

**CASE STUDY 2:
THE IMPACT OF PHARMACOLOGIC TREATMENT OF
ALZHEIMER'S DISEASE ON COGNITION, BEHAVIOR, AND
ACTIVITIES OF DAILY LIVING**

Michael W. Jann, PharmD, FCCP, FCP, BCPP

Patient Presentation

Chief Complaint: “I am more forgetful now than before.”

History/Physical Findings: MJK is an 80-year-old white male who resides with his daughter and her family. The family members reported that MJK has had short-term memory problems over the past 4–5 months. These cognitive symptoms have included forgetting times and places once familiar to him, missing appointment dates and calendar days, and misplacing a house key on several occasions during the past few weeks. The family became alarmed when MJK didn't remember what the house key was used for. He becomes angry and irritable when these incidents occur. Yesterday, MJK became angry at the grocery-store clerk when MJK was unable to understand the amount of correct change from the grocery bill and accused the clerk of “stealing.” Over the past few weeks, his daughter noticed that he paces or wanders around the house at night for a few hours before going to his bedroom.

MJK served in the Air Force during WWII in Europe and obtained a bachelor's degree and a doctorate in engineering. He was a faculty member in the department of mechanical engineering at the local university and is now retired.

MJK's parents are deceased, reasons unknown, but both lived well into their 80s. His spouse died 5 years ago.

Review of Systems (ROS): Osteoarthritis in both knees for 7 years (complains of occasional knee pain and takes ibuprofen 200 mg prn); no previous history of psychiatric problems; no known allergies (NKA); no history of psychiatric problems; no daily medications.

Physical Exam: General appearance: white male's appearance is consistent with his 80 years. Vital signs: BP 138/88 sitting; pulse 78; respiratory rate 18; temperature 36.6°C; Weight 167 lbs.; height 5' 10". Skin: normal texture and color. HEENT: within normal limits. Lungs: clear, normal breath sounds. Cardiovascular: regular rhythm and rate (RRR), no murmurs. Musculo-skeletal and extremities: normal.

Neurologic Exam: Motor, sensory, cerebellar, and gait are within normal limits. Folstein Mini-Mental Status Exam (MMSE) score, 24/30. Disoriented to date and day of the week, good registration but impaired ability to complete serial 7s, impaired attention, and very poor short-term memory. Unable to recall any three items after 3 minutes. Able to draw interlocking pentagons.

Laboratory Assessments

CT scan: Mild generalized cerebral cortical atrophy.

ECG: Normal sinus rhythm. Ventricular rate 78 bpm, PR interval 134 msec, QRS duration 83 msec, QT 344 msec.

Chemistry panel: Na 132 mEq/L, K 4.0 mEq/L, Cl 102 mEq/L, CO₂ 26 mEq/L, BUN 10 mg/dL, SCr 1.0 mg/dL, Glucose 98 mg/dL.

Complete blood count: Hgb 14.0 g/dL, Hct 42.0%, RBC 4.48 x 10⁶/mm³, Platelets 420 x 10³/mm³, WBC 6500/mm³, Neutrophils 60%, Lymphocytes 27%, and Monocytes 5%.

Liver function tests: AST 34 U/L, ALT 23 U/L, Alk Phos 76 U/L, GGT 22 U/L, LDH 88 U/L, Tot. Bilirubin 1.0 mg/dL. Tot. Protein 7.4 g/dL, Albumin 4.8 g/dL, Chol 176 mg/dL, Ca 8.8 mg/dL, Trigly 161 mg/dL, and Phos 4.2 mg/dL.

Thyroid function test: TSH 2.2 µU/mL, T₄ 7.2 µg/dL, B₁₂ 458 pg/mL; Folate 6.1 ng/mL.

Urinalysis: Appearance clear, specific gravity 1.020, pH 7.8, glucose, protein, ketone, and occult blood results were all negative. RBC, WBC: none were seen.

ASSESSMENT

Probable AD: mild stage 3 on the global deterioration scale (GDS). Some behavioral symptoms present without psychosis or depression.

