TITLE: Acetylcholinesterase Inhibitors for Traumatic Brain Injury

DATE: 17 April 2007

CONTEXT AND POLICY ISSUES:
Traumatic brain injury (TBI) is an acute injury to the brain resulting from external physical forces. It is characterized by one or more of the following: confusion or disorientation, loss of consciousness, post-traumatic amnesia and other neurological abnormalities such as focal neurological signs, seizures, and/or intra-cranial lesions. This definition excludes injury due to poisoning, anoxia, stroke, and other cardiovascular events.\(^1\) In Canada, during fiscal year 2003-2004, there were 16,811 hospitalizations as a result of traumatic head injuries, the equivalent of 46 admissions per day, with an overall crude rate of 53 per 100,000 persons. Mean age of the admitted was 41 years with 30% being children and youth (age 0-19 years) and 91% being diagnosed with TBI.\(^2,3\) Since these estimates are derived from hospital admissions, they are underestimates as persons with TBI may not survive to be admitted, may not require admission, or may not even be seen at a hospital.\(^1,2\)

The most common method of assessing the severity of injury is the Glasgow Coma Scale score which ranges from 3 (worst score) to 15 (best score) and is derived from evaluating eye, verbal and motor ability. Scores are categorized as mild (13-15), moderate (9-12), or severe (3-8) injury. Another indicator of severity is the duration of post-traumatic amnesia from the time of injury including any period of loss of consciousness or coma. Again, duration of post-traumatic amnesia is categorized as mild (<24 hrs), moderate (1-6 days), or severe (7 days or more) injury. In the presence of disagreement between the two methods of classification, it is appropriate to use the more severe category.\(^1\)

Disclaimer: The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information on available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
Although mild TBIs have a good prognosis with a minority experiencing residual deficits, the outcomes for moderate to severe TBIs are more dire. For example, between 50 to 90% of children and adolescents with severe TBI will require help, to various degrees, in bathing, dressing, and walking for varying periods of time after the injury. Furthermore, carers of people with TBI have significantly poorer quality of life and more psychiatric morbidity than the general population.

Cognitive impairments are among the most common neurological sequelae of TBIs of all severity levels and can include difficulties in comprehension, communication, attention, memory, concentration, initiating and planning daily activities, reasoning, judgement, problem solving, decision making, arousal, and speed of information processing.

Animal and human data implicate post-traumatic cholinergic dysfunction as a cause of cognitive impairment. The cholinergic system is a system of nerve cells that uses acetylcholine. Acetylcholine is a neurotransmitter associated with arousal, attention, memory and other aspects of cognition. Because of the structure of the skull cavity, TBI frequently results in injury to acetylcholine-rich regions of the brain.

Similarities between Alzheimer and TBI patients with respect to cognitive impairments and their physiological basis combined with the success of acetylcholinesterase inhibitors (AI) in Alzheimer’s disease, has resulted in AIs being considered for the treatment of cognitive impairments secondary to TBI. In Canada, there are three approved AIs (donepezil hydrochloride, rivastigmine hydrogen tartrate, and galantamine hydrobromide) specifically indicated for symptomatic treatment of mild to moderate dementia of Alzheimer’s type. These AIs enhance cholinergic function by slowing the degradation of acetylcholine by acetylcholinesterase (an enzyme that breaks down acetylcholine). Although AIs have demonstrated clear cognitive benefit in Alzheimer’s disease, generalizations to other patient populations should be made cautiously. For example, Cochrane systematic reviews of double-blind randomized placebo-controlled trials have not found donepezil or galantamine clinically effective for patients with mild cognitive impairment defined as problems with memory and other cognitive abilities without a diagnosis of dementia (a heterogeneous population which could include those who deteriorate to Alzheimer’s disease, stroke sufferers, and individuals who may actually improve). In fact, an unexplained statistically significant elevated death rate in mild cognitive impairment patients treated with galantamine relative to placebo has resulted in Loy and Schneider not recommending galantamine use in this patient population. Furthermore, AIs should not be perceived as panaceas. Based on published literature and clinical experience, Arciniegas and Silver conclude that post-traumatic impairments in arousal and speed of processing would be expected to respond best to catecholaminergic augmentation (i.e. dopamine and norepinephrine) whereas memory impairments would be expected to respond to cholinergic augmentation strategies. Unfortunately, simple, inexpensive, and widely available methods of quantifying in vivo neurotransmitter function are presently lacking.

