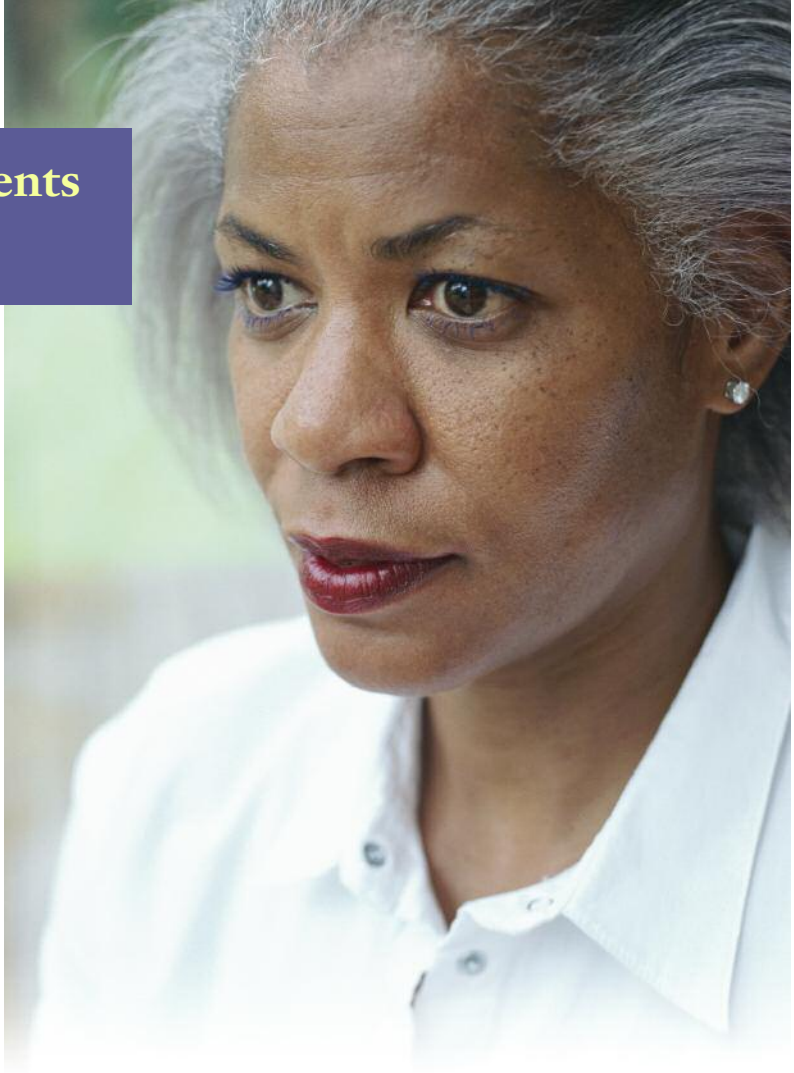


Current Treatments for Patients With Alzheimer Disease

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There is neither proven effective prevention for Alzheimer disease nor a cure for patients with this disorder. Nevertheless, a spectrum of biopsychosocial therapeutic measures is available for slowing progression of the illness and enhancing quality of life for patients. These measures include a range of educational, psychological, social, and behavioral interventions that remain fundamental to effective care. Also available are a number of pharmacologic treatments, including prescription medications approved by the US Food and Drug Administration for Alzheimer disease, "off-label" uses of medications to manage target symptoms, and controversial complementary therapies. Physicians must make the earliest possible diagnosis to use these treatments most effectively. Physicians' goals should be to educate patients and their caregivers, to plan long-term care options, to maximally manage concurrent illnesses, to slow and ameliorate the most disabling symptoms, and to preserve effective functioning for as long as possible. The authors review the various current treatments for patients with Alzheimer disease.

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Alzheimer disease is a fatal progressive neurodegenerative illness and the most common form of dementia, affecting as many as 25 million people worldwide.¹⁻³ The exact etiologic and pathophysiologic mechanisms of this disorder are the object of intense scientific investigation. The most common pathologic findings include neuritic plaques of β -amyloid protein—the residue of

degenerated neurons—and neurofibrillary tangles, which contain hyperphosphorylated tau protein.⁴

The most promising Alzheimer disease research involves investigation of aberrant β -amyloid production/aggregation and the role of β -amyloid in the immune system-associated inflammatory process.^{5,6} The cascade of damage originates in the entorhinal cortex and hippocampus and inexorably progresses to other regions of the brain. The disease process becomes well-established before clinical signs and symptoms appear.