CLINICAL COURSE

Family members met with MJK's primary care physician and discussed the diagnosis of probable AD and its current treatment regimen with cholinesterase inhibitors (ChEIs). The family desired to keep MJK at home and manage his symptoms. The physician explained the fluctuating symptoms of the disease that could include memory impairment, behavioral changes, and alterations in daily functional activities.

MEDICATIONS

Donepezil 5 mg daily for 3 months. Increase the dose to 10 mg donepezil daily if no significant adverse events present and add vitamin E 1000 IU twice a day.

FOLLOW-UP EVALUATIONS DURING CLINICAL COURSE

Three months later, MJK experienced no significant adverse events except mild nausea during the first week of donepezil. This effect was well tolerated, and no concomitant medications were needed for the nausea. Donepezil was increased to 10 mg. The family noticed a slight improvement in MJK's nightly wandering and noticed a decrease in his irritability. Also, the family mentioned that MJK's misplacement of keys and other items has not occurred as often. The physician's MMSE score at 3 months was 23. At a subsequent follow-up evaluation at 6 months, the family reported no significant changes in his behavior and MJK continues to function appropriately at home without assistance from family members. His activities include toileting, using the telephone, self-dressing,

eating, interest in finances and hobbies (e.g., watching baseball, playing golf). MMSE score at 6 months was 24.

CASE DISCUSSION

MJK displayed the typical symptoms and time course found in patients with probable AD. Although family members noticed memory problems over the past 4–5 months, these problems most likely started earlier. The onset of symptoms with cognitive impairment often begin at least several months (in some cases even years) prior to others noticing memory problems. Impaired memory or cognitive impairment is the hallmark characteristic of the disease. Specifically, the short-term memory becomes the most affected in the early stages of AD. Forgetting dates or the day of week is common, but the patient often defensively dismisses these incidents as ordinary lapses in memory. Anyone can misplace a household item. However, one of the main features of AD regarding cognitive impairment is the patient forgetting the function of a common household item, such as, in this case, the front-door house key.

Behavioral or personality changes often occur with the disease. Irritability, anger, and nighttime wandering occurred in MJK over this time period. In other cases, hallucinations, delusions, and depression can be found. MJK accused the grocery store clerk of “stealing,” but since this was a one-time occurrence (in the course of his disease), one cannot conclude that delusions are a part of his behavioral disturbance at this time. However, family members need to know that these psychiatric symptoms can appear with the disease and that other concomitant medications, such as antipsychotics or antidepressants, may be needed at some time during this chronic illness. MJK’s ability to function in the course of daily activities (e.g., toileting, dressing, etc.) has not yet been affected due the early nature of the disease.

The diagnostic evaluations of MJK’s primary care physician are a typical work-up recommended by many experts who treat AD. When these tests are

completed, there is about a 90% reliability that the patient who has a cognitive impairment has probable AD. Epidemiologic data also indicate that in persons aged 75–80 years the incidence of AD is about 35%–40%. AD, as one form of cognitive problems also known as dementias, is by far the most common form of dementia and comprises 65% of all dementias (Small et al 1997).

MJK's primary care physician placed him on donepezil 5 mg daily. Donepezil was approved by the FDA in 1996 for the treatment of mild-to-moderate AD. MJK's MMSE score of 24 points and his GDS score of 3 indicate that he is in the mild stage of the illness. The earlier work of many scientists has shown that AD affects many different brain areas but most notably the cholinergic neurons (Van Den Berg et al 2000). Cholinesterase inhibitors (ChEIs) are the only class of medications approved by the FDA for the treatment of AD. ChEIs main pharmacologic action is to prevent the breakdown of the neurotransmitter acetylcholine by inhibition of the enzyme acetylcholinesterase (AChE). AChE is present in the brain and binds to the acetylcholine and produces a rapid breakdown of the neurotransmitter. ChEIs, like donepezil, bind to AChE to prevent its action on acetylcholine, thereby allowing the neurotransmitter to function longer at the synaptic cleft.

ChEIs are the most rigorously studied class of medications with well-documented, placebo-controlled studies. Tacrine (Cognex[®]) was the first ChEI approved by the FDA in 1993. However, its adverse-effect profile involving hepatic dysfunction, necessitating constant liver function tests, and its high incidence of gastrointestinal problems of nausea and vomiting limit its efficacy in patients with AD (Van Den Berg et al 2000).

Donepezil 5 mg was prescribed for MJK for the first 3 months. This is the typical starting dose for donepezil. Due to its long elimination half-life (mean 70 hours), donepezil can be administered on a once-a-day basis that is convenient for patients, their caregivers, and prescribers.

At 3 months, MJK's family noticed no significant changes in his memory, but more importantly, no decline in cognitive impairment. Donepezil 5 mg daily was reported in clinical trials at 15 weeks to significantly differ from the placebo group in MMSE scores ($P = 0.004$) and global improvement was noted (Rogers et al 1998a). The drug dose was increased, and at 6 months, MJK's MMSE score remained unchanged since starting donepezil. This finding is typical with these medications, indicating that memory or cognitive function is not declining. Placebo-controlled studies indicated that at the 3- and 6-month time periods patients who received placebo showed significant decline compared with patients taking donepezil 5 mg and 10 mg (Rogers et al 1998ab). This important finding indicates that donepezil can maintain cognitive function compared with untreated patients who decline. Scientists and clinicians consider this maintenance of cognitive function a clear improvement (Table 1).

Interestingly, behavioral symptoms such as nighttime wandering also improved for MJK. Recent evidence indicates that ChEIs may possess psychotropic properties that improve common behavioral problems found in patients with AD (Cummings 2000). A recent study reported that donepezil improved restlessness, overactive behavior without a clear purpose, and wandering (Weiner et al 2000). Further, irritability also improved with ChEIs and is specifically reported with donepezil (Cummings 2000; Weiner et al 2000). These improvements in behavioral symptoms were noted to occur at 3 months and remained constant 12 months later (Weiner et al 2000).

Cognitive function and behavioral problems are commonly found in patients with AD. These two factors affect the patient's overall daily activities and his ability to function at home or in other living arrangements. Maintenance of cognitive function and improvement in behavioral symptoms can translate into maintaining MJK's status at home, his ability to care for himself in daily functions, such as dressing, and his interest in hobbies.

Only very mild nausea was reported during MJK's first week of treatment with donepezil. It was tolerated by the patient and required no therapeutic interventions. This can occur with ChEIs by their pharmacologic actions on the gastrointestinal system. The incidence of gastrointestinal problems associated with ChEIs is lowest with donepezil, where a slow dosage titration minimizes these side effects (Barner and Gray 1998; Dooley and Lamb 2000; Van Den Berg et al 2000). Donepezil has not displayed any hepatotoxicity as is reported with tacrine (Barner and Gray 1998).

Vitamin E 1000 IU twice a day is commonly recommended by many clinicians to be taken with ChEIs. This vitamin was shown to benefit patients with AD and is relatively safe and inexpensive (Sano et al 1997).

At this time, MJK does not need other medications to treat other psychiatric problems, such as depression, hallucinations, or delusions commonly found in patients with AD. However, if these psychotropic medications or other drugs frequently prescribed for medical illnesses found in the elderly are needed, the likelihood of any clinically significant drug-drug interaction with donepezil is negligible.

Donepezil is metabolized by cytochrome P 450 (CYP) isozymes 3A4 and 2D6. However, donepezil's effect on these isozymes is minimal due to its low binding affinity (50–130 μmol), relative to the drug's plasma concentration of 164 nmol usually found in patients (Dooley and Lamb 2000). For example, risperidone 1.0 mg (an atypical antipsychotic commonly prescribed for patients with AD with agitation and psychosis) was coadministered with donepezil 5 mg for 14 consecutive days into healthy volunteers (Pesco-Koplowitz et al 2000). No significant differences in risperidone or donepezil pharmacokinetics were found. Adverse effects of headache, nervousness, and somnolence were similar with risperidone alone, donepezil alone, or in combination. Other drug-drug

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Table 2.

Drug	Enzyme Selection	Side Effects	Precautions	Drug Interactions	Metabolism	Effect of Food	Comments
Tacrine	ChE> AchE	Elevated transaminase, nausea, vomiting, diarrhea, dizziness, confusion, headache, myalgia	ALT levels must be monitored Should be taken without food if tolerated	Yes Theophylline, Amitriptyline & Tricyclic Anti-depressants may counteract effects of tacrine	Hepatic (2D6, 3A4)	Decreases effectiveness	Must be administered at regular intervals. Rash, jaundice, change in stool color may occur with prolonged treatment
Donepezil	ChE> AchE	Nausea, vomiting, diarrhea, headache, insomnia, dizziness, pain in various locations	Take without regard to food	Yes	Hepatic (1A2, 2D6)	None	
Rivastigmine	AChE> ChE	Nausea, vomiting, diarrhea, dizziness, headache, insomnia, accidental trauma, fatigue, UTI, asthenia	Should be taken with food	No	Nonhepatic	Decreases C max, increases AUC	Nicotine increases clearance by 25%
Galantamine HBr	AChE> ChE	Nausea, vomiting, diarrhea, anorexia, weight loss	Concentrations increase rapidly in the elderly	Yes, however, no interaction with warfarin or digoxin	Hepatic (2D6, 3A4)	Decreases C max, delays T	Dose cautions for renal impaired and elderly

Sey 2000; Wick et al 2000; Galantamine PI.

ChEIs

Most of the cholinesterase inhibiting compounds induce limiting adverse effects that are characterized by cholinergic overstimulation at inhibition levels of 30%–50%. There is really no reported consistent threshold cholinesterase inhibition level, which is correlated with cholinergic side effects. Therefore, differing tolerability profiles of ChEIs are thought to be determined more by pharmacodynamic and pharmacokinetic peculiarities rather than by the fact acetylcholinesterase is inhibited.

The only consistent tolerability determinant of ChEIs appears to be the rate of change in cholinesterase activity in the daily profile. Most evidence suggests that some levels of inhibition are better tolerated if peak inhibitions is protracted as opposed to or compared with rapid drops from baseline to peak inhibition. Signs of cholinesterase overstimulation are usually transient even if inhibition is maintained for long periods with drugs such as donepezil and matrifonate.

Rapid metabolism and, thus, excretion of ChEIs for long-term therapy in Alzheimer's patients should optimally not involve the cytochrome P-450 systems. Alzheimer's patients frequently take several medications in parallel. A cytochrome P-450 dependent metabolism and strong binding to plasma proteins would unnecessarily increase the risk of potential pharmacokinetic drug-to-drug interactions between the ChEIs and additional therapies.

ChEIs as a whole are the most successful agents for symptomatic treatment of Alzheimer's disease. Clinical results with some of the second-generation drugs such as AchE-I/BuChEs (butyrylcholinesterase) indicate that the disadvantages might be overcome by improving CNS selectivity and, as such, decrease the peripheral cholinergic effects and toxicity discussed in other presentations.

interaction studies have been completed, comparing cimetidine, theophylline, and ketoconazole. Each of these agents did not produce clinically significant changes in donepezil pharmacokinetics (Tiseo et al 1998abc). Ketoconazole is a CYP 3A4 isozyme inhibitor and, when coadministered with donepezil, resulted in only 26% increase in donepezil area under the plasma concentration time curve (AUC) (Tiseo et al 1998a). Cimetidine is a commonly tested compound in drug-drug interaction studies known to interact with many different drugs (Table 2). Yet, cimetidine produced only 20% increase in donepezil AUC (Tiseo et al 1998b). Both of these interaction studies were conducted in healthy volunteers and, in the clinical situation, in patients with AD. These donepezil AUC changes are not likely to be clinically significant.

When digoxin was coadministered with donepezil, the pharmacokinetic disposition of either drug remained unaltered during coadministration (Tiseo et al 1998d). Donepezil is highly bound to plasma proteins (96%) (Van Den Berg et al 2000; Barner and Gray 1998). However, protein binding displacement drug-drug interactions are also unlikely to occur as donepezil is only 75% bound to albumin and 21% to alpha-one acid glycoprotein (Van Den Berg et al 2000). When coadministered with warfarin, donepezil resulted in no significant changes in R or S warfarin pharmacokinetics (Tiseo et al 1998e).