Consequently, clinicians select pharmacotherapies on the basis of the hypothesized link
between neurotransmitters and the most prominent cognitive impairments exhibited by TBI patients. To enable more evidence-based decision making, this report examines the empirical data regarding AIs in the treatment of cognitive impairments arising from TBI.

RESEARCH QUESTION:
What is the clinical efficacy and safety of AIs in the treatment of cognitive impairments secondary to TBI?

METHODS:
A limited literature search was conducted on key health technology assessment resources, including PubMed, EMBASE, PsycINFO, The Cochrane Library (Issue 1, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI’s HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1997 and the present, and are limited to English language publications only.

SUMMARY OF FINDINGS:
No health technology assessment reports, systematic reviews, or meta-analyses examining the use of AIs in patients with TBI were identified.

Guidelines
One guideline, published in July 2006, by the New Zealand Guideline Group was identified. Based on a systematic search and critical review of relevant research by a multidisciplinary team of medical, rehabilitation, and research specialists, the group concluded that a trial of donepezil hydrochloride may be considered for adults with deficits in memory and sustained attention following TBI, and that the evidence for children and young adults was inadequate necessitating cautious application of the adult recommendations. Due to a dearth of relevant research, these recommendations were supported by international expert opinion rather than high quality research.

Randomized Controlled Trials
One small (10 patients/group), double-blind, cross-over, randomized block, placebo-controlled trial published in 2004 was identified (see Table A1 in Appendix for study details). Adult TBI patients, 2 to 24 months post injury and suffering from attention or short-term memory impairment, were randomly assigned to one of two groups. One group received 10 weeks of donepezil followed by 10 weeks of placebo separated by a 4 week washout period while a second group received 10 weeks of placebo followed by 10 weeks of donepezil separated by a 4 week washout period. After 10 weeks of donepezil treatment, statistically significant substantial within group improvements were noted, relative to baseline, in short-term memory measured with the Auditory Immediate Index and Visual Immediate Index of the Wechsler Memory Scale-III, and sustained attention/information processing measured with the Paced Auditory Serial Addition test. The Wechsler Memory Scale III is valid and sensitive in detecting and monitoring changes in cognitive deficits in patients with moderate to severe TBI and the Paced...
Auditory Serial Addition test is sensitive to attention deficits in mild and severe TBI. At the 10 week mark, the donepezil treatment group had statistically significant better scores on all outcomes relative to the placebo group. However, at 24 weeks, no statistically significant between group differences were noted on any of the outcomes suggesting a carryover effect of donepezil. To explain the prolonged effect, the authors hypothesized that donepezil may increase the activity of choline acetyltransferase, a primary enzyme in the biosynthesis of acetylcholine. One patient withdrew due to increased bowel frequency and incontinence after one week on donepezil. The improvements noted in both groups at the 24 week mark were impressive in that the mean short-term memory scores actually approached or exceeded a score of 100 which defines average performance in a healthy population. Although this study is of higher quality on the hierarchy of research designs, its relatively small size, unclear quality of allocation concealment, stringent inclusion/exclusion criteria, narrow range of outcome measures, and short duration limits conclusions regarding generalizability to the heterogeneous TBI population, the impact of donepezil on other cognitive/behavioural impairments, and the long-term therapeutic/adverse effects.

Observational Studies
Other than small case series (n≤4), six observational studies published between 2000 and 2005 were identified (see Table A1 in Appendix for study details) and are briefly summarized below. A primary limitation of all observational studies is their inability to disentangle the potential effects of placebo, spontaneous recovery, and the impact of concurrent treatments. Thus, they should be viewed as hypothesis generating activities requiring more rigorous experimental evaluation.

