

**Giacino JT, Whyte J, et al. Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury. N Engl J Med 2012;366:819-26.**

Design: Randomized clinical trial

Population/sample size/setting:

- 184 severe TBI patients (133 men, 51 women, men age 36) treated at 11 inpatient rehabilitation sites in 3 countries
- Eligible patients were age 16 to 65, with nonpenetrating TBI 4 to 16 weeks previous to enrollment; all were in a vegetative or minimally conscious state as indicated by a Disability Rating Scale (DRS) score > 11, with an inability to follow commands and engage in functional communication as assessed by the Coma Recovery Scale-Revised (CRS-R)
- Exclusion criteria were pre-existing nervous system disability, medical instability, pregnancy, renal disease, seizure within the previous month, prior treatment with amantadine, or allergy to amantadine

Main outcome measures:

- Randomization was stratified on diagnosis (vegetative/minimally conscious) and on interval from injury to enrollment (28 to 70 days vs. 71 to 112 days)
- Amantadine (n=87) and identical appearing placebo (n=97) were titrated on an identical schedule (100 mg bid for 14 days, then 150 bid at week 3 and 200 mg bid at week 4 if the DRS score had not improved at least 2 points from baseline); after week 4, study drug was discontinued after a 2-3 day taper; the study continued until week 6, when neither group took any study drug
- Principal outcome was the rate of change in the DRS during the first 4 weeks, when either amantadine or placebo was being given
- Secondary outcome was the rate of change in DRS during the final 2 weeks, testing the durability of the effect of amantadine after it was discontinued
- CRS-R was used to better understand the effects of study drug on key behaviors, but was conducted for descriptive purposes only, and was not analyzed as an outcome
- Both amantadine and placebo groups had improvements in the DRS during the 4 weeks of drug treatment, but the improvements were not equal
- Amantadine group had more rapid decline in the DRS than the placebo group (difference in slope of DRS was 0.24 points per week)
  - o The effect of amantadine was consistent across the planned subgroups, even though the patients with the shorter interval between injury and enrollment had faster recovery than their counterparts who had a longer interval between injury and enrollment
  - o Similarly, the patients with minimally conscious state had a faster rate of improvement than their vegetative counterparts
- The amantadine and placebo groups were balanced with respect to the vegetative state at baseline (36% vs. 34%); at 4 weeks, the amantadine group had reduced this to 18.6%, but the placebo group still had 31.6% in the vegetative state

- During the two-week follow-up after the discontinuation of the study drugs, the placebo group had continued improvement in the DRS, but the amantadine group improvement was significantly lower during the same 2 weeks; the amantadine group maintained its DRS status, but without real improvement
- No patient in either group attained a DRS score consistent with no-to-moderate disability (0 to 6 on DRS); 25.6% of the amantadine group and 16.8% of the placebo group attained a status of moderately-severe to severe disability (DRS of 7-13)
- Adverse events were common, and were equally distributed between groups; some complications were expected due to the seriousness of the TBI

#### Authors' conclusions:

- During 4 weeks of amantadine treatment, the rate of functional recovery was significantly greater than during 4 weeks of placebo treatment
- Functionally meaningful changes included consistent responses to verbal commands, intelligible speech, and functional-object use
- Due to the continued improvement in the placebo group between 4 and 6 weeks of the study, and the lack of significant improvement in the same period for the amantadine group, the amantadine and placebo groups were nearly indistinguishable on the DRS at the end of 6 weeks
- Amantadine can be used safely at doses of 200 to 400 mg in patients with severe TBI

#### Comments:

- Overall the study was conducted well, with a clear protocol which was adhered to, and clearly specified primary and secondary outcomes
- The duration of the drug treatment was only 4 weeks; the results lead the reader to wonder what may happen with longer treatment times, and whether continued amantadine treatment would have led to continued improvement at 6 weeks or longer
- There is some discussion of the subgroup analyses in the text which does not seem to match the graphs in the supplementary appendix
  - o The text states that the advantage of amantadine was stronger in the patients who were enrolled later than those enrolled earlier after the injury, and refers the reader to Figure S4 in the appendix
  - o The same figure appears to show a greater response for patients with earlier than with later enrollment (inspection of the graph appears to show about a 4.9 point decline in DRS for the early group and 2.4 points for the later group)
  - o Unfortunately, there is no Table to correspond to the graphic in Figure S4; this illustrates the desirability of having both graphic and tabular displays of numerical data in a study
- However, the main outcome analysis appears to be adequate, with a low risk of bias for the comparison between treatment groups

- The discussion section says that the findings are consistent with observational reports that show deceleration or loss of function after amantadine is discontinued; however, the amantadine group maintained, and did not lose, DRS functional gains obtained during treatment
- The outcomes, while better for amantadine than for placebo, remain pessimistic, with great residual severe disability
- A study with longer duration of amantadine treatment is imperative

Assessment: Adequate for evidence that short-term use of amantadine improves disability more than placebo