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Drugs for Cognitive Loss and Dementia

Revised 10/16/17: See page 160

Alzheimer's disease (AD) is the most common cause of dementia, but cognitive loss is also associated with other neurological conditions such as Parkinson's disease, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia.

Mild cognitive impairment (MCI) is generally defined as cognitive decline that is greater than expected for an individual's age and education, but does not interfere with activities of daily living (ADLs); it may be a transitional state between the cognitive changes of normal aging and dementia. No drugs are approved for treatment of MCI.

Treatment of reversible dementia due to drug toxicity, infection, or metabolic disorders is not included here.

NONPHARMACOLOGIC INTERVENTIONS

Patients with AD should be provided with a stable, nonconfrontational environment, a level of stimulation and autonomy commensurate with their stage of disease, and frequent reminders and orientation cues. Behavioral and psychiatric symptoms such as sleep disturbances, wandering, and agitation should be managed by addressing the causative personal or environmental factors when possible.^{1,2} Other interventions such as light, music, aroma, acupuncture, or massage therapy can also be tried.³ Education and support of caregivers has been shown to improve their skill and quality of life and to delay patient institutionalization.⁴

Recommendations for Treatment of Alzheimer's Disease

- ▶ Currently available drugs for treatment of Alzheimer's disease (AD) and other dementias do not slow, stop, or reverse the underlying neurodegenerative process.
- ▶ The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine can modestly improve symptoms of dementia. Transdermal rivastigmine causes fewer gastrointestinal adverse effects than the oral formulation.
- ▶ The NMDA-receptor antagonist memantine may provide some modest benefit in patients with moderate to severe AD. It causes fewer adverse effects than acetylcholinesterase inhibitors.
- ▶ Whether adding memantine to an acetylcholinesterase inhibitor is more effective than an acetylcholinesterase inhibitor alone remains to be established.

ACETYLCHOLINESTERASE INHIBITORS

Cognitive loss in AD is associated with depletion of acetylcholine, which is involved in learning and memory.⁵ Acetylcholinesterase inhibitors increase acetylcholine concentrations in the brain and have been shown to produce modest improvements in dementia symptoms, but they do not slow, stop, or reverse progression of AD.

All three of the acetylcholinesterase inhibitors in Table 1 (p 157) are Health Canada- and FDA-approved for treatment of AD dementia, but few trials have been conducted in patients >85 years old, and data on their use for >1 year are lacking.⁶ Rivastigmine is the only acetylcholinesterase inhibitor approved for treatment of mild to moderate dementia associated with Parkinson's disease. None of these drugs are approved for treatment of vascular dementia.

Gastrointestinal (GI) adverse effects are common with these agents, particularly during drug initiation and dose escalation. Bradycardia and syncope can occur, and an increased incidence of falls and hip fractures has been reported in elderly patients taking these drugs. They should be used with caution in patients who are at an increased risk for peptic ulcers and/or GI bleeding and in those with asthma or COPD.

Concurrent use of drugs with anticholinergic effects, including first-generation antihistamines such as diphenhydramine (*Benadryl*, and others), drugs for overactive bladder such as oxybutynin (*Ditropan*, and others), and tricyclic antidepressants such as imipramine (*Tofranil*, and others; only generics in Canada) might decrease the efficacy of acetylcholinesterase inhibitors.

DONEPEZIL — Donepezil (*Aricept*, and generics) is a centrally active, reversible inhibitor of acetylcholinesterase.⁷ It is Health Canada- and FDA-approved for treatment of mild, moderate, and severe AD dementia.

Pharmacokinetics — Donepezil is rapidly absorbed from the gastrointestinal (GI) tract, reaching peak plasma concentrations in 3-4 hours with the 10-mg tablet and in ~8 hours with the 23-mg tablet. Donepezil has a half-life of about 70 hours. It is metabolized primarily by CYP2D6 and 3A4 and is excreted in urine.

