Rivastigmine treatment in cognitive and behavioral deficits after TBI.

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Orbito-frontal and temporo-hippocampal lesions may be predominant after TBI, with prevalent involvement of cholinergic pathways.
Donepezil mediated memory improvement in traumatic brain injury during post acute rehabilitation

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Donepezil in the Treatment of Cognitive Dysfunction Associated with Traumatic Brain Injury

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Cholinesterase inhibitors are known to enhance cognitive function among patients with dementia of the Alzheimer's type. It is quite possible that this clinical benefit may extend to other patient groups, yet this issue awaits further exploration. This study examined the use of the cholinesterase inhibitor donepezil in the treatment of patients with a history of traumatic brain injury and subsequent cognitive impairment. The sample was comprised of 24 ambulatory psychiatric patients who were receiving care for psychotropic sequelae of brain injury. In this sample, residual cognitive impairment was treated with adjunctive donepezil. This study reports the clinical assessments of this patient sample in outpatient follow-up for up to 10 years duration. Assessments of cognition with the Wechsler Adult Intelligence Scale-Revised and the Hooper Visual Organization Test were obtained on a subset of this sample (N = 22). Clinician assessment ratings were analyzed for the entire sample. Results indicated improvement in full-scale IQ (z = 2.5, p = .002) scores as well as clinician-based ratings (z = 2.4, p < .0001). Further research will likely delineate whether specific types of brain injuries are most responsive to cholinesterase inhibitors. These findings suggest that donepezil may enhance clinical response by complementing the medication management of other concomitant psychiatric disturbances related to brain injury.

Subject Review

Attention and memory dysfunction after traumatic brain injury: cholinergic mechanisms, sensory gating, and a hypothesis for further investigation

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Cognition-enhancing effects of donepezil in traumatic brain injury.

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The purpose of this study was to investigate the effects of donepezil, a cholinergic agent, on chronic cognitive impairment due to traumatic brain injury (TBI). Chronic patients underwent two standardized neuropsychological evaluations—one before and the other 3 months following treatment with donepezil. Together with global inventories that appraised behaviour, fatigue, anxiety and depression, these evaluations also assessed executive functioning, memory and attention. Of the 10 patients who followed the therapy, 8 reported subjective improvement in at least one cognitive domain following therapy and most of them reported better functioning in everyday activities. This effect was supported by a slight global improvement when considering the global score of the different affectivo-behavioural scales. At the neuropsychological level, although we could observe a slight improvement in the majority of the considered tests, significant positive changes were mainly found in tests assessing speed of processing, learning and divided attention. These findings suggest that donepezil may lead to better general functioning and improve attentional skills in patients with chronic TBI.

2005 S. Karger AG, Basel
Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury-clinical experience in 111 patients.

Tenovuo O. (2005)
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PURPOSE: Theoretically, central acetylcholinesterase inhibitors (CAIs) could alleviate at least some of the main symptoms of chronic traumatic brain injury (TBI). The aim of this report is to describe clinical experience of the treatment of chronic TBI with these drugs.

GENERAL METHODS: From an outpatient clinic material, 111 patients were selected having chronic stable TBI with at least one of the following target symptoms: fatigue, poor memory, diminished attention or diminished initiation. Patients received in random donepezil, galantamine or rivastigmine. The evaluation of the treatment response was based on the subjective view of the patient.

FINDINGS: As first treatment, 27 patients received donepezil, 30 galantamine and 54 rivastigmine. Altogether 41 patients tried more than one drug, but only three patients tried all three alternatives. In total, 61% of patients had a marked positive response and 39% a modest or no response. The clearest effect was in almost all responders a better vigilance and attention causing better general function. About half of the patients (55%) wanted to continue therapy with one of these drugs. The therapeutic response became very quickly and at low doses. There were no significant differences between the three drugs either in effect or tolerability. The age, sex, type of injury, severity of TBI or elapsed time after injury did not affect the response. The mean dose in maintenance therapy was 7.2 mg od for donepezil, 5.0 mg bid for galantamine and 2.3 mg bid for rivastigmine. Side effects or inadequate therapeutic response were the main causes for discontinuation with nearly equal frequency. Paradoxical responses were seen in some patients.

