# Practical Principles for the Management of Alzheimer's Disease

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Alzheimer's disease is a complex disorder that is particularly challenging to treat and manage. Early recognition of Alzheimer's disease is the first step toward providing patients with optimal therapy and the best opportunity for treatment response. Subsequently, physicians will need to address issues that emerge as the disease inevitably progresses. As the number of elderly patients with Alzheimer's disease increases, it becomes increasingly important for the primary care physician—usually the first line of patient contact—to diagnose Alzheimer's disease early, and initiate and manage appropriate long-term cholinesterase inhibitor therapy, which has been shown to provide significant benefits to Alzheimer's disease patients. In this article, discussions of individual patients illustrate commonly encountered situations in the primary care setting.

*(Primary Care Companion J Clin Psychiatry 2002;4:63–69)*

*Received Feb. 27, 2002; accepted June 13, 2002. From the University Neuropsychiatric Institute, University of Utah, Salt Lake City.*

*Supported by PPS International Communications, Stanford, Conn.*

*Dr. Christensen has received research support from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Novartis, Organon, Sandoz, Solvay, Wyeth Ayerst, Designer Genes, and the Eccles Institute of Human Genetics; has been a consultant for Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Lilly, Pfizer, Solvay, Wyeth Ayerst, and Designer Genes; and has been a member of the speakers bureau for Abbott, Bayer, Bristol-Myers Squibb, Eisai Pharmaceuticals, GlaxoSmithKline, Janssen, Lilly, Pfizer, Sandoz, Solvay, Upjohn, and Wyeth Ayerst.*

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Alzheimer's disease is a progressive, debilitating disease marked by unrelenting cognitive and functional decline, and it represents a significant societal burden. The prevalence of dementia increases with age, with 10% of the population 65 years and older and 30% of those aged 85 years and older developing the disease.[1] A dramatic rise in the number of Alzheimer's disease cases is expected over the next few decades as both life expectancies and the population of people reaching their 60s and 70s increase.[1]

## DIAGNOSIS OF ALZHEIMER'S DISEASE

Early and accurate detection of Alzheimer's disease is important for successful treatment. However, Alzheimer's disease is commonly undiagnosed, misdiagnosed, or diagnosed late in the course of disease[1] even though symptoms are often present for 2 or more years before identification.[2] Since the publication of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria, the diagnosis of Alzheimer's disease has become one of inclusion rather than exclusion.[3] Using these criteria, the diagnosis of Alzheimer's disease has been shown to be accurate in 75% to 97% of cases.[4–7]

### Symptoms of Alzheimer's Disease

Many patients with Alzheimer's disease visit physicians at the request of concerned family members and are not brought in specifically for problems with cognition. It is therefore important to be alert for symptoms of possible dementia that may be evident clinically or in conversation with patients and family members. Signs of cognitive decline include memory loss affecting job performance, functioning, and social skills; mood and personality changes (e.g., apathy, depression, irritability); and difficulty with familiar tasks. The patients described in this section illustrate the importance of being alert to early warning signs of Alzheimer's disease, some of which may not overtly indicate memory loss.

A patient who illustrates the typical presentation of dementia in a primary care setting, Mr. A, a 65-year-old businessman, had no complaints and could give no reason for seeing a physician. Over the previous 2 years, his wife had made annual appointments for him to see a physician regarding what she considered uncharacteristic behavior. Ms. A had not accompanied her husband to previous appointments, assuming that he would mention the cognitive problems or that the physician would detect them. Determined to have an accurate history taken, Ms. A accompanied her husband to his third annual appointment. She complained of Mr. A's uncharacteristic mistakes at work (e.g., transposing numbers, losing track of files) and voiced the concerns of his coworkers, who described Mr. A as "more irritable and edgy."

Because patients often attend appointments alone, the ability to make a diagnosis may be impeded by the patient's lack of awareness or denial of cognitive, functional, or behavioral problems. For this reason, it is imperative to obtain information from someone who is familiar with the patient.

