OFF-LABEL USES OF DONEPEZIL:

A FOCUS ON SAFETY AND EFFICACY IN TRAUMATIC BRAIN INJURY AND POST STROKE APHASIA

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September 11th, 2015

OBJECTIVES

- Review the use of donepezil in traumatic brain injury and post stroke aphasia.
- Summarize the epidemiology, pathophysiology, and treatment recommendations.
- Analyze several clinical trials for the efficacy and safety of using donepezil for traumatic brain injury and post stroke aphasia.
- Identify potential areas for future research.
- Evaluate the clinical benefit versus risk.

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DONEPEZIL

- Approved in December 1996
- Indications
  - Mild, moderate, and severe Alzheimer's dementia
- Adverse effects
  - Insomnia (2-14%)
  - Nausea (3-19%)
  - Diarrhea (5-15%)

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Lexi-Comp Online™, Lexi-Drugs Online™. (2015). Hudson, OH: Lexi-Comp, Inc.

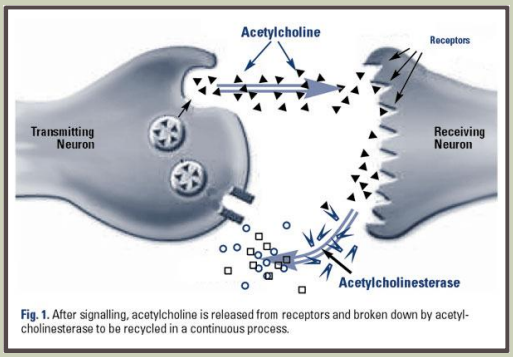

Fig. 1. After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.

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http://peaknootropics.com/using-acetylcholinesterase-inhibitors-nootropics/.

DONEPEZIL OFF-LABEL USES

- Traumatic Brain Injury (TBI)
- Post Stroke Aphasia
- Dementia associated with Parkinson's Disease
- Lewy Body Dementia
- Mood Disorders
- Autism Spectrum Disorder

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OFF-LABEL MEDICATIONS

- No approved medications for the specific populations
- Similar medication has been approved for the indication
- Pathologic or physiologic features of conditions are similar
- Health care professionals should weigh the risks and benefits of using an off-label medication

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Wittich CM, et al. Mayo Clin Proc. October 2012;87(10):982-990.

TRAUMATIC BRAIN INJURY

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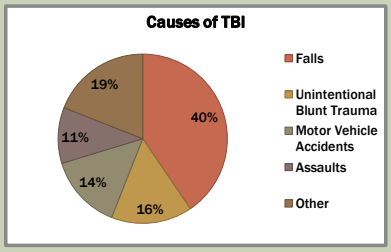
EPIDEMIOLOGY

- Approximately 2.5 million people sustained a TBI in 2010



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Injury Prevention & Control: Traumatic Brain Injury. *CDC*.

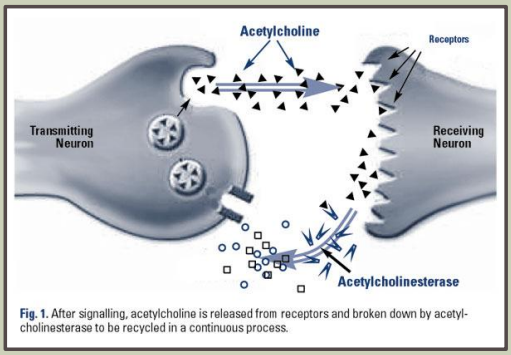

Fig. 1. After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.

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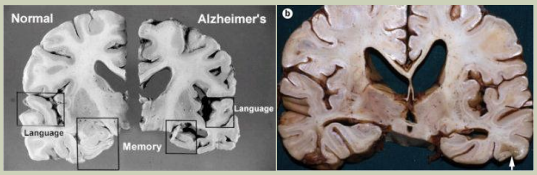
http://peaknootropics.com/using-acetylcholinesterase-inhibitors-nootropics/.

ATROPHY IN THE BRAIN



- Comparison of a normal brain, Alzheimer's brain, and brain 4 years after TBI

10

Dementia. Available at: http://www.upright-health.com/dementia.html.
Smith DH, et al. Available at: http://www.nature.com/nrneurol/journal/v9/n4/fig_tab/nrneurol.2013.29_F1.html

SEVERITY OF TRAUMATIC BRAIN INJURY

- TBI severity classification
  - Glasgow Coma Scale

Severity	Glasgow Coma Scale Score	Post-traumatic amnesia	Loss of consciousness
Mild	13-15	< 1 hour	< 30 minutes
Moderate	9-12	1-24 hours	1-24 hours
Severe	< 8	> 24 hours	> 24 hours

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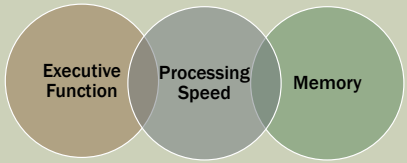
Scher, LM, et al. *Current Psychiatry*. 2011;10:21-37.

