A 76-year-old woman presents with her husband for her annual evaluation for long-standing, advanced dementia, probable Alzheimer’s disease (AD). Her examination reveals a declining cognitive score of 10/38 on her Short Test of Mental Status, and her husband confirms she is having increasing difficulties with even some basic tasks of activities of daily living. She has been on donepezil 10 mg daily and memantine 10 mg twice daily for several years, yet she continues to decline. Her husband asks about raising the dosages of these drugs in an effort to improve her functional abilities. You have recently read that donepezil has been approved for a higher dosing formulation and wonder if a higher dose would be an effective treatment strategy for this patient. As a nurse practitioner (NP) interested in using an evidence-based approach to answering a clinical question, you begin a search for evidence to guide you and your patient’s caregiver.

BACKGROUND AND SIGNIFICANCE
AD is the most common dementia in the elderly, affecting over 30 million people worldwide, with current estimates expecting to triple by 2040. It has become an urgent public health problem as the population continues to age, with a prevalence that doubles every 5 years after age 65. The complexity of this neurodegenerative disease is manifested in the loss of function of memory, language, visuospatial and executive functions, and behavioral symptoms that include apathy, agitation, anxiety, irritability, disinhibition, delusions, and hallucinations. The patient’s progressive disability and eventual incapacity results in increasing psychological and economic burden on caregivers and, ultimately, society.

While the etiology of the condition remains poorly understood, progress has been made in understanding the neuropathology of AD, and, as a result, drugs for its treatment have become available. The disease is characterized...
by early loss of basal forebrain cholinergic neurons, leading to decreased cholinergic transmission. The development and approval of cholinesterase inhibitors (ChEIs), which increase the availability of acetylcholine by preventing its hydrolysis in central synapses, have become the main approach to symptomatic treatment of the disease. \(^3\)

Donepezil was the second ChEI to receive regulatory approval for the treatment of mild to moderate AD. It has a long half-life, allowing for once-daily dosing. The standard titration schedule was based upon the pivotal clinical trials that led to its original approval by the Food and Drug Administration (FDA) and begins at 5 mg/day with titration to 10 mg/day. \(^3\) Rivastigmine and galantamine are two subsequently approved ChEIs with analogous titration schedules and similar efficacy as donepezil. \(^4\)

A systematic review reveals that ChEI inhibitors reduce the cognitive impairment and improve overall function in patients with mild to moderate AD. \(^4\) Safety and tolerability of the ChEIs in the review showed that donepezil has a more advantageous tolerability profile at the standard dose of 10 mg/d. \(^4\) However, the guidelines published by the American College of Physicians and the American Academy of Family Physicians for the pharmacologic treatment of dementia concluded that there is not enough evidence to recommend one agent over another. \(^5\)

Since their introduction, new formulations of these medications have emerged, including the rivastigmine transdermal patch and extended-release galantamine. New generic forms of ChEIs are available. A higher dosing formulation of donepezil recently received FDA approval for moderate to severe AD. Will a higher dose result in improved cognition and functional ability for patients in the advanced stage of AD?

**FOCUSED EVIDENCE-BASED CLINICAL QUESTION**

To answer the clinical question, a focused question was developed to guide the literature search. In patients suffering from moderate to severe AD (Population), is a higher dose of donepezil (Intervention) compared to standard dosing (Comparison) effective in improving cognitive and functional abilities (Outcome)?

**SEARCH STRATEGY**

Multi-databases were searched in Ovid, MEDLINE, EMBASE, and PsyINFO for the period between 1950 and November 2010. The MeSH (Medical Subject Heading) term “donepezil” was used and combined using Boolean operator “and” with the text words “high dose” and yielded 63 citations. The filters “English language” and “human” were applied and 29 citations were identified. A review of the abstracts of these articles led to the selection of one article by Farlow and colleagues \(^6\) because it was the highest level of evidence (a randomized controlled trial) comparing the higher dose of donepezil to the standard dose.