Clinical Studies — In a randomized, double-blind, 3-year trial comparing donepezil 10 mg/day, vitamin E 2000 IU/day, and placebo in 769 patients with **MCI**, there were no significant differences in the probability of progression to AD at 3 years. The donepezil group had a significantly lower rate of progression during the first year of the study.⁸

In short-term, randomized, double-blind trials in patients with **mild to moderate AD dementia**, donepezil 5 or 10 mg/day improved scores on neuropsychological tests, assessments of behavior and ADLs, and patient-, clinician-, and caregiver-rated measures of global change.^{9,10} In one randomized, double-blind, placebo-controlled trial, however, in 565 patients with mild to moderate AD dementia, donepezil had no effect on institutionalization or progression of disability at 3 years.¹¹

Health Canada and FDA approval of donepezil for treatment of **severe AD dementia** was based on the results of two clinical trials. In one, a randomized, double-blind, placebo-controlled, 24-week trial in 248 nursing-home patients with severe AD dementia, donepezil improved ADLs, cognition, and global function, but not behavior.¹² In the other, a randomized, double-blind, 24-week trial in 343 ambulatory outpatients with severe AD dementia, donepezil was more effective than placebo in improving measures of cognition and global function.¹³ In a trial in patients with **moderate to severe AD dementia**, those who continued taking donepezil had slightly higher mental status scores than those who stopped taking it.¹⁴

The results of some small, short-term (10-26 weeks), placebo-controlled trials have suggested a modest improvement in cognition, global function, and ADLs with donepezil in patients with **dementia associated with PD** and in those with **dementia associated with Lewy bodies**.¹⁵⁻¹⁷ There is no evidence that donepezil improves cognition or global functioning in patients with **vascular dementia**.

Dosage — The recommended starting dosage of donepezil is 5 mg once daily. After 4-6 weeks, the dose can be increased to 10 mg daily. If treatment is interrupted for several days, donepezil should be restarted at the lowest daily dose. The drug is also available in the US in 23-mg tablets for patients with a suboptimal response to lower doses, but the larger dose has marginal benefits at best and causes substantially more GI adverse effects.^{18,19}

Adverse Effects — The most common adverse effects of donepezil have been nausea, vomiting, and diarrhea, particularly with drug initiation or dose escalation. Urinary incontinence, vivid dreams, bradycardia, and syncope have also occurred. Fatigue and muscle cramps have been reported. Higher plasma levels of the drug and possibly a higher incidence of adverse effects might occur in CYP2D6 poor metabolizers.

Drug Interactions — In addition to interactions with drugs that have cholinergic or anticholinergic effects, donepezil may interact with inhibitors of CYP3A4 or 2D6, or with inducers of CYP3A4.²⁰

GALANTAMINE — Galantamine (*Razadyne*, *Razadyne ER*, and generics; only generic extended-release products available in Canada) is a reversible, competitive inhibitor of acetylcholinesterase. It also acts on nicotinic acetylcholine receptors; the clinical significance of its nicotinic activity remains to be established. Galantamine is Health Canada- and FDA-approved for treatment of mild to moderate AD dementia.

Pharmacokinetics — Galantamine is rapidly absorbed from the GI tract. Serum concentrations of the immediate-release (IR) formulation peak in about 1 hour when taken without food and in about 2.5 hours with food. With the extended-release (ER) formulation, serum concentrations peak 4.5-5 hours after administration. Galantamine has a half-life of about 7 hours. It is metabolized in the liver by CYP2D6 and 3A4 to metabolites that have little anticholinesterase activity.

Clinical Studies — In two randomized, 2-year trials in a total of 2048 patients with **MCI**, there was no difference in the rate of progression to AD dementia between galantamine- and placebo-treated patients.²¹

