ORIGINAL ARTICLE

Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury

Joseph T. Giacino, Ph.D., John Whyte, M.D., Ph.D., Emilia Bagiella, Ph.D.,
Kathleen Kalmar, Ph.D., Nancy Childs, M.D., Allen Khademi, M.D.,
Bernd Eifert, M.D., David Long, M.D., Douglas I. Katz, M.D., Sooja Cho, M.D.,
Stuart A. Yablon, M.D., Marianne Luther, M.D., Flora M. Hammond, M.D.,
Annette Nordenbo, M.D., Paul Novak, O.T.R., Walt Mercer, Ph.D.,
Petra Maurer-Karattup, Dr.Rer.Nat., and Mark Sherer, Ph.D.

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.)

From the JFK Johnson Rehabilitation Institute, Edison, NJ (J.T.G., K.K., A.K.); Spaulding Rehabilitation Hospital and Department of Physical Medicine and Rehabilitation, Harvard Medical School (J.T.G.), and Department of Neurology, Boston University School of Medicine (D.I.K.) — all in Boston; Moss Rehabilitation Research Institute, Albert Einstein Healthcare Network, Elkins Park (J.W., S.C.), and Brain Injury Program, Bryn Mawr Rehab Hospital, Malvern (D.L.) — both in Pennsylvania; Department of Biostatistics, Mailman School of Public Health, Columbia University, New York (E.B.); Texas NeuroRehab Center, Austin (N.C., W.M.); SRH Fachkrankenhaus Neresheim, Neresheim (B.E., P.M.-K.), and Schön Klinik Bad Aibling, Bad Aibling (M.L.) — both in Germany; Braintree Rehabilitation Hospital, Braintree, MA (D.I.K.); Methodist Rehabilitation Center, Jackson, MS (S.A.Y., M.S.); Division of Physical Medicine and Rehabilitation, University of Alberta, Edmonton, Canada (S.A.Y.); Department of Physical Medicine and Rehabilitation, Carolinas Rehabilitation, Charlotte, NC (F.M.H.); Indiana University School of Medicine, Indianapolis (F.M.H.); Department of Neurorehabilitation, Traumatic Brain Injury Unit at Copenhagen University Hospital, Glostrup, and Hvidovre Hospital, Hvidovre — both in Denmark (A.N.); Sunnyview Rehabilitation Hospital, Schenectady, NY (P.N.); and TIRR Memorial Hermann, Houston (M.S.). Address reprint requests to Dr. Giacino at the Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, 125 Nashua St., Boston, MA 02114, or at jgiacino@partners.org.

Drs. Giacino and Whyte contributed equally to this article.

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SEVERE TRAUMATIC BRAIN INJURY IS A CATastrophic event that frequently has devastating familial, economic, and societal consequences. Traumatic brain injury is the most common cause of death and disability in persons between 15 and 30 years of age.[1] The most severe injuries can result in prolonged disorders of consciousness. Approximately 10 to 15% of patients with severe traumatic brain injury are discharged from acute care in a vegetative state,[2] a condition in which there is wakefulness without behavioral evidence of conscious awareness.[3] The estimated prevalence of a minimally conscious state,[4] which is distinguished from a vegetative state by the presence of at least one clearly discernible behavioral sign of consciousness, is 8 times as high as the prevalence of a vegetative state.[5] Of patients who are in a vegetative state for at least 4 weeks, approximately 50% will regain consciousness by 1 year.[2] Outcomes are generally more favorable for patients who are in a minimally conscious state, although approximately 50% remain severely disabled at 1 year.[6-9]

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 neurotransmitter systems can be improved through supplementation.

Amantadine hydrochloride is one of the most commonly prescribed medications for patients with disorders of consciousness who are undergoing inpatient neurorehabilitation.[10] The mechanism of action is unclear, although amantadine appears to act as an N-methyl-D-aspartate antagonist and indirect dopamine agonist.[11] The results of two randomized trials involving patients with traumatic disorders of consciousness suggested that amantadine was effective,[12,13] although methodologic limitations, including small samples and unbalanced groups, precluded definitive conclusions.[14,15]

In 1998, a consortium of brain-injury rehabilitation centers conducted an observational pilot study designed to establish the rate of spontaneous recovery from vegetative and minimally conscious states and provide the basis for a multicenter clinical trial.[10] A multiple-regression analysis exploring the effect of cognition-enhancing medications at 16 weeks after injury on scores on the Disability Rating Scale (DRS),[16] a measure 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, randomized, placebo-controlled trial to determine the effectiveness of amantadine in promoting recovery from a post-traumatic vegetative or minimally conscious state. We hypothesized that 4 weeks of treatment with amantadine administered between 4 and 16 weeks after injury in patients with traumatic disorders of consciousness would improve the rate of functional recovery during the treatment interval, that the improvement would be maintained 2 weeks after drug washout, and that amantadine would be well tolerated.