CONCLUSIONS: CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences between the three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed.
Effects of rivastigmine on cognitive function in patients with traumatic brain injury

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Objective: To compare the efficacy and safety of rivastigmine (3 to 6 mg/day) vs placebo over 12 weeks in patients with traumatic brain injury and persistent cognitive impairment.

Methods: This prospective, randomized, double-blind, placebo-controlled study was conducted in 157 patients at least 12 months after injury. The primary efficacy measures were the Cambridge Neuropsychological Test Automated Battery (CANTAB) Rapid Visual Information Processing (RVIP) A’ subtest and the Hopkins Verbal Learning Test (HVLT). The primary efficacy outcome was the proportion of patients who demonstrated 1.0 SD or greater improvement from baseline at week 12 on CANTAB RVIP A’ or HVLT.

Results: The percentage of responders at week 12 on either the CANTAB RVIP A’ or HVLT was 48.7% for rivastigmine and 49.3% for placebo (p = 0.940). Furthermore, for the overall study population, there were no significant differences for any of the secondary efficacy variables. In a subgroup of patients with moderate to severe memory impairment (n = 81), defined as 25% impairment or greater on HVLT at baseline, rivastigmine was significantly better than placebo for a number of measures, including the proportion of HVLT responders and CANTAB RVIP mean latency.

Conclusions: Rivastigmine was safe and well tolerated in patients with traumatic brain injury with cognitive deficits. Rivastigmine shows promising results in the subgroup of patients with traumatic brain injury with moderate to severe memory deficits.
Study protocol

Goal
• Evaluation of rivastigmine efficacy in reducing cognitive and behavioral deficits in the chronic post-rehabilitation phase after TBI

Methods
• TBI Patients’ recruitment at a chronic stage
• Inclusion / exclusion criteria
• Informed consent of patient and GP
• Pre-treatment evaluation (T0)
  – Neuropsychological Battery
  – Neuropsychiatric Inventory Behavioral Test (to caregiver)
  – EEG and ECG
  – Extensive clinical evaluation
• Rivastigmine treatment 1,5 mg b.i.d. for 4 weeks
• Subsequently 3 mg b.i.d. for additional 20 weeks
• Post-treatment evaluation (T1)
  – NP Battery
  – NIB Test
-- Evaluation of side effects and subjective complaints / improvements
Inclusion criteria

- Male / Female patients
- Age 18 / 65 ys.
- GCS < 8 in the first 24h after trauma
- Diminuished score at NP Battery and NB Scale
- At least 1 year post-trauma
- At least 24 weeks after ending Medical / NP Rehabilitation
Exclusion Criteria

**Specific**
- Severe motor impairment with lack of sufficient motor skill to complete NP battery
- Severe communication deficit or aphasia
- MMSE below 14
- Multiple TBIs
- Persistent PTA (GOAT cut off = 75%)

**Aspecific**
- Diabetes mellitus
- Chronic Bronchopneumopathy
- Alterations of cardiac electrophysiological conduction
- Peptic ulcer
- Positivity to familial glaucoma
- Pregnancy
- Uncontrolled epilepsy
- Alcohol or substance abuse
- Major Psychiatric Pathology (1 of DSM IV-R)
- Neuroleptic or BD use
Evaluation Protocol

COGNITIVE
- M.I.D.A. (Reaction time / attention)
- Trail Making A and B
- Bisyllabic Word Span
- Rey 15 Words Test
- Corsi Span
- Corsi Supra Span
- Rivermead Behavioral Memory Test

OVERALL OUTCOME
- G.O.S.E. (Glasgow Outcome Scale Extended)
- D.R.S. (Disability Rating Scale)

QUALITY OF LIFE
- Test Euro Q.o.L.