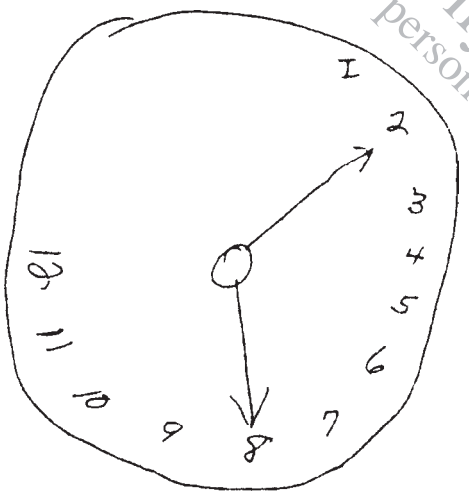
Being alert to symptoms that could represent early dementia, such as depression or apathy, can facilitate a

**Table 1. Steps Toward a Diagnosis of Dementia[a]**

| Action | Comment | Administered by |
|---|---|---|
| 1. Clinical history | Input from family member or friend is critical | Physician alone or with assistance from nurse or clinical assistant |
| 2. Complete physical examination | Exclude other causes of dementia (eg, tertiary syphilis, hypothyroidism, $B_{12}$ deficiency) | Physician alone or with assistance from nurse or clinical assistant |
| 3. Laboratory tests | Exclude other causes of dementia (eg, tertiary syphilis, hypothyroidism, $B_{12}$ deficiency) | Physician alone or with assistance from nurse or clinical assistant |
| Complete blood count | | |
| Thyroid-stimulating hormone and thyroxine ($T_4$) measurement | | |
| Rapid plasma reagin | | |
| 4. Neurologic examination | Exclude other causes of dementia (eg, tertiary syphilis, hypothyroidism, $B_{12}$ deficiency) | Physician alone or with assistance from nurse or clinical assistant |
| Cerebral, cerebellar, cranial nerve, and motor-sensory function | | |
| 5. Cognitive assessments | | |
| MMSE[8] | Limited sensitivity in patients with a high level of education | Trained medical assistant or physician |
| Clock-drawing test[9] | | Trained medical assistant or physician |
| 6. Functional assessments | | |
| FAQ[10] | Completed by caregiver | Medical assistant or physician |
| 7. Interpretation of results | | |
| Clinical examination | | Physician |
| Cognitive assessment | | Physician |

[a]Abbreviations: FAQ = Functional Activities Questionnaire, MMSE = Mini-Mental State Examination.

**Figure 1. Results of the Clock-Drawing Test[a]**



[a]The patient was instructed to draw a clock face displaying the time as 2:30. The clock draw was scored on a scale of 0 to 4. A score of 4 reflects an accurate representation of the clock and time, with lower scores indicating increasing distortion of the requested drawing. A score of 2 was recorded for this patient.

diagnosis. For instance, Mr. B brought in his wife, a 71-year-old retired bookkeeper, because "she seemed depressed." While Ms. B actually appeared jovial, she was often at a loss for words and seemed apathetic and emotionally detached. On the basis of these observations, questions about her cognitive functioning were asked. Ms. B denied any problems. In private, her husband disclosed that he had recently taken the checkbook away from her, having noticed a number of errors including "paying the same bill over and over again."

**Table 2. Recognizing Early Signs of Dementia[a]**

| |
|---|
| Routinely screen patients 65 years and older for symptoms of memory loss and functional impairment |
| Be alert to the possibility of early dementia in patients presenting with symptoms of depression, apathy, personality change, or uncharacteristic behaviors |
| Specifically question patient and family about cognitive and functional performance |
| Obtain a collateral history |
| Perform simple screening tests (eg, MMSE, clock-drawing test, FAQ) |

[a]Abbreviations: FAQ = Functional Activities Questionnaire, MMSE = Mini-Mental State Examination.

## Diagnosing Alzheimer's Disease in a Primary Care Setting

Routine questioning of older patients (65 years and older) and their relatives will quite likely reveal any cognitive difficulties and can facilitate the early detection of Alzheimer's disease. In fact, input from family members is critical in the diagnostic process, as they often are the first to notice symptoms. A complete physical examination with laboratory testing (Table 1) should follow the taking of a patient's history. This aspect of the workup allows the physician to diagnose or rule out potentially reversible causes of cognitive decline, such as $B_{12}$ deficiency, brain tumor, or hypothyroidism. Cognitive and functional ability may be assessed with the Mini-Mental State Examination (MMSE),[8] the clock-drawing test,[9] and the Functional Activities Questionnaire (FAQ)[10] (see Table 1)—all instruments that can be readily administered in a primary care setting. The clock-drawing test takes only minutes to administer and provides objective information about a patient's memory, comprehension, planning, and visuospatial skills.