Table 1. Dosage and Cost of Drugs for Alzheimer's Disease

Drugs	Formulations	Usual Dosage	Starting Dosage/Titration	US Cost ¹	CAN Cost ¹¹
Acetylcholinesterase Inhibitors					
Donepezil – generic	5, 10, 23 mg tabs ^{2,12}	5-10 mg once/d in the evening	5 mg once/d; after 4-6 wks increase to 10 mg once/d;	\$5.50	\$24.80
Aricept (Pfizer; Eisai in US)			after an additional 3 months, can increase to 23 mg once/d ¹³	506.10	164.10
orally disintegrating – generic	5, 10 mg orally disintegrating tabs			31.80	108.50
Aricept RDT				N.A.	164.10
Galantamine – generic ¹⁴	4, 8, 12 mg tabs;	8-12 mg bid, preferably with meals ⁴	4 mg bid; after 4 wks increase to 8 mg bid; after an additional 4 wks can increase to 12 mg bid	135.10	N.A.C.
Razadyne (Janssen)	4 mg/mL soln ^{3,15}			320.20	N.A.C.
extended-release – generic	8, 16, 24 mg ER caps	16-24 mg once/d, preferably with the AM meal	8 mg once/d; after 4 wks increase to 16 mg once/d; after an additional 4 wks can increase to 24 mg once/d	140.00	39.10
Razadyne ER (Janssen)				320.20	N.A.C.
Rivastigmine – generic	1.5, 3, 4.5, 6 mg caps	4.5-6 mg bid with meals	1.5 mg bid; increase in increments of 1.5 mg bid every 2 wks ⁵ to 6 mg bid	105.30	39.10
Exelon (Novartis)	1.5, 3, 4.5, 6 mg caps; 2 mg/mL soln			N.A.	171.40
transdermal – generic ¹⁴	4.6 mg/24 hrs,	9.5 mg or 13.3 mg once/d	4.6 mg once/d; after 4 wks increase to 9.5 mg once/d; after an additional 4 wks can increase to 13.3 mg once/d	372.90	N.A.C.
Exelon Patch	9.5 mg/24 hrs, 13.3 mg/24 hrs patches			593.70	148.10
NMDA-Receptor Antagonist					
Memantine – generic	5, 10 mg tabs;	10 mg bid ⁶	5 mg once/d; increase in increments of 5 mg/wk to 10 mg bid	25.80	98.10
Ebixa (Lundbeck); Namenda (Allergan) in US	2 mg/mL soln ^{3,15}			406.20	155.50
extended-release – Namenda XR	7, 14, 21, 28 mg ER caps ⁷	28 mg once/d ⁶	7 mg once/d; increase in increments of 7 mg/wk to 28 mg once/d	387.60	N.A.C.
NMDA-Receptor Antagonist/Acetylcholinesterase Inhibitor					
Memantine/donepezil – Namzaric (Allergan) ⁸	7/10, 14/10, 21/10, 28/10 mg ER caps ⁷	28/10 mg once/d in the evening ⁹	See footnote 10	385.90	N.A.C.

ER = extended-release; N.A.C. = Not available in Canada; N.A. = Not available in the US

1. Approximate WAC for 30 days' treatment at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. September 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.

2. The 23-mg tablet should not be split, crushed, or chewed.

3. The oral solution is only available generically.

4. In patients with CrCl 9-59 mL/min or moderate hepatic impairment, dosage should not exceed 16 mg/day. Patients with CrCl <9 mL/min or severe hepatic impairment should not take galantamine.

5. Every 4 weeks for dementia associated with Parkinson's disease.

6. In patients with severe renal impairment (CrCl 5-29 mL/min), the target dosage is 5 mg bid for immediate-release formulation and 14 mg once/day for the extended-release formulation.

8. Approved for patients previously stabilized on donepezil 10 mg once/d.

9. Contents of capsules can be sprinkled on applesauce and consumed immediately. Capsules should not be divided, crushed, or chewed.

10. The recommended dosage of Namzaric is 14/10 mg once/day for patients with severe renal impairment (CrCl 5-29 mL/min) previously stabilized on memantine 5 mg bid or 14 mg once/day and donepezil 10 mg once/day.

11. For patients who were taking donepezil 10 mg once/d without memantine, the recommended starting dosage is 7/10 mg once/d in the evening; the memantine daily dose can be increased in increments of 7 mg/week. For patients previously stabilized on donepezil 10 mg once/d and memantine 10 mg bid or 28 mg once/d, the recommended starting dosage is 28/10 mg once/d in the evening.

