

## CASE STUDY 1: UNDERSTANDING THE GOALS OF THERAPY

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### Patient Presentation

*Chief Complaint:* Concern about memory lapses and thinking process.

*History/Physical Findings:* Mrs. B is a 75-year-old white female who was referred to a neurologist because of concerns about her memory and thinking process. She reported to her primary care doctor that on a recent vacation trip to Europe she developed a flu-like illness that lasted for three days. Along with a headache, slight fever, and upset stomach, she found that she had great difficulty with memory and thinking during the illness and could not remember much for about 2 days. She recovered from the flu but, on returning to the United States, noticed that she was having frequent memory lapses and had become quite concerned. Her primary care physician referred her to a neurologist for further evaluation.

Mrs. B gave the following information during her first visit to the neurologist. She has been married for 47 years to her 77-year-old husband. They have two grown children, one of whom lives nearby and the other 500 miles away. Mrs. B completed high school and two years of college before taking a job as a secretary for a law firm. She devoted a number of years to child-rearing but eventually returned to increasingly responsible positions in several law firms until retirement at age 65 from her position as executive assistant to the senior partner of a major firm. Her husband was a successful attorney who retired at age 70. Both Mrs. B and her husband are active in community affairs and travel frequently.

Mrs. B is a member of the board of trustees for a community college and chair of the fund-raising committee for a local charity. Since her return from Europe she has had increasing difficulty keeping up with these outside activities. She has

missed appointments with administrators at the community college and failed to bring important records to meetings of the fund-raising committee. She also said that she presented a report on fund-raising activities that contained major errors. These were very embarrassing lapses/errors that caused her great anxiety because she was noted for being able to keep track of many things simultaneously. She reports that she now feels somewhat overwhelmed with all her responsibilities and has begun making extensive notes to remind herself of appointments and tasks.

Mr. B agrees that his wife seems to be having some memory problems but attributes them to overwork. He reports that she has become more anxious and irritable, but pinpoints these changes before the recent trip to Europe. He has to remind his wife more frequently about appointments but that, in other ways, she remains very capable. She has always been very careful about her appearance and about having a neat and attractive home. Mr. B acknowledges that this has not changed, but that Mrs. B occasionally seems preoccupied. Mrs. B continues to enjoy contact with family and friends, and enjoys a close relationship with both of her children and talks to them frequently.

There have been no other significant changes in Mrs. B's medical condition recently. She had minor surgery 4 years ago and recovered completely. She takes a diuretic for mildly elevated blood pressure and occasionally takes anti-inflammatory medication for arthritis. Mrs. B scored 26 out of a possible 30 on the Mini-Mental Status Examination. She missed the date, was able to recall only one of three objects after a delay in time, and made one error on the serial 7s task. Mrs. B reports no close relatives with any significant memory problems.

Because Mrs. B has experienced a gradual but significant change in her memory and, possibly, in her ability to make judgments and do calculations, the neurologist ordered additional laboratory tests and targeted neuropsychological

testing. Routine biochemical screening tests were all within normal limits, and an MRI scan of the brain showed no lesions or other abnormalities. A neurological exam was unremarkable with no abnormalities in gait, movement, or posture. Neuropsychologic testing revealed that Mrs. B scored within the normal range on tests of expressive and receptive language and tests of praxis but scored below the 20th percentile on a test of verbal memory. The neuropsychologist also noted that, although Mrs. B's overall language scores were within the normal range, she had some difficulty with naming uncommon objects and compensated with circumlocutions.

## ASSESSMENT

The neurologist concluded that Mrs. B is in the very early stages of Alzheimer's disease (AD) and decided to start her on donepezil hydrochloride (Aricept®). In addition, the neurologist counseled Mrs. B and her husband about the disease and lifestyle changes they should consider, and gave them information about local resources for patients with AD.

