Current PSYCHIATRY

Prevent drug-drug interactions with cholinesterase inhibitors

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Avoid adverse events when prescribing medications for patients with dementia

Mr. B, age 78, has a long history of well-controlled bipolar disorder and was diagnosed with Alzheimer's dementia 6 months ago. He is living at home and has been taking donepezil, 10 mg/d, and lamotrigine, 100 mg bid.

This morning Mr. B's wife calls and reports that he is experiencing sudden difficulty walking, dizziness, and "feeling drunk." When you ask about Mr. B's medications, his wife says that her husband's internist had prescribed itraconazole, 200 mg/d, for onychomycosis, and Mr. B has taken 1 dose. You promptly discontinue the itraconazole, and Mr. B's symptoms resolve.

Drug-drug interactions (DDIs) in Alzheimer's disease (AD) patients such as Mr. B can be serious and even life-threatening. On average, persons age ≥65 use 4.5 prescription agents and 2 over-the-counter preparations per day,[1] and the number of concurrently used medications is a significant predictor of adverse drug reactions.[2]

Cognitive enhancers, including acetylcholinesterase inhibitors (AChEIs) and memantine, are the most widely prescribed agents for AD patients. The FDA has approved galantamine and rivastigmine for mild to moderate dementia, memantine for moderate to severe dementia, and donepezil for mild to severe dementia (***Table 1, page 58***).[3-5]

To help you minimize adverse DDIs in AD patients, this article describes:

- pharmacokinetic and pharmacodynamic effects of cognitive enhancers used in AD management
- DDIs with medications commonly prescribed to AD patients
- how to avoid adverse events related to antipsychotics, antidepressants, and benzodiazepines.

Pharmacologic changes with aging

Pharmacokinetics is the study of the time course of drugs and their metabolites through the body. Pharmacokinetic interactions involve alterations in the plasma concentration of a drug by a second agent.[3]

Absorption of medications is decreased in the elderly because of reduced intestinal blood flow and motility. Absorption further decreases if patients concomitantly take antacids, high-fiber supplements, or anticholinergic medications.

Distribution. With aging, lean body mass typically decreases and adipose tissue increases. Because most psychotropics are lipid-soluble, their volume of distribution increases with age. This leads to drug accumulation and longer half-lives. On the other hand, water-soluble medications such as lithium distribute in a smaller volume and pose a higher risk of toxicity.

continued

Table 1

Pharmacokinetic features of cognitive enhancers

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

CYP-450: cytochrome P-450; AChEIs: acetylcholinesterase inhibitors; NMDA: N-methyl-D-aspartate
Source: References 3-5

Clinical Point

Age-associated decline in renal clearance leads to decreased excretion of active metabolites and lithium

In plasma, drugs circulate freely or bound to proteins—mainly albumin and α1-acid glycoprotein. Aging can cause decreased plasma albumin and increased α1-acid glycoprotein.[6] Additionally, malnutrition, diabetes mellitus, and hepatic and renal disease—all more common with advancing age—may cause hypoalbuminemia, which increases the free fraction of drugs bound to albumin.[6] ***Table 1*** includes information about cognitive enhancers' protein binding.

When 2 or more highly protein-bound drugs are coadministered, mutual displacement occurs and the free fraction of each drug increases. A recent case report described valproate toxicity with dizziness, ataxia, and falling in a 76-year-old man after aspirin was added to his regimen.[7] The mechanism appeared to be mutual displacement from albumin combined with metabolism of valproate inhibited by aspirin.[7]

Metabolism. Liver size and hepatic blood flow decrease with aging.[6] Cytochrome P-450 3A4 pathway activity slows, but the 2D6 pathway is not affected.[4] Oxidative metabolism through CYP pathways is slower, but conjugation reactions are not.[6] ***Table 2*** [3,5,7,8] lists major substrates and inhibitors of CYP enzymes.

Azole antifungals are potent inhibitors of CYP 3A4,[4] of which both donepezil and lamotrigine are substrates (***Table 2***). In Mr. B's case, lamotrigine and donepezil levels increased because of this pharmacokinetic interaction. Because donepezil also is metabolized by the CYP 2D6 pathway, the increase in concentration is unlikely to modify the drug effect. Mr. B experienced symptoms consistent with lamotrigine toxicity.