12. Approximate WAC for 30 days' treatment at the lowest usual dosage, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, September 2017).

13. 23-mg tabs not available in Canada.

14. Maximum dose in Canada is 10 mg/d.

15. Approved but not yet marketed in Canada.

16. The oral solution is not available in Canada.

In short-term (4-6 months) trials in patients with **mild to moderate AD dementia**, galantamine modestly improved cognitive and clinical global measures compared to placebo.^{22,23} In a randomized, placebo-controlled, 2-year trial in 2045 patients with mild to moderate AD dementia or mixed AD/vascular dementia, patients taking background memantine did not benefit from addition of galantamine. Among 1549 patients not taking memantine, mortality rates were lower and there was less cognitive and functional loss with galantamine than with placebo.²⁴

Several trials (6-12 months) in AD dementia patients with **cerebrovascular disease** have shown significant

improvements in cognition, behavior, and ADLs with galantamine treatment.^{25,26}

Dosage — The recommended starting dosage of galantamine is 8 mg daily (4 mg twice daily with the IR formulation or 8 mg once daily with the ER formulation) taken with food. The daily dose can be increased to 16 mg after 4 weeks and then to 24 mg after another 4 weeks. The maximum daily dose is 16 mg in patients with moderate hepatic or renal impairment; the drug should not be used in patients with severe hepatic or renal impairment. If treatment is interrupted for several days, galantamine should be restarted at the lowest daily dose.

Adverse Effects — Nausea, vomiting, diarrhea, dizziness, anorexia, and weight loss are common with rapid dose escalation of galantamine, and less common during maintenance treatment. Bradycardia and syncope can occur. Depression, fatigue, and somnolence have been reported. Higher plasma levels of the drug and possibly a higher incidence of adverse effects may occur in CYP2D6 poor metabolizers.

Drug Interactions — In addition to interactions with drugs that have anticholinergic or cholinergic effects, galantamine may interact with drugs that inhibit CYP3A4 or 2D6 or induce CYP3A4.²⁰

RIVASTIGMINE — Rivastigmine is a carbamate-based, slowly reversible, noncompetitive cholinesterase inhibitor with good CNS penetration.²⁷ It is Health Canada- and FDA-approved for treatment of mild to moderate dementia associated with AD or Parkinson's disease. The transdermal patch (*Exelon Patch*, and generics) is also approved for use in patients with severe AD dementia in the US.

Pharmacokinetics — The oral formulation of rivastigmine is rapidly absorbed from the GI tract, reaching peak plasma concentrations in about 1 hour without food and in about 2.5 hours with food. The drug binds weakly to plasma proteins and has a short half-life in plasma (1.5 hours), but it has a half-life for cholinesterase inhibition in the CNS of about 10 hours. Rivastigmine is metabolized mainly through hydrolysis by esterases and is excreted in urine.

Clinical Studies — In a randomized, double-blind trial of up to 48 months in 1018 patients with **MCI**, there was no significant difference between rivastigmine and placebo in cognitive function or rate of progression to AD.²⁸

A review of 13 randomized, double-blind, placebo-controlled, 12- to 52-week trials involving 4775 patients with **mild to moderate AD dementia** found that oral and transdermal rivastigmine slowed the rate of cognitive function decline and improved ADLs, but the effects were small and the clinical significance was unclear. The transdermal patches were better tolerated than the oral formulation.²⁹

In a 24-week trial in 1195 patients with **severe AD dementia**, transdermal rivastigmine (9.5 mg/24 hours) was as effective as oral rivastigmine (12 mg/day), and the incidence of nausea and vomiting was about two-thirds lower with the patch.³⁰ In another 24-week trial, 716 patients with severe AD dementia were randomized to receive rivastigmine patches containing 4.6 or 13.3 mg/24 hours; at the end of the study, the mean

decline from baseline on assessments of cognition and overall function was significantly less with the 13.3-mg patch.³¹