## DISCUSSION

Mrs. B is typical of many patients diagnosed with AD. Less than 1% of new cases are found in persons younger than 65 and the likelihood of developing the disease rises steadily with age. The percentage of the population with AD also rises steadily with age from about 1% at age 65 to approximately 35% of all 90-year-olds. Men and women are equally vulnerable to AD but, since women typically live longer than men, there are more women than men with AD in the population. Studies investigating different ethnic and cultural groups have found that AD is common in elderly persons from all ethnic and socioeconomic backgrounds, but there may be some Asian ethnic groups that are less vulnerable to AD.

While old age is by far the most important risk factor for AD, there are other risk factors for developing the disease. Like Mrs. B, most patients who develop AD have no close relatives with the disease. However, people who have a parent or other close relative with AD are more likely to develop the disease. Additionally, people who inherit one form of the gene for apolipoprotein E (the APOE4 form) are at increased risk for AD compared with those who inherit APOE2 and/or APOE3. While APOE genotype influences risk, it does not determine who gets the disease. Many patients with AD do not carry the APOE4 gene, and people with the APOE4 gene do not always get AD. Because the gene is not a determinant for contracting AD, it is not used as a diagnostic test. Educational level is also related to the risk for AD. Studies have shown quite consistently that persons with less education are more likely to develop AD in old age. The reason for this relationship has not been determined.

## CLINICAL COURSE

After discussing the diagnostic findings with Mrs. B and her husband, the neurologist prescribed treatment with donepezil 5 mg/day for 4 weeks and then increased the dose to 10 mg/day.

The neurologist explained that AD affects the brain and gradually destroys some of the important cells that are necessary for learning, memory, and thinking. With donepezil, the treatment expectations are to slow that process. Donepezil is in the class of cholinesterase inhibitors (ChEIs). It is thought that cognitive signs and symptoms of AD are linked to a deficiency of cholinergic neurotransmission. Donepezil acts by enhancing cholinergic function with a mechanism that increases the concentration of acetylcholine through reversible inhibitions of the enzyme acetylcholinesterase. Donepezil is indicated in mild-to-moderate AD. The most common of the adverse events is nausea, vomiting, and diarrhea.

The neurologist described the variability of the course of AD from one patient to the next and explained that nearly all patients with the disease can expect to decline over a period of years. As the disease progresses, patients have more problems with memory and with using language. Those cognitive problems can make it more difficult to do such ordinary things as handle money, find one's way in unfamiliar surroundings, or find words in ordinary speech.

The main goal of treatment with ChEIs is to minimize the loss of memory and other cognitive functions and to preserve Mrs. B's ability to think, function independently, and to engage in favorite activities of daily living. Studies have shown that cognitive functions, such as memory and language, often improve when patients start treatment. Over time, however, those functions may worsen, but at a slower rate than they do in patients treated with placebo. Patients treated with ChEIs are more likely to retain their ability to perform common tasks, such as manage money, pursue hobbies and leisure activities, do household tasks, and follow conversations than are patients treated with placebo. The neurologist explained that Mrs. B should be able to continue doing many of the things she likes to do, though she may want to give up some of the very demanding responsibilities that make her anxious.

The neurologist addressed the issue of using the ChEI donepezil with regard to mild GI problems (eg, nausea and diarrhea) and encouraged Mrs. B to call if the side effects became a problem. Studies have shown that donepezil does not increase symptoms of anxiety, irritability, or apathy. Along with a follow-up visit, the couple was provided with information about community resources for patients with mild AD.

## CONCLUSION

When patients are first diagnosed with AD, they and their family are usually not ready to consider the long-term effects of the disease and all the complications

that might arise throughout the course of the disease. Clinicians, however, should understand the impact of AD and consider how therapy might affect long-term disease outcome. Patients with AD often require extensive medical services during the course of their illness. AD is associated with increased rates of hospitalization, more emergency room visits, greater use of home health services, and a high likelihood of eventual nursing home placement. At each stage in the disease, patient, family, and physician must reassess the patient's need for medical care and support services. Usually a patient's need for such services and the cost of those services become greater as a patient becomes more severely impaired. Table 1 lists several pivotal studies of the long-term use of cholinesterase inhibitors. Not included on the table is galantamine hydrobromide, a reversible, competitive acetylcholinesterase inhibitor. In a study of 21 weeks duration, 978 patients were randomized to doses of 8, 16, or 24 mg of galantamine per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to galantamine and increased by 8 mg/day every 4 weeks. The maximum titration phase was, therefore, 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day). At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for galantamine-treated patients compared with placebo-treated patients were 1.7, 3.3, and 3.6 units for the 8, 16, 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups (galantamine prescribing information).

