Texas Vendor Drug Program

Drug Use Criteria: Acetylcholinesterase Inhibitors

- Developed April 2006.
- Revised May 2019; May 2017; June 2015; October 2013; December 2011; January 2010.

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Alzheimer's disease is associated with significant losses in cholinergic neurons and decreased concentrations of acetylcholine, a neurotransmitter significantly involved in learning and memory processes. Acetylcholinesterase inhibitors (ACIs) exert pharmacologic effects by increasing availability of intrasynaptic acetylcholine in the presence of intact cholinergic neurons. All available ACIs are FDA-approved in adults for the management of mild to moderate Alzheimer's dementia, while donepezil is also FDA-approved for management of severe Alzheimer's disease. Additionally, rivastigmine (Exelon®) is FDA-approved for use in mild-to-moderate dementia associated with Parkinson's disease.

Recently, a combination product containing donepezil and memantine extended-release (Namzaric®) has been FDA-approved for use in patients with moderate to severe Alzheimer's dementia stabilized on donepezil and memantine. Memantine, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, exerts pharmacologic effects by blocking glutamate activity, the key excitatory neurotransmitter in the central nervous system. Glutamate is released into synapses when certain neurons die and activates NMDA receptors, causing overexcitation, an influx of calcium ions and, ultimately, death of downstream neurons. NMDA receptor activation is thought to be one of the main causes of neurodegeneration in various types of dementia, including Alzheimer's-associated dementia. ACI monotherapy and combination therapy recommended dosages are summarized in Tables 1 and 2, respectively. Dosages exceeding these recommendations will be reviewed.

Table 1. Recommended Adult Dosages for ACIs

Therapy Type	Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
Mono	mild to moderate Alzheimer's	donepezil (Aricept®, generics)	tablets (5 mg, 10 mg, 23 mg) orally disintegrating tablets (5 mg, 10 mg)	10 mg/day, as a single dose
Mono	moderate to severe Alzheimer's	Donepezil		23 mg/day, as a single dose
Mono	mild to moderate Alzheimer's	galantamine (Razadyne®, Razadyne® ER, generics)	immediate-release tablets (4 mg, 8 mg, 12 mg); oral solution (4 mg/ml)	24 mg/day, in 2 divided doses
Mono	mild to moderate Alzheimer's	Galantamine	extended-release capsules (8 mg, 16 mg, 24 mg)	24 mg/day once daily
Mono	mild/moderate Alzheimer's, Parkinson's disease dementia	Rivastigmine (Exelon®, generics)	immediate-release capsules (1.5 mg, 3 mg, 4.5 mg, 6 mg)	12 mg/day, in 2 divided doses
Mono	mild/moderate Alzheimer's, Parkinson's disease dementia	Rivastigmine	transdermal (extended-release) patch (4.6 mg/24 h, 9.5 mg/24 h, 13.3 mg/24 h)	13.3 mg/24 h
Combination	moderate to severe Alzheimer's dementia in patients stabilized on memantine and donepezil:	memantine extended-release/donepezil (Namzaric®)	capsules (7 mg/10 mg, 14 mg/10 mg, 21 mg/10 mg, 28 mg/10 mg)	28 mg/10 mg once daily

Table 2: Recommended Adult Dosages for ACIs: Combination Therapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
moderate to severe Alzheimer's dementia in patients stabilized on donepezil alone or memantine and donepezil	memantine extended-release/donepezil (Namzaric®)	capsules (7 mg/10 mg, 14 mg/10 mg, 21 mg/10 mg, 28 mg/10 mg)	28 mg/10 mg once daily

Although not FDA-approved, ACIs have also been evaluated for use in vascular dementia, dementia with Lewy bodies, post stroke aphasia, and memory improvement in multiple sclerosis patients.

1.1.1 Renal Impairment

Patients prescribed galantamine with moderate renal impairment [creatinine clearance (CrCl) 9-59 ml/min] should have doses titrated cautiously; dosages should not exceed 16 mg daily. Galantamine is not recommended for use in patients with severe renal impairment (CrCl less than 9 ml/min). Patients with severe renal impairment (CrCl 5-29 ml/min) stabilized on memantine 5 mg twice daily immediate-release or 14 mg daily extended-release and donepezil 10 mg daily or donepezil 10 mg once daily without memantine may utilize memantine/donepezil combination therapy in doses not exceeding 14 mg/10 mg daily.

1.2 Pediatrics

ACIs and memantine/donepezil combination therapy are not recommended for use in children, as adequate, well-controlled clinical trials have not documented safety and efficacy of these agents for any disease state in the pediatric population.

2 Duration of Therapy

ACIs do not alter the long-term progressive decline of Alzheimer's disease, but have been shown to delay time to institutionalization, which may be cost-effective. ACIs may be prescribed to stabilize dementia in Alzheimer's patients, as determined by periodic assessment of functional and cognitive ability. ACIs should be discontinued when dementia becomes unresponsive to therapy and progressively severe, as the efficacy of these agents diminishes due to loss of intact cholinergic neurons.

3 Duplicative Therapy

Combined use of two or more ACIs does not provide enhanced therapeutic benefit and may result in additive adverse effects. Concurrent administration of two or more ACIs is not recommended and will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for ACIs are summarized in Table 3. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 3: Drug-Drug Interactions for ACIs

Target Drug	Interacting Drug	Interaction	Recommendations	Clinical Significance[+]
ACIs	anticholinergics	potential for reduced cholinergic activity with centrally acting anticholinergics, which may manifest as reduced activities of daily living but not cognitive function; peripherally acting anticholinergics less likely to attenuate ACI therapeutic effects	monitor for diminished cholinergic effects; choose agents with less centrally acting anticholinergic activity	moderate (DrugReax) 3- moderate (CP)
ACIs	cholinergic agents and other cholinesterase inhibitors	enhanced cholinergic/ adverse effects	avoid combination, if possible; if combination needed, monitor for enhanced cholinergic effects; may adjust doses to achieve tolerable clinical effects	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendations	Clinical Significance[+]
ACIs	drugs that lower seizure threshold (e.g., bupropion)	concurrent use may increase seizure risk as seizures observed with ACIs	use cautiously together; begin with low ACI doses and titrate slowly	major (DrugReax)
ACIs	NSAIDs	potential for additive gastrointestinal effects	monitor for gastrointestinal intolerance and/or bleeding	3-moderate (CP)
ACIs	beta blockers	increased risk of bradycardia when prescribed concurrently; ACIs may increase vagal tone, resulting in bradycardia, hypotension, and syncope	monitor blood pressure, heart rate during therapy	3-moderate (CP)
donepezil	QT interval-prolonging medications	adjunctive use may increase risk of QT interval prolongation and torsades de pointes as donepezil has increased risk of QT interval prolongation and torsades de pointes	avoid combined use; if used together, monitor patients for efficacy and cardiovascular adverse outcomes	contraindicated (DrugReax) 1-severe (CP)
donepezil, galantamine	CYP3A4 and CYP2D6 inducers	potential for reduced donepezil serum concentrations and decreased efficacy	monitor for reduced donepezil efficacy	3-moderate (CP)
donepezil, galantamine	CYP3A4 and CYP2D6 inhibitors	potential for increased donepezil and galantamine serum concentrations	monitor for increased cholinergic effects	major**,** moderate (DrugReax) galantamine: 2-major; donepezil, galantamine: 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendations	Clinical Significance[+]
donepezil/ memantine	alkalinizing agents (e.g., select carbonic anhydrase inhibitors, sodium bicarbonate)	memantine clearance reduced by about 80% in alkaline conditions (pH ≥ 8); adjunctive administration with alkalinizing agents may decrease memantine elimination and increase memantine serum levels and potential for increased pharmacologic/adverse effects	administer drug combination cautiously together; monitor patients for increased pharmacologic/adverse effects	moderate (DrugReax) 3-moderate (CP)
donepezil/ memantine	other drugs excreted by renal tubular secretion (e.g., amiloride, cimetidine, dofetilide, nicotine, quinidine, ranitidine)	memantine eliminated by renal tubular cationic transport; combined administration may result in altered serum levels of both memantine and other drugs excreted by renal tubular secretion due to competition for transport system; elevated dofetilide levels may increase potential for arrhythmias, including torsades de pointes	monitor patient responses, observe for adverse effects or loss of efficacy, and adjust doses as necessary	moderate (DrugReax) dofetilide, procainamide, quinidine: 2-major; all other drugs: 3-moderate (CP)
rivastigmine	metoclopramide	combined use may increase risk of extrapyramidal effects as both agents associated with extrapyramidal signs/ symptoms	avoid concurrent use; monitor closely for extrapyramidal effects if combined therapy necessary	contraindicated (DrugReax) 2-major (CP)

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: May 21, 2019).

2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed May 21, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; May 21, 2019.
4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at: http://online-statref-com.libproxy.uthscsa.edu/. Accessed May 21, 2019.
5. Rivastigmine transdermal system (Exelon® Patch) package insert. Novartis, December 2018.
6. Galantamine extended-release capsules, tablets and oral solution (Razadyne® ER, Razadyne®) package insert. Janssen Pharmaceuticals, May 2018.
7. Donepezil tablets, orally disintegrating tablets (Aricept®, Aricept® ODT) Package Insert. Eisai Inc., December 2018.
8. Memantine extended-release/donepezil capsules (Namzaric®) package insert. Allergan USA, Inc., January 2019.
9. Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med. 2007; 120:388-97.
10. Blennow K, deLeon MJ, Zetterberg H. Alzheimer's disease. Lancet. 2006; 368:387-403.
11. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006, Issue 1. Art. No.: CD005593. DOI: 10.1002/14651858.CD005593.
12. Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on May 21, 2019.)
13. Mayeux R. Clinical practice. Early Alzheimer's disease. N Engl J Med. 2010;362(23):2194-201.
14. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148(5):379-97.
15. Deardorff WJ, Grossberg GT. A fixed-dose combination of memantine extended-release and donepezil in the treatment of moderate-to-severe Alzheimer's disease. Drug Des Devel Ther. 2016; 10:3267-79.
16. Szeto JY, Lewis SJ. Current treatment options for Alzheimer's disease and Parkinson's disease dementia. Curr Neuropharmacol. 2016;14(4):326-38.

17. Ehret MJ, Chamberlin KW. Current practices in the treatment of Alzheimer disease: where is the evidence after the phase III trials? Clin Ther. 2015;37(8):1604-16.
18. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep. 2015;67(2):195-203.
19. Howard E, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012;366(10):893-903.
1. Epperly T, Dunay MA, Boice JL. Alzheimer disease: pharmacologic and nonpharmacologic therapies for cognitive and functional symptoms. Am Fam Physician. 2017;95(12):771-8.