**Table 3. Efficacy and Dosing of the ChE Inhibitors[a]**

| Variable | Donepezil | Galantamine | Rivastigmine |
|---|---|---|---|
| Efficacy for mild-to-moderate symptoms | Yes[15] | Yes[16] | Yes[17] |
| Long-term efficacy | Yes (DB[18,19] and OL[20,21]) | Yes (OL[22]) | Yes (OL[23]) |
| Dosing | | | |
| Starting dose | 5 mg qd[15] | 4 mg bid[16] | 1.5 mg bid[17] |
| Schedule to reach maximum dose | May be increased to 10 mg qd after 4 weeks, as per physician's judgment[15] | Increased after 4 weeks or more as tolerated by 4-mg bid increments to a maximum dose of 12 mg bid[16] | Increased after 2 weeks or more as tolerated by 1.5-mg bid increments to a maximum dose of 6 mg bid[17] |

[a]Abbreviations: ChE = cholinesterase, DB = double-blind, OL = open-label.

**Table 4. Incidence of Gastrointestinal Adverse Events With the ChE Inhibitors[a]**

| | Incidence of Gastrointestinal Adverse Events (%) | | | |
|---|---|---|---|---|
| Drug | Nausea | Diarrhea | Vomiting | Anorexia |
| Donepezil[15] | | | | |
| 5 mg/d | 5 | 8 | 3 | 3 |
| 10 mg/d (6-week escalation) | 6 | 9 | 5 | 3 |
| Placebo | 6 | 5 | 3 | 2 |
| Galantamine[16b] | | | | |
| 16 mg/d | 13 | 12 | 6 | 7 |
| 24 mg/d (titrated monthly) | 17 | 6 | 10 | 9 |
| Placebo | 5 | 6 | 1 | 3 |
| Rivastigmine[17c] | | | | |
| 6–12 mg/d (titrated weekly) | 47 | 19 | 31 | 17 |
| Placebo | 12 | 11 | 6 | 3 |

[a]Abbreviation: ChE = cholinesterase.
[b]Galantamine is not recommended in patients with severe renal or hepatic impairment.[16]
[c]There is 1 postmarketing report of severe vomiting and esophageal rupture following reinitiation of rivastigmine treatment with an inappropriately high dose.[17]

Recall Ms. B, who had denied having cognitive problems. Initial assessments of her cognitive and functional abilities provided the following scores: clock-drawing test, 2 out of 4 (Figure 1); MMSE, 18 out of 30; and FAQ, 14 out of 30. These scores are indicative of moderate impairment. Ms. B's test results prompted a more comprehensive workup, which led to a diagnosis of Alzheimer's disease. The workup included the taking of additional clinical and family histories, physical examination, collection of laboratory data, magnetic resonance imaging brain scan, neurologic examination, and administration of the Hachinski Ischemic Scale[11] to rule out vascular factors. This case illustrates that a physician who is alert to early changes can employ a few simple objective measures to facilitate an early and accurate diagnosis (Table 2).

## PHARMACOLOGIC TREATMENT

Given that there is presently no cure for Alzheimer's disease, the goal of treatment is to improve, stabilize, or slow the cognitive, functional, and behavioral decline. Pharmacologic treatments for Alzheimer's disease recommended by the American Academy of Neurology include the cholinesterase (ChE) inhibitors as a treatment standard and vitamin E (1000 IU p.o. b.i.d.) as a treatment guideline.[12] Although the role of this antioxidant in Alzheimer's disease is unclear, vitamin E has been shown to delay the time to clinical worsening in a double-blind trial.[13]

Currently, the ChE inhibitors (tacrine hydrochloride, donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide) are the only U.S. Food and Drug Administration–approved drugs for the treatment of mild-to-moderate Alzheimer's disease. The widely accepted cholinergic hypothesis attributes the cognitive decline associated with Alzheimer's disease in part to a loss of cholinergic neurons in the basal forebrain.[14] By inhibiting enzymes that metabolize acetylcholine (ACh), ChE inhibitors increase ACh levels and thereby enhance cholinergic neurotransmission.

The ChE inhibitors (Tables 3 and 4) have been shown to improve or slow decline in the cognitive, functional, and behavioral symptoms associated with Alzheimer's disease.[15–18,24–26] Importantly, studies have shown that early initiation of ChE inhibitor therapy, followed by continuous long-term treatment, provides patients with the greatest benefits.[20] Therefore, starting treatment early and maintaining patients on an effective and well-tolerated therapy are important to ensure maximum benefit and may delay nursing home placement,[27] for example.

