

**Meythaler JM, Brunner RC, et al. Amantadine to Improve Neurorecovery in Traumatic Brain Injury—Associated Diffuse Axonal Injury: A Pilot Double-blind Randomized Trial. J Head Trauma Rehabil 2002;17(4):300-313.**

Design: Randomized crossover trial

Population/sample size/setting:

- 35 patients (9 women, 26 men, mean age 31) treated for motor vehicle-related TBI (GCS $\leq$ 10) at the University of Alabama

- Inclusion criteria required age 16-75, GCS of 10 or less in the first 24 hours of injury, posttraumatic amnesia of at least 1 week, loss of consciousness immediately after a motor vehicle crash, informed consent by a legal representative of the patient, and feasibility of giving medication by nasogastric tube
- Exclusion criteria were life-threatening disease before the head injury, any penetrating head injury, severe medical comorbidity which would affect assessment of therapy, prior significant TBI or other brain insult, chronic steroid therapy, or renal failure

Main outcome measures:

- All patients received both amantadine (200 mg/d in divided doses in the morning and at noon) and placebo, with the sequence determined by a random process
- First dose was administered as soon as the patients were no longer on pressors and their acute care team deemed them able to tolerate amantadine; no patient started treatment earlier than 4 days or later than 6 weeks after the injury
- The study lasted for 12 weeks, with 6 weeks of amantadine and 6 weeks of placebo for each patient (no washout period between study medications)
- Group 1 (n=15) received amantadine first, then placebo; group 2 received placebo first, then amantadine
- Principal outcome measures included the Disability Rating Scale (DRS) and the Mini-mental Status Examination (MMSE)
  - o MMSE improved by 14.3 points in Group 1 during the first 6 weeks on amantadine, but by only an additional 2.4 points while on placebo
  - o MMSE improved by 10.5 points in Group 2 during the first 6 weeks on placebo, and by an additional 6.3 points during the second 6 weeks on placebo
  - o DRS improved by 9.8 points during the first 6 weeks in Group 1 but by only 0.15 points during the second 6 weeks
  - o DRS improved by 9.4 points during the first 6 weeks in Group 2 and by another 3.8 points during the second 6 weeks
  - o The DRS scores were unequal at baseline (15.5 in Group 1 and 21.7 in group 2); the final DRS score was 5.5 in Group 1 and 8.5 in Group 2
- Some additional scales were also measured with similar improvements in the first 6 weeks and with smaller improvements in the second 6 weeks for both groups

- Lab values (CUN, creatinine, Hgb/HCT) over the course of the study in both groups, and no seizures were reported during the study

Authors' conclusions:

- There was a consistent trend toward a more rapid improvement when patients were on amantadine; this was apparent in Group 2, which had more improvement during the second 6 weeks on amantadine than Group 1 had during the second 6 weeks on placebo
- The study could not absolutely demonstrate that early treatment with amantadine was more effective than later treatment, but patients did seem to improve more rapidly when taking amantadine
- A larger multicenter double-blind trial of amantadine is indicated, because amantadine was well-tolerated and demonstrated improvement in TBI patients

Comments:

- The condition being studied is unsuitable for a crossover design
  - o Crossover designs are used when the treated condition is stable; immediately after a TBI patient is taken off pressors, the condition is expected to improve in subsequent weeks (as happened with the lab values for this patient population)
  - o This accounts for why the improvement on placebo in Group 2 during the first 6 weeks was greater than its improvement on amantadine in the second 6 weeks
  - o There was no washout period between amantadine and placebo; however, because the rate of improvement in Group 1 was slower in the second 6 weeks, the carryover effect is unlikely to bias the estimate of its effect greatly
- Because the study cannot be interpreted as a crossover trial, the treatment effect can be guessed at by comparing the improvements in the first 6 weeks as a parallel group randomized trial; Group 1 and Group 2 responses were similar during this period
- The study should be seen as hypothesis-generating rather than as evidence in support of the hypothesis that amantadine is effective for severe TBI; the hypothesis is plausible, given that Group 2 had some additional improvement when taking amantadine, but is very far from being demonstrated

Assessment: Inadequate as evidence that amantadine is effective for the cognitive effects of TBI (crossover design not suited to the condition being treated, small and uncertain differences between amantadine and placebo)