Excretion. The age-associated decline in renal clearance related to a diminished glomerular filtration rate leads to decreased excretion of active metabolites and lithium, making older patients more susceptible to lithium toxicity. The magnitude of the decline in renal clearance varies among patients and is exacerbated by concomitant conditions—such as diabetes and hypertension—and medications—such as nonsteroidal anti-inflammatory drugs (NSAIDs).[4] Thiazide diuretics, angiotensin-converting enzyme inhibitors, and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib may elevate lithium levels.[3]

Pharmacokinetics of AChEIs. AChEIs have relatively few pharmacokinetic interactions, although donepezil and galantamine are metabolized through the liver's CYP 2D6 and 3A4 pathways.

Because rivastigmine does not undergo hepatic metabolism, it is least likely of the cognitive enhancers to have pharmacokinetic interactions with other medications. Rivastigmine did not lead to increased adverse events when administered concomitantly with 22 different classes of medications—including antidiabetics, cardiovascular drugs, gastrointestinal agents, and NSAIDs.[9]

Pharmacodynamics is the study of the time course and intensity of drugs' pharmacologic effects. Pharmacodynamic interactions involve changes in a drug's action at a receptor or biologically active site.[3] Pharmacodynamic interactions may result from an antagonistic

Table 2

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

	CYP 2D6	CYP 3A4
Substrates (substances metabolized by enzyme)	Second-generation antipsychotics Citalopram Donepezil Duloxetine Galantamine Haloperidol Tricyclic antidepressants Trazodone Venlafaxine	Second-generation antipsychotics Benzodiazepines Buspirone Carbamazepine Donepezil Galantamine Haloperidol Lamotrigine Mirtazapine Nefazodone Sertraline Tricyclic antidepressants Trazodone Zolpidem
Inhibitors	Bupropion Cimetidine Duloxetine Fluoxetine Paroxetine Sertraline	Erythromycin Fluconazole Fluvoxamine Grapefruit juice Itraconazole Nefazodone

* All cytochrome P (CYP) 450 enzymes are induced by barbiturates, phenytoin, carbamazepine, and rifampicin. Smoking also induces CYP 1A2.
DDIs: drug-drug interactions; AD: Alzheimer's disease
Source: References 3,5,7,8

Table 3

Potential drug-drug interactions in AD patients taking cognitive enhancers

Interaction	Mechanism	Potential sequela(e)
AChEIs + anticholinergics	↓ Acetylcholine in CNS	Cognitive worsening, delirium
AChEIs + beta blockers	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

AChEIs: acetylcholinesterase inhibitors; PNS: peripheral nervous system
Source: References 3,5,10

or synergistic mechanism (***Table 3***).[3,5,10] Dopamine neurons degenerate with aging, particularly after age 70, and the number of cholinergic receptors decreases in AD patients. As a result, these patients may become more sensitive to antipsychotics, selective serotonin reuptake inhibitors (SSRIs)—which indirectly reduce dopamine outflow—and medications with anticholinergic effects.[4]

Memantine, an amantadine derivative and N-methyl-D-aspartate (NMDA) receptor antagonist, is a weak dopaminergic agonist with atropinic effects.[11] Because memantine is not metabolized by the CYP-450 pathway, it lacks pharmacokinetic DDIs.[12] However, combining memantine

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Clinical Point

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

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Table 4

Medications with moderate to strong anticholinergic activity

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

Source: References 5,13,14

Clinical Point

Concurrent use of anticholinergics and AChEIs is fairly common but is rarely appropriate because of pharmacologic antagonism

with other NMDA antagonists—such as amantadine or dextromethorphan—could cause hallucinations, dizziness, headache, fatigue, and confusion.[11] Concurrent use with drugs that lower seizure threshold, such as tricyclic antidepressants, may increase the risk of seizures.

