

Silver JM, Koumaras B et al. Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology 2006;67:748-755.

Design: Randomized clinical trial

Population/sample size/setting:

- 157 patients (106 men, 51 women, mean age 37) treated for sequelae of mild TBI at 19 centers in the USA
- Eligible patients were 18 to 50 years old, nonpregnant, with nonpenetrating head injury and at least 1 standard deviation difference between Wechsler adult intelligence test and their current attention, as determined by the Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing (CANTAB RVIP) or verbal memory, as determined by the Hopkins Verbal Learning Test (HVLТ)
- Exclusion criteria were concurrent medical, psychiatric, or substance problem which could interfere with the conduct of the trial, concurrent medications known to affect cognition, MRI-documented brain hemorrhage, neurodegenerative disorder, or brain surgery

Main outcome measures:

- Patients randomized to rivastigmine (n=80) or placebo (n=77)
- Starting dose of rivastigmine was 1.5 mg bid with food; after at least 4 weeks on starting dose, the dose could be increased to 3 mg bid, but could not exceed daily dose of 6 mg
- Treatment was continued for 12 weeks from the first dose
- Primary outcome measures were CANTAB RVIP (attention) and HVLТ (verbal memory), which were administered at weeks 4, 8, and 12
 - o A treatment “response” was defined as at least a 1 standard deviation improvement from baseline on either test
- Numerous secondary analyses were conducted, including measures of mood and additional neuropsychological testing (Trail Making tests)
- At week 12, the percentage of responders was similar in the rivastigmine (48.7%) and placebo (50.7%) groups; percentage of responders were similar at 4 and 8 weeks
- There were no significant differences between rivastigmine and placebo in the secondary outcome measures either
- One post hoc subgroup analysis was done on patients with at least 25% impairment in HVLТ at baseline, and showed a trend ($p < .05$) in favor of rivastigmine in the change from baseline for the CANTAB RVIP
- Only one serious adverse event was reported, which was an episode of noncardiac substernal chest pain in the rivastigmine group, not considered to be related to the medication

Authors' conclusions:

- Rivastigmine was safe and well-tolerated during the study

- The post hoc analysis of the subgroup with more severe memory impairment suggested positive effects in favor of rivastigmine, but since p values were not adjusted for multiple comparisons, this may have arisen by chance
- Further studies are needed to determine the patient population likely to achieve a favorable response to rivastigmine

Comments:

- The limitations of a post hoc analysis of a subgroup without adjustment for multiple comparisons are acknowledged by the authors, and the lack of a difference between rivastigmine and placebo in the primary outcomes should guide the interpretation of the study
- The study lasted for 12 weeks, but the protocol at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00171795) (NCT00171795) called for 20 weeks of treatment with rivastigmine or placebo
- Although the analysis is stated to be intention to treat, the statistical paragraph of the methods section states that patients were required not to miss a dose of study medication in the 3 days before assessment in order to be included in the primary analysis; this is analysis based on treatment adherence and not based on treatment assignment

Assessment: Inadequate for evidence of effectiveness of rivastigmine for TBI cognitive impairment