Agents Used in the Treatment of Alzheimer's Disease
Monograph
July 2011

Introduction:[1-6]

Alzheimer's disease, the most common form of dementia, currently affects an estimated 5.4 million Americans of all ages.[1] Sixty to eighty percent of all dementia cases are diagnosed as Alzheimer's disease. According to 2000 Census data, 90% percent of all cases of Alzheimer's exist in patients 75 years or older and roughly two-thirds of all Americans with Alzheimer's are women.[2] The cause of Alzheimer's is not definitely known. Alzheimer's is distinguished from other forms of dementia by the accumulation of the protein beta-amyloid outside nerve cells (neurons) in the brain and protein tau inside neurons. The most trademark clinical sign of Alzheimer's disease is the gradual decline in the ability to remember new information due to disruption of brain cell function that commonly begins in regions of the brain involved in forming new memories. As the damage spreads to other parts of the brain, motor ability, speech, senses, and emotions can be adversely affected.

Risk factors for Alzheimer's includes age (>64 years of age), family history, genetics, history of head trauma or injury, and existing cognitive impairment. The number of deaths due to Alzheimer's disease has increased by 66% between 2000 and 2008. In 2007, Alzheimer's disease was listed as the fifth leading cause of death in adults age 65 years or older.[3] Current Healthy People 2020 goals for dementia, including Alzheimer's, is to increase the proportion of patients who are aware of their dementia diagnosis and to decrease the proportion of preventable hospitalizations in patients with known Alzheimer's disease and other dementias.[4]

Very little is known about the prevalence and incidence of Alzheimer's disease in the American Indian and Alaska native population as only few population studies have been performed regarding this disease state. As life expectancy in the Native population increases, the new cases of Alzheimer's disease are expected to increase. In a study comparing 65 year and older Cree Indians to Caucasians in Winnipeg, investigators found a 0.5% rate of Alzheimer's in the Cree Indians compared to a 3.5% rate in the English group.[5] According to the IHS Division of Program Statistics, the American Indian/Alaska Native age-adjusted death rates for Alzheimer's disease for years 2002-2004 is one-half that of the all-race rate in the United States.[6] Currently, there is no treatment available to cure or stop the progression of the disease; however, there are medications available to slow the worsening of brain deterioration and help preserve brain function.

Pharmacology/Pharmacokinetics: [7-11]

Cholinesterase Inhibitors

As discussed in the introduction, hallmark pathophysiology of Alzheimer's disease involves a deficit in neural acetylcholine production/action. Due to this pathophysiology, cholinesterase inhibitors are considered first-line therapy for Alzheimer's disease.

There are currently three available cholinesterase inhibitors approved for treatment of Alzheimer's disease. Tacrine is also classified as a cholinesterase inhibitor, but due to tolerability issues, it is not marketed for use in Alzheimer's disease.

Mechanisms of Action:
Aricept (donepezil)**:** reversibly and noncompetitively inhibits centrally-active acetylcholinesterase, thus resulting in increased availability of neuronal acetylcholine.

Razadyne (galantamine): reversible and competitive inhibitor of central acetylcholinesterase. In addition, galantamine also stimulates central nicotinic acetylcholine receptors and may affect glutamine and serotonin levels.

Exelon (rivastigmine): reversible inhibitor of neural acetylcholinesterase.

Table 1: Pharmacokinetics of Cholinesterase Inhibitors

Drug	Absorption	Distribution	Metabolism	Elimination
Donepezil	Well absorbed orally 100% bioavailable Time to peak: 10 hours for 10 mg tablet.	Vd: 12-16 L/kg 96% protein bound (75% to albumin, 21% to alpha$_1$-acid glycoprotein)	CYP2D6 and 3A4 to four metabolites, two of which are active; hepatic glucuronidation	Half-life: 70 hours; 15 days to steady state 57% Urine (17% as unchanged drug) 15% fecally
Galantamine	Rapid and complete with ~90% bioavailability Time to peak: 1 hour for immediate release tablet (2.5 hours if taken with food), 4-5.5 hours for extended release formulation	Vd: ~175 L, Levels in brain are 2-3 times higher than plasma 18% protein bound	CYP2D6 and 3A4 including 2 mildly active metabolites (metabolite activity 130 times less than parent compound) Linear kinetics	Half-life: 7 hours 25% eliminated by urine
Rivastigmine	Rapid and complete within 1 hour if fasting 36%-40% bioavailablity Time to peak: 1 hour if given po; 10-16 hours transdermally following first dose	Vd: 1.8-2.7 L/kg CSF levels are ~40% if serum levels	Primarily central cholinesterase-mediated hydrolysis Metabolite undergoes N-demethylation and/or hepatic sulfate conjugation Linear kinetics at doses up to 3 mg twice daily; non-linear kinetics at higher doses	Half-life: 1.5 hours oral; 3 hours for transdermal Primarily as urine (97% as metabolites); 0.4% eliminated fecally