## TREATMENT RESPONSE

Given the progressive degeneration that is characteristic of Alzheimer's disease, decline is inevitable. Thus, it is important to have informed expectations of ChE inhibitor therapy (i.e., improvement, stabilization, or slowed progression of symptoms) and to educate the patient and caregiver about realistic expectations of treatment. Some patients experience marked symptomatic improvement with a ChE inhibitor; others, only modest improvement; and some, a stabilization or less progression of symptoms than would be expected without treatment. However, even relatively small effects on cognition, function, and behavior may provide valuable benefits over the long term, such as prolonging a patient's stay at home. Unrealistic expectations may lead to inappropriate discontinuation of the drug, resulting in loss of therapeutic benefit. A study has demonstrated that interruption of ChE inhibitor treatment

often leads to a loss of cognitive and functional benefits, which are not fully recovered when medication is restarted.[20]

### Slowing Symptomatic Decline

The ChE inhibitors have been shown to slow the cognitive and functional decline associated with Alzheimer's disease.[18,20,24–26] The benefits of slowing decline in a progressive illness such as Alzheimer's disease are illustrated in the case of Mr. C, a 71-year-old retired farmer whose cognitive difficulties first became apparent when he could not remember how to start his tractors. Despite initiation of rivastigmine treatment (1.5 mg b.i.d. for 1 month; titrated monthly by 1.5-mg b.i.d. increments to 6.0 mg b.i.d.), Mr. C's cognitive function slowly deteriorated, with a drop in MMSE score from 21 to 19 over a 6-month period. His family discontinued ChE inhibitor therapy without physician consultation. Three weeks later, the family reported that the patient was doing "much worse" since stopping the medication. Therapy was reinitiated and, fortunately, Mr. C returned to the level of cognitive function observed just prior to discontinuation of ChE inhibitor treatment. At follow-up, the family remarked that the medicine was "doing more than we thought it was." In addition to illustrating the cognitive benefits of continuous ChE inhibitor treatment, this case stresses the importance of communicating realistic expectations of therapy to the caregivers.

### Stabilizing Symptomatic Decline

Stabilization of symptoms is also recognized as a beneficial treatment outcome. Ms. D, an 83-year-old woman, presented with memory problems and an increasing inability to care for herself. Her family was prepared to place her in a nursing home. After a diagnosis of Alzheimer's disease, Ms. D began donepezil treatment (5 mg/day for 1 month; 10 mg/day thereafter). At her 1-year follow-up, the cognitive and functional decline she had experienced before treatment initiation had stabilized and she continued to live independently.

### Improving Symptoms

Some patients experience improvement in cognitive functioning in response to ChE inhibitor treatment. Ms. E was one such patient, an 88-year-old woman whose son recognized her difficulty with memory and simple tasks as early signs of Alzheimer's disease. He recalled that ChE inhibitor treatment had benefited his father. A workup was requested, Ms. E was diagnosed with Alzheimer's disease, and ChE inhibitor therapy was initiated (rivastigmine, 1.5 mg b.i.d. for 1 month; titrated monthly by 1.5-mg b.i.d. increments to 6 mg b.i.d.). After 3 months of treatment, Ms. E's MMSE scores improved from 15 to 21. The patient was able to recall her grandchildren's names, talk accurately about world events, and help prepare family meals. After 1 year of treatment, Ms. E's MMSE score remained at 19.

It is important to note, however, that the proportion of patients demonstrating this type of treatment response varies. In clinical trials of the ChE inhibitors, drug effects on cognitive functioning are assessed with the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). In U.S. trials of 24 or 26 weeks' duration, the percentages of drug-treated versus placebo-treated patients achieving a ≥ 4-point improvement from baseline (considered to represent a moderate improvement) on the ADAS-cog have been reported as follows: donepezil (10 mg/day), 58% versus 28%[15]; rivastigmine (6–12 mg/day), 25% versus 7%[17]; and galantamine (24 mg/day), 34% versus 17%.[16]