Early-onset and aggressive variants of Alzheimer disease have stronger genetic correlations than the more common, late-onset form of this illness, but genetic vulnerability is also a component of the common form. Because of the typical onset of symptoms later in

life, many patients will have comorbid illnesses, which complicate clinical presentation, diagnosis, and management. Onset of clinical signs and symptoms is insidious, evolving over several years. Alzheimer disease begins with mild memory impairment and gradually progresses through stages of increasing cognitive decline, diminishing executive functioning, compromised judgment, deterioration in self-care, and eventually the complete inability to manage life independently. In many cases, the course of Alzheimer disease is complicated further by disturbances in mood and behavior.

Treatment for particular symptoms of Alzheimer disease is available. However, specific "disease-modifying" treatments aimed at preventing or reversing the basic pathophysiologic processes of

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Alzheimer disease remain in investigational stages.⁷ In the present article, we review current treatment approaches for patients with Alzheimer disease, including behavioral assessment and interventions, cognitive and neuropsychiatric rating instruments, medications approved for the disease, medications for neuropsychiatric symptoms, and alternative and complementary therapies.

Psychosocial and Behavioral Therapies

Alzheimer disease has sweeping effects extending far beyond the afflicted individuals, and care must be addressed in a coordinated “systems” approach involving many resources. Although the US Food and Drug Administration (FDA) has approved medications for Alzheimer disease, psychosocial and behavioral therapies represent the mainstay of treatment for patients. Such therapies must begin immediately after diagnosis, and effects of therapy should be reviewed periodically to make adjustments for the inevitable decline in patients’ abilities to function. Treatment strategies must be sufficiently flexible to account for the nuanced problematic situations that are likely to arise for individual patients and their families.

Long-time evidence indicates that nonpharmacologic interventions must always precede, and run concurrently with, pharmacologic interventions to maximize outcomes.⁸

Therapeutic Alliance

Given the complicated nature of care in Alzheimer disease, the establishment and maintenance of a therapeutic alliance involving the patient, family, and caregivers is of vital importance.⁹ Family members and caregivers eventually become the primary reliable sources of information about patients and the individuals responsible for implementing treatment interventions and monitoring outcomes. Clear lines of communication need to be established early between physicians and caregivers to facilitate decision-making and best outcomes.

Education

Educating patients and their families about the nature and course of Alzheimer

disease is crucial to facilitate the careful planning that is necessary for ongoing effective care. While the autonomy of the patient with Alzheimer disease is still intact, expeditious decisions need to be made. It is the time for the patient, family, and caregivers to “get things in order,” including reviewing family finances (eg, for in-home care and extended care placement) and preparing living wills, trusts, and durable power of attorney documents.¹⁰⁻¹¹ Expansive family discussions should be encouraged, especially in regard to settling disputes and disagreements that often flare up with the stress of caretaking.

Patients must confront the difficult task of making their wishes and preferences known to family members. Especially important are patients’ preferences about medical procedures in emergency care situations (eg, cardiopulmonary resuscitation, intubation, emergency surgery) and end-of-life care (eg, feeding tubes, intravenous hydration, treatment for infections). End-stage Alzheimer disease qualifies for hospice care, which provides comfort measures for the patient and strong emotional support for the family.¹² Soon after diagnosis and during the course of the illness, referral of patients and families for counseling, psychotherapy, and participation in Alzheimer disease support groups can help to reduce inevitable stresses.¹³

Physical Health

The fundamentals of health are especially important for patients with Alzheimer disease. Exercise performed in a manner, intensity, and duration that the patient can tolerate should be part of the overall treatment plan. Exercise has been demonstrated to improve physical functioning and mood in patients with Alzheimer disease.¹⁴ For patients who also have arthritis, swimming is especially helpful.

The US Department of Agriculture’s “food pyramid” provides the basis for a healthy diet, with an emphasis on fruits and vegetables high in phenolic antioxidant content.¹⁵ Such foods include almonds, apples, blueberries, grapes, green tea, pomegranates, tomatoes, and walnuts. Nutritional supplementation, discussed later in the present article, may

also be helpful. Concurrent chronic illnesses must be maximally managed and monitored regularly.

Behavioral Assessment and Interventions

Patients will inevitably present certain behaviors that will complicate their care. For specific problematic