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Potential drug interactions with cholinesterase inhibitors in Alzheimer patients: A guideline for Neurologists

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ABSTRACT

Cholinesterase inhibitors are used for the symptomatic treatment of patients with Alzheimer's disease (AD). This population often has numerous comorbidities and is treated with multiple medications, which leads to polypharmacy. Possible pharmacokinetic and pharmacodynamic drug interactions may occur with this type of concomitant treatment, such as interactions with antipsychotics, antidepressants, anticholinergics, and cardiovascular and urinary disorder medications. Drug interactions should always be considered to reduce the risk of side effects and other problems for patients and also to increase the effectiveness of therapeutic drugs for AD.

INTRODUCTION

Cholinesterase is a family of enzymes that catalyzes the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation. These enzymes break down acetylcholine in the brain; if their action is inhibited, more acetylcholine is available for communication between brain cells (Colovic *et al*., 2013). Patients with Alzheimer disease (AD) have reduced cerebral production of choline acetyl transferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function, therefore Cholinesterase inhibitors (ChEIs) were the first medication approved by the Food and Drug Administration (FDA) for the treatment of cognitive deficits in AD (Lopez *et al*., 2002). Commonly prescribed medications, such as antihistamines and tricyclic antidepressants (TCAs), often have anticholinergic properties that alone or in combination with other medications can antagonize the effects of CEIs. Other medication classes, such as antipsychotics and cholinergic agents, may also result in pharmacodynamic interactions (Tavassoli *et al*., 2007). One of the crucial consequences of an aging population (older than 65 years of age) is the higher prevalence of age-related disorders. Hence, the negative impact of polypharmacy , the use of multiple medications, generally ranges from 5 to 10, by a patient, is an inevitable phenomenon of this change in the health condition of the elderly in general and in AD patients specifically (Campanelli, 2012; Fick *et al*., 2003; Linjakumpu *et al*., 2002).

Considering the importance of drug interactions in these frail patients, professionals who work in geriatric field should pay more attention to this issue, especially in developing countries that have health systems with limited resources (Narayan *et al*., 2013; Roe *et al*., 2002). The aim of this mini review was to provide a practical study about important drug interactions with AD medications, such as ChEIs, for professionals who work in the field of dementia.

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Method

The PubMed and Elsevier databases were searched for surveys published during the last five years. Other applicable resources, such as the UpToDate subscription-based resource database, Lexicomp (a clinical drug information database), and the American Geriatric Society Updated Beers Criteria, were used. The interaction between ChEIs and Memantine with current medications prescribed for the treatment of common chronic disorders in elderly patients with AD have been studied. We selected medications that are approved for use in elderly patients with AD. Therefore, any medications that are contraindicated or should be avoided (like clidinium-C and cimetidine) have not been included in this review.

Results

The AD population often has many comorbidities and receives treatment with multiple medications. The astute clinician should remain mindful of possible drug interactions (both pharmacokinetic and pharmacodynamic) that may occur with concomitant treatment.

We have listed the drug interactions between ChEIs and Memantine with medications used for common chronic disorders in AD patients along with their pharmaceutical applications, such as UpToDate, Lexicomp, and a few books in the field of drug-drug interactions, such as Drug Interaction Facts.

Tables 1–4 have also been included to show possible interactions in these diverse classes of medications. As shown in table 5, some of these interactions have been reported so important that patients who use these medications should be advised to consider therapy modification to prevent deleterious effects. Other drug combinations should be avoided, while still others carry the recommendation for closely monitoring the patient's therapy.

Table 1: Drug interactions between AChE-Is and Memantine with antidepressants.

Interactions	Rivastigmine	Donepezil	Galantamine	Memantine
TCAs	Tertiary TCAs decrease pharmacologic effects of AChEIs; Exception: Desipramine and Nortriptyline with caution			No interaction
SSRIs	Paroxetine should be avoided, its anticholinergic effect may diminish efficacy of Rivastigmine.	Paroxetine should be avoided, its anticholinergic effect may diminish efficacy of Donepezil	Fluvoxamine, Fluoxetine and Paroxetine should be avoided, Fluoxetine and Fluvoxamine can increase galantamine plasma concentration; anticholinergic effect of paroxetine may diminish efficacy of donepezil	No interaction
Bupropion	Increase risk of seizure			Reduce renal clearance of memantine

Online drug information database, Lexi-Interact™ Online

Table 2: Drug interactions between AChE-Is and Memantine with urinary anticholinergics.

Interactions	Rivastigmine	Donepezil	Galantamine	Memantine
Propantheline	Urinary anticholinergic agents may antagonize therapeutic efficacy of acetylcholinesterase inhibitors. Solifenacin and Darifenacin has the least interaction and is drug of choice in these patients.			No interaction
Oxybutynin				No interaction
Tolterodine				No interaction
Solifenacin				No interaction

Online drug information database, Lexi-Interact™ Online

Table 3: Drug interactions between AChE-Is and Memantine with antipsychotics.

