

**Zhang L, Ptokin RC et al. Cholinergic Augmentation With Donepezil Enhances Recovery in Short-Term Memory and Sustained Attention After Traumatic Brain Injury. Arch Phys Med Rehabil 2004;85:1050-1055.**

Design: Randomized crossover trial

Population/sample size/setting:

- 18 patients (13 men, 5 women, mean age 32) treated for rehabilitation of TBI at university departments of rehabilitation medicine in San Antonio and Philadelphia
- Eligibility criteria were a history of TBI (regardless of severity) and deficits of attention or short-term memory shown by the auditory and visual indices of the Wechsler Memory Scale (WMS) or the Paced Auditory Serial Addition Test (PASAT)
  - o PASAT tests attention, working memory, and speed by verbally presenting a series of digits to the patient and requiring the patient to add a digit to the preceding digit verbally; the test is presented 4 times at 4 presentation rates (2.4 sec, 2.0 sec, 1.6 sec, and 1.2 sec)
- Exclusion criteria were extensive, and included medical or psychiatric complications of TBI (cardiac, seizures, endocrine, infection, GI bleeding, electrolyte imbalance, stroke, major depression), cognitive or behavioral function at level V (confused, non-agitated) on the Rancho Los Amigos scale, use of antidepressants, anticonvulsants, antipsychotics, or neurostimulants, and communication disorders (aphasia or dysarthria) which would interfere with neuropsychologic testing

Main outcome measures:

- 20 patients entered the study, and 18 completed the 24 week study
- The 18 patients each took donepezil for 10 weeks and placebo for 10 weeks in an order determined by randomization; there was a 4 week washout period at the end of the first 10 week period
- Titration of donepezil was done with a starting dose of 5 mg/d for 2 weeks and 10 mg/d for the remaining 8 weeks; identical appearing placebos were titrated in the same way
- The main outcomes were the change in the visual and auditory components of the WMS, and the change in the PASAT
- The group which received donepezil first (n=9) improved the auditory score of the WMS from 63.7 to 95.4 in the first 10 weeks, and maintained the improvement during the 10 weeks on placebo (final score 105.9)
- The group which received placebo first improved its auditory WMS score from 62.3 to 73.6 in the first 10 weeks, and improved to a score of 102.4 during the 10 weeks on placebo
- These scores showed an advantage for donepezil over placebo
- Similar patterns of improvement were shown for the visual component of the WMS and for the four presentations of the PASAT; improvement under donepezil was superior to improvement under placebo

- The improvements in the group which took donepezil first were sustained during the 10 week washout for the visual WMS and the PASAT, just as was the case for the auditory WMS improvement
- One patient withdrew during titration of donepezil due to increased bowel frequency and incontinence

Authors' conclusions:

- Cholinergic augmentation with donepezil improves cognitive function in postacute TBI patients
- There appears to be a carryover effect of donepezil which extends to the second testing period following 10 weeks of placebo; this far exceeds the 70 hour half-life of donepezil
- The generalization of the results to the mild TBI population may be limited by the fact that the patients in this study had predominantly moderate to severe TBI

Comments:

- The patients took the WMS and the PASAT as a condition of entry into the study; they took these tests again twice after the randomization had been done
- The second and third tests may show changes from baseline as a result of both treatment effects from donepezil and from practice effects from taking the test repeatedly
  - o The practice effects are difficult to estimate, but the changes from baseline in the patients who took placebo first may provide an approximation
  - o For the PASAT and for the visual component of the WMS, the practice effects appear to be very small; for the auditory component of the WMS, they appear to exist, but to be small in relation to the treatment effect of donepezil
- The average score on the auditory component of the WMS (from Table 2) appears to improve during placebo treatment by about 10 points, but this is reported as non-significant by the authors
  - o This apparent improvement may indeed not be significant, since the estimate of improvement depends on a paired t-test for each patient; one would need the raw data to test the changes during placebo treatment for statistical significance
  - o However, paired t-tests are generally have more power than independent-samples t-tests, and it would be surprising if the placebo improvement for the auditory WMS did not exist
- The study may not have had the stated 90% power to detect a treatment effect size of 0.93 standard deviations, but an inflation of the donepezil effect is not likely

Assessment: Adequate for evidence that donepezil may improve working memory and sustained attention in patients with subacute moderate to severe TBI