In a randomized, double-blind, placebo-controlled, 24-week trial in 541 patients with **dementia associated with PD**, rivastigmine produced statistically significant improvements in attention and cognition.³² In a double-blind, 20-week trial in 120 patients with **dementia with Lewy bodies**, rivastigmine produced significant improvement in behavior compared to placebo.³³ In a randomized, double-blind, 24-week trial in 710 patients with **vascular dementia**, oral rivastigmine significantly improved performance on measures of cognition compared to placebo, but not global impression of change or ADLs.³⁴

Dosage — The recommended starting dosage of **oral** rivastigmine is 1.5 mg twice daily with food. The daily dose can be increased in 1.5-mg increments at 2-week intervals, up to a maximum dose of 12 mg. If treatment is interrupted for several days, rivastigmine should be restarted at the lowest daily dose.

The **transdermal** patch may be a more reliable method of administration in patients with dementia.³⁵ The initial dose is one 4.6 mg/24 hours patch, placed on the back, chest, or upper arm; the application site should be rotated daily. After one month, the dose can be increased to 9.5 mg/24 hours; subsequent escalation 4 weeks later to a 13.3 mg/24 hours patch (not approved in Canada) may provide additional benefit.³⁶ If treatment is interrupted for >3 days, it should be restarted with the lowest-dose patch.

Adverse Effects — Oral rivastigmine commonly causes nausea, vomiting, and diarrhea; GI tolerability can be improved if titration is slow and the drug is taken with food. These effects appear to be substantially less frequent with the transdermal formulation. Bradycardia and syncope can occur with either formulation of the drug.

Drug Interactions — Except for interactions with drugs that have anticholinergic or cholinergic effects, rivastigmine has no well-documented drug interactions.

CHOICE OF DRUG — Donepezil, galantamine, and rivastigmine appear to be similar in efficacy and safety in patients with AD dementia, but comparative trials are lacking. Transdermal rivastigmine may be better tolerated than the oral formulation. Both donepezil and rivastigmine have documented efficacy in dementia associated with Parkinson's disease and with Lewy body disease. Rivastigmine has improved cognitive performance in patients with vascular dementia.

AN NMDA-RECEPTOR ANTAGONIST

MEMANTINE — An *N*-methyl-D-aspartate (NMDA)-receptor antagonist, memantine (*Ebixa* [*Namenda* in US], and generics) is approved by Health Canada and the FDA for oral treatment of moderate to severe AD dementia.³⁷ Its mechanism of action in AD is unclear; it may reduce glutamatergic overstimulation at the NMDA receptor, which could have symptomatic benefits.³⁸

Pharmacokinetics — Memantine is well absorbed from the GI tract, reaching peak plasma concentrations in about 3-7 hours with the IR formulation and about 9-12 hours with the ER formulation. The terminal elimination half-life is 60-80 hours. Memantine is excreted primarily in urine.

Clinical Studies — Memantine is approved only for treatment of moderate to severe AD dementia.

In a double-blind, 28-week trial in 252 patients with **moderate to severe AD dementia**, memantine treatment produced modest, but statistically significant benefits in global, functional, and cognitive scores, compared to placebo.³⁹

In one randomized trial in patients with **moderate to severe AD dementia taking donepezil**, addition of memantine led to significantly better outcomes on measures of cognition, behavior, ADLs, and global improvement, compared to addition of placebo.⁴⁰ In another randomized trial, however, in 295 patients with moderate to severe AD dementia taking donepezil, addition of memantine did not significantly improve measures of cognition and ADLs compared to addition of placebo.¹⁴

There is no acceptable evidence that memantine is effective in **mild AD**. In a prospective, double-blind, 24-week study in 433 patients with **mild to moderate AD dementia taking a cholinesterase inhibitor**, addition of memantine was no more effective than addition of placebo.⁴¹

Memantine is available in an extended-release, fixed-dose combination with donepezil (*Namzaric*; not approved in Canada) that is approved for once-daily treatment of moderate to severe AD; its efficacy is unclear and it is expensive.⁴²

Memantine has been reported to improve cognition in patients with mild to moderate **vascular dementia**.^{43,44} It has not been shown to be effective in **dementia associated with PD or Lewy bodies**.⁴⁵

Dosage — The recommended starting dosage of IR memantine is 5 mg once daily. The daily dose can be

increased in weekly increments of 5 mg to a total of 20 mg, usually divided twice daily. The initial dosage of ER memantine (not approved in Canada) is 7 mg once daily; the dose can be increased in weekly increments of 7 mg to a target dose of 28 mg. The maximum recommended dosage in patients with severe renal impairment is 5 mg of the IR formulation twice daily or one 14-mg ER tablet daily.