In a small retrospective case series (n=53) examining the therapeutic impact of donepezil in adult brain injury patients over a follow up period ranging from 2 to 25 months, Whelan et al.\textsuperscript{14} demonstrated a statistically significant increase in the Clinical Improvement Scale (mean change (sd)=2.77 (1.65)) which considers mood, affect, energy, interest in daily activities, grooming, and social interaction. Conversely, no statistically significant improvements in intellectual function or ability to organize visual stimuli were found. Study limitations included an impure TBI patient population; a considerable number of patients missing outcome scores; the use of additional vitamins/medications; and inconsistent follow-up periods.

In a small heterogeneous case series (n=10) examining the effect of an 8 week course of donepezil in adult TBI patients, Kaye et al.\textsuperscript{15} reported improvements in the Clinical Global Improvement rating and patient self-reports of focus, attention, clarity of thought, and speed of processing, but not in neuropsychological tests of memory. One patient withdrew due to intolerable nausea. Study limitations included a small heterogeneous sample; lack of details regarding outcome measures; lack of statistical analysis; and a short treatment duration.

In a very small prospective observational study (n=7), Morey et al.\textsuperscript{16} examined the impact of different doses of donepezil on adult TBI patients at least 1.5 years post injury. Patients were exposed to primarily 10 mg/day of donepezil for 6 months followed
by a 6 week wash-out period, and an additional 6 months of donepezil at 5mg/day. Statistically significant mean differences were found in several measures of visual learning and memory after the first 6 months of treatment relative to baseline (brief visual memory test total score mean difference = -8.71 and delayed recall mean difference = -9.71) but not in the second 6 months of treatment relative to baseline. Statistically significant changes were not observed in measures of verbal learning and memory, immediate memory and working memory, verbal fluency, or self-perception of memory abilities. The authors suggested that the lack of effect during the second treatment period indicated a dose-response effect. Study limitations included a small sample size with substantial withdrawals (2 dropped out secondary to lethargy and somnolence).

In a small (n=18 per group) retrospective case-control study, Walker et al.\textsuperscript{17} examined the impact of donepezil in addition to inpatient rehabilitation relative to rehabilitation alone in adult veterans and military personnel with moderate to severe TBI admitted within 3 months of injury. No statistically significant between group differences were noted in any of the Functional Independence Measure cognitive scores, but a statistically significant negative correlation was noted between the Functional Independence Measure cognitive efficiency score (change score/days in rehabilitation) and the number of days from admission to initiation of donepezil (r = -0.52, p = 0.026). That is, the sooner donepezil was initiated after admission, the greater the daily rate of improvement in the Functional Independence Measure cognitive score. Study limitations included a small sample size; lack of standardization with respect to time to initiation of donepezil, dosing changes, or number of days on donepezil; and the lack of information on rehabilitation program components.

In a moderate sized (n=111) retrospective case series, Tenovuo\textsuperscript{5} examined the impact of donepezil (n=27), galantamine (n=30), or rivastigmine (n=54) on mild to severely injured, stable adult TBI patients with at least one of four symptoms: fatigue, poor memory, diminished attention, or problems with initiation. Fifty-five percent of patients reported a good (clearly positive response helping to cope with everyday life) to excellent (remarkably enhanced functional ability measured by ability to work or study) response. The most frequently reported areas of subjective improvement included vigilance 56%, concentration 18%, initiation 14%, general functioning 12%, memory 9%, and clearness of thought 6%. Drug responders were not more likely to return to work, study or otherwise productive daily life relative to non-responders, but did have a statistically significant higher mean Glasgow Outcome Scale-Extended score (means 5.4 vs 5.0, p < 0.05). There were no statistically significant differences between drugs with respect to patient self-report of improvement or adverse effects. Nonetheless, 26% of patients reported persisting or disturbing adverse effects, the most frequent being nausea 24%, tiredness 12%, headache 8%, and insomnia 8%. Study limitations included concurrent use of other centrally acting drugs in nearly half the patients; and outcomes not being measured at standardized points.