### Follow-Up

Routine follow-up is an integral part of disease management in a chronic disorder such as Alzheimer's disease. Follow-up visits should include a physical assessment and interim history, assessment of patient and caregiver perceived benefit, administration of cognitive and functional assessment scales, and inquiry into any emerging behavioral disturbances or caregiver concerns. Maintaining open communication with the patient and family, as well as sensitivity to developing concerns and symptoms, is also vital. In addition, adverse events should be monitored and treated appropriately. Gastrointestinal (GI) effects, such as nausea, diarrhea, and vomiting, are the most common adverse events and are usually transient and mild.[15–17] To minimize GI events, many clinicians increase the drug dose slowly, usually after 4 weeks at the previously tolerated dose. While the ChE inhibitors may exacerbate asthma, obstructive pulmonary disease, sick sinus syndrome, and bradycardia, cholinomimetic effects can also include GI bleeding and urinary obstruction. Effective management of Alzheimer's disease patients through follow-up visits and appropriate caregiver support can help ensure that patients obtain the best possible care and outcome.

## LONG-TERM, UNINTERRUPTED TREATMENT

The goal of improved or stabilized cognition, function, and behavior is best achieved by long-term, uninterrupted ChE inhibitor therapy. In 1-year, double-blind, placebo-controlled trials, donepezil treatment was shown to maintain higher levels of cognitive and global functioning[18] and delay functional decline[19] compared with placebo. Clinical studies have also shown that interruption of ChE inhibitor therapy for 6 weeks causes a loss of treatment benefit that may not be fully regained when drug treatment is reinitiated.[20] Recall the situation with Mr. C: his family had terminated his treatment, believing that it was not effective. Fortunately, therapy was reinitiated before

the critical period had elapsed, and Mr. C was able to regain treatment benefit.

The ChE inhibitors have been shown to be safe and well tolerated over the long term. Ms. F, who is 76 years old and holds a doctorate in economics, was diagnosed with mild Alzheimer's disease (MMSE score of 28) after her family noticed that she easily became disinterested and often seemed less able to express herself. For the past 4 years, Ms. F has taken donepezil (5 mg/day for 1 month; 10 mg/day thereafter) and vitamin E (1000 IU/day) and has experienced a decline of only 4 points in MMSE score (average deterioration is 2–3 points per year[28]). At 4-year follow-up, Ms. F was living independently and largely managing her own affairs.

Some patients may have trouble tolerating even the initial low starting dose of a ChE inhibitor due to GI adverse events. Patients who do not tolerate the lowest dose of a ChE inhibitor will often tolerate the drug after a rechallenge at the same dose or at a dose lower than the usual starting dose. Ms. G, who is 70 years old, is one such patient who had not previously tolerated donepezil therapy (5 mg/day). A full discussion with her husband was required before he agreed to initiate treatment with a lower-than-usual donepezil dose of 1.25 mg/day, followed by weekly increases of 1.25 mg/day. After 1 month at 5 mg/day, the maximal dose of 10 mg/day was given. Ms. G tolerated the new dosing regimen and, after 2 years, remains on therapy with no noticeable deterioration of symptoms. Her level of cognitive functioning has remained relatively stable, with MMSE scores consistently ranging from 18 to 20.

## MANAGEMENT OF BEHAVIORAL AND NEUROPSYCHIATRIC DISTURBANCES

Alzheimer's disease patients commonly experience neuropsychiatric and behavioral disturbances such as agitation, depression, apathy, and wandering.[29] Physicians should probe the development of behavioral disturbances with the caregiver and patient, as attending to these disturbances is crucial to successful management of Alzheimer's disease. Generally, depressive symptoms manifest in early Alzheimer's disease, while agitation, insomnia, fearfulness, and psychoses develop in moderate-to-severe stages.[29] Behavioral symptoms may reemerge throughout the course of the disease.

Neuropsychiatric and behavioral disturbances are a particularly distressing aspect of Alzheimer's disease and are often the precipitant for nursing home placement.[29] This is a significant issue for caregivers, who prefer to have their loved ones at home for as long as possible. Importantly, slight improvements in behavior may facilitate patient manageability and delay placement into nursing facilities. Accordingly, family intervention programs[30] and ChE inhibitor treatment[27,31] have been demonstrated to keep patients at home longer.

Mr. H, a 90-year-old Alzheimer's disease patient who showed cognitive improvement with rivastigmine treatment (1.5 mg b.i.d.; titrated monthly by 1.5-mg b.i.d. increments to 6 mg b.i.d.), provides an illustration of the potential behavioral benefits of ChE inhibitors. This patient remained on therapy over the final 3 years of his life despite a gradual loss of cognition and functioning, eventual placement into a nursing home, and progression to severe Alzheimer's disease stages. The decision to continue treatment was based on the fact that Mr. H's family recognized that the course of his disease lacked the behavioral and temperament problems exhibited by an uncle with Alzheimer's disease.