NMDA Antagonists
Research into the pathophysiology of Alzheimer's disease suggests that, in addition to the role of acetylcholine, glutamate may also be involved in the disease progression of Alzheimer's. The mechanism for this progression involves stimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate causing a long-term influx of calcium into the neuron. Inhibition of this calcium influx is thought to possibly slow the progression of Alzheimer's-induced dementia. Targeting this mechanism is the lone agent in the NMDA antagonist class, Namenda (memantine).

Mechanism of Action
Memantine is an uncompetitive antagonist at the N-methyl-D-aspartate subgroup of glutamate receptors. NMDA receptor ion channels, in the inactivated, non-stimulated state, are normally blocked by magnesium ions until stimulated by glutamate. Upon glutamate stimulation, magnesium is displaced and calcium may freely flow into the neuron. Memantine binds to the intra-pore Mg site thus preventing calcium influx during abnormal glutamate stimulation. Memantine does not interfere with normal glutamate function.

Memantine also shows low to negligible affinity for GABA, benzodiazepine, dopamine,

adrenergic, histamine and glycine receptors and for voltage-dependent Ca2+, Na+ or K+ channels. Memantine also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

Pharmacokinetics:
Absorption: Well absorbed with peak concentrations reached in 3-7 hours.
Distribution: Vd=9-11 L/kg, 45% plasma protein bound.
Metabolism: Memantine does not undergo significant metabolism by CYP450 enzymes. Various hepatic conjugations form three different metabolites with minimal activity.
Elimination: Urine (74%, 48% as unchanged drug; undergoes active tubular secretion moderated by pH-dependent tubular reabsorption; excretion reduced by alkaline urine pH)

FDA Approved Indications:[7-10]

Donepezil:

Treatment of mild, moderate, or severe dementia of the Alzheimer's type

Galantamine:

Treatment of mild-to-moderate dementia of Alzheimer's disease.

Rivastigmine:

Treatment of mild-to-moderate dementia associated with Alzheimer's disease or Parkinson's disease.

Memantine:

Treatment of moderate to severe dementia of Alzheimer's type.

Current National Core Formulary Alternatives: [12]

There are currently no agents on the National Core Formulary (NCF) that are FDA-approved for treatment of Alzheimer's disease.

Dosage and Administration: [7-10, 13-16]

Dosages Available
Donepezil: Tablets: 5 mg, 10 mg, 23 mg; ODT: 5 mg and 10 mg

Galantamine: Immediate release tablets: 4 mg, 8 mg, 12 mg; Extended release capsules: 8 mg, 16 mg, 24 mg; Oral solution: 4 mg/mL

Rivastigmine: Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg; Oral solution: 2 mg/mL with dosing syringe included; Transdermal patch: 4.6 mg/24 hours, 9.5 mg/24 hours

Memantine: Tablets: 5 mg, 10 mg, a titration pack is also available that contains a combination of both strengths; Oral solution: 2 mg/mL; an extended release capsule for once-daily administration has been approved, but availability has yet to be determined.

Administration

Donepezil: Take once daily in the evening without regard to meals. The 23 mg tablet should not be split, crushed, or chewed due to an increase in rate of absorption. ODT should be placed on tongue, allowed to dissolve, and followed with water.

Galantamine: Immediate release oral formulation to be taken with food in two daily doses. Extended release capsules should be taken once daily with morning meal. Patients and caregivers should be instructed on proper administration of liquid formulation (refer to instruction sheet included in product packaging).

Rivastigmine: Oral formulations should be taken with food in divided doses. Patients and caregivers should be educated in the use of the included syringe for the liquid formulation; liquid may be mixed in other beverage, but should be consumed within 4 hours. Patch should be placed for 24 hours on upper or lower back, chest, or upper arm. Rotate application sites and do not use the same site twice in less than 14 days.

Memantine: May be taken without regard to meals; XR capsule may be taken whole or sprinkled over food and taken by mouth without chewing; the package insert does not prohibit the splitting of memantine tablets.