Finally, in a small (n=15) prospective case series, Khateb et al\textsuperscript{4} examined the impact of donepezil on adult patients with moderate to severe TBI at least 6 months post injury.
Treatment consisted of 5 mg/day for one month followed by 10 mg/day for 2 months and outcomes were measured pre- and post intervention. Eight of the 10 patients completing the study reported improvement in at least one cognitive or behavioural domain and statistically significant improvements were noted in neuropsychological tests of processing speed (pre/post mean (sd): 87.3 (22.9), 79.5 (19.1)), learning (47.7 (6.9), 53.5 (5.0)) and divided attention (5.8 (3.3), 2.9 (2.7)). No significant improvements were noted in anxiety and depression, troubles associated with emotional, personality, motivational, behavioural and cognitive changes, or fatigue. Four patients withdrew due to side effects including nausea, sleep disorders, anxiety, excitability, cramps and dizziness. Study limitations included the small sample size with considerable withdrawals (5 in total).

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The prevalence and adverse consequences of TBIs are substantial and cognitive impairments are among the most common neurological sequelae.

A small randomized controlled trial and several observational studies have indicated that AIs, primarily donepezil, may be clinically effective in the treatment of TBI related cognitive impairments such as memory, attention, information processing speed, learning, and clearness of thought. Nevertheless, this research has limitations such as small sample sizes, stringent inclusion/exclusion criteria, cointerventions, narrow range of outcome measures, short duration, inconsistent follow-up periods, loss to follow-up, and no information on the effect of AIs in children with TBI. Accordingly, larger, higher quality, randomized controlled trials are required to confirm the findings and optimize the treatment protocol with respect to such factors as ideal patient groups, time period of administration relative to injury, dosage and treatment duration. For example, TBI specific research has suggested a carryover effect and low threshold effect while research involving Alzheimer patients has suggested that lower doses may be just as effective as higher doses potentially sparing patients from the adverse side-effects of AIs. Once AIs have been found clinically effective relative to placebo, head to head trials would be useful in determining if differences exist among the AIs with respect to efficacy and safety. To ensure high-quality research, future randomized controlled trials should acknowledge the following methodological recommendations detailed by Griffen et al.:

1) Ensuring that inclusion criteria include specific cognitive impairments hypothesized to be responsive to AIs.
2) Adequate length trials to detect improvement in cognition and function.
3) Using outcome measures that are sensitive to changes in the types of cognitive impairments detailed in inclusion criteria and targeted by AIs.
4) Addressing behavioural outcomes in addition to cognition.

Further, agreement on a standard set of reliable and valid outcome measures which include meaningful measures of function and quality of life would facilitate inter-study comparisons, meta-analyses, and the identification of consequential treatment effects.
Finally, it should be remembered that none of the medications evaluated in this health technology inquiry service report have been approved for the treatment of cognitive deficits following TBI and that adverse effects of AIs have been noted in certain patient populations. Hence, assumptions regarding efficacy should be guarded and off-label use of AIs should be judicious.

PREPARED BY:
Dianne Zakaria Ph.D., Epidemiologist
Melissa Severn, MIST - Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
### APPENDIX

Table A1: Clinical Efficacy of Acetylcholinesterase Inhibitors in the Treatment of Traumatic Brain Injury Sequelae