**SUMMARY OF STUDY FINDINGS**

The randomized, double-blind study by Farlow et al. \(^6\) sought to assess whether patients with moderate to severe AD, who are presumed to have greater loss of brain cholinergic functional and therefore reduced acetylcholine production, would respond to higher doses of a ChEI. The effectiveness and safety profile of high-dose donepezil (23 mg/d) was compared to the standard donepezil (10 mg/d). The main outcome measures were changes in cognition and global functioning assessed using the Severe Impairment Battery (SIB) and the Clinician’s Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+; global function rating) at week 24. Treatment emergent adverse events (TEAEs) were assessed using spontaneous patient/caregiver reporting and open-ended questioning; clinical laboratory testing (hematology, biochemistry, and urinalysis panels analyzed by a central laboratory); 12-lead ECG; and physical and neurologic examinations, including vital sign measurement. The study was sponsored by Eisai Inc. \(^6\)

**Population:** The study was conducted at 219 sites in Asia, Europe, Australia, North America, and South America. It included 1371 randomly assigned patients (mean age, 73.8 years; 62.8% female; 73.5% white; weight range, 34.0–138.7 kg) with moderate to severe probable AD who had received donepezil 10 mg once daily for ≥ 12 weeks before the start of the study. \(^6\) Baseline disease severity scores did not differ between the two groups determined by the Mini–Mental State Examination (MMSE) scores 0 to 20 and Severe Impairment Battery (SIB) score ≤ 90. A total of 296 of 981 patients (30.2%) withdrew from the donepezil 23-mg/d group; 87 of 486 patients (17.9%) withdrew from the donepezil 10-mg/d group. \(^6\)

**Intervention:** Patients were randomly assigned to receive high-dose donepezil (23 mg once daily) or standard-dose donepezil (10 mg once daily). \(^6\)

**Comparison of Outcomes:** At study end (week 24), the least squares mean changes from baseline (LSM [SE]) in SIB score were significantly greater with
donepezil 23 mg/d than with donepezil 10 mg/d \( \left( H_1 \leq 0.001 \right) \), the between-treatment difference in CIBIC+ score was non-significant (4.23 \( \pm \) 1.07 vs 4.29 \( \pm \) 1.07). In post-hoc analysis, LSM Delta in SIB score and CIBIC+ treatment effect at end point were greater with donepezil 23 mg/d than 10 mg/d in patients with more advanced AD compared with less impaired patients (SIB, \( \pm \) 1.6 \[0.78\] vs \( \pm \) 1.5 \[0.88\], respectively \( [P < 0.001] \); CIBIC+, 4.31 \[1.09\] vs 4.42 \[1.10\] \( [P = 0.028] \)).

TEAEs were reported in 710 of 963 patients (73.7%) who received donepezil 23 mg/d and in 300 of 471 patients (63.7%) who received donepezil 10 mg/d. With higher-dose donepezil, mild, moderate, and severe TEAEs were reported in 297 (30.8%), 332 (34.5%), and 81 (8.4%) patients, respectively; with lower-dose donepezil, these proportions were 147 (31.2%), 119 (25.3%), and 34 (7.2%).

The three most common severe AEs reported with the 23-mg/d dose were nausea (9 patients [0.9%] vs 1 [0.2%] with the 10-mg/d dose), dizziness (7 [0.7%] vs 1 [0.2%]), and vomiting (6 [0.6%] vs 0). The most commonly reported TEAEs considered probably related to treatment with the 23 mg/d dose were nausea (59 patients [6.1%] vs 9 [1.9%] with the 10 mg/d dose), vomiting (48 [5.0%] vs 4 [0.8%]), and diarrhea (31 [3.2%] vs 7 [1.5%]). Thirteen deaths were reported during the study or within 30 days of study discontinuation (23 mg/d, 8 patients [0.8%]; 10 mg/d, 5 patients [1.1%]); all were considered unrelated to the study medication.