Adverse Effects — Memantine is usually well tolerated. Confusion and agitation can occur. Other adverse effects have included dizziness, insomnia, hallucinations, and delusions.

Drug Interactions — Memantine does not affect the activity of acetylcholinesterase inhibitors. Amantadine, which is used to treat Parkinson's disease, is also an NMDA-receptor antagonist and could theoretically have undesirable additive effects if taken with memantine.

ANTIPSYCHOTICS

Antipsychotic drugs are widely used off-label to treat agitation and other behavioral symptoms in elderly patients, especially those with dementia.⁴⁶ In Canada, risperidone is indicated for the symptomatic management of aggression and psychotic symptoms associated with severe AD dementia. Second-generation antipsychotics used in low doses have generally been preferred because they have fewer extrapyramidal effects than first-generation drugs.

Efficacy in AD Dementia — Although many clinicians believe that use of second-generation antipsychotics such as quetiapine (*Seroquel*, and generics) to calm agitated or aggressive patients with dementia is beneficial, controlled-trial evidence for the efficacy of antipsychotic medications in dementia is limited. In one placebo-controlled, 36-week trial in 421 outpatients with AD dementia, antipsychotic treatment produced modest improvement in behavioral symptoms such as anger, aggression, and paranoid ideation, but did not improve functioning, care needs, or quality of life.⁴⁷

Adverse Effects — Common adverse effects of antipsychotic drugs include somnolence and gait changes. Extrapyramidal effects can occur and may be more severe in patients also taking an acetylcholinesterase inhibitor.⁴⁸ In one study in 421 patients with AD dementia, cognitive function declined more in patients taking an antipsychotic than in those taking placebo.⁴⁹

Risk of Death — Health Canada and the FDA require manufacturers of all antipsychotic drugs to include a warning in the labeling about an increased risk of death among elderly patients with dementia treated with antipsychotics. In randomized trials, elderly patients with

dementia taking second-generation antipsychotics had a higher mortality rate than those taking placebo (4.5% vs 2.6% in a typical 10-week controlled trial); most of the deaths were due to cardiovascular or infectious causes. The mortality risk with first-generation antipsychotics has not been adequately evaluated, and may be higher than the risk with second-generation drugs.

ANTIDEPRESSANTS

In addition to treating depression, antidepressants are used off-label to treat agitation and other behavioral symptoms in patients with dementia. A review of 9 trials in a total of 692 patients with dementia found that the selective serotonin reuptake inhibitors (SSRIs) sertraline (*Zoloft*, and generics) and citalopram (*Celexa*, and generics) significantly improved agitation, but not other behavioral symptoms.⁵⁰ In a randomized, double-blind, 9-week trial in 186 patients with AD dementia and clinically significant agitation, citalopram significantly improved measures of agitation compared to placebo, but was also associated with worsening of cognition and QT interval prolongation.⁵¹

OTHER DRUGS

Dextromethorphan/quinidine (*Nuedexta*; not approved in Canada) is FDA-approved for pseudobulbar affect, which occurs in a range of neurological disorders.⁵² Quinidine is a strong CYP2D6 inhibitor²⁰; it boosts serum concentrations of the CYP2D6 substrate dextromethorphan. In a randomized, placebo-controlled trial in 194 patients with Alzheimer's-related agitation, measures of agitation and aggression were modestly but significantly improved in those receiving the combination. Adverse effects were infrequent, but included dizziness, falls, diarrhea, and urinary tract infection.⁵³