COGNITIVE IMPAIRMENT

- Up to 70% of TBI patients



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Scher, LM, et al. *Current Psychiatry*. 2011;10:21-37.

CURRENT RECOMMENDATIONS

- No approved medications to treat cognitive impairment associated with TBI
- Treatment should be **symptom-based**

Impairment	First Line Medication	Side Effects	Other treatment options
Executive function	Amantadine 200-400 mg/day	CNS depression, peripheral edema, hypotension, anorexia	Bromocriptine, pramipexole, carbidopa/levodopa
Processing speed	Methylphenidate 0.3 mg/kg twice daily	Tachycardia, insomnia, decreased appetite, nausea, anxiety	Dextroamphetamine
Memory	Donepezil 5-10 mg/day	Nausea, insomnia, diarrhea, fatigue	Rivastigmine, galantamine, physostigmine

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Scher, LM, et al. *Current Psychiatry*. 2011;10:21-37.

EARLY LITERATURE

Study	Design	Population	Dose	Results
Whelen, et al. 2000	Retrospective case series Cognitive dysfunction	N=53	5 mg daily titrated to 10 mg if tolerated	Improvement: daily functioning
Masanic, et al. 2001	Open label retrospective study Memory, behavior, global function	N=4 ≥ 2 years post injury	5 mg daily x 8 wk 10 mg daily x 4 wk Washout x 4 wk	Improvements: verbal/visual memory, behavior
Morey, et al. 2003	Single-subject retrospective study Memory	N=7 ≥ 1.5 years post injury	5 mg daily x 4 wk 10 mg daily x 5 mo Washout x 6 wk 5 mg daily x 6 mo	Improvement: visual memory Only seen with 10 mg

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Whelen FJ., et al. *Ann Clin Psychiatry*. 2000;12(3):131-5
Masanic CA., et al. *Arch Phys Med Rehabil*. 2001;82:896-901
Morey CE., et al. *Brain Injury*. 2003;17:809-15

LIMITATIONS

- Very few patients
- Adverse effects not reported in detail
- Placebo effect
- Retrospective cases
- Different assessment tools and primary outcomes

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ZHANG, ET AL. 2004

- 24-week randomized, placebo-controlled, double-blind crossover trial
- Short-term memory and sustained attention
- Inclusion criteria:
  - Short-term memory impairment
  - Participants were 2-24 months post TBI

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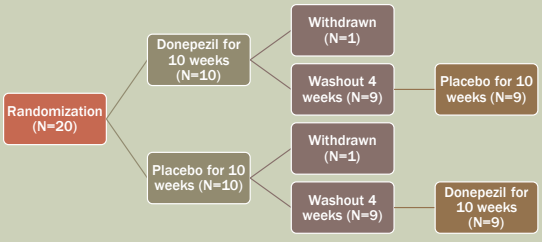
Zhang L, et al. *Arch Phys Med Rehabil*. 2004;85:1050-5.

METHODS
ZHANG, 2004



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Zhang L, et al. *Arch Phys Med Rehabil*. 2004;85:1050-5.

ASSESSMENT TOOLS
ZHANG, 2004

- Wechsler Memory Scale (WMS–III)
  - Auditory Immediate Index (AII)
  - Visual Immediate Index (VII)
  - Indexes have a mean of 100 and a standard deviation of 15
- Paced Auditory Serial Addition Test (PASAT)
  - Sustained attention, working memory, and information-processing speed
  - Maximum of 60

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Zhang L, et al. *Arch Phys Med Rehabil*. 2004;85:1050-5.

RESULTS
ZHANG, 2004

- Auditory Immediate Index

	Group A Donepezil first	Group B Placebo first	p value
Baseline	63.7 ± 2.5	62.3 ± 2.0	0.611
Week 10	95.4 ± 4.5	73.6 ± 4.5	**0.002**
Week 24	105.9 ± 4.5	102.4 ± 4.5	0.588

Score of 100 defines average performance in a healthy population

19 Zhang L, et al. *Arch Phys Med Rehabil.* 2004;85:1050-5.

RESULTS
ZHANG, 2004

- Visual Immediate Index

	Group A Donepezil first	Group B Placebo first	p value
Baseline	65.9 ± 2.6	63.3 ± 3.2	0.116
Week 10	93.5 ± 3.0	64.9 ± 3.0	**< 0.001**
Week 24	91.3 ± 3.0	94.9 ± 3.0	0.397

