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High-dose donepezil or memantine: Next step for Alzheimer's disease?

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Larger dosages may benefit patients who have 'maxed out' existing therapies

Although cholinesterase inhibitors (ChEIs) and memantine at standard doses may slow the progression of Alzheimer's disease (AD) as assessed by cognitive, functional, and global measures, this effect is relatively modest. For the estimated 5.4 million Americans with AD[1]—more than one-half of whom have moderate to severe disease[2]—there is a great need for new approaches to slow AD progression.

High doses of donepezil or memantine may be the next step in achieving better results than standard pharmacologic treatments for AD. This article presents the possible benefits and indications for high doses of donepezil (23 mg/d) and memantine (28 mg/d) for managing moderate to severe AD and their safety and tolerability profiles.

Current treatments offer modest benefits

AD treatments comprise 2 categories: ChEIs (donepezil, rivastigmine, and galantamine) and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (***Table 1***).[3,4] All ChEIs are FDA-approved for mild to moderate AD; donepezil also is approved for severe AD. Memantine is approved for moderate to severe AD, either alone or in combination with ChEIs. Until recently, the maximum FDA-approved doses were donepezil, 10 mg/d, and memantine, 20 mg/d. However, these dosages are associated with only modest beneficial effects in managing cognitive deterioration in patients with moderate to severe dementia.[5,6] Studies have reported that combining a ChEI, such as donepezil, and memantine is well tolerated and may result in synergistic benefits by affecting different neurotransmitters in patients with moderate to severe AD.[7,8]

Table 1

FDA-approved treatments for Alzheimer's disease

Drug	Maximum daily dose	Mechanism of action	Indication	Common side effects/comments
Tacrine	160 mg/d	ChEI	Mild to moderate AD	Nausea, vomiting, loss of appetite, diarrhea. First ChEI to be approved, but rarely used because of associated possible hepatotoxicity
Donepezil	10 mg/d	ChEI	All stages of AD	Nausea, vomiting, loss of appetite, diarrhea, sleep disturbance
Rivastigmine	12 mg/d	ChEI	Mild to moderate AD	Nausea, vomiting, diarrhea, weight loss, loss of appetite
Galantamine	24 mg/d	ChEI	Mild to moderate AD	Nausea, vomiting, diarrhea, weight loss, loss of appetite
Memantine	20 mg/d	NMDA receptor antagonist	Moderate to severe AD	Dizziness, headache, constipation, confusion
Galantamine ER	24 mg/d	ChEI	Mild to moderate AD	Nausea, vomiting, diarrhea, weight loss, loss of appetite
Rivastigmine transdermal system	9.5 mg/d	ChEI	Mild to moderate AD	Nausea, vomiting, diarrhea, weight loss, loss of appetite
Donepezil 23	23 mg/d	ChEI	Moderate to severe AD	Nausea, vomiting, diarrhea
Memantine ER	28 mg/d	NMDA receptor antagonist	Moderate to severe AD	Dizziness, headache, constipation, confusion

AD: Alzheimer's disease; ChEI: cholinesterase inhibitor; ER: extended release; NMDA: *N*-methyl-D-aspartate

Source: References 3,4

Clinical Point

AChE inhibition may be suboptimal with donepezil, 10 mg/d, and higher doses may be beneficial for patients with advanced AD

Recently, the FDA approved higher daily doses of donepezil (23 mg) and memantine (28 mg) for moderate to severe AD on the basis of positive phase III trial results.[9-11] Donepezil, 23 mg/d, currently is marketed in the United States; the availability date for memantine, 28 mg/d, was undetermined at press time.

High-dose donepezil (23 mg/d)

Cognitive decline with AD has been associated with increasing loss of cholinergic neurons and cholinergic activities, particularly in areas associated with memory/cognition and learning, including cortical areas involving the temporal lobe, hippocampus, and nucleus basalis of Meynert.[12-14] In addition, evidence suggests that increasing levels of acetylcholine by using ChEIs can enhance cognitive function.[13,15]

Donepezil is a selective, reversible ChEI believed to enhance central cholinergic function.[15] Randomized clinical trials assessing dose-response with donepezil, 5 mg/d and 10 mg/d, have demonstrated more benefit in cognition with either dose than placebo. The 10 mg/d dose was more effective than 5 mg/d in patients with mild to moderate and severe AD.[16-18] In patients with advanced AD who are stable on 5 mg/d, increasing to 10 mg/d could slow the progression of cognitive decline.[18]

Rationale for higher doses. Positron emission tomography studies have shown that at stable doses of donepezil, 5 mg/d or 10 mg/d, average cortical acetylcholinesterase (AChE) inhibition was <30%.[19,20] Based on these findings, researchers thought that cortical AChE inhibition may be suboptimal with donepezil, 10 mg/d, and that higher doses of ChEI may be required in patients with more advanced AD—and therefore more cholinergic loss—for adequate cholinesterase inhibition. In a pilot

High-dose Alzheimer's drugs

Clinical Point

Patients receiving donepezil, 23 mg/d, showed a statistically significant improvement in cognition compared with 10 mg/d