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 traumatic brain injury 4 to 16 weeks before enrollment, and were receiving usual inpatient rehabilitation 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 consistently and to engage in functional communication, as assessed by the score on the Coma Recovery Scale–Revised (CRS-R).[17]

The DRS includes measures of eye opening, verbalization, and motor response (derived from the Glasgow Coma Scale); cognitive understanding of feeding, dressing, and grooming; degree of assistance and supervision required; and employability.[16] Scores range from 0 to 29, with higher values indicating greater disability (see the Supplementary 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-

matic brain injury, medical instability, pregnancy, serious renal disease (estimated creatinine clearance, less than 60 ml per minute), more than one seizure in the previous month, prior treatment with amantadine, and allergy to amantadine. In the case of patients who were undergoing evaluation for ventricular shunt placement or receiving a psychoactive medication, enrollment was deferred until shunt placement had been completed or psychoactive medications discontinued.

Demographic characteristics and baseline functional scores on the DRS and CRS-R were submitted to the data coordinating center through an online portal. Treatment was assigned within centers in random blocks of four or six, with stratification for diagnosis (vegetative state vs. minimally conscious state) and interval between injury and enrollment (28 to 70 days vs. 71 to 112 days), which are factors shown to be predictive of outcomes.[3,6,10]

STUDY OVERSIGHT

The protocol was approved by the institutional review boards at all participating sites, and written informed consent was obtained from each patient's legally authorized representative. Independent oversight was provided by an external data and safety monitoring board. All data were stored and analyzed by a data coordinating center at Columbia University. The study was conducted in adherence to the protocol, available at NEJM.org. The first and second authors designed the study. All the authors vouch for the accuracy and completeness of the data and for the analysis. The National Institute on Disability and Rehabilitation Research provided all financial support for this study, including funds to purchase amantadine.

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 re-

Table 1. Demographic and Clinical Characteristics at Baseline.*		
Characteristic	Amantadine (N=87)	Placebo (N=97)
Age — yr	35.5±15.3	37.2±15.4
Male sex — no. (%)	64 (74)	69 (71)
Race or ethnic group — no. (%)†		
Asian	1 (1)	1 (1)
Black	10 (11)	6 (6)
White	73 (84)	87 (90)
Other	3 (3)	3 (3)
Hispanic		
Yes	5 (6)	11 (11)
No	82 (94)	86 (89)
Education — no. (%)		
High school or less	57 (66)	57 (59)
At least some college	29 (33)	34 (35)
At least some graduate school	1 (1)	5 (5)
Unknown	0	1 (1)
Time from injury to randomization — days		
Median	48	47
IQR	38–66	37–65
Time from rehabilitation admission to randomization — days		
Median	13	12
IQR	6–20	6–19
Score on Disability Rating Scale‡	21.8±2.0	22.2±2.1
Score on Coma Recovery Scale–Revised§	9.6±3.8	9.2±4.4
Minimally conscious state — no. (%)	56 (64)	64 (66)
Vegetative state — no. (%)	31 (36)	33 (34)

* 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.

ceived 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.

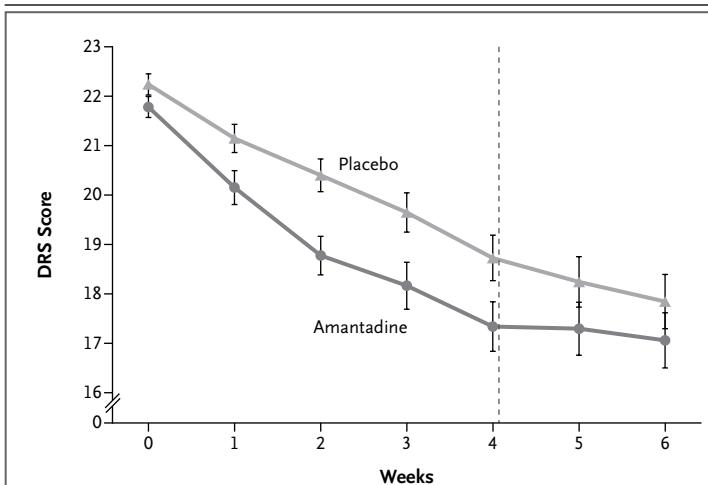To minimize exposure to confounding psychoactive medications during the treatment phase,