Initially, nondrug approaches (e.g., music, light exercise) may be effective in managing mild behavioral disturbances typically seen in early Alzheimer's disease. The ChE inhibitors have been shown to be effective in attenuating behaviors such as anxiety, wandering, agitation, and depression.[24,29] Selective serotonin reuptake inhibitors are effective for treating the depression commonly seen in Alzheimer's disease.[12,32] Although typical and conventional antipsychotics can be efficacious for improving agitation and psychotic symptoms (e.g., delusions and hallucinations), the atypical agents may be better tolerated.[12] Other medications (e.g., trazodone, buspirone, bupropion) may also be effective in treating behavioral disturbances associated with Alzheimer's disease.[32]

Frequently, families fail to seek medical help until behavioral problems become unmanageable. Mr. I sought treatment for his wife only after her behavior became intolerable, even though she had exhibited cognitive signs of Alzheimer's disease for a few years. Ms. I, who was 83 years old, became insistent that she and her husband were living in a hotel and needed to return home. Ms. I also claimed that she was single and only dating Mr. I. Her behaviors became predictably out of control and occasionally threatening between 6 p.m. and midnight. Following a diagnostic workup, Ms. I was started on donepezil (5 mg/day for 1 month; 10 mg/day thereafter). Over the first 6 weeks of treatment, Ms. I became less agitated, less boisterous, and more easily distracted from delusional concerns. Trazodone was subsequently added to settle the remaining mild agitation and insomnia. This case illustrates the potential benefits of ChE inhibitor therapy and other medications for the behavioral symptoms associated with Alzheimer's disease.

## CARING FOR THE CAREGIVER

Providing support for caregivers is essential to the successful treatment of Alzheimer's disease (Table 5). While a variety of support systems are available to caregivers and patients, the primary care physician is frequently the family's first-line resource, thus providing these physicians ample opportunity to promote family contact with

**Table 5. Taking Care of the Caregiver**

| |
|---|
| Include the caregiver in discussions of patient treatment, progress, and course of disease |
| Be alert to and treat symptoms of depression, grief, and stress in the caregiver |
| Refer to support resources, such as the Alzheimer's Association Web site (www.alz.org), which contains links to local, state, federal, and national resources for caregivers and patients |
| Identify coping strategies. Education and support can reduce caregiver depression, anger, and fatigue[12] |

community support services. Furthermore, as half of all caregivers will suffer from depression associated with caring for an Alzheimer's disease patient, the physician should be alert to symptoms of depression in the caregiver.[1]

The following case illustrates depression in a caregiver. Mr. J, who is 70 years old, began showing signs of depression 6 months after his wife was diagnosed with Alzheimer's disease. These signs were evident in his apathy and his comments, such as there being "no use" in her treatment. He displayed less interest in their children and a lower level of daily care for his wife. Additionally, Mr. J was frequently still in pajamas in the late afternoon and stopped preparing meals. He was diagnosed with major depression and started on antidepressant therapy. His daughter moved into the house, and his wife began attending adult day care 3 days per week. Gradually, Mr. J's desire to care for his wife returned. He began to attend caregiver support groups and modified his duties to allow assistance from his daughter and a home health care nurse. This case illustrates that providing proper support and health care services to caregivers is a major aspect of managing Alzheimer's disease.

## CONCLUSIONS

As illustrated by the patients presented in this review, individual response to ChE inhibitor treatment varies greatly. Effective management of the Alzheimer's disease patient is multifaceted. Nonpharmacologic treatments, such as behavioral and environmental interventions, can augment pharmacologic therapies. Successful pharmacologic treatment of Alzheimer's disease requires early detection and diagnosis of symptoms, followed by prompt initiation of a well-tolerated and effective dose of a ChE inhibitor. Optimal treatment benefits are obtained with sustained long-term therapy. Furthermore, short- and long-term treatment response must be monitored, and functional decline and behavioral symptoms must be addressed as they emerge. Finally, addressing caregiver issues and concerns is critical in the successful management of Alzheimer's disease.

*Drug names:* bupropion (Wellbutrin), donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon), tacrine (Cognex).



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