Target Dose

Donepezil:

Mild to Moderate Alzheimer's: 5 mg-10 mg daily

Moderate to Severe Alzheimer's: 10 mg-23 mg daily

Dose should be titrated starting at 5 mg daily x 4-6 weeks, then may be increased to 10 mg daily if needed. If the 23 mg dose is desired, patents should be on the 10 mg daily dose for a minimum of 3 months

Galantamine:

Mild to Moderate Alzheimer's: Extended release: Start at 8 mg/day x 4 weeks. Dose may be titrated to a target dose of 16 mg-24 mg daily by increasing daily dose by 8 mg every 4 weeks.

Immediate release and liquid: Start with 4 mg given BID for a minimum of 4 weeks, after which the dose may be increased to the minimum effective dose of 8 mg BID. Dose may be further increased (if needed) to 12 mg BID after 4 weeks of taking the 16 mg daily dose.

Rivastigmine:

Mild to Moderate Alzheimer's: Start at 1.5 mg BID. If this dose is well tolerated, after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. Max dose is 12 mg daily.

Mild to Moderate Dementia associated with Parkinson's: starting dose of Exelon is 1.5 mg BID; subsequently, the dose may be increased to 3 mg BID and further to 4.5 mg BID and 6 mg BID, based on tolerability, with a minimum of 4 weeks at each dose.

Memantine:

Moderate to Severe Alzheimer's: The recommended starting dose of Namenda is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

Special Populations

Pregnancy

Donepezil: Category C
Galantamine: Category B
Rivastigmine: Category B
Memantine: Category B

Hepatic

Donepezil:

In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Galantamine:

Moderate liver dysfunction (Child-Pugh score 7-9): Maximum dose: 16 mg/day
Severe liver dysfunction (Child-Pugh score 10-15): Use is not recommended.

Rivastigmine:

Clearance is significantly reduced in mild to moderately impaired patients. Although dosage adjustments are not recommended, use lowest possible dose and titrate according to individual's tolerance. Consider intervals of >2 weeks between dosage adjustments.

Memantine: No dosage adjustments needed. Use caution with severe disease.

Renal

Donepezil:

In a study of 11 patients with moderate to severe renal impairment (Cl_C < 18 mL/min/1.73 m^2) the clearance of donepezil did not differ from 11 age- and sex-matched healthy subjects.

Galantamine:

Moderate renal impairment: Maximum dose: 16 mg/day.
Severe renal dysfunction (Cl_{cr} <9 mL/minute): Use is not recommended

Rivastigmine:

Dosage adjustments are not recommended; however, titrate the dose to the individual's tolerance.

Memantine:

Mild-Moderate impairment: No adjustment required.
Severe impairment: Cl_{cr} 5-29 mL/minute: Immediate release: Initial: 5 mg once daily; after at least 1 week of therapy and if tolerated, may titrate up to 5 mg twice daily; Extended release: Target dose of 14 mg/day

Meta-analyses & Systematic Reviews:

In March, 2011, an updated systematic review of the agents used in the treatment of Alzheimer's disease by the National Institute of Clinical Excellence (NICE) was published. [17] This document reviewed the data released after its initial appraisal of the topic in 2006 and focused on randomized clinical trials for donepezil, galantamine, rivastigmine and memantine. Pooled data from 12 trials comparing donepezil to placebo showed a statistically significant improvement in MMSE score from baseline for donepezil at 12 and 24 weeks (1.165, p<0.001; 1.206, p<0.001). Similar numbers were seen with galantamine versus placebo with statistically signification functional benefit with the galantamine arm at 12-13 and 21-26 weeks using the Alzheimer's Disease Cooperative Study-

Activities of Daily Living (ADCS-ADL) scale (1.394, p<0.001; 2.234, p<0.001). Pooled multiple outcome measure analysis showed statistically significant improvements in function with galantamine versus placebo. Pooled data for rivastigmine versus placebo, revealed statistically significant improvements in cognition as measured by MMSE and ADAS-cog score respectively at 24-26 weeks (1.022, p<0.001; -2.44, p<0.001). They noted a high number of adverse effects, primarily gastrointestinal, but noted reduced adverse effects with the 9.5mg/day patch versus the 12mg capsule. This review recognized 4 head-to-head randomized clinical trials (RCT), but considered only one (donepezil versus rivastigmine) to be sufficient quality for inclusion. The included study found no statistically significant difference between the two products at 2 years for cognitive outcomes (MMSE and SIB) behavioral outcomes (NPI). However, a statistically significant difference was seen with rivastigmine for functional outcomes (p=0.007-0.047) and global outcomes (GDS). For memantine versus placebo, the pooled data for cognitive measure using SIB reported statistically significant benefit at 12 weeks, but was not maintained at 24-48 weeks. For functional outcomes measured by ADCS-ADL19, the results were not statistically significant at 12 weeks, but modestly significant at 24-28 weeks (0.877, p<0.075; 1.408, p=0.044). When adding memantine to AChE, pooled data did not show additional benefit from the combination. The guidance did note a lack of robust evidence, especially with respect to head-to-head trials and that important gaps remain.

