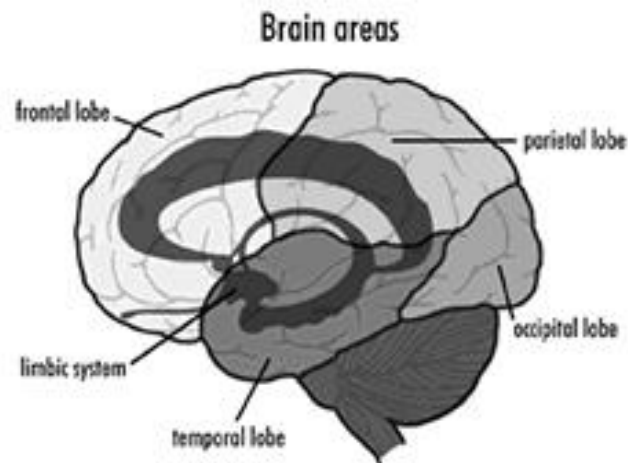


“Normal Aging” versus Alzheimer Disease
Drugs to treat the symptoms that are not due to old age.

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Alzheimer Disease is a form of dementia that affects 5% of men and women over age 65 and 50% of people over age 85.^{1,2} Dementia is a neurological disorder that severely obstructs a person's ability to perform normal activities of daily living such as feeding, dressing, and bathing oneself.^{1,2,3,4,13} Alzheimer Disease gradually, but progressively, impairs memory, learning, reason, judgment, and communication skills. Alzheimer Disease most commonly occurs sporadically but in some cases it is hereditary.^{2,3,4} The cause of Alzheimer Disease is unknown, however, it is known that damage to the brain occurs several years or even decades before symptoms appear. Once Alzheimer Disease becomes symptomatic irreversible damage has already occurred.^{2,3} Symptoms such as changes in behavior occur because of damage to certain areas of the brain.⁴

The brain is composed of five general regions: the limbic system, the temporal lobes, the parietal lobes, the frontal lobe, and the occipital lobe.⁴



The limbic system, where memory and emotion originate, is affected early on. This often results in difficulty finding objects and/or forgetting where objects were placed.⁴ The temporal lobes are the area where learning and short term memory are processed. Damage to this region can result in lapses in a person's recent memory and the inability to recognize familiar faces and places.⁴ The parietal lobes control spatial information and make a person able to put activities into sequence. Damage to these lobes by Alzheimer Disease leaves a person unable to clearly express his or her thoughts, get dressed or find his or her way.⁴ The frontal lobe is needed to plan and organize activities, it also regulates behavior; once damaged a person may lose interest in favorite activities and may behave in inappropriate ways.⁴ The occipital lobe is generally not affected by Alzheimer Disease, however, the surrounding visual areas may be affected which can lead to loss of depth vision and/or the inability to see movement.⁴

Physical changes occur in the brain either as a result of damage or they may actually cause the damage. Under the microscope there are four different findings that are indicative of Alzheimer Disease: plaques, tangles, beta-amyloid, and degenerated nerve cells.^{1,2,3,4} Plaques are clumps of abnormal protein that accumulate outside nerve cells, whereas tangles are composed of a different protein that twists together and deposits inside nerve cells.^{2,3} Beta-amyloid is an atypical protein that is formed when something triggers a normal protein to be cut incorrectly. Beta-amyloid tends to accumulate within plaques.⁵

Patients with Alzheimer Disease have irregular concentrations of several neurotransmitters that are important for proper brain function.³ Acetylcholine is important for stimulating muscle contraction and the release of hormones involved in wakefulness, attentiveness, anger, aggression, sexuality, and thirst.⁶ Norepinephrine is a neurotransmitter that is important for attentiveness, emotions, sleeping, dreaming, and learning.⁶ Serotonin

contributes to the regulation of body temperature, sleep, mood, appetite, and pain.⁶ Glutamate is associated with learning and memory.⁶

Early warning signs of Alzheimer Disease include: memory loss that affects daily functioning, difficulty performing familiar or routine tasks, language problems, disorientation with regards to time and place, poor judgment, problems with abstract thinking, misplacing things, changes in mood and/or behavior, changes in personality, and/or loss of interest in favorite pastimes.⁴ It is important to remember that these are not normal signs of aging and Alzheimer Disease can only be diagnosed by a qualified health care professional.¹ Diagnosis of Alzheimer Disease is made following a systematic assessment that rules out other possibilities by looking at medical history, mental status, physical examination, laboratory tests, and psychiatric and/or psychological evaluations.^{4,7,17}