Interactions	Rivastigmine	Donepezil	Galantamine	Memantine
Quetiapine	Anticholinergic effects of these medications can diminish therapeutic effects of Acetylcholinesterase inhibitors. Increase risk of QT interval prolongation and torsade de pointes.			No interaction
Olanzapine				No interaction
Risperidone				No interaction
Aripiprazole				No interaction
Clozapine				No interaction
Haloperidol				No interaction
Trifluoperazine				No interaction
Chlorpromazine				No interaction
Ziprasidone				No interaction

Online drug information database, Lexi-Interact™ Online

Table 4: Drug interactions between AChE-Is and Memantine with cardiovascular drugs.

Interactions	Examples	Rivastigmine	Donepezil	Galantamine	Memantine
Beta Blockers	Atenolol, Carvedilol, Metoprolol,Sotalol	Vagotonic effects of AchEIs on SA and AV nodes with concomitant use of these medications can cause bradycardia and heart block. The most vagotonic effect has seen with rivastigmine and the least effect has seen with galantamine. Monitor patient regularly.			No interaction
Non-Dihydropyridine CCBs	Diltiazem Verapamil				No interaction
Digitalis Preparation	Digoxin				No interaction
Antiarrhythmic Agents	Disopyramide, Procainamide, Quinidine, Amiodarone				No interaction
Diuretics	HCTZ Furosemide	No interaction			Altered plasma levels of memantine and HCTZ, not clinically important

Online drug information database, Lexi-Interact™ Online

Table 5: Examples of some potential drug-drug interactions in Alzheimer's patients taking cognitive enhancers.

Interaction	Mechanism	Results Articles	Description	Ref
AChEIs + anticholinergics	↓ Acetylcholine in CNS	Anticholinergic drugs may antagonize the effects of cholinesterase inhibitors.	This drug combination should be avoided.	(Johnell and Fastbom, 2008).
		dual use of ChEIs and bladder anticholinergics may result in decline activity of daily living function .	bladder anticholinergics such as oxybutynin or tolterodine with ChEIs may result in greater rates of functional decline than use of ChEIs alone.	(Sink *et al*., 2008)
AChEIs + Beta Blockers	Vagal Stimulation and Sympathetic blockade	Concurrent use of AChEIs and beta blockers could worsen bradycardia and cause syncope.	In patients taking these cardiovascular drugs, make sure that heart rate is >60 bpm before AChEI treatment, and monitor regularly.	(Paulison and Léos, 2010)
AChEIs + Antipsychotics	This interaction produces an extrapyramidal syndrome and worsening of extrapyramidal adverse effects	This interaction may be attributable to a relative imbalance of cholinergic and dopaminergic activity in the striatum, which may occur following concomitant administration of a dopaminolytic and a cholinesterase inhibitor.	For example,Donepezil significantly potentiated bradykinesia induction with a low dose of haloperidol and worsening of extrapyramidal adverse effects in patients receiving a combination of donepezil and risperidone.	(Shimizu *et al*., 2015) (Magnuson *et al*., 1998) (Liu *et al*., 2002) (Pasqualetti *et al*., 2015)

DISCUSSION

The neuropsychiatric symptoms in AD and other types of dementia are extremely common and often much more troubling than amnestic symptoms. Depression is also a frequent psychiatric disorder in this group of patients (Lyketsos and Lee, 2003), and drugs to treat this and other symptoms are often prescribed to AD patients. For example, selective serotonin reuptake inhibitors (SSRIs) are useful in the management of agitation and paranoia in the AD population (Seitz *et al*., 2011).

The selection of a specific SSRI is generally based upon its side effect profile, any drug interactions, and cost. Fluvoxamine, fluoxetine, and paroxetine are not good choices due to drug interactions that result from their inhibition of CYP 2C9, which reduces the metabolism of some drugs prescribed concomitantly; paroxetine in particular has significant anticholinergic effects (Preskorn, 1997).

Among the drugs in this category, citalopram and s-citalopram are the most suitable choice for these patients because they produce fewer drug interactions; however, due to the increased risk of cardiac arrhythmia in patients using citalopram (especially in the elderly at higher doses), any dose higher than 20 mg daily is not recommended in these patients (Porsteinsson *et al*., 2014). The anticholinergic properties of TCAs can increase confusion and reduce the positive effects of the ChEIs (Table 1); therefore, nortriptyline should be considered due to its lower incidence of adverse anticholinergic effects compared to other TCAs, as it is typically a better tolerated choice (Taragano *et al*., 1997). Sleep disturbances are also common in patients with AD. Drugs prescribed to treat these disturbances may also interact with other drugs that elderly patients are taking. Usually, for overcome of sleep disorders, medications such as antipsychotic and/or anti-depressant drugs are prescribed by physician for AD patients. Therefore, the interaction between these drugs with the class of ChEIs should be kept in mind (Katz *et al*., 1998).

Antipsychotics are often used in concomitant with ChEIs to treat the behavioral and psychological symptoms of dementia. The practitioners should take in consideration the interactions between ChEIs and antipsychotic drugs. It is important to consider the interactions between ChEIs and antipsychotic drugs to obtain the most effective treatment for patients with AD. It is thought that the co-prescription of ChEIs and dopamine D2 receptor blockers may induce an acetylcholine/dopamine imbalance in the striatum, producing an extrapyramidal syndrome and making extrapyramidal adverse effects worse (Table 3). Agitation and aggression are frequently occurring and distressing behavioral and psychological symptoms of dementia. The most widely prescribed pharmacological treatments for these symptoms are atypical antipsychotics (Ballard *et al*., 2009).

CONCLUSION

An interdisciplinary "geriatric assessment" is essential for a comprehensive evaluation of the prescriptions in the patients with AD who receive ChEIs and Memantine. Moreover raising awareness of the professionals and families about careful drug regimen review is essential to identify potentially inappropriate or hazardous medications to modify the treatment protocol (Tanaka *et al*., 2009). This assessment might reduce the length of hospital admissions, related costs and patient mortality and morbidity.

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REFERENCES

Ballard C, Corbett A, Chitramohan R, Aarsland D. Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions. Curr Opin Psychiatry, 2009; **22**:532-540.

Campanelli CM. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc, 2012; **60**:616-631.

Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol, 2013; **11**:315-335.

Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication

use in older adults: results of a US consensus panel of experts. Arch Intern Med, 2003; **163**:2716-2724.

Johnell K, Fastbom J. Concurrent Use of Anticholinergic Drugs and Cholinesterase Inhibitors. Drugs Aging, 2008; **25**:871-877.

Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc, 1998; **46**:8-13.

Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol, 2002; **55**:809-817.

Liu HC, Lin SK, Sung SM. Extrapyramidal side-effect due to drug combination of risperidone and donepezil. Psychiatry Clin Neurosci, 2002; **56**:479-479.

Lopez O, Becker J, Wisniewski S, Saxton J, Kaufer D, DeKosky S. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry, 2002; **72**:310-314.

Lyketsos CG, Lee HB. Diagnosis and treatment of depression in Alzheimer's disease. Dement Geriatr Cogn Disord, 2003; **17**:55-64.

Magnuson TM, Keller BK, Burke WJ. Extrapyramidal side effects in a patient treated with risperidone plus donepezil. Am J Psychiatry, 1998; 155: 1458-1459.

Narayan SW, Hilmer SN, Horsburgh S, Nishtala PS. Anticholinergic component of the Drug Burden Index and the Anticholinergic Drug Scale as measures of anticholinergic exposure in older people in New Zealand: a population-level study. Drugs Aging, 2013; **30**:927-934.

Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F. Potential drug–drug interactions in Alzheimer patients with behavioral symptoms. Clin Interv Aging, 2015; **10**:1457-1466.

Paulison B, Léos CL. Potential cardiotoxic reaction involving rivastigmine and beta-blockers: a case report and review of the literature. Cardiovasc Toxicol, 2010; **10**:306-310.

Porsteinsson AP, Drye LT, Pollock BG, Devanand D, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA, 2014; 311:682-691.

Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. Clin Pharmacokinet, 1997; **32**:1-21.

Roe CM, Anderson MJ Spivack B. Use of anticholinergic medications by older adults with dementia. J Am Geriatr Soc, 2002; **50**:836-842.

Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev, 2011; **16, 2**: CD008191.

Shimizu S, Mizuguchi Y, Sobue A, Fujiwara M, Morimoto T, Ohno Y. Interaction between anti-Alzheimer and antipsychotic drugs in modulating extrapyramidal motor disorders in mice. J Pharmacol Sci, 2015; **127**:439-445.

Sink KM, Thomas J, Xu H, Craig B, Kritchevsky S, Sands LP. Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes. J Am Geriatr Soc, 2008; **56**:847-853.

Tanaka A, Koga S, Hiramatsu Y. Donepezil-induced adverse side effects of cardiac rhythm: 2 cases report of atrioventricular block and Torsade de Pointes. Intern Med, 2009; **48**:1219-1223.

Taragano FE, Lyketsos CG, Mangone CA, Allegri RF, Comesaña-Diaz E. A double-blind, randomized, fixed-dose trial of fluoxetine vs. amitriptyline in the treatment of major depression complicating Alzheimer's disease. Psychosomatics, 1997; **38**:246-252.

Tavassoli N, Sommet A, Lapeyre-Mestre M, Bagheri H, Montrastruc JL. Drug Interactions with Cholinesterase Inhibitors. Drug safety, 2007; **30**:1063-1071.

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