20 Zhang L, et al. *Arch Phys Med Rehabil.* 2004;85:1050-5.

RESULTS
ZHANG, 2004

	Group A	Group B	p value
2.4 seconds			
Week 10	42.7 ± 1.95	29.08 ± 1.95	**< 0.001**
Week 24	44.8 ± 1.95	46.53 ± 1.95	0.545
2.0 seconds			
Week 10	37.74 ± 1.2	26.48 ± 1.2	**< 0.001**
Week 24	37.97 ± 1.2	35.03 ± 1.2	0.102
1.6 seconds			
Week 10	31.44 ± 1.39	21.89 ± 1.39	**< 0.001**
Week 24	32.78 ± 1.39	32.22 ± 1.39	0.783
1.2 seconds			
Week 10	21.98 ± 1.11	14.69 ± 1.11	**0.001**
Week 24	21.64 ± 1.11	23.02 ± 1.11	0.41

21 Zhang L, et al. *Arch Phys Med Rehabil.* 2004;85:1050-5.

CONCLUSION
ZHANG, 2004

- Auditory and visual immediate memory and attention
- Improvement continued after washout
- Limitations
  - Spontaneous recovery
  - Small number of patients
  - 1 patient dropped out due to adverse effects

22 Zhang L, et al. *Arch Phys Med Rehabil.* 2004;85:1050-5.

WHAT ABOUT THE OTHER ACETYLCHOLINESTERASE INHIBITORS (AI)?

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TENOVUO, ET AL. 2004

- Retrospective, open cohort study with 3 arms
- Treatment response between donepezil, galantamine, and rivastigmine
- 111 patients
  - 1 year post injury, with symptoms of fatigue, poor memory, diminished attention, or initiation problems

24 Tenovuo O. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2005;29:61-67

ASSESSMENT TOOLS
TENOVUO, 2004

- Response based on **subjective** assessment
  - Graded as none, modest, good, or excellent
- Glasgow Outcome Scale, extended (GOS-E) form was also determined
  - Functional outcome scale that rates patient status from 1-8

25 Tenovuo O. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005;29:61-67

	Positive Overall Response	Continuing treatment	Marked Adverse Effects
Donepezil (N=27)	41% (N=11)	33% (N=9)	26% (N=9)
Galantamine (N=30)	60% (N=18)	50% (N=15)	23% (N=7)
Rivastigmine (N=54)	59% (N=32)	48% (N=26)	28% (N=15)

- GOS-E was significantly better in responders
  - 5.4 versus 5.0, $p < 0.05$
- 37.7% of those who responded to at least one drug improved one step in the GOS-E scale

26 Tenovuo O. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005;29:61-67

RESULTS
TENOVUO, 2004

- No difference between groups
- Increase in general functioning
- No wearing off of response
- Extra benefit with dose increase
- Response to one acetylcholinesterase inhibitor and not another
- Adverse effects were persisting in 26% of patients

27 Tenovuo O. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005;29:61-67

LIMITATIONS
TENOVUO, 2004

- 39% of patients had a modest or no response
- Improvement was based on subjective assessment
- Difference in the number of patients in each arm
- Placebo effect

28 Tenovuo O. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005;29:61-67

KHATEB, ET AL. 2005

Study	Population	Dose	Endpoint	Results
Khateb, et al. Prospective case series	N=10 Mod/severe, > 6 months post injury	5 mg daily x 1 month, 10 mg daily x 2 months	Behavior	Improved
			Executive functioning	Not significant
			Learning/Memory	Improved
			Attention	Improved

29 Khateb A, et al. *European Neurology*. 2005;54:39-45.

SAFETY
KHATEB, 2005

- Side effects:
  - Nausea, sleep disorders, anxiety, excitability, cramps, dizziness
  - 4/15 patients stopped the drug
  - Side effects subsided in 2-3 weeks for some patients

30 Khateb A, et al. *European Neurology*. 2005;54:39-45.

FINAL CONCLUSIONS

- Acute and late phases of memory and attention improved
- Positive effects after treatment discontinuation
- Possible improvement in processing speed and learning
- No significant difference between donepezil and other acetylcholinesterase inhibitors
- Adverse effects were often transient

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FUTURE STUDIES

- Large scale randomized placebo-controlled trial
- Effectiveness based on time since TBI, severity of TBI, and location of injury
- Clinical observation

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POST STROKE APHASIA

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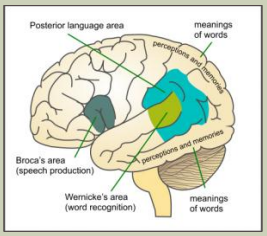
APHASIA

- Loss or impairment of language due to brain damage
- Affects about 20-40% of all stroke patients
- Aphasia recovery tends to plateau by 1 year after onset



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Teasell R, et al. *Clinician Handbook. 2014:1-41*

CLASSIFICATIONS OF APHASIA

Broca's	• Nonfluent aphasia • Speech production is halting
Wernicke's	• Fluent aphasia • Comprehension is poor
Global	• Severe impairment of both expressive and receptive skills