A randomized, placebo-controlled trial in 613 patients with mild to moderate AD compared 2000 IU/d of **vitamin E**, 20 mg of memantine, a combination of both vitamin E and memantine, and placebo. Functional decline was significantly slower, compared to placebo, with vitamin E, but not with memantine or the combination of vitamin E and memantine.⁵⁴

The dietary supplement **Ginkgo biloba** is heavily promoted in the US for memory support. In several randomized, double-blind trials, it was not effective in preventing or treating dementia or for preventing cognitive decline in older adults.⁵⁵⁻⁵⁸ ■

Additional Content Available Online

Drugs for Alzheimer's Disease

<http://medicalletter.org/TML-article-1530c>

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▶ Tocilizumab (Actemra) for Giant Cell Arteritis

The FDA has approved the interleukin-6 (IL-6) receptor antagonist tocilizumab (*Actemra* – Genentech) for subcutaneous (SC) treatment of giant cell arteritis in adults (not approved for this indication in Canada). It is the first drug to be approved in the US for this indication. Tocilizumab is also approved for treatment of rheumatoid arthritis, polyarticular or systemic juvenile idiopathic arthritis, and cytokine release syndrome (not approved for this indication in Canada).¹

Pronunciation Key

Tocilizumab: toe" si liz' ue mab *Actemra*: ac tem' ra

THE DISEASE – Giant cell arteritis is a systemic large vessel vasculitis that usually occurs in adults >50 years old. It can cause blindness, stroke, and aortic aneurysm or dissection. High-dose corticosteroid therapy has been effective in inducing remission, but treatment must be continued for months or years, adverse effects can be severe, and relapses are common.² Alternatives to glucocorticoid therapy have not been found to be effective in randomized, controlled trials.

MECHANISM OF ACTION — Tocilizumab is a humanized IL-6 receptor monoclonal antibody that competitively inhibits the binding of IL-6 to its receptors. IL-6 is a pro-inflammatory cytokine that is overproduced in patients with giant cell arteritis.

CLINICAL STUDIES — FDA approval of tocilizumab for giant cell arteritis was based on the results of a double-blind trial in 251 adults ≥ 50 years old with newly diagnosed or relapsing giant cell arteritis. Patients were randomized to tocilizumab 162 mg SC every week (n=100) or every other week (n=50) plus a 26-week prednisone taper, or to placebo plus a 26- (n=50) or 52-week (n=51) prednisone taper. The rate of sustained glucocorticoid-free remission (remission from week 12 through 52 and adherence to prednisone taper) was significantly greater in patients who received tocilizumab once weekly (56%) or every other week (53%) than in those who received placebo plus 26 weeks (14%) or 52 weeks (18%) of prednisone taper. The cumulative prednisone dose over the 52-week period was $\sim 50\%$ lower in those receiving tocilizumab than in those receiving placebo.³

The effect of IL-6 inhibition with tocilizumab on vision loss and other ischemic events remains to be determined.⁴

ADVERSE EFFECTS — Adverse effects in the clinical trial were similar in all of the groups. Serious adverse events occurred less frequently in patients treated with tocilizumab. Serious bacterial, fungal, and viral infections have been reported with use of tocilizumab. Testing for latent tuberculosis is required before starting the drug. Live vaccines should not be administered during tocilizumab therapy.

Neutropenia, thrombocytopenia, and serum hepatic transaminase elevations have been reported with tocilizumab; dosage adjustment and/or discontinuation of the drug may be needed, based on severity. Use of tocilizumab for other indications has been associated with GI perforation; patients with a history of diverticulitis are at increased risk.

DRUG INTERACTIONS — *In vitro* data indicate that tocilizumab may reverse IL-6-mediated suppression of CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4, potentially decreasing serum concentrations of other drugs taken concurrently.⁵ *In vivo* studies have found that concurrent use of tocilizumab resulted in decreased serum concentrations of simvastatin (Zocor, and others) and omeprazole (Losec [Prilosec in US], and others). Other biologic agents should not be used concomitantly with tocilizumab.