Figure 1. Mean Disability Rating Scale (DRS) Scores during the 6-Week Assessment Period, According to Study Group.

DRS scores range from 0 to 29; lower scores indicate less severe functional disability (see Fig. S7 in the Supplementary Appendix for the DRS syllabus). DRS scores improved significantly faster in the amantadine group than in the placebo group during the 4-week treatment interval. During the washout interval (weeks 5 and 6), the rate of recovery was significantly slower in the amantadine group, and mean DRS scores were similar for the two groups at the 6-week mark. I bars denote the standard error.

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.[17] 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,[10] 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
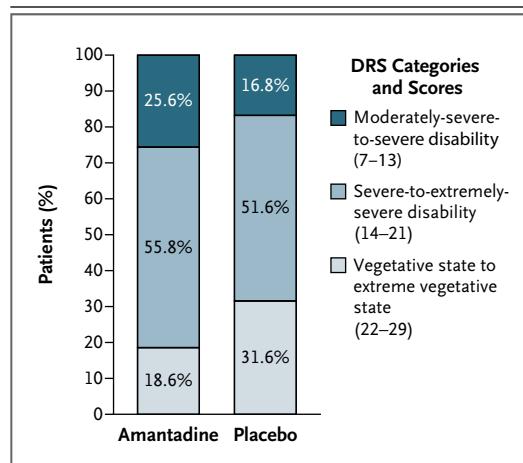

Figure 2. Post hoc Analysis of the Distribution of DRS Scores by Outcome Category.

DRS scores are represented as follows: moderately-severe-to-severe disability (range, 7 to 13), severe-to-extremely-severe disability (range, 14 to 21), and vegetative state to extreme vegetative state (range, 22 to 29). DRS score ranges were slightly modified from the original version of the DRS[16] to allow disability outcome ratings to be directly compared with those reported by Giacino and Kalmar in 1997.[6] After 4 weeks of treatment, the proportion of patients with DRS scores falling in the category for vegetative state to extreme vegetative state was higher in the placebo group. Conversely, the proportion of patients with scores in the category for moderately-severe-to-severe disability (i.e., least unfavorable) was greater in the amantadine group. At week 4, there were no patients with DRS scores between 0 and 6 (indicating no-to-moderate disability).