Overall, this guidance concluded that "each of the AChE inhibitors offers benefits over best supportive care, for cognitive, functional and global outcomes, although the nature and extent of behavioral benefits are uncertain owing to mixed results from available evidence" and the data is insufficient to detect differences between products clinically. The guidance also noted no effect on survival with AChE use based on available data. It was noted that the rivastigmine patches reduced the adverse effects as compared to oral capsules. For memantine, the guidance noted benefit in cognitive, functional, global and behavioral outcomes, as well as "NPI score on agitation, aggression and/or psychotic symptoms." The guidance concluded "combination treatment with memantine and AChE inhibitors could not be recommended because of a lack of evidence of additional clinical efficacy compared to memantine monotherapy."

Note: Pooled data includes 2006 guidance data plus data from trials published since 2006 document

A Cochrane systematic review of rivastigmine in Alzheimer's disease was published in 2009 by Birks and colleagues.[18] The goal of this review was to determine the safety and efficacy of rivastigmine from the available data. Nine (9) trials (published and unpublished), with 4775 patients, were included in this review. Benefit was seen with high dose rivastigmine (6-12mg daily) versus placebo with cognitive function via the ADAS-Cog score (-1.99, 95% CI -2.49 t0 -1.50) and with ADL via the PDS (-2.15, 95% CI -3.16 to -1.13) at 26 weeks. Statistically significant differences were seen with cognitive function for low dose rivastigmine as compared to placebo. Adverse effects were significantly higher than placebo, but some evidence suggests reduced adverse effects with lower, but more frequent dosing. Additionally, data for each patch was reviewed finding the lower dose patch (9.6mg/day) was as effective as the higher dose patch (17.4mg/day) and similarly dosed capsules, but had lower adverse events.

In 2009, Rodda and colleagues published a systematic review of RCT to assess the efficacy of the AChE inhibitor agents in the treatment of behavioral and psychological symptoms (BPSD) in Alzheimer's disease.[19] Fourteen studies met their criteria for inclusion. Most studies focused on cognitive function, with few studies looking specifically at individual behavioral symptoms indicating an area for future study in the future. Three (3) of 14 studies showed improvement in overall NPI score or in the agitation/aggression item of NPI (donepezil, 2 studies; galantamine, 1 study). The authors conclude that the evidence for AChE inhibitors for BPSD is modest, but due to a "lack of safe

and effective alternative options, a trial of a cholinesterase inhibitor is an appropriate pharmacological strategy in the management of PBSD in Alzheimer's disease and may be suitable as first line pharmacotherapy."

A systematic review and meta-analysis was published in 2008 by Hansen and colleagues, to assess the safety and efficacy of cholinesterase inhibitors in Alzheimer's disease.[20] They analyzed data from 26 studies, 22 of which were RCT. The ADAS-Cog score was used for assessment of cognition with 14 trails reporting this outcome, MMSE for function, NPI for behavior and CIBIC+ for global assessment of change. Pooled weighted difference between active agents versus placebo revealed:

- **Cognition:** -2.67 (95% CI, -3.28 to -2.06) for donepezil, -2.76 (95% CI, -3.17 to -2.34) for galantamine and -3.01 (95% CI, -3.80 to -2.21) for rivastigmine. Fourteen studies assessed cognition.
- **Function:** 0.31 (95% CI, 0.21 to 0.4) for donepezil, 0.27 (95% CI, 0.18 to 0.26) for galantamine and 0.26 (95% CI 0.11 to 0.40) for rivastigmine. Fourteen studies assessed function.
- **Behavior:** -4.3 (95% CI, -5.95 to -2.65) for donepezil and -1.44 (95% CI, -2.39 to -0.48) for galantamine. Seven studies were assessed, with no articles for rivastigmine.
- **Global assessment of change:** RR 1.88 (95% CI, 1.50 to 2.34) for donepezil, 1.15 (95% CI, 0.96 to 1.39) for galantamine and 1.64 (95% CI, 1.29 to 2.09) for rivastigmine. Nine studies were included.