<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 2004</td>
<td>-study sample: adult TBI patients from 2 neurorehabilitation clinics in 2 teaching hospitals -inclusion criteria: attention or short-term memory impairment; 2 to 24 months after brain injury -exclusion criteria: medical complications; cognitive and behavioural functioning at level V or below on the Rancho Los Amigos levels of cognitive functioning; neurological or psychiatric complications or comorbidity; taking psychotropic medications; communication impairment that would interfere with neuropsychologic testing -sample size: n_A=10, n_B=10 -intervention: group A underwent a 10 week donepezil phase and 10 week placebo phase separated by a 4 week wash out period; group B underwent the same phases in reverse order; donepezil was started at 5 mg/day for the first 2 weeks and 10 mg/day for the remaining 8 weeks -outcomes (measured at baseline, 10 weeks and 24 weeks): the Auditory Immediate Index and the Visual Immediate Index of the Wechsler Memory Scale-III to assess short-term auditory and visual memory, respectively, and the Paced Auditory Serial Addition Test to assess sustained attention, working memory and information processing speed -primary statistical techniques: mixed linear model</td>
<td>-2 patients did not complete the study: one was transferred to an assisted living facility in another city and a second withdrew due to increased bowel frequency and incontinence after one week on donepezil -SS within group improvements were seen in all outcomes after donepezil treatment relative to baseline scores -at the 10 week mark the donepezil treatment group had SS better scores on all outcomes relative to the placebo group -at the 24 week mark, no SS differences were noted between groups on any of the outcomes indicating a carryover effect of donepezil -over the 24 week period, the Auditory Immediate index increased from a mean (sd) of 63.7 (2.5) to 105.9 (4.5) in group A and 62.3 (2.0) to 102.4 (4.5) in group B; the visual immediate index increased from 65.9 (2.6) to 91.3 (3.0) in group A and 63.3 (3.2) to 94.9 (3.0) in group B; and, with a presentation rate of 2.4 seconds, the Paced Auditory Serial Addition Test increased from 24.11 (1.65) to 44.80 (1.95) in group A and 27.22 (1.73) to 46.53 (1.95) in group B -to explain the prolonged effect, the authors hypothesized that donepezil may increase the activity of choline acetyltransferase, a primary enzyme in the biosynthesis of acetylcholine</td>
</tr>
<tr>
<td>Author/Year/Design</td>
<td>Methodology</td>
<td>Results</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| **Observational Studies** | - **study sample:** adult outpatients of a neurology clinic with moderate to severe TBI for at least 6 months  
- **exclusion criteria:** history of other previous central nervous system injury or disease; ongoing alcohol or drug abuse; speech or language disorders severe enough to affect study participation; unstable psychiatric disorders; compliance difficulties; current use of AI  
- **sample size:** n=15  
- **intervention:** donepezil 5mg/day for 1 month and 10 mg/day over the next 2 months  
- **outcomes** (measured at baseline and 3 months): Hospital Anxiety and Depression Scale to assess anxiety and depression; Dysexecutive Questionnaire to assess troubles associated with emotional, personality, motivational, behavioural and cognitive changes; fatigue questionnaire to assess fatigue; a neuropsychological battery of standardized tests to assess cognitive issues of executive functioning, learning, memory, and attention; and patient subjective impression about the effect of medication on language, memory, attention, emotion and fatigue  
- **primary statistical techniques:** non-parametric Wilcoxon test for matched pairs | - 5 patients did not complete the study: 4 discontinued due to side-effects (nausea, sleep disorders, anxiety, excitability, cramps and dizziness) and 1 had compliance issues  
- 8 of 10 patients reported improvement in at least one cognitive or behavioural domain  
- no SS effects were noted with the Hospital Anxiety and Depression Scale, the Dysexecutive Questionnaire, or the fatigue questionnaire  
- SS improvements were noted in neuropsychological tests of processing speed (pre/post means (sd): 87.3 (22.9), 79.5 (19.1)), learning (47.7 (6.9), 53.5 (5.0)), and divided attention (5.8 (3.3), 2.9 (2.7)) |
<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Tenovuo® 2004     | **study sample:** adult TBI patients attending one outpatient clinic; severity varied from mild to extremely severe as measured with GCS or duration of PTA  