**Time:** The study was conducted over 24 weeks.

## Table 1. Rapid Critical Appraisal Checklist for Randomized Controlled Clinical Trials

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1. Are the Study Findings Valid?
   A. Were the subjects randomly assigned to the experimental and control groups? The authors described their randomization methodology through centralized, computer-generated, randomized codes to prevent bias and enhance the generalizability of the findings.
   B. Were the follow-up assessments conducted long enough to fully study the effects for the intervention? The study intervention lasted 24 weeks, which is a common period in most drug trials. However, there was a trend toward declining effectiveness at 24 weeks in all the outcome data reported by the authors.
   C. Did at least 80% of the subjects complete the study? In the 23-mg/d dosing group, 70% of the subjects completed the study; in the standard dosing of donepezil, 83% of the subjects completed the study. This loss to follow-up in the group of interest can distort the assessment and weaken conclusions. The authors reported the withdrawal from intolerance to be 32% (23 mg/d) versus 17% (10 mg/d).
   D. Was random assignment concealed from the individuals who were first enrolling subjects into the study? Computer-generated randomization codes were used to assign who received which dose of donepezil.
   E. Were the subjects analyzed in the group to which they were randomly assigned? All baseline characteristics were comparable between the two treatment groups. Baseline disease severity was not appreciably different. Concurrent use of medication classes seemed proportionally similar. Treatment compliance rates were reported to be comparable. TEAEs occurring in > 2% of patients were reported in both groups. Primary (SIB and CIB+) and secondary outcomes (ADCS-ADL or MMSE) were reported in both groups.
   F. Was the control group appropriate? Both groups were screened for selection using the same criteria.
   G. Were the subjects and providers kept blinded to study group? The authors described that the study personnel were blinded to treatment assignment. In order to maintain blinding of the subjects to the drug dosage size, a double-dummy design was used by the researched ChEIs.
   H. Were instruments used to measure the outcomes valid and reliable? The co-primary outcome measures for cognition changes were assessed using the SIB, and global functioning was assessed using the CIBIC+ global function rating. The SIB is a 40-item instrument to evaluate cognitive function in advanced dementia patients. The CIBIC+ is a semi-structured tool administered by an independent clinician interviewing the patient and caregiver that assesses overall change and change in various domains of patient functioning. The authors did not report the validity or reliability of these tools but did cite the original studies on the instruments. In order to judge the validity of the study, it is helpful if authors include this information in their method explanation.
   I. Were the subjects in each of the groups similar in demographic and baseline clinical variables? The authors provided a detailed description of the demographic and clinical characteristics of both study groups. The demographic characteristics were similar in both groups, except the 23-mg/d group had a higher rate of Hispanics (18 [5.8]) than the 10-mg/d (7 [4.8]) in the US study groups.

2. What Are the Results, and Are They Important?
   A. How large is the intervention or treatment effect (number needed to treat [NNT], number needed to harm [NNH] and effect size?)
Statistical analysis was conducted using the ANCOVA model with terms for baseline score and treatment used as the primary model for testing treatment effects on SIB score. The least square of means was used to compare treatment groups.

Unfortunately for the clinician wishing to determine the study’s clinical significance, the data were not presented by the authors, nor were the data reported in a manner that would allow for additional calculations of the clinical effect size or the NNT.

**B. How precise is the intervention or treatment (confidence interval)?** None were reported, reducing the clinician’s ability to estimate the treatment effect.

**3. Will the Results Help in Caring for the Patient?**

**A. Were all clinically important outcomes measured?** The study population appeared representative of community-dwelling patients with severe AD most often seen in a community office practice.

**B. What are the treatment risks and benefits?** Tolerability of the higher dose is an important concern in this vulnerable population because the disease severity limits their ability to convey the symptoms they may be experiencing. Potential treatment side effects not only can affect the patient but add to the caregiver burden in trying to manage unrecognized side effects. The inattention to drug side effects by the clinician could lead to iatrogenic polypharmacy problems. TEAs occurring in > 2% of the patients were reported at a higher frequency in the higher dose group (73.7%) and 63.7% in the standard dose group. In the donepezil 23-mg/d group, those with lower weight (< 55 kg) had more TEAs than those with higher weight (81.7% vs 71.4%).