As previously mentioned, head-to-head data is limited, but this review included 2 trials comparing donepezil with galantamine and 2 trials comparing donepezil to rivastigmine. Only one was randomized. Adjusted indirect comparisons revealed less deterioration in behavior with donepezil versus galantamine ($p=0.003$) and global assessment favored donepezil and rivastigmine versus galantamine (RR=1.63, $p<0.005$; RR 1.42, $p<0.05$). Overall adverse effect frequency was lowest with donepezil and highest with rivastigmine. The authors concluded, "no clear evidence exists to determine whether one of these drugs is more efficacious than another, although adjusted indirect comparisons suggest that donepezil and rivastigmine may be slightly more efficacious than galantamine, at least as reflected by some outcome measures" and that "common adverse events appears to be lowest with donepezil and highest with rivastigmine."

A Cochrane systematic review of memantine for dementia was published in 2006 (updated 2009) by McShane et al.[22] This review identified 12 trials that met the pre-defined criteria being RCT that were double-blind, placebo controlled for patients with dementia and included memantine as the active agent. Three trials were in moderate to severe Alzheimer's disease at 24-28 weeks using memantine 20mg/day. The SIB was used to assess cognition, NPI for behavior, ADCS-ADL for function and CIBIC+ for global assessment. The data revealed:

- **Cognition:** memantine group improved 2.97 points (95% CI, 1.68 to 4.26; $p <0.00001$)
- **Function:** memantine group improved 1.27 points (95% CI, 0.44 to 2.09; $p<0.003$)
- **Behavior:** Less worsening of mood and behavior with memantine group, 2.76 points (95% CI, 0.88 to 4.63; $p<0.004$). Agitation occurred less in memantine group, OR 0.6 (95% CI, 0.42 to 0.86; $p=0.005$)
- **Global assessment of change:** 0.28 points (95% CI, 0.15 to 0.41, $p<0.0001$) in favor of memantine group

Three trials included patients with mild to moderate Alzheimer's disease with memantine 20mg/day or placebo at 24 weeks. These data revealed:

- **Cognition:** 0.99 points (95% CI, 0.21 to 1.78; $p=0.01$)
- **Function:** non-significant findings, 0.20 points (95% CI, -0.87 to 21.27, $p=0.72$)
- **Behavior:** non-significant findings, -0.25 points (95% CI, -1.48 to0.98; $p=0.69$)

- **Global assessment of change:** modest improvement with memantine group, 0.13 points (95% CI, 0.01 to 0.25; p=0.03)

Adverse events were assessed for the moderate to severe and the mild to moderate groups with memantine being well tolerated.

The authors concluded that "memantine 20mg/day caused clinically noticeable reduction in deterioration over 28 weeks" in moderate to severe Alzheimer's disease based upon function and cognitive measures. These patients also were less likely to become agitated. Patients receiving 20mg/day for mild to moderate disease had less deterioration at 28 weeks, but overall, the data would only justify use in those with moderate to severe dementia.

A Cochrane systematic review of cholinesterase inhibitors in Alzheimer's disease was originally published by Birks in 2006 with edits (no changes in conclusions) published in 2009.[23] This review included 10 randomized, double-blind, placebo controlled trials that were 6 months in duration. Similar to those previously noted above, this review noted improvements in cognitive function, ADL and behavior for patients receiving active agent. Adverse events were noted more frequently in those receiving AChE inhibitors with fewer noted with donepezil than rivastigmine. The authors concluded that all three AChE inhibitors are efficacious in mild to moderate disease with no difference between products in efficacy.