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Teasell R, et al. *Clinician Handbook. 2014:1-41*

NON-PHARMACOLOGICAL INTERVENTIONS

- Speech language therapy
- Group therapy
- Communication partner training
- Computer-Based Training

36

Teasell R, et al. *Clinician Handbook. 2014:1-41*

PHARMACOLOGIC THERAPY

- Bromocriptine – no significant impact on aphasia
- Amphetamines – improved aphasia recovery when combined with language therapy
- Donepezil – positive effect on global language function during active treatment

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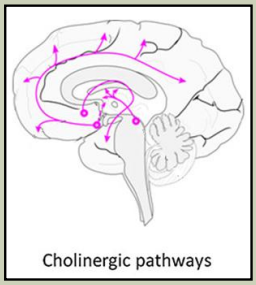
Teasell R, et al. *Clinician Handbook. 2014:1-41*
Walker-Batson D, et al. Stroke. 2001;2093-2098.

MECHANISM OF EFFECT



- Vascular lesions interrupt cholinergic pathways
- Cerebral circulation is influenced by cholinergic mechanisms

38

Berthier ML, et al. *Neuropsychol Rev.* 2011;21:302-317.

ASSESSMENT TOOLS

- Tests used to assess aphasia
  - Communication, linguistic ability, comprehension
- Western Aphasia Battery (WAB)
- Psycholinguistic Assessment of Language Processing in Aphasia (PALPA)

39

Aphasia Assessment and the ICF. Australian Aphasia Rehabilitation Pathway.

BERTHIER, ET AL. 2006

- 20 week double-blind, randomized, placebo-controlled study
- Primary endpoint: aphasia severity
- Inclusion criteria:
  - < 70 years
  - Chronic aphasia (1 year since onset)
  - Unilateral stroke lesion

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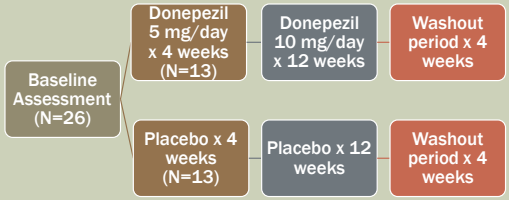
Berthier ML, et al. *Neurology.* 2006;67:1687-1689.

METHODS
BERTHIER, 2006



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Berthier ML, et al. *Neurology.* 2006;67:1687-1689.

RESULTS
BERTHIER, 2006

- Significant improvement
  - Aphasia severity (p = 0.037)
  - Picture naming subtest of PALPA (p = 0.025)
- Adverse events not significant

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Berthier ML, et al. *Neurology.* 2006;67:1687-1689.

CONCLUSION
BERTHIER, 2006

- Between group differences no longer significant after washout period
- Only enhances language and communication performance during treatment

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Berthier ML, et al. *Neurology*. 2006;67:1687-1689.

CHEN, ET AL. 2010

Study	Population	Dose	Assessment
Chen, et al. 2010 Pilot case-control study	N=60 Treatment group versus control group	5 mg daily x 12 wks	Western Aphasia Battery measured at baseline and 12 weeks

44

Chen Y., et al. Zhonqhua Nei Ke Za Zhi. 2010;49(2):115-8

RESULTS
CHEN, 2010

- Aphasia Quotient was significantly greater ($p = 0.004$)
- Significant recovery in spontaneous speech, comprehension, repetition, and naming functions ($p = 0.05$)

45

Chen Y., et al. Zhonqhua Nei Ke Za Zhi. 2010;49(2):115-8

FINAL CONCLUSION

- Speech and language therapy is the mainstay of treatment
- Recovery in spontaneous speech, comprehension, repetition, and naming functions
- Presents a good option for patients that require augmentation to speech and language therapy

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FUTURE STUDIES

- Large scale randomized placebo-controlled trial
- Determine if aphasia type or severity is linked to effectiveness of donepezil to better target certain patient populations
- Compare donepezil with the other acetylcholinesterase inhibitors

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DISCUSSION: TRAUMATIC BRAIN INJURY

- Use is controversial
- Available trials are limited by design
- Improvement in memory and attention for many patients
- Positive effects remained after discontinuation
- Adverse events may limit use
- Donepezil should be used to treat memory impairment following traumatic brain injury
  - 10 mg daily

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DISCUSSION: POST STROKE APHASIA

- No pharmacological treatment for post stroke aphasia
- Few clinical trials
- Significant recovery in speech and comprehension
- Positive effects did not remain after discontinuation
- Donepezil should be used to treat post stroke aphasia
  - 5-10 mg both showed improvement

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ACKNOWLEDGEMENTS

- Special thanks to:
  - Tamara Knight, Pharm.D., BCPS
  - Lyndsi Meyenburg, Pharm.D., BCPS

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