitoring to detect seizures; however, a high incidence of amantadine...

### Table 2. Adverse Events, According to Treatment Group.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Amantadine (N = 97)</th>
<th>Placebo (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Changes on electroencephalography</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (11)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other gastrointestinal event</td>
<td>4 (5)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Elevated liver-function tests†</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>7 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Agitation</td>
<td>12 (14)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (14)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Involuntary muscle contractions</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertonia or spasticity</td>
<td>18 (21)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Other motor problems</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* There were no significant differences between the study groups (P≥0.05). † Liver-function tests were conducted at the discretion of the treating physician and commonly included measurements of γ-glutamyltransferase, serum alanine aminotransferase, and serum aspartate aminotransferase. Results were interpreted according to local norms.
induced subclinical seizures would be expected to slow rather than accelerate functional recovery.

We conclude that amantadine is effective in accelerating the pace of recovery during acute rehabilitation in patients with prolonged post-traumatic disturbances in consciousness. Exposure to amantadine is associated with more rapid emergence of cognitively mediated behaviors that serve as the foundation for functional independence. The rate of recovery in the amantadine group slowed and between-group behavioral differences diminished during the washout period, suggesting that the response is drug-dependent. Whether treatment with amantadine, as compared with placebo, improves the long-term outcome or simply accelerates recovery en route to an equivalent level of function remains unknown. In view of health care cost constraints and declining lengths of stay for inpatient rehabilitation, amantadine-induced acceleration of recovery may represent an important advance. Future research should focus on determining the pathophysiological characteristics of patients who have a response to amantadine, the most effective dosage and duration of treatment and timing of its initiation, and the effectiveness of amantadine in patients with non-traumatic brain injuries.

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REFERENCES


