

Long-Term Cognitive Impact of Anticholinergic Medications in Older Adults

Polypharmacy is a major health concern as older adults typically take multiple medications, prescribed by several physicians, and often filled at different pharmacies. This scenario complicates the

physician's ability to anticipate potentially harmful interactions or adverse effects of medications. The drugs with anticholinergic (AC) properties are a class of medications that may lead to adverse effects,

particularly for the older adult population. These central nervous system side effects can lead to cognitive impairments which further complicate treatment.

Table 1. Pharmacokinetic features of cognitive enhancers

	Agent	Protein Binding	CYP-450 activity	Other features
AChHIs	Donepezil	96%	CYP 2D6, 3A4 substrate	Once-daily dosing
	Rivastigmine	40%	None	Metabolized by cholinesterase
	Galantamine	18%	CYP 2D6, 3A4 substrate	Nicotinic cholinergic receptor modulation
NMDA receptor antagonist	Memantine	45%	None	No hepatic metabolism

CYP450: cytochrome P450; AchEIs: acetyl cholinesterase inhibitors; NMDA: N-methyl-D-aspartate

Table 2. DDIs in AD patients: CYP-450 substrates and inhibitors*

	CYP 2D6	CYP 3A4
Substrates (metabolized by enzyme)	Second-generation antipsychotics Citalopram Donepezil Duloxetine Galantamine Haloperidol Tricyclic antidepressants Trazadone Velafaxine	Second-generation antipsychotics Benzodiazepines Buspirone Carbamazepine Donepezil Galantamine Haloperidol Lamotrigine Mirtazapine Nefazodone Sertraline Tricyclic antidepressants Trazadone
Inhibitors	Bupropion Cimetidine Duloxetine Fluoxetine Paroxetine Sertraline	Erythromycin Fluconazole Fuvoxamine Grapfruit juice Ltraconazole Nefazodone

Table 3. Medications with moderate to strong ACH activity

Class	Examples
Antiarrhythmics	Disopyramide
Antiemetics	Meclizine
Antiparkinsonians	Benzotropine, biperiden, trihexyphenidyl
Antipsychotics	Chlorpromazine, clozapine, olanzapine, pimozide, thioridazine
Antihistamines	Chlorpheniramine, cyprheptadine, diphenhydramine, hydroxyzine, promethazine
H2 histamine blockers	Cimetidine, ranitidine
Muscle relaxants	Cyclobenzaprine
Gastrointestinal/urinary antispasmodics	Atropine, belladonna, alkaloids, dicyclomine, hyoscyamine, oxybutynin, scopolamine, tolterodine
Tricyclic Antidepressants	Amitriptyline, amoxapine, imipramine, clomipramine, doxepin, protriptyline

• All cytochrome P (CYP) 450 enzymes are induced by barbituates, phenytoin, carbamazepine, and rifampicin. Smoking also induces CYP 1A2.

• DDIs: drug-drug interactions; AD: Alzheimer's Disease

NOTE: Combining memantine with other NMDA antagonists could cause hallucinations, dizziness, headache, and confusion

Interaction	Mechanism	Potential Sequela(e)
AchEIs + anticholinergics	↓ Acetylcholine in CNS	Cognitive worsening, delirium
AchEIs + beta blocker	Vagal stimulation and sympathetic blockade	Bradycardia, syncope
AchEIs + cholinergics	↑ Acetylcholine in PNS	Cholinergic Crisis: hypersalivation, abdominal pain, diarrhea
AchEIs + antipsychotics (rare)	↑ Acetylcholine/↓ dopamine in striatum	Parkinsonian syndrome, rigidity
Ginkgo biloba + warfarin	Antiplatelet aggregation and anticoagulation	Gastrointestinal bleeding, hematuria, subcutaneous ecchymosis

Medications

Anticholinergics

Because anticholinergic drugs can worsen cognitive impairment and cause delirium they are contraindicated in older patients, especially those with AD. Antihistamines, histamine H2 blockers, low potency first-generation anti-psychotics (FGAs), and tricyclic antidepressants are common medications with anticholinergic effects. Anticholinergics can counteract AchEIs beneficial effect.

Antiparkinsonian agents

Interaction of antiparkinsonian medications with AchEIs could limit the efficacy of either drug when treating comorbid AD and Parkinson's disease (PD).

Cardiovascular agents

MAKE SURE that heart rate is > 60 bpm before AchEI treatment, and monitor regularly. Concurrent use of AchEIs and beta blockers, calcium channel inhibitors, or digoxin could worsen bradycardia and cause syncope. The risk is higher in patients:

- with sick sinus syndrome or other bradyarrhythmias
- taking antipsychotics that could induce torsades de pointes, such as ziprasidone or haloperidol

AchEIs inhibit the metabolism of suc-

cinyllcholine and therefore augment and prolong this drug's neuromuscular blockade.

Antidepressants

Up to 30% of AD patients experience major depression. SSRIs are the antidepressants most often used to treat depression and anxiety in AD patients. Citalopram, escitalopram, or venlafaxine are good choices for patients with AD because of minimal CYP inhibitory activity. Fluvoxamine, fluoxetine, and paroxetine inhibit CYP 2C9, through which warfarin and some other drugs with a narrow therapeutic index are metabolized.

Benzodiazepines

Contraindicated in elderly patients (especially those with AD) because of the high risk of delirium, worsened cognitive function, paradoxical disinhibition, and falls. If benzodiazepines are necessary to control anxiety, use intermediate-duration agents that do not undergo oxidative metabolism and have no active metabolites, such as lorazepam, oxazepam, or temazepam.

Herbal Supplements

Ginkgo biloba and huperzine A (Chinese club moss) are the herbal supplements commonly used by dementia patients.

Ginkgo inhibits platelet aggregation and

can cause bleeding complications, with or without concomitant antiplatelet or anticoagulant therapy such as aspirin, warfarin, and NSAIDs. Huperzine A is a natural cholinesterase inhibitor and should not be combined with AchEIs because of the risk of additive adverse effects.

References (available upon request)
 American Journal of Geriatric Psychiatry Vol. 14, No. 11 November 2006: Long Term Cognitive Impact of Anticholinergic Medications
 Current Psychiatry, Vol. 7, No. 2 February 2008: Prevent drug-drug interactions with cholinesterase inhibitors; Andreea L. Seritan, M.D.