**C. Is the treatment feasible in my clinical setting?** The new higher dosing is now available for clinical use.

**D. What are my patient’s/family’s values and expectations for the outcome that is trying to be prevented and treatment itself?** This requires individual family dialogue to ascertain the patient’s known values and the values and preferences of the caregiver/family. The side-effect profile would likely play a role in the decision to use the higher dose. In the case presented, increased functionality was an important value to this caregiver. The goal of evidence-based practice is to gain information about the patient’s values and provide him or her with the information necessary to make a decision based on the best evidence available.

**KEY CLINICAL POINTS**

In patients with severe stage AD who are already receiving standard-dose donepezil, a higher formulation has shown statistical efficacy on cognitive testing (SIB) with the greatest difference in those with more severe impairment (MMSE0-16).

There was no difference between groups in functional abilities overall (CIBIC+).

Mild to severe side effects were reported with the increased higher dose in a highly vulnerable population.

**DISCUSSION**

Through the well-designed randomization process, the clinical characteristics between both intervention groups were representative of the population seen in most clinical settings, whether private or tertiary. Over 90% of the participants were community dwelling. It is unclear how the authors arrived at the higher dosing strategy of 23 mg/d. They did not offer an explanation of the science behind this decision. While the study provided evidence of a cognitive benefit (SIB) over 24 weeks, provided data suggested a downward trend in the SIB scores that raises the question of long-term outcome of such high dose treatment.

While the SIB and CIBIC are common clinical outcome measures in dementia drug trials, there is little consensus as to what magnitude of change from baseline is required to represent a clinically meaningful outcome for the patient and caregivers. Only the cognitive signs (SIB)
showed improvement, and that was a difference of less than 3 points. It is unclear if this result would represent a meaningful clinical improvement to caregivers. Functional disabilities remain a key cause of caregiver stress, and there was no difference found with the higher dosing schedule as measured by the CIBIC.

The authors focused on statistical analysis and did not provide a more clinically meaningful effect size. A key component of the critical appraisal process in evidence-based process is evaluating the statistical analyses reported in a study. The clinician is impeded in this process when the authors do not report simple effect size. The effect size is a measure of the clinical magnitude or impact of the treatment on the outcome of interest (the higher dose donepezil). It has been pointed out that the omission of effect sizes in research is a major contributor to practice gap. In this article we are lacking important information that would allow the clinician to assess the NNT and NNH. These clinically meaningful measures allow the clinician to communicate the significance of the research in a common sense manner.

A cost analysis was not included in the study design. The generic form of donepezil in 5 mg and 10 mg tablets is now available at reduced cost. However, the 23-mg tablet (brand name Aricept) is not available in a generic formulation and will cost about $260 per month.

The reported increase in side effects was especially worrisome in this cohort because of the advance nature of their disabilities. In the advance stage of the disease, these patients are unable to clearly articulate new onset symptoms that may be distressing them. Cholinergic side effects have been noted to cause nausea, vomiting, diarrhea, muscle cramps, and urinary incontinence. Syncopal episodes have been reported and are included in the safety information provided by the company. The study identified an increased in the risk of falls in the higher dosing of donepezil. Clinicians and families wishing to try this higher formulation need to be aware of the possibility of increased side effects and have the ability to assess the patient for signs of difficulty.

CONCLUSION

The applicability of the modest findings of this study rests with the dialogue each caregiver and clinician will have as this new drug dose comes to market. Consumer values and preferences are integral parts of applying evidence-based practice. There is insufficient evidence at this time that would assure both the clinician and caregiver that the higher dosing of donepezil will result in a meaningful improvement in the quality of life for the patient with advanced stage AD. The authors correctly point out that additional research is warranted to identify the long-term outcome of higher dosing schedules.

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