CONCLUSIONS

Donepezil is a ChEI, the only class of medications approved by the FDA for the treatment of mild-to-moderate Alzheimer's disease. It has been available since 1996, and its safety is well established in clinical practice (Table 3). Clinical trial data show that cognitive function is maintained with donepezil while placebo-treated patients declined. Maintenance of cognitive function is a clear improvement compared with decline rates among untreated patients. ChEIs may also possess psychotropic actions and improve behavioral symptoms commonly found in patients with Alzheimer's. These two factors can positively affect the daily activities and functioning in these patients while lessening the

burden on caregivers. Donepezil is unlikely to have clinically significant drug-drug interactions.

Table 3. Alzheimer's Treatment

<ul style="list-style-type: none"> • ChEIs are well tolerated with extended use • Residency environment is not a barrier to use • Dementia patients also respond • Certain ChEIs may decrease the amount of antipsychotics • Early treatment results in better long-term benefits • ChEIs continue to be mainstay of treatment • No reliable data exists for nicotine, estrogen as treatments • NSAIDs are not currently recommended for AD prevention or treatment • Vitamin E 2000IU per day may be prudent in newly diagnosed patients • Alzheimer vaccines and stem cell transplants remain in early research

Wick et al 2000.

REFERENCES

Barner EL, Gray SL. Donepezil use in Alzheimer's disease. *Ann Pharmacother.* 1998;32:70-77.

Cummings JL. Cholinesterase inhibitors: a new class of psychotropic compounds. *Am J Psychiatry.* 2000;157:4-15.

Dooley M, Lamb HM. Donepezil. *Drugs Aging.* 2000;16:199-226.

Galantamine Prescribing Information.

Pesco-Koplowitz L, Parier JL, Zhao Q, et al. Pharmacokinetics of risperidone/donepezil combination. *Biol Psychiatry*. 2000;47:167S.

Rogers SL, Doody RS, Mohs RC, et al. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med*. 1998a;158:1021-1031.

Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998b;50:136-145.

Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med*. 1997;336:1216-1222.

Sey M. The importance of early detection in the treatment of Alzheimer's disease. Based on Sey's presentation at the 31st Annual Meeting and Exhibition of the American Society of Consultant Pharmacists, November 1-4, 2000 at Hynes Convention Center, Boston, MA.

Small GW, Rabins PV, Barry PP, et al. Diagnosis and treatment of Alzheimer's disease and related disorders. *JAMA*. 1997;278:1363-1371.

Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and ketoconazole: assessment of pharmacokinetic changes following single and multiple doses. *Br J Clin Pharmacol*. 1998a;46:30-34.

Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and cimetidine: assessment of pharmacokinetic changes following single and multiple doses. *Br J Clin Pharmacol*. 1998b;46:25-29.

Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and theophylline: assessment of pharmacokinetic changes following multiple-dose administration in healthy volunteers. *Br J Clin Pharmacol*. 1998c;46:35-39.

Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and digoxin: assessment of pharmacokinetic changes. *Br J Clin Pharmacol*. 1998d;46:41-44.

Tiseo PJ, Perdomo CA, Friedhoff LT. The effect of multiple doses of donepezil HCl on the pharmacokinetics and pharmacodynamics of warfarin. *Br J Clin Pharmacol*. 1998e;46:45-50.

Van Den Berg CM, Kazmi Y, Jann MW. Cholinesterase inhibitors for the treatment of Alzheimer's disease in the elderly. *Drugs Aging*. 2000;16:123-138.

Weiner MF, Martin-Cook K, Foster BM, et al. Effects of donepezil on emotional/behavioral symptoms in Alzheimer's disease patients. *J Clin Psychiatry*. 2000;61:487-492.

Wick JY, Zanni GR. Alzheimer's Disease: Pathogenesis and Pharmacotherapy. Clinical newsletter of the American Society of Consultant Pharmacists. 2000;15.