DDIs with cognitive enhancers

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 antipsychotics (FGAs), and tricyclic antidepressants are common medications with anticholinergic effects (***Table 4***).[5,13,14]

Anticholinergics can counteract AChEIs' beneficial effect. Concurrent use of anticholinergics and AChEIs is fairly common in clinical practice but is rarely appropriate because of pharmacologic antagonism. In a retrospective study of 836 community-living older adults (age ≥65) with probable dementia, Roe et al[13] compared anticholinergic use in 418 who were taking donepezil with 418 matched controls who were not taking donepezil. They found:

- 33% of those taking donepezil also were receiving anticholinergics, compared with 23% of controls
- 26% of all patients in the study used multiple anticholinergic medications.

Similarly, a study of pharmacy claims for AChEIs among 557 Medicaid beneficiaries aged ≥50 found that 35% of patients taking AChEIs also received at least 1 anticholinergic drug.[14]

Antiparkinsonian agents. Interaction of antiparkinsonian medications with AChEIs could limit the efficacy of either drug when treating comorbid AD and Parkinson's disease (PD),[5] although in practice, clinical deterioration of parkinsonism has not been reported.[15] In one study, 25 PD patients stabilized on levodopa/carbidopa were given donepezil, 5 mg/d, or placebo for two 2-week courses separated by a washout of at least 2 weeks. At steady state, pharmacokinetic parameters were unchanged and no clinically significant DDIs were observed.[16]

Cardiovascular agents. 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,[11] such as ziprasidone or haloperidol.

In patients taking these cardiovascular drugs, make sure that heart rate is >60 bpm before AChEI treatment, and monitor regularly.

Other agents. AChEIs inhibit the metabolism of succinylcholine and therefore augment and prolong this drug's neuromuscular blockade. Discontinue AChEIs before administering succinylcholine for

anesthesia, such as for electroconvulsive treatment.

AChEIs may lead to toxicity when added to cholinergic agents such as bethanechol.[11] Similarly, AChEIs may precipitate a cholinergic crisis—with increasing weakness, hypersalivation, abdominal pains, and diarrhea—when used in conjunction with peripheral acetylcholinesterase inhibitors such as the myasthenia gravis agents pyridostigmine and neostigmine. The mechanism is increased acetylcholine available at the neuromuscular junction.

DDIs with other psychotropics

Antipsychotics. Nearly one-half of AD patients experience delusions, often in the middle stage of the disease, and many are prescribed second-generation antipsychotics (SGAs) to control delusions, hallucinations, sundowning, agitation, or aggression. Concomitant use of AChEIs and antipsychotics may increase the risk of extrapyramidal symptoms by disrupting the acetylcholine/dopamine balance in the striatum.[5]

In AD patients taking donepezil and risperidone, case reports describe parkinsonian syndrome and rigidity with immobility, which resolved after the antipsychotic was discontinued.[5,11] When rivastigmine and risperidone were coadministered, however, no clinically relevant adverse interactions were noted in a 20-week, open-label trial of 65 patients with AD, 10 with vascular dementia, and 10 with both.[17]

The FDA has warned of increased risk of death when SGAs are used to treat behavioral disturbances in dementia patients. In a recent meta-analysis of 15 placebo-controlled trials, cognitive tests scores worsened when AD patients took aripiprazole, olanzapine, quetiapine, or risperidone. A significant risk for cerebrovascular events was seen, especially with risperidone, although no clear causal relationship was established.[18] Falls, injury, and syncope were not increased, and patients with less severe dementia, outpatients, and those selected for psychosis were less affected. Thus, provide careful follow-up and avoid long-term unwarranted antipsychotic use in AD patients.

continued

Related Resources

- Jacobson SA, Pies RW, Greenblatt DJ. *Handbook of geriatric psychopharmacology*. Washington, DC: American Psychiatric Publishing; 2002.
- Sandson, NB. *Drug-drug interaction primer*. Washington, DC: American Psychiatric Publishing; 2007.

Drug Brand Names

Amantadine • Symmetrel
Amitriptyline • Elavil
Amoxapine • Asendin
Aripiprazole • Abilify
Atropine • Sal-Tropine
Benztropine • Cogentin
Bethanechol • Urecholine
Biperiden • Akineton
Bupropion • Wellbutrin
Buspirone • BuSpar
Carbamazepine • Tegretol
Celecoxib • Celebrex
Chlorpheniramine • Chlor-Trimeton
Chlorpromazine • Thorazine
Cimetidine • Tagamet
Citalopram • Celexa
Clomipramine • Anafranil
Clozapine • Clozaril
Cyclobenzaprine • Flexeril
Cyproheptadine • Periactin
Dextromethorphan • Benylin, Delsym, others
Dicyclomine • Bentyl
Digoxin • Lanoxin
Diphenhydramine • Benadryl
Disopyramide • Norpace
Donepezil • Aricept
Doxepin • Adapin, Sinequan
Duloxetine • Cymbalta
Escitalopram • Lexapro
Erythromycin • E-Mycin
Fluconazole • Diflucan
Fluvoxamine • Luvox
Fluoxetine • Prozac
Galantamine • Reminyl, Razadyne
Haloperidol • Haldol
Hydroxyzine • Vistaril
Hyoscyamine • Anaspaz, Levbid, Levsin
Imipramine • Tofranil
Itraconazole • Sporanox
Lamotrigine • Lamictal
Levodopa/carbidopa • Sinemet
Lithium • Eskalith, Lithobid
Lorazepam • Ativan
Meclizine • Antivert
Memantine • Namenda
Mirtazapine • Remeron
Nefazodone • Serzone
Neostigmine • Prostigmin
Olanzapine • Zyprexa
Oxazepam • Serax
Oxybutynin • Ditropan
Paroxetine • Paxil
Pimozide • Orap
Promethazine • Phenergan
Protriptyline • Vivactil
Pyridostigmine • Mestinon
Quetiapine • Seroquel
Ranitidine • Zantac
Risperidone • Risperdal
Rivastigmine • Exelon
Scopolamine • Scopace
Sertraline • Zoloft
Succinylcholine • Anectine
Temazepam • Restoril
Thioridazine • Mellaril
Tolterodine • Detrol
Trazodone • Desyrel
Trihexyphenidyl • Artane
Valproate • Depakote
Venlafaxine • Effexor
Warfarin • Coumadin
Ziprasidone • Geodon
Zolpidem • Ambien

Disclosure

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

The herbal supplement ginkgo biloba inhibits platelet aggregation and can cause bleeding complications

Highly anticholinergic FGAs such as chlorpromazine are not recommended for AD patients (***Table 4, page 64***).

Antidepressants. Up to 30% of AD patients experience major depression.[19] 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.[4] Fluvoxamine, fluoxetine, and paroxetine inhibit CYP 2C9, through which warfarin and some other drugs with a narrow therapeutic index are metabolized.[6]

Benzodiazepines are contraindicated in elderly patients (especially those with AD) because of the high risk of delirium, worsened cognitive function, paradoxical disinhibition, and falls.[20] 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.[19] See ***Table 2*** for more information on benzodiazepine DDIs.

Herbal supplements. Ginkgo biloba and huperzine A (Chinese club moss) are the herbal supplements used most commonly by dementia patients. Ginkgo inhibits platelet aggregation and can cause bleeding complications, with or without concomitant antiplatelet or anticoagulant

Bottom Line

Alzheimer's disease patients are at risk for pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs). When using potent cytochrome P-450 inhibitors, be aware of medications the patient is taking that are substrates of these enzymes. Avoid concomitant use of acetylcholinesterase inhibitors (AChEIs) and anticholinergics. Other DDIs, such as AChEIs with antipsychotics or antiparkinsonian drugs, are rarely clinically significant. Periodic follow-up and close monitoring of side effects may help prevent iatrogenic adverse events.

therapy such as aspirin, warfarin, and NSAIDs. Enzyme induction of CYP 2C19 by ginkgo, leading to subtherapeutic levels of anticonvulsants, has been implicated in a report of fatal seizures. Huperzine A is a natural cholinesterase inhibitor and should not be combined with AChEIs because of the risk of additive adverse effects.[10]

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