**inclusion criteria:** fairly stable phase after trauma (one year or more from trauma); one of four symptoms (fatigue, poor memory, diminished attention, problems with initiation) caused by the TBI  
**exclusion criteria:** children; uncertain diagnosis; other possible causes for chronic symptoms; contraindications for AI; suspicion of degenerative dementia  
**sample size:** n=111  
**intervention:** patients received one of three AI (donepezil n=27, galantamine n=30, or rivastigmine n=54) depending on availability of sample packages; dosing started at the lowest recommended dose (donepezil 5mg/day, galantamine 8mg/day, rivastigmine 3mg/day) and was increased thereafter depending on tolerability and response  
**outcomes:** patient self-report (none, no effect; modest, slight or uncertain benefit without marked effect on everyday life; good, clearly positive response helping to cope with everyday life; and excellent, remarkably enhanced functional ability measured by ability to work or study); number of patients returning to work, study or otherwise productive daily life; and Glasgow Outcome Scale-Extended form  
**primary statistical techniques:** ANOVA, chi-square test, Kruskal-Wallis test, and logistic regression | - no SS differences between drugs with respect to patient self-report or adverse effects  
- 55% of patients reported a good or excellent response  
- most frequently reported areas of subjective improvement (% reporting) were as follows: vigilance (56%), concentration (18%), initiation (14%), general functioning (12%), memory (9%), and clearness of thought (6%)  
- logistic regression indicated treatment response was not associated with the patient’s age or sex, the mechanism of injury, the severity of TBI or the elapsed time from the injury  
- drug responders were not more likely to return to work, study or otherwise productive daily life relative to non-responders  
- drug responders had a SS higher Glasgow Outcome Scale-Extended relative to non-responders (means 5.4 vs 5.0)  
- 26% of patients reported persisting or clearly disturbing adverse effects  
- most frequently reported adverse effects (% reporting) were as follows: nausea (24%), tiredness (12%), headache (8%), and insomnia (8%)  
- it was noted by the author that favourable effects occurred quickly with low doses and therapeutic response appeared to continue beyond discontinuation of treatment |
<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Walker et al. 2004 retrospective case-control study | **-study sample:** adult veterans and military personnel with TBI  
**-inclusion criteria:** moderate to severe TBI; age ≤ 65 years; acute rehabilitation admission within 3 months of injury; no prior acute rehabilitation; ≥ 3 week acute rehabilitation length of stay  
**-sample size:** n_t=18, n_c=18  
**-intervention:** treatment group received donepezil (initially 5 mg/day and increased to 10 mg/day depending on perceived clinical response) in addition to inpatient rehabilitation; control group received inpatient rehabilitation alone  
**-controls** were calliper matched by age at admission and baseline cognitive impairment to treatment patients  
**-outcomes** (pre/post-intervention): FIM cognitive total score, FIM cognitive change score, and FIM efficiency score (FIM cognitive change score/days in rehabilitation)  
**-primary statistical techniques:** ANOVA and Pearson’s product moment correlation coefficient | **-no side effects were reported**  
**-no SS differences in any of the main outcomes** (treatment vs control mean): FIM cognitive total (24.8 vs 22.4), FIM cognitive change (13.9 vs 11.3), FIM cognitive efficiency (0.25 vs 0.23)  
**-sub-group analyses of the donepezil group did not indicate a dose-response relationship**  
**-a significant negative correlation was observed between FIM cognitive efficiency score and the number of days between admission to initiation of donepezil (r = -0.52, p=0.026), i.e. the sooner donepezil was initiated the greater the daily rate of improvement in the FIM cognitive score** |
<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Morey et al. 2003  | -study group: former adult patients of a hospital who had sustained a TBI and were at least 1.5 years post-injury  
-exclusion criteria: taking anti-cholinergic medications, history of substance abuse, compliance issues, medical or psychological diagnoses other than TBI, physical complications precluding the patient’s ability to perform the test battery, and patients demonstrating language deficits or adequate memory functioning on baseline testing  
-sample size: n=7  