Table 2

High-dose vs standard-dose donepezil: Treatment-emergent adverse events

Adverse event	Donepezil, 23 mg/d	Donepezil, 10 mg/d
Nausea	12%	3%
Vomiting	9%	3%
Diarrhea	8%	5%
Anorexia	5%	2%
Dizziness	5%	3%
Weight decrease	5%	3%
Headache	4%	3%
Insomnia	3%	2%
Urinary incontinence	3%	1%
Fatigue	2%	1%
Weakness	2%	1%
Somnolence	2%	1%
Contusion	2%	0%

Source: Reference 22

study of patients with mild to moderate AD, higher doses of donepezil (15 mg/d and 20 mg/d) were reported to be safe and well tolerated.[21]

The 23-mg/d donepezil formulation was developed to provide a higher dose administered once daily without a sharp rise in peak concentration. The FDA approved donepezil, 23 mg/d, for patients with moderate to severe AD on the basis of phase III trial results.[9,22] In a randomized, double-blind, multicenter, head-to-head clinical trial, >1,400 patients with moderate to severe AD (Mini-Mental State Exam [MMSE]: 0 to 20) on a stable dose of donepezil, 10 mg/d, for ≥3 months were randomly assigned to receive high-dose donepezil (23 mg/d) or standard-dose donepezil (10 mg/d) for 24 weeks.[9,22] Patients in the 23-mg/d group showed a statistically significant improvement in cognition compared with the 10-mg/d group. The difference between groups on

a measure of global improvement was not significant.[9,22] However, in a post-hoc analysis, it was demonstrated that a subgroup of patients with more severe cognitive impairment (baseline MMSE: 0 to 16), showed significant improvement in cognition as well as global functioning.[9]

Overall, treatment-emergent adverse events (TEAEs) during the study were higher in patients receiving 23 mg/d (74%) than those receiving 10 mg/d (64%). The most common TEAEs in the 23-mg/d and 10-mg/d groups were nausea (12% vs 3%, respectively), vomiting (9% vs 3%), and diarrhea (8% vs 5%) (***Table 2***).[22] These gastrointestinal adverse effects were more frequent during the first month of treatment and were relatively infrequent beyond 1 month. Serious TEAEs, such as falls, urinary tract infection, pneumonia, syncope, aggression, and confusional state, were noted in a similar proportion of patients in the 23-mg/d and 10-mg/d groups; most of these were considered unrelated to treatment. No drug-related deaths occurred during the study. High-dose (23 mg/d) donepezil generally was well tolerated, with a typical ChEI safety profile but superior efficacy.

A recent commentary discussed the issue of effect size and whether a 2.2-point difference on a 100-point scale (the Severe Impairment Battery [SIB]) is clinically meaningful.[23] As with all anti-dementia therapies, in any cohort some patients will gain considerably more than 2.2 points on the SIB, which is clinically significant. A 6-month trial is recommended to identify these optimal responders.

Table 3

High-dose memantine: Treatment-emergent adverse events[a]

Adverse event	Placebo (n = 335)	Memantine ER (n = 341)
Any TEAE	214 (63.9%)	214 (62.8%)
Fall	26 (7.8%)	19 (5.6%)
Urinary tract infection	24 (7.2%)	19 (5.6%)
Headache	17 (5.1%)	19 (5.6%)
Diarrhea	13 (3.9%)	17 (5.0%)
Dizziness	5 (1.5%)	**16 (4.7%)**
Influenza	9 (2.7%)	15 (4.4%)
Insomnia	16 (4.8%)	14 (4.1%)
Agitation	15 (4.5%)	14 (4.1%)
Hypertension	8 (2.4%)	13 (3.8%)
Anxiety	9 (2.7%)	12 (3.5%)
Depression	5 (1.5%)	**11 (3.2%)**
Weight increased	3 (0.9%)	**11 (3.2%)**
Constipation	4 (1.2%)	**10 (2.9%)**
Somnolence	4 (1.2%)	**10 (2.9%)**
Back pain	2 (0.6%)	**9 (2.6%)**
Aggression	5 (1.5%)	8 (2.3%)
Hypotension	5 (1.5%)	7 (2.1%)
Vomiting	4 (1.2%)	7 (2.1%)
Abdominal pain	2 (0.6%)	7 (2.1%)
Nasopharyngitis	10 (3.0%)	6 (1.8%)
Confusional state	7 (2.1%)	6 (1.8%)
Weight decreased	**11 (3.3%)**	5 (1.5%)
Nausea	7 (2.1%)	5 (1.5%)
Irritability	**8 (2.4%)**	4 (1.2%)
Cough	**8 (2.4%)**	3 (0.9%)

[a]Data [n (%)] include all adverse events experienced by ≥2% patients in either group (safety population). Adverse events that were experienced at twice the rate in 1 group compared with the other are indicated by bold type

ER: extended-release (28 mg); TEAE: treatment-emergent adverse event

Source: Reference 11

High-dose memantine

Memantine is an NMDA receptor antagonist, which works on glutamate, an ubiquitous neurotransmitter in the brain that serves many functions. For reasons that are not fully understood, in AD glutamate becomes excitotoxic and causes neuronal death.