In 2006, a Drug Effectiveness Research Project (DERP) drug class review on Alzheimer's drugs was published by the Oregon Health & Science University, Center for Evidence-Based Policy.[24] The writing group sought to answer key questions regarding donepezil, galantamine, rivastigmine, tacrine and memantine alone or in combination:

-Data was insufficient to draw conclusions about effectiveness comparing one product to the others. Overall, the AChE inhibitors are "modestly effective in reducing the rate of decline in cognition" with a NNT to yield one global responder of 12 and NNT to yield a cognitive response, 10. They noted some benefit on symptom stabilization, behavior and functional status. Data for memantine showed improved cognitive symptoms, daily function and caregiver dependence as compared to placebo. When added to donepezil, benefit was seen in function, behavior and caregiver dependence versus placebo.
-Similar to other systematic reviews, this review noted a relatively high overall incidence of adverse events with these medications, but the data was insufficient to compare the incidence of specific adverse events between the different drugs. The AChE inhibitors tended to having higher incidence of vomiting and nausea, with the highest rates associated with rivastigmine. Memantine adverse events were relatively low.
-Little data was available to assess age. However, subgroup analysis of pooled rivastigmine use reported greater benefit in patients older than 75 years.
-Little data was available to fully assess race as the majority of available clinical trials were conducted in the Caucasian population. One study reported some pooled non-Caucasian data, but no difference in response between populations.
-No studies specifically looked gender, but most studies included more females than males. No conclusions were drawn from the available information.

<u>Adverse Events:</u> [7-10]

Donepezil:

>10%:

Central nervous system: Insomnia (2% to 14%)

Gastrointestinal: Nausea (3% to 19%; dose related), diarrhea (5% to 15%; dose related)

Miscellaneous: Accident (7% to 13%), infection (11%)

1% to 10%:

Cardiovascular: Hypertension (3%), chest pain (2%), hemorrhage (2%), syncope (2%), hypotension, atrial fibrillation, bradycardia, ECG abnormal, edema, heart failure, hot flashes, peripheral edema, vasodilation

Central nervous system: Headache (3% to 10%), pain (3% to 9%), fatigue (1% to 8%), dizziness (2% to 8%), abnormal dreams (3%), hostility (3%), nervousness (1% to 3%), hallucinations (3%), depression (2% to 3%), confusion (2%), emotional lability (2%), personality disorder (2%), fever (2%), somnolence (2%),

Dermatologic: Bruising (4% to 5%), eczema (3%), pruritus, rash, skin ulcer, urticaria

Endocrine & metabolic: Dehydration (1% to 2%), hyperlipemia (2%), libido increased

Gastrointestinal: Anorexia (2% to 8%), vomiting (3% to 9%; dose related), weight loss (3% to 5%; dose related), abdominal pain, bloating, constipation, dyspepsia, epigastric pain, fecal incontinence, gastroenteritis, GI bleeding, toothache

Genitourinary: Urinary frequency (2%), urinary incontinence (1% to 3%), cystitis, hematuria, glycosuria, nocturia, UTI

Hematologic: Contusion (≤2%), anemia

H*epatic*: Alkaline phosphatase increased

Neuromuscular & skeletal: Muscle cramps (3% to 8%), back pain (3%), CPK increased (3%), arthritis (1% to 2%), ataxia, bone fracture, gait abnormal, lactate dehydrogenase increased, paresthesia, tremor, weakness (1% to 2%)

Ocular: Blurred vision, cataract, eye irritation

Respiratory: Bronchitis, cough increased, dyspnea, pharyngitis, pneumonia, sore throat

Miscellaneous: Diaphoresis, fungal infection, flu symptoms, wandering

Galantamine:

>10%:

Gastrointestinal: Nausea (6% to 24%), vomiting (4% to 13%), diarrhea (6% to 12%)

1% to 10%:

Cardiovascular: Bradycardia (2% to 3%), syncope (0.4% to 2.2%: dose related), chest pain (≥1%)

Central nervous system: Dizziness (9%), headache (8%), depression (7%), fatigue (5%), insomnia (5%), somnolence (4%)

Gastrointestinal: Anorexia (7% to 9%), weight loss (5% to 7%), abdominal pain (5%), dyspepsia (5%), flatulence (≥1%)

Genitourinary: UTI (8%), hematuria (<1% to 3%), incontinence (≥1%)

Hematologic: Anemia (3%)

Neuromuscular & skeletal: Tremor (3%)

Respiratory: Rhinitis (4%)

Rivastigmine:

>10%:

Central nervous system: Dizziness (2% to 21%), headache (3% to 17%)

Gastrointestinal: Nausea (7% to 47%), vomiting (6% to 31%), diarrhea (5% to 19%), anorexia (3% to 17%), abdominal pain (1% to 13%)

1% to 10%:

Cardiovascular: Syncope (3%), hypertension (3%)