-intervention: donepezil for 6 months (initially 5 mg/day for 4 weeks and increased to 10 mg/day for the final 5 months) followed by a 6 week wash-out period and an additional 6 months of donepezil at 5mg/day  
-outcomes (completed at baseline and at the end of each phase): Brief Visual Memory Test-Revised to assess visual learning and memory; Hopkins Verbal learning test to assess verbal learning and memory; Digit Span test to provide a measure of immediate memory and working memory; Letter-Number Sequence test to measure working memory; Controlled Oral Word Association Test to measure verbal fluency; and the Memory Functioning Questionnaire to assess self-perceptions of memory abilities  
-primary statistical techniques: repeated measures ANOVA to compare T1 with T2 (end of first 6 month treatment), T1 with T3 (end of washout period), and T1 with T4 (end of second treatment period) | -2 of 7 participants dropped out during the first treatment phase after reaching a 10 mg dose with complaints of lethargy and somnolence  
-SS mean differences were found between T1 and T2 for the Brief Visual Memory Test-Revised scores (total score mean difference= -8.71; delayed recall mean difference= -9.71)  
-no other SS differences were found for other measures across all other testing intervals  
-authors suggested that the lack of SS findings between T1 and T4 indicates a dose-response effect |
<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Kaye et al., 2003  | study group: adult TBI patients receiving treatment in one out-patient practice; study includes first 10 TBI patients receiving donepezil; heterogeneous group with respect to age, severity of injury, and time since head injury  
- sample size: n=10  
- intervention: 5 mg/day donepezil for first 4 weeks and 10 mg daily for subsequent 4 weeks  
- outcomes (pre- and post-intervention): Clinical Global Improvement ratings conducted by two independent raters and “a symptom focused neuropsychological test battery”  
- primary statistical techniques: not specifically stated | - 1 subject was lost to follow-up and another subject withdrew due to intolerable nausea  
- the Global Memory Scale of the Memory Assessment Scale did not improve  
- Clinical Global Improvement rating showed improvement  
- in most cases (7/8), patients rated themselves somewhat improved, but not necessarily in the memory domain as expected, i.e. improvements were reported in focus, attention, clarity of thought, and speed of processing  
- family members reported improved socialization  
- 7/8 patients completing the study continued taking donepezil |
<table>
<thead>
<tr>
<th>Author/Year/Design</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
</table>
| Whelan et al. 2000 retrospective case series | **-study group:** non-elderly adult brain injury patients with clinically apparent cognitive dysfunction and psychiatric symptoms seen at two ambulatory psychiatric treatment settings; group involved brain injury from trauma, anoxia, or vascular event  
**-sample size:** n=53  
**-intervention:** donepezil 5 mg/day and titrated to 10 mg/day as tolerated; adjunctive preventive measures included vitamin E 400 IU twice daily for its potential neuroprotective effects and enteric-coated aspirin daily for its anti-inflammatory and vasoprotective benefits; furthermore, the majority of patients received a combination of antidepressant, anxiolytic, and mood stabilizer therapy  
**-outcomes** (measured at baseline and, for a sub-sample, at 2 to 25 months follow-up): Wechsler Adult Intelligence Scale-Revised to provide a comprehensive estimate of intellectual function; the Hooper Visual Organization Test to measure ability in organizing visual stimuli; and the Clinical Improvement Scale which was based on two rater’s observations and considered improvement in mood, affect, energy, interest in daily activities, grooming, and social interaction  
**-primary statistical techniques:** paired t-test | **-SS improvements in the Wechsler Adult Intelligence Scale-Revised full-scale IQ score (n=22, mean change score (sd)=2.5 (4.6)) and the Clinical Improvement Scale (n=53, mean change score (sd)=2.77 (1.65))**  
-Bonferroni correction for multiple comparisons resulted in non-significant results for IQ testing |

**Note.** TBI = traumatic brain injury, SS = statistically significant (p ≤ 0.05), AI = acetylcholinesterase inhibitor, GCS = Glasgow coma scale, PTA = post traumatic amnesia, ANOVA = analysis of variance, n_t = number in treatment group, n_c = number in control group, FIM = functional independence measure, IQ = intelligence quotient
REFERENCES:


