

## Acetylcholinesterase Inhibitors

[Developed, April 2006]

### MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with [\*].

#### 1.\* Dosage

Acetylcholinesterase inhibitors (ACIs) are indicated for the management of mild to moderate Alzheimer's dementia. Alzheimer's disease is associated with significant losses in cholinergic neurons and decreased concentrations of the neurotransmitter, acetylcholine, which is significantly involved in learning and memory processes. Acetylcholinesterase inhibitors exert pharmacologic effects by increasing availability of intrasynaptic acetylcholine in the presence of intact cholinergic neurons. Recommended dosages are summarized in Table 1.

<i>Drug Name</i>	<i>Maximum Recommended Dosage</i>
Donepezil (Aricept®)	10 mg/day, as a single dose
Galantamine (Razadyne®)	24 mg/day, in 2 divided doses
Rivastigmine (Exelon®)	12 mg/day, in 2 divided doses
Tacrine (Cognex®)**	160 mg/day, in 4 divided doses

*\*\*This agent has largely been replaced with other available acetylcholinesterase inhibitors with more favorable dosage regimens and adverse event profiles.*

Although not FDA-approved, ACIs have also been evaluated for use in vascular dementia, dementia with Lewy bodies, and Parkinson's-induced dementia.

#### 2. Duration of Therapy

Acetylcholinesterase inhibitors do not alter the long-term progress of Alzheimer's disease, but have been shown to delay the time to institutionalization, which may be cost-effective. Acetylcholinesterase inhibitors may be prescribed to stabilize dementia in Alzheimer's patients, as determined by periodic assessment of functional and cognitive ability. Acetylcholinesterase inhibitors 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.

The following drug-drug interactions are considered clinically significant for ACIs. 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:

- a. **Tacrine and Fluvoxamine (Luvox®)** [clinical significance level – 2 (Hansten & Horn); 2 (DIF); moderate (CPonline)]

Concurrent administration of tacrine and fluvoxamine may result in increased tacrine plasma concentrations and the potential for increased pharmacologic and adverse effects. This interaction is most likely due to fluvoxamine inhibition of cytochrome P450 1A2, the enzyme responsible for tacrine metabolism. Alternative selective serotonin reuptake inhibitors that are not metabolized by CYP1A2 should be considered (e.g., fluoxetine) to avoid potential adverse effects. If this drug combination cannot be avoided, monitor patients for tacrine adverse effects, including hepatotoxicity.

- b. **Anticholinergic Agents (e.g., cyclobenzaprine, sedating H<sub>1</sub>-blockers, tricyclic antidepressants)** [clinical significance level – 3 (Hansten & Horn); high (CPonline)]

Adjunctive administration of ACIs and anticholinergic agents may result in mutually antagonistic pharmacologic effects. Agents with central anticholinergic activity (e.g., scopolamine, benztropine) have the propensity to inhibit the beneficial pharmacologic effects of ACIs in Alzheimer's disease, while peripherally acting anticholinergic agents (e.g., glycopyrrolate) would not be expected to interfere with ACI therapeutic effects. Likewise, the impact of ACIs on agents exhibiting anticholinergic effects could be beneficial if the anticholinergic effect is unwanted (e.g., antihistamines, phenothiazines), or undesirable if the therapeutic response requires an anticholinergic effect (e.g., Parkinson's disease). If the ACI-anticholinergic drug combination is necessary, monitor patients for reduced anticholinergic effects and modify dosages or discontinue therapy as necessary.

- c. **Cholinergic Agents (e.g., bethanechol -Urecholine®, pyridostigmine -Mestinon®)** [clinical significance level – 3 (Hansten & Horn); high (CPonline)]

Cholinergic agents administered concomitantly with ACIs may result in enhanced pharmacologic and adverse effects. If concurrent prescriptions of ACIs and other cholinergic agents are necessary, monitor for enhanced cholinergic response and adjust doses as necessary.

## REFERENCES

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