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).
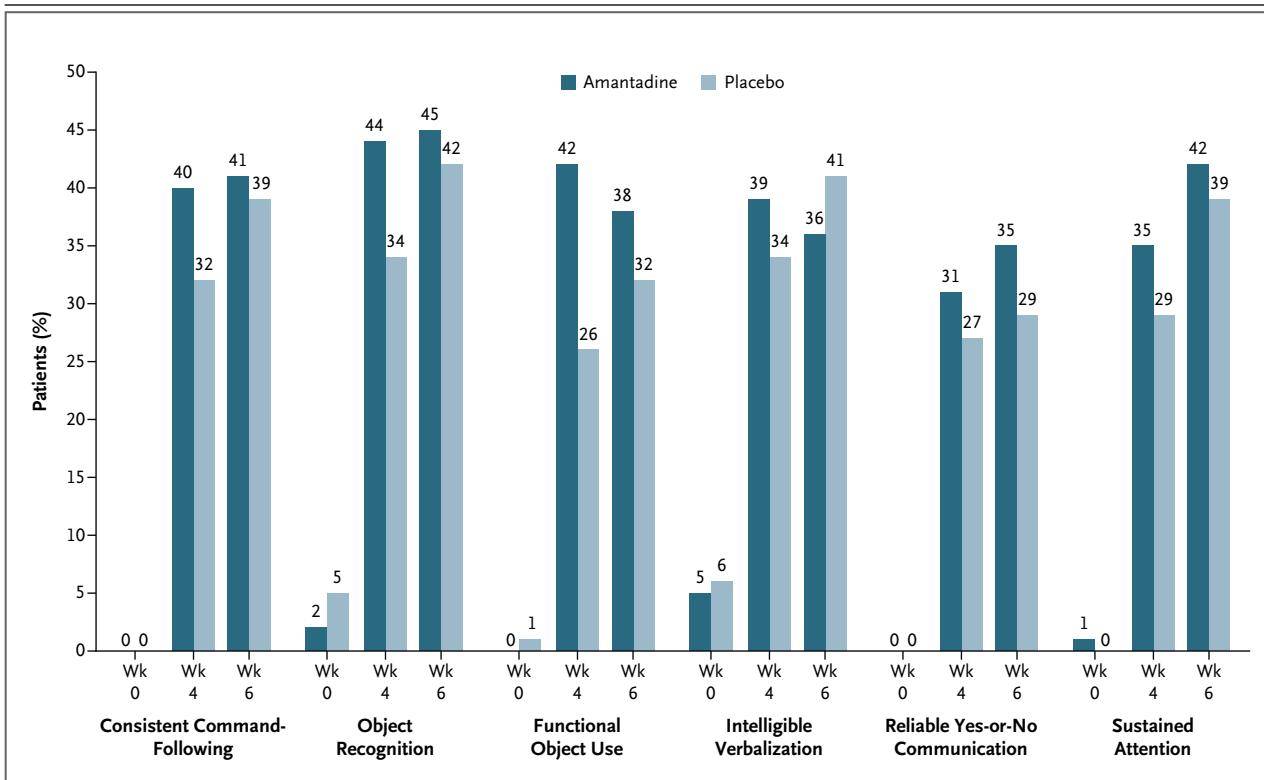
Figure 3. Frequency of Recovery of Key Behavioral Benchmarks on the Coma Recovery Scale–Revised (CRS-R).

At baseline (week 0), very few patients in either study group had behaviors associated with normal consciousness. By the end of week 4, recovery of key behavioral milestones was common in both groups (range, 26 to 44% of all cases). However, patients who received amantadine had a higher rate of recovery across all six behaviors. After washout, at week 6, behavioral recovery remained more favorable in the amantadine group across five of the six behaviors monitored. (See Fig. S8 in the Supplementary Appendix for the CRS-R syllabus.)

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-

sistent, regardless of the interval since injury or whether patients were in a vegetative state or a minimally conscious state at enrollment. Although gains were generally well maintained in the amantadine group after the washout period, the rate of recovery attenuated substantially after treatment was discontinued, and scores on the DRS were largely indistinguishable between the amantadine and placebo groups at the 6-week follow up assessment. During the 6-week observation period, exposure to amantadine did not increase the risk of adverse medical, neurologic, or behavioral events, including those of greatest concern to clinicians treating this population (e.g., seizure). These findings suggest that amantadine can be used safely at doses between 200 mg and 400 mg in patients with severe traumatic brain injury.

Our findings are consistent with observational reports[12,19] 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.[20,21] The favorable neurobehavioral effects of amantadine may reflect enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, and frontostriatal circuits that are responsible for mediating arousal, drive, and attentional functions.

Two case studies that used serial ^{18}F-fluorodeoxyglucose–positron-emission tomography to evaluate the effects of amantadine showed significant increases in prefrontal cortical metabolism[22,23] 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

Table 2. Adverse Events, According to Treatment Group.*		
Adverse Event	Amantadine (N=87)	Placebo (N=97)
	number (percent)	
Seizure	2 (2)	4 (4)
Changes on electroencephalography	1 (1)	0
Nausea	1 (1)	1 (1)
Vomiting	10 (11)	8 (8)
Constipation	2 (2)	3 (3)
Diarrhea	5 (6)	5 (5)
Other gastrointestinal event	4 (5)	11 (11)
Elevated liver-function tests†	3 (3)	3 (3)
Restlessness	7 (8)	9 (9)
Agitation	12 (14)	11 (11)
Insomnia	12 (14)	14 (14)
Involuntary muscle contractions	2 (2)	0
Hypertonia or spasticity	18 (21)	14 (14)
Other motor problems	1 (1)	1 (1)
Rash	5 (6)	6 (6)
Congestive heart failure	0	1 (1)

* 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.

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-

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,[24] 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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