Central nervous system: Fatigue (2% to 9%), insomnia (1% to 9%), confusion (8%), depression (4% to 6%), anxiety (2% to 5%), malaise (5%), somnolence (4% to 5%), hallucinations (4%), aggressiveness (3%), parkinsonism symptoms worsening (2% to 3%), vertigo (≤2%)

Gastrointestinal: Dyspepsia (9%), constipation (5%), flatulence (4%), weight loss (3% to 8%), eructation (2%), dehydration (2%)
Genitourinary: Urinary tract infection (1% to 7%)
Neuromuscular & skeletal: Weakness (2% to 6%), tremor (1%; up to 10% in Parkinson's patients)
Respiratory: Rhinitis (4%)
Miscellaneous: Diaphoresis (4%), flu-like syndrome (3%)

Memantine:

1% to 10%:

Cardiovascular: Hypertension (4%), hypotension (2%), cardiac failure, cerebrovascular accident, syncope, transient ischemic attack
Central nervous system: Dizziness (5% to 7%), confusion (6%), headache (6%), anxiety (4%), depression (3%), hallucinations (3%), pain (3%), somnolence (3%), fatigue (2%), aggressive reaction (1% to 2%), ataxia, vertigo
Dermatologic: Rash
Gastrointestinal: Constipation (3% to 5%), diarrhea (5%), weight gain (3%), vomiting (2% to 3%), abdominal pain (2%), weight loss
Genitourinary: Urinary incontinence (2%), micturition
Hematologic: Anemia
Hepatic: Alkaline phosphatase increased
Neuromuscular & skeletal: Back pain (3%), hypokinesia
Ocular: Cataract, conjunctivitis
Respiratory: Cough (4%), dyspnea (2%), pneumonia
Miscellaneous: Influenza (4%)

Precautions/Contraindications: [7-10]

Donepezil:

Contraindications: hypersensitivity to donepezil, piperidine derivatives, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Anorexia/weight loss: May cause anorexia and/or weight loss (dose-related).
• GI effects: May cause dose-related diarrhea, nausea, and/or vomiting; usually resolves in 1-3 weeks.
• Vagotonic effects: Cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease; syncopal episodes have been associated with donepezil.

Disease-related concerns:

• Cardiac conduction abnormalities: Use with caution in patients with sick-sinus syndrome, bradycardia, or conduction abnormalities. Alzheimer's treatment guidelines consider bradycardia to be a relative contraindication for use of centrally-active cholinesterase inhibitors.
• Peptic ulcer disease: Use with caution in patients at risk of ulcer disease (eg, previous history or NSAID use); cholinesterase inhibitors may increase gastric acid secretion. Monitor for symptoms of bleeding.
• Respiratory disease: Use with caution in patients with COPD and/or asthma.

• Seizure disorder: Use with caution in patients with a history of seizure disorder; cholinomimetics may potentially cause generalized seizures, although seizure activity may also result from Alzheimer's disease.

• Urinary tract obstruction: Use with caution in patients with bladder outlet obstruction or prostatic hyperplasia; cholinomimetics may cause or worsen outflow obstructions, including possible exacerbation of BPH symptoms.

Concurrent drug therapy issues:

• Depolarizing neuromuscular-blocking agents: May exaggerate neuromuscular blockade effects of depolarizing neuromuscular-blocking agents (eg, succinylcholine).

Galantamine:

Contraindications:

Hypersensitivity to galantamine or any component of the formulation
Severe liver dysfunction (Child-Pugh score 10-15)
Severe renal dysfunction (Cl_{cr} <9 mL/minute)

Same precautions as stated above for donepezil

Rivastigmine:

Contraindications:

Hypersensitivity to rivastigmine, other carbamate derivatives (eg, neostigmine, pyridostigmine, physostigmine), or any component of the formulation

Same precautions as listed for donepezil with addition of:

Special populations:

• Low body weight (<50 kg): Use caution due to increased risk of adverse reactions.

Other warnings/precautions:

• Appropriate use: Post-market cases of overdose (including a few fatalities) have been reported in association with medication errors/improper use of rivastigmine transdermal patches. No more than 1 patch should be applied daily and existing patch must be removed prior to applying new patch.

• Initiation/interruption of therapy: Should be started at lowest dose and titrated; if treatment is interrupted for more than several days, reinstate at the lowest daily dose.

Memantine:

Contraindications:

Hypersensitivity to memantine or any component of the formulation

Warnings/Precautions

Disease-related concerns:

• Cardiovascular disease: Use with caution in patients with cardiovascular disease; although adverse cardiac events were infrequent in clinical trials, an increased incidence of cardiac failure, angina, bradycardia, and hypertension (compared with placebo) was observed.