BEHAVIORAL
- N.P.I. (Neuropsychiatric Inventory)
Sample description

- **14 Subjects** (10 M ; 4 F)
- **Av. Age** 34.5 +/- 11.1 ys.
- **Av. School** 11.1 +/- 2.9 ys.
- **Av. 24h GCS** 5.00 +/- 1,10
- **Av. Coma Duration** 26 +/- 14.1 days
- **Av. Time Post-injury** 51.1 +/- 33.8 months
# Results

<table>
<thead>
<tr>
<th>MIDA (reaction time)</th>
<th>T0 msec</th>
<th>T1 msec</th>
<th>Delta T0 / T1</th>
<th>p</th>
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<tbody>
<tr>
<td>Run in</td>
<td>457.08±-222.91</td>
<td>348.92±-140.12</td>
<td>-108.15±-185.55</td>
<td>0.0105</td>
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<tr>
<td>Simple Central position</td>
<td>347.69±-76.35</td>
<td>340.29±-120.24</td>
<td>-7.40±-89.20</td>
<td>0.235</td>
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<tr>
<td>Simple Extended field</td>
<td>396.00±-103.14</td>
<td>368.00±-106.60</td>
<td>-28.00±-61.34</td>
<td>0.1060</td>
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<tr>
<td>Complex</td>
<td>497.70±-50.77</td>
<td>475.80±-58.97</td>
<td>-21.90±-65.19</td>
<td>0.3223</td>
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<table>
<thead>
<tr>
<th>TRAIL MAKING</th>
<th>T0 sec</th>
<th>T1 sec</th>
<th>Delta T0 / T1</th>
<th>p</th>
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<tbody>
<tr>
<td>Part A</td>
<td>71.90±34.06</td>
<td>69.98±32.77</td>
<td>-1.92±-32.63</td>
<td>0.8945</td>
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<tr>
<td>Part B</td>
<td>181.39±101.02</td>
<td>154.76±86.87</td>
<td>-26.63±-57.48</td>
<td>0.1189</td>
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</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Test</th>
<th>T0</th>
<th>T1</th>
<th>Delta T0 / T1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis. Word Span</td>
<td>3.75±1.01</td>
<td>3.96±0.92</td>
<td>0.21</td>
<td>0.50</td>
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<tr>
<td>Corsi Span</td>
<td>4±1.03</td>
<td>3.75±0.76</td>
<td>-0.25</td>
<td>0.77</td>
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<tr>
<td>Corsi Supra Span immediate</td>
<td>3.75±8.42</td>
<td>5.68+/-7.88</td>
<td>1.93</td>
<td>0.2676</td>
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<tr>
<td>15 Rey Words Immediate</td>
<td>28.93+/-9.75</td>
<td>32.71±10.00</td>
<td>+ 3.79</td>
<td>0.0291</td>
</tr>
</tbody>
</table>
### Results

<table>
<thead>
<tr>
<th></th>
<th>Total T0</th>
<th>Total T1</th>
<th>Delta T0 T1</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>RIVERMEAD-S</td>
<td>5.14± 3.63</td>
<td>6.64 ±3.50</td>
<td>1.50</td>
<td>0.0352</td>
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<tr>
<td>G.O.S.E.</td>
<td>4.29± 2.13</td>
<td>4.36± 2.13</td>
<td>0.07</td>
<td>1.000</td>
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<tr>
<td>D.R.S.</td>
<td>4.08</td>
<td>4.28</td>
<td>0.20</td>
<td>0.41</td>
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<td>N.P.I.</td>
<td>33.29± 24.22</td>
<td>24.93± 20.88</td>
<td>-8.36</td>
<td>0.0010</td>
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</tbody>
</table>

#### Rivermead

- Total: 5.14 ± 3.63
- Delta: 1.50
- p-value: 0.0352

#### Neuro Psychiatric Inventory

- Total: 33.29 ± 24.22
- Delta: -8.36
- p-value: 0.0010
Conclusions

Measured observations

• Overall reduction of reaction time (not stat.s.)
• Improvement in verbal learning (close to stat.s.)
• Positive behavioral results with better social integration (stat.s.)
• Memory improvement in daily life activities (stat.s.)
• No correlation with GOSE or DRS

Subjective observations

• Less burden on caregiver
• No relevant side effects
• Tendency to return to baseline, with worsening of function, after therapy withdrawal
GRAZIE!