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**Table 1. Studies of Long-Term Cholinesterase Inhibitor Use**

Study	Design/Data Collection Technique	Number of Participants	Limitations	Findings
<i>Tacrine</i>				
Gifford <sup>33</sup>	Retrospective review of Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database, 1992–95.	1,640	<ul style="list-style-type: none"> <li>• Not all residents had a diagnosis of AD</li> <li>• Only 8% of those reviewed reached a dose of 120 mg/day</li> <li>• Limited to nursing home residents in four U.S. states</li> <li>• Used ITT analysis in attempt to combine data; includes some very short duration studies</li> </ul>	A significant proportion of those nursing home residents who received tacrine were unlikely to benefit due to low doses employed.
Qizibash et al. <sup>31</sup>	Meta-analysis of 12 clinical trials with doses of 20–160 mg over 3–36 weeks	1,984	<ul style="list-style-type: none"> <li>• Most studies used the patient's best dose rather than predetermined endpoint</li> <li>• Lack of controlled data on clinically significant endpoints</li> </ul>	Revealed some impact on intellectual function, although the changes were often small.
Knapp et al. <sup>25</sup>	Randomized, double-blind, placebo-controlled parallel group trial over 30 weeks.	653	<ul style="list-style-type: none"> <li>• A large portion of data (400 of 663 patients) are based on ITT analysis</li> <li>• 28% of participants had asymptomatic liver transaminase elevations; 16% had GI complaints</li> </ul>	Tacrine produced statistically significant dose-related improvements on performance-based tests and quality of life.
<i>Donepezil</i>				
Rogers et al. <sup>34</sup>	Randomized, double-blind, placebo-controlled, up to 254 weeks	133		<ul style="list-style-type: none"> <li>• In the first 6–9 months, mean ADAS-Cog and CDR-SB scores increased over baseline</li> <li>• Overall decline was less than that in patients not treated</li> <li>• Over time, gradual deterioration was noted</li> </ul>
Burns et al. <sup>34</sup>	Placebo-controlled, parallel group study over 30 weeks.	818 patients randomised to either 5 or 10 mg		<ul style="list-style-type: none"> <li>• The 10 mg group did significantly better than the 5 mg group</li> <li>• No lab abnormalities were noted</li> <li>• Donepezil judged effective in mild to moderate AD</li> </ul>
<i>Rivastigmine</i>				
Corey-Bloom et al. <sup>35</sup>	Double-blind, placebo-controlled over 52 weeks.	532		<ul style="list-style-type: none"> <li>• In first 26 weeks, ADAS-Cog scores in placebo patients declined an average of 4 points, while rivastigmine patients gained 1 point over baseline. In second 26 weeks, rivastigmine patient maintained function</li> <li>• After 40 weeks, decline was observed in all groups</li> </ul>
Rosler. <sup>36</sup>	Prospective, double-blind, placebo-controlled using 1–4 mg (lower dose) or 6–12 mg (higher dose) daily for six months.	725		<ul style="list-style-type: none"> <li>• Cognitive function declined most in the placebo group</li> <li>• Significantly more patients in the higher dose group improved by 4 or more points on ADAS-Cog</li> <li>• Concluded that rivastigmine improves ADLs and global evaluation ratings in patients with mild to moderate AD</li> </ul>

AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale Cognition Component; ADLs = activities of daily living; CDR-SB = Clinical Dementia Rating (sum of boxes); ITT = intent to treat.

Wick et al 2000.

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