DOSAGE, ADMINISTRATION, AND COST — The recommended dosage of tocilizumab for treatment of giant

cell arteritis is 162 mg injected SC once weekly. Administration every other week may be considered for some patients. Tocilizumab should be given in combination with a tapering course of a glucocorticoid. The labeling states that it can be used alone after discontinuation of glucocorticoid therapy, but the duration of treatment is unclear. A 28-day supply of once-weekly tocilizumab (four 162-mg prefilled syringes) costs CAN\$1514.60⁶ (US\$3647.10⁷).

CONCLUSION — In one controlled trial in patients with newly diagnosed or relapsing giant cell arteritis (not approved for this indication in Canada), addition of tocilizumab (Actemra) to tapered prednisone was significantly more effective than addition of placebo in achieving sustained remission and in reducing the cumulative dosage of prednisone. Its effect on the most serious complications of giant cell arteritis (blindness, stroke) remains to be determined. More data are needed to clarify the place of tocilizumab in the treatment of giant cell arteritis. ■

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7. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly September 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.

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1. Explain the current approach to the management of Alzheimer's disease dementia and mild cognitive impairment.
2. Discuss the pharmacologic options available for treatment of Alzheimer's disease dementia and mild cognitive impairment and compare them based on their efficacy, dosage and administration, potential adverse effects, and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient with Alzheimer's disease or mild cognitive impairment.
4. Review the efficacy and safety of tocilizumab (*Actemra*) for treatment of giant cell arteritis.

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Issue 1530 Questions

(Correspond to questions #61-70 in Comprehensive Exam #77, available January 2018)

Drugs for Cognitive Loss and Dementia

1. Alzheimer's disease may be accompanied by:
 - a. sleep disturbances
 - b. wandering
 - c. agitation
 - d. all of the above
2. The most common adverse effects of acetylcholinesterase inhibitors are:
 - a. urinary
 - b. gastrointestinal
 - c. metabolic
 - d. CNS-related
3. Donepezil is FDA-approved for which severity of AD dementia?
 - a. only mild
 - b. only mild to moderate
 - c. only moderate to severe
 - d. mild, moderate, and severe
4. An 87-year-old man with AD has been taking donepezil for 2 years without any signs of improvement. He has had some GI adverse effects and his daughter wants to know if he should continue taking the drug. You could tell her that:
 - a. stopping the drug may result in lower mental status scores
 - b. the efficacy of donepezil increases over time
 - c. stopping the drug could make his GI symptoms worse
 - d. all of the above
5. A 76-year-old woman with moderate to severe AD has been treated with oral rivastigmine 12 mg/day for about 18 months, with some improvement in her activities of daily living (ADLs). In recent weeks, however, she has developed severe nausea and vomiting. The best approach for this patient would probably be to:
 - a. decrease her dose of rivastigmine
 - b. switch her to the rivastigmine patch
 - c. switch her to galantamine
 - d. start her on a phenothiazine

6. Galantamine should not be used in patients with:
 - a. G6PD deficiency
 - b. gluten sensitivity
 - c. severe hepatic or renal impairment
 - d. any of the above
7. The efficacy and tolerability of the acetylcholinesterase inhibitors used to treat AD could be summarized as follows:
 - a. donepezil, galantamine, and rivastigmine appear to be similar in efficacy and adverse effects
 - b. rivastigmine has been more effective than donepezil and better tolerated than galantamine
 - c. galantamine has been no more effective than the others, but much better tolerated
 - d. donepezil has been the least effective, but the best tolerated
8. Memantine:
 - a. may have a modest benefit on symptoms of moderate to severe AD
 - b. has not been shown to have any effect on mild AD dementia
 - c. is usually well tolerated
 - d. all of the above
9. Use of second-generation antipsychotic drugs in patients with AD dementia has been shown to:
 - a. improve quality of life
 - b. improve functioning
 - c. increase the risk of death
 - d. all of the above

Tocilizumab (Actemra) for Giant Cell Arteritis

10. Approximately what percentage of patients with giant cell arteritis treated with tocilizumab achieved sustained glucocorticoid-free remission at 52 weeks?
 - a. 30%
 - b. 50%
 - c. 70%
 - d. 90%

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