Once diagnosed, Alzheimer Disease is categorized into 7 different stages:^{2,3,4}

STAGE 1	None	No problems with activities of daily living
STAGE 2	Very mild	Forgetting names, trouble finding words
STAGE 3	Mild	Difficulty traveling to new location or dealing with problems
STAGE 4	Moderate	Difficulty with complex tasks i.e. shopping
STAGE 5	Moderately severe	Needs help choosing clothing and prompting to bathe
STAGE 6	Severe	Requires assistance dressing, bathing & toileting
STAGE 7	Very severe	Limited vocabulary, loss of ability to walk and sit, unable to smile

The goal of therapy for patients with Alzheimer Disease is first and foremost to slow progression of the disease, it is also important to lighten the burden placed on caregivers by treating cognitive, behavioral and psychological symptoms.^{7,17} Currently there are two types of drugs that are approved for use in Alzheimer Disease. Three of the drugs are used to treat patients with mild to moderate Alzheimer Disease by increasing acetylcholine levels in the brain, the fourth drug is used to treat patients with moderate to severe Alzheimer Disease by decreasing glutamate levels (glutamate is an excitatory amino acid found in the brain, over stimulation of glutamate receptors leads to toxicity and nerve cell death).^{16,17} None of the four Alzheimer Disease drugs is a cure; they are used to decrease symptoms and slow progression of the disease.^{1,2,3,8,10,13,15,17}

In Alzheimer Disease acetylcholine, a neurotransmitter that is important for memory, undergoes substantial degradation by an enzyme called acetylcholinesterase. Cholinesterase inhibitors are a class of drugs that inhibit the breakdown of acetylcholine by blocking acetylcholinesterase.⁸ Compared to placebo cholinesterase inhibitors have been shown to be effective at improving cognitive function, activities of daily living capability, and behavior.⁸ All three are fairly well tolerated. Donepezil and rivastigmine have been directly compared to one

another and there is no significant difference in efficacy although donepezil has fewer incidences of adverse effects.⁸ Unfortunately there is no evidence that any of the cholinesterase inhibitors can alter the course of the underlying dementia, thus they are not a cure for Alzheimer Disease.^{10,13,15} The efficacy of various treatments is measured using two different scales: Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) which assesses memory, orientation, attention, reasoning, and language, and Clinician’s Interview Based Impression of Change (CIBIC-plus) which evaluates the following four areas: general, cognitive, behavioral and activities of daily living.^{10,13,15,17} Clinical studies have shown that all four drugs approved for use in Alzheimer Disease have statistically significantly improved the above two measures of efficacy as compared to placebo.^{10,13,15,17}

Aricept® or donepezil is a cholinesterase inhibitor that is indicated for mild to moderate Alzheimer Disease.^{9,10} Donepezil reversibly inhibits acetylcholinesterase which results in an increased concentration of acetylcholine that is available for nerve impulses in the brain.^{1,9,10} Orally donepezil is 100% bioavailable. Drug concentrations peak in 3 to 4 hours and it takes 15 days to reach steady state because the half life is 70 hours. Donepezil is 96% bound to plasma proteins. Four metabolites are formed via CYP2D6/3A4 metabolism and 57% of the drug is renally excreted. No dosage adjustments are required for either renal or hepatic impairment.^{9,10} Donepezil is dosed once daily starting with 5mg at bedtime and increasing to 10 mg at bedtime after four weeks.^{1,7,9,10} Common side effects of donepezil (greater than 5%) include: insomnia, nausea, vomiting, diarrhea, dizziness, anorexia, fatigue, headache, and muscle cramps.^{7,8,9,10} A one month supply of donepezil costs approximately \$180.¹⁸ Donepezil is not on the Saskatchewan Drug Formulary but coverage may be obtained pending approval via Exceptional Drug Status (EDS).¹¹

Exelon® or rivastigmine is a cholinesterase inhibitor that is indicated for treatment of mild to moderate Alzheimer Disease.^{12,13} Rivastigmine reversibly inhibits acetylcholinesterase and butyrylcholinesterase.^{1,7,12,13} Rivastigmine is only 40% orally bioavailable. Rivastigmine concentrations peak one hour after administration and the half life is 1.5 hours thus the drug needs to be dosed twice daily. Rivastigmine is 40% bound to plasma proteins. Rivastigmine undergoes minimal metabolism in the liver, it is 97% renally excreted. The initial dose of rivastigmine is 1.5 mg twice daily which should be increased to 3 mg twice daily after one month (the maximum dose is 6 mg twice daily).^{12,13} The most common side effects of rivastigmine (greater than 5%) are more extensive in both number and magnitude than the other two cholinesterase inhibitors: dizziness, headache, nausea, vomiting, diarrhea, anorexia, abdominal pain, fatigue, insomnia, confusion, depression, anxiety, malaise, somnolence, dyspepsia, constipation, urinary tract infection and falls.^{1,7,9,12,13} Rivastigmine has significant gastrointestinal adverse effects, for example 47% of patients develop nausea and 31% of patient experience vomiting.¹³ No dosage adjustment is required in renal or hepatic impairment.¹³ A one month supply of rivastigmine costs about \$750.00.¹⁸ Rivastigmine is not on the Saskatchewan Drug Formulary but coverage may be obtained pending approval via EDS.¹¹

Reminyl*ER or galantamine is a long acting cholinesterase inhibitor that is indicated for the treatment of mild to moderate Alzheimer Disease.^{14,15} Galantamine prevents the breakdown of acetylcholine by inhibiting acetylcholinesterase, it also stimulates nicotinic receptors to release more acetylcholine. Thus the drug has dual mechanisms that work to increase acetylcholine levels in the brain.^{1,7,14,15} Galantamine has an oral bioavailability of 80-100%. Drug concentrations peak one hour after administration, it takes less than 6 days to reach steady state. The half life is 7 hours and the drug is 18% plasma protein bound. Galantamine should be taken in the morning with food. Galantamine is dosed once daily due to the extended release nature of the product formulation. This drug is extensively metabolized in the liver by CYP2D6/3A4 and 25% is excreted in the urine. Dose adjustments are indicated in both hepatic

and renal disease.^{14,15} The initial dose of galantamine is 8 mg daily, the dose can be increased by 8 mg daily every 4 weeks to a maximum daily dose of 24 mg. The most common side effects of galantamine (greater than 5%) are nausea, vomiting, dizziness, headache, anxiety and depression.^{14,15} A one month supply of galantamine costs \$210.00-\$220.00.¹⁸ Galantamine is not on the Saskatchewan Drug Formulary but coverage may be obtained pending approval via EDS.¹¹

Ebixa® or memantine is used to treat moderate to severe dementia by inhibiting the stimulation of receptors in the brain by glutamate thus resulting in decreased nerve cell toxicity and nerve cell death.^{16,17} Memantine does not disrupt normal nerve cell function as it only exerts its inhibitory effect under conditions of excessive glutamate stimulation. Memantine is 100% bioavailable. Peak concentrations are reached after 3 to 7 hours. The half life is 60 to 80 hours, thus steady state concentrations are not reached until day eleven. The drug has been found to be 45 % bound to plasma proteins. Memantine is 57-82% excreted in the urine and dose adjustments are required if the patient has reduced renal function. The initial dose of memantine is 5 mg daily, the dose can be increased by 5 mg each week to a maximum dose of 20 mg daily.^{16,17} The most common side effects of memantine (greater than 5%) are dizziness, confusion, headache, and constipation.^{16,17} A one month supply of memantine 10 mg per day costs \$195.00.¹⁸ Memantine is not on the Saskatchewan Drug Formulary, nor is there EDS criteria.¹¹

The EDS criteria required by Saskatchewan Health is as follows for all cholinesterase inhibitors indicated for treatment of mild to moderate dementia of the Alzheimer type.¹¹ A physician must diagnose Alzheimer Disease using criteria set by the American Psychiatric Association which includes development of memory impairment as well as the loss of word comprehension, muscle coordination and/or the ability to interpret sensory stimuli. Diagnosis also requires a gradual and continual decline in function that results in significant impairment and is not due to any other disease, condition or medication.¹⁹ Furthermore, the patient must not be concurrently taking any other anticholinergic medication.¹¹ Lastly in order for Saskatchewan Health to provide EDS coverage for donepezil, galantamine, or rivastigmine a Mini-Mental State Examination (MMSE) score of 10 to 26²⁰ (Appendix 1), and the completion of a Functional Activities Questionnaire are required. Part one of the MMSE tests vocal responses involving orientation, memory, and attention, while part two of the MMSE tests the patient's ability to name, follow verbal and written commands and to write spontaneous sentences as well as copy a complex polygon. The maximum total score possible is 30.²⁰

Alzheimer Disease is a devastating condition in which a person progressively loses the ability to function independently and self-sufficiently. The cause of Alzheimer Disease is currently unknown thus it is virtually impossible to prevent or cure the disease. There are currently four pharmaceutical agents on the market which target two distinct mechanisms in order to alleviate some of the symptoms of Alzheimer Disease and potentially slow disease progression. A search of the Cochrane Database of Systematic Reviews found one article in which the author has compared the three cholinesterase inhibitors.⁸ The article reviewed numerous studies in the literature that focused on donepezil, rivastigmine, and galantamine versus placebo. One study compared donepezil and rivastigmine. The author concluded that all three acetylcholinesterase inhibitors are effective in reducing the symptoms of Alzheimer Disease. It is difficult to say which agent is the best because there was only one head-to-head trial. However, donepezil and galantamine are both once daily dosing which makes administration simpler and easier. In the trial that compared donepezil and rivastigmine, the two drugs were found to be comparable in efficacy but donepezil had significantly less frequent and less severe side effects.⁸ Patients should not take more than one of donepezil, rivastigmine or galantamine at the same time due to the similarities in mechanism of action. If a patient does not

respond to or cannot tolerate one of the acetylcholinesterase inhibitors then they may be switched to another. Memantine has a completely different mechanism of action so it may be used in combination with any of the other three drugs, however it is not eligible for EDS coverage. Alzheimer Disease is a progressively debilitating disease with no cure. Four drugs (Table 1) are available to assist in reducing progression of the disease and to alleviate symptoms thus improving the quality of life of both the patient and the caregiver.

Table 1 Comparison of available medications for Alzheimer Disease

	Aricept ^{9,10} (Donepezil)	Exelon ^{12,13} (Rivastigmine)	Reminyl ^{14,15} (Galantamine)	Ebixa ^{16,17} (Memantine)
Mechanism of Action	Inhibits acetylcholinesterase	Inhibits acetylcholinesterase	Inhibits acetylcholinesterase	Inhibits N-methyl-D-aspartate type glutamate receptors
Efficacy	Effective in reducing progression and symptoms in mild to moderate Alzheimer Disease	Effective in reducing progression and symptoms in mild to moderate Alzheimer Disease	Effective in reducing progression and symptoms in mild to moderate Alzheimer Disease	Effective in reducing progression and symptoms in moderate to severe Alzheimer Disease
Side effects (≥5%)	Insomnia, nausea, vomiting, diarrhea, dizziness, anorexia, fatigue, headache, and muscle cramps	Dizziness, headache, nausea, vomiting, diarrhea, anorexia, abdominal pain, fatigue, insomnia, confusion, depression, anxiety malaise, somnolence, dyspepsia, constipation, urinary tract infection	Nausea, vomiting, diarrhea, dizziness, headache, depression, fatigue, insomnia, anorexia, weight loss, abdominal pain, flatulence	Dizziness, confusion, headache, constipation
Cost	\$180 per month	\$207-\$750 per month	\$210 - \$220 per month	\$195 per month

Appendix 1 Mini Mental Status Examination²⁰

APPENDIX

Patient.....
Examiner

Date

"MINI-MENTAL STATE"

Maximum
Score Score

ORIENTATION

- 5 () What is the (year) (season) (date) (day) (month)?
5 () Where are we: (state) (county) (town) (hospital) (floor).

REGISTRATION

- 3 () Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he learns all 3. Count trials and record.

Trials

ATTENTION AND CALCULATION

- 5 () Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world" backwards.

RECALL

- 3 () Ask for the 3 objects repeated above. Give 1 point for each correct.

LANGUAGE

- 9 () Name a pencil, and watch (2 points)
Repeat the following "No ifs, ands or buts." (1 point)
Follow a 3-stage command:

"Take a paper in your right hand, fold it in half, and put it on the floor"
(3 points)

Read and obey the following:

CLOSE YOUR EYES (1 point)

Write a sentence (1 point)

Copy design (1 point)

----- Total score

ASSESS level of consciousness along a continuum-----

Alert Drowsy Stupor Coma

INSTRUCTIONS FOR ADMINISTRATION OF MINI-MENTAL STATE EXAMINATION

ORIENTATION

(1) Ask for the date. Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?" One point for each correct.

(2) Ask in turn "Can you tell me the name of this hospital?" (town, county, etc.). One point for each correct.

REGISTRATION

Ask the patient if you may test his memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him to repeat them. This first repetition determines his score (0-3) but keep saying them until he can repeat all 3, up to 6 trials. If he does not eventually learn all 3, recall cannot be meaningfully tested.

ATTENTION AND CALCULATION

Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.

If the patient cannot or will not perform this task, ask him to spell the word "world" backwards. The score is the number of letters in correct order. E.g. dlrow = 5, dlrow = 3.

RECALL

Ask the patient if he can recall the 3 words you previously asked him to remember. Score 0-3.

LANGUAGE

Naming: Show the patient a wrist watch and ask him what it is. Repeat for pencil. Score 0-2.

Repetition: Ask the patient to repeat the sentence after you. Allow only one trial. Score 0 or 1.

3-Stage command: Give the patient a piece of plain blank paper and repeat the command. Score 1 point for each part correctly executed.

Reading: On a blank piece of paper print the sentence "Close your eyes", in letters large enough for the patient to see clearly. Ask him to read it and do what it says. Score 1 point only if he actually closes his eyes.

Writing: Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence, it is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.

Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 in., and ask him to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

Estimate the patient's level of sensorium along a continuum, from alert on the left to coma on the right.

References

1. National Institute for Health. 1 June 2006 <www.nia.nih.gov/Alzheimers/>.
2. Alzheimer's Association. 1 June 2006 <www.alz.org>.
3. Young, Koda-Kimble. Applied Therapeutics: The Clinical Use of Drugs. 6th ed.
4. Alzheimer Society of Canada. 1 June 2006 <www.alzheimers.ca>.
5. "Experimental Alzheimer Drugs Targeting Beta-Amyloid and the "Amyloid Hypothesis""
Alzheimer's Association. 1 June 2006 <www.alz.org>.
6. McGill University. 9 June 2006
<http://www.thebrain.mcgill.ca/flash/i/i_01/i_01_m/i_01_m_ana/i_01_m_ana.html>
7. Canadian Pharmacists Association. "Therapeutic Choices." Dementias. 2005. 31-41.
8. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD0055593. DOI: 10.1002/14651858.CD005593.
9. Lexi-Comp (Lexi-Drugs – Donepezil) [computer program]. Lexi-Comp; April 18, 2006.
10. *Aricept®*, *donepezil hydrochloride*. [product monograph]. Kirkland (QC): Pfizer Canada, 2005 July 5.
11. Saskatchewan Health. Formulary. July 2005. 1 June 2006
<<http://formulary.drugplan.health.gov.sk.ca>>.
12. Lexi-Comp (Lexi-Drugs – Rivastigmine) [computer program]. Lexi-Comp; April 18, 2006.
13. *Exelon®*, *rivastigmine tartarate*. [product monograph]. East Hanover (NJ): Novartis, 2005 October.
14. Lexi-Comp (Lexi-Drugs – Galantamine) [computer program]. Lexi-Comp; April 18, 2006.
15. *Reminyl**, *galantamine hydrobromide extended release capsule*. [product monograph]. Toronto (ON): Janssen-Ortho Inc, 2001 July 19.
16. Lexi-Comp (Lexi-Drugs – Memantine) [computer program]. Lexi-Comp; April 18, 2006.
17. *Ebixa®*, *memantine*. [product monograph]. Denmark: Lundbeck, 2002.
18. Stueck Pharmacy, Leader, SK. Retail Drug Prices.
19. American Psychiatric Association, "The diagnostic and Statistical Manual." Criteria for Diagnosis of Dementia of the Alzheimer's Type.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.