Some researchers have hypothesized that if safe and well tolerated, a memantine dose >20 mg/d may have better efficacy than a lower dose. Memantine's manufacturer has developed an extended-release (ER), once-daily formulation of memantine, 28 mg/d, to improve adherence and possibly increase efficacy.[10,11] Because of memantine ER's relatively slow absorption rate and longer median $T_{max,}$ of 12 hours, there is minimal fluctuation in plasma levels during steady-state dosing intervals compared with the immediate-release (IR) formulation.[10]

continued

Clinical Point

Memantine ER may be better tolerated than the IR formulation because of less plasma fluctuation during steady-state dosing intervals

High-dose Alzheimer's drugs

Clinical Point

Donepezil, 23 mg/d, and memantine, 28 mg/d, could improve adherence because they are once-daily formulations

Related Resources

- Alzheimer's Disease Education and Referral Center. www.nia.nih.gov/Alzheimers.
- Lleó A, Greenberg SM, Growdon JH. Current pharmacotherapy for Alzheimer's disease. Annu Rev Med. 2006;57:513-533.

Drug Brand Names

Donepezil • Aricept
Galantamine • Razadyne
Memantine • Namenda
Rivastigmine • Exelon
Tacrine • Cognex

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In a phase I study of 24 healthy volunteers that investigated the safety, tolerability, and pharmacokinetics of memantine ER, 28 mg/d, TEAEs were mild; the most common were headache, somnolence, and dizziness.[10] During memantine treatment, there were no serious adverse events, potential significant changes in patients' vital signs, or deaths.

Memantine ER plus ChEI. A multicenter, multinational, randomized, double-blind study compared memantine ER, 28 mg/d, and placebo in patients with moderate to severe AD (MMSE: 3 to 14).[11] All patients were receiving concurrent, stable ChEI treatment (donepezil, rivastigmine, or galantamine) for ≥3 months before the study. Patients treated with memantine ER, 28 mg/d, and ChEI (n = 342) showed a significant improvement compared with the placebo/ChEI group (n = 335) in cognition and global functioning. Patients receiving memantine/ChEI also showed statistically significant benefits on behavior and verbal fluency testing compared with patients receiving placebo/ChEI. Memantine was well tolerated; most adverse events were mild or moderate. The most common adverse events in the memantine/ChEI group that occurred at a higher rate relative to the placebo/ChEI group were headache (5.6% vs 5.1%, respectively), diarrhea (5.0% vs 3.9%), and dizziness (4.7% vs 1.5%). There were no deaths related to memantine (***Table 3, page 23***).[11]

Memantine ER, 28 mg/d, may be tolerated better than the IR formulation because of less plasma level fluctuation during the steady-state dosing interval. Also, memantine ER, 28 mg/d, may offer better efficacy over memantine IR, 20 mg/d, because of dose-dependent cognitive, global, and behavioral effects. In addition, once-daily dosing of memantine ER may improve adherence compared with the IR formulation.[24]

In patients with severe renal impairment, dosage of memantine IR should be reduced from 20 mg/d to 10 mg/d.[25] However, there is no available information regarding the dosing, safety, and tolerability of memantine ER, 28 mg/d, in patients with renal disease.

Recommendations

Because there are few FDA-approved treatments for AD, higher doses of donepezil or memantine may be an option for patients who have "maxed out" on their AD therapy or no longer respond to lower doses. Higher doses of donepezil (23 mg/d) and memantine (28 mg/d) could improve medication adherence because both are once-daily preparations. In clinical trials, donepezil, 23 mg/d, was more effective than donepezil, 10 mg/d.[9] Whether memantine ER, 28 mg/d, is superior to memantine IR, 20 mg/d, needs to be investigated in head-to-head, double-blind, controlled studies.

For patients with moderate to severe AD, donepezil, 23 mg, is associated with greater benefits in cognition compared with donepezil, 10 mg/d.[9] Similarly, because of potentially superior efficacy because of a higher dose, memantine ER, 28 mg, might best help patients with moderate to severe AD, specifically those who either don't respond or lose response to memantine IR, 20 mg/d. Combining a ChEI, such as donepezil, with memantine is associated with slower cognitive decline and short- and long-term benefits on measures of cognition, activities of daily living, global outcome, and behavior.[7,26] However,

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additional clinical trials are needed to assess the safety, tolerability, and efficacy of combination therapy with higher doses of donepezil and memantine ER.

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Bottom Line

High doses of donepezil (23 mg/d) or memantine (28 mg/d) may help patients with moderate to severe Alzheimer's disease. These doses are associated with an increased rate of adverse events, such as nausea and vomiting, compared with lower doses of the same drug. Higher-dose formulations may be an option for patients who do not respond or no longer respond to lower doses.

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Clinical Point

Whether memantine, 28 mg/d, is superior to memantine IR, 20 mg/d, needs to be evaluated in head-to-head, controlled trials