• Hepatic impairment: Use with caution in patients with severe hepatic impairment.

• Ophthalmic disease: Worsening of corneal condition has been observed in a clinical trial; periodic ophthalmic exams during use are recommended (Canadian labeling).
• Renal impairment: Use with caution in patients with moderate-to-severe renal impairment; dose adjustments may be required.
• Seizure disorder: Use with caution in patients with a history of seizure disorder; may increase risk of seizures.

Other warnings/precautions:

• Urine pH: Clearance is significantly reduced by alkaline urine; use caution with medications, dietary changes, or patient conditions which may alter urine pH.

Look-alike/Sound-alike Error Risk Potential: [7-10]

Donepezil:

Aricept® may be confused with AcipHex®, Ascriptin® and Azilect®

Galantamine:

Razadyne® may be confused with Rozerem™
Reminyl® may be confused with Amaryl®, Robinul®
Due to patient safety concerns regarding prescribing and dispensing errors between Reminyl® and Amaryl®, Reminyl® (galantamine) is being renamed to Razadyne® (immediate-release) and Razadyne® ER (extended-release). The brand name Reminyl® was discontinued with the July, 2005 distribution of Razadyne®.

Rivastigmine:

None documented

Memantine:

Memantine may be confused with mesalamine

FDA Risk Evaluation and Mitigation Strategy (REMS): [25]

There are currently no REMS requirements for any agent in this class.

Drug Interactions: [7-10, 13]

Donepezil:

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Management: Upon completion/discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates. Risk D: Consider therapy modification

Succinylcholine: Acetylcholinesterase Inhibitors may increase the serum concentration of Succinylcholine. Management: Consider alternatives to this combination due to a risk of prolonged neuromuscular blockade. Risk D: Consider therapy modification

Herb/Nutraceutical: St John's wort may decrease donepezil levels. Ginkgo biloba may increase adverse effects/toxicity of acetylcholinesterase inhibitors. Galantamine:

Succinylcholine: Acetylcholinesterase Inhibitors may increase the serum concentration of Succinylcholine. Management: Consider alternatives to this combination due to a risk of prolonged neuromuscular blockade. Risk D: Consider therapy modification

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Management: Upon completion/discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates. Risk D: Consider therapy modification

Herb/Nutraceutical: St John's wort may decrease galantamine serum levels; avoid concurrent use.

Rivastigmine:

Succinylcholine: Acetylcholinesterase Inhibitors may increase the serum concentration of Succinylcholine. Management: Consider alternatives to this combination due to a risk of prolonged neuromuscular blockade. Risk D: Consider therapy modification

Memantine:

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of memantine.

Conclusions:

AChE agents show improvement in cognition, function and behavior, but the data is inconclusive to identify a clinically superior product within the AChE class. Donepezil is FDA approved for mild to moderate and moderate to severe Alzheimer's disease and was well tolerated in studies. Memantine provides an alternative mechanism for the treatment of Alzheimer's disease. Memantine is indicated for moderate to severe Alzheimer's disease and shows benefit in cognitive, function and behavior, but did not show additive benefits when added to donepezil.

Recommendations:

Based upon these findings, it is recommended that an AChE be added to the NCF based upon its place in therapy as a first line agent in the management of Alzheimer's disease. Donepezil may be a reasonable option if a specific agent is named to the IHS NCF because of its use in mild, moderate and severe Alzheimer's disease and adverse effect profile. While memantine has a specific place in therapy, it would not be recommended to add memantine at this time as it does not meet the usual NCF criteria.

Acronyms:

AChE	Acetylcholinesterase
NICE	National Institute of Clinical Excellence
ADAS-Cog	Alzheimer's Disease Assessment Scale
MMSE	Mini Mental State Examination
CAS	Caregiver Activity Survey
NPI	Neuropsychiatric Instrument
GDS	Global Deterioration Scale
CIBIC-Plus	Clinician's Interview-Based Impression of Change scale
PDS	Progressive Deterioration Scale
ADCS-ADL	Alzheimer's Disease Cooperative Study activities of daily living
SIB	Severe Impairment Battery
CGIC	Clinical Global Impression of Change
WMS-R	Revised Wechsler Memory Scale
BPSD	Behavioral and Psychological Symptoms of Dementia

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Note: Information within this document is current as of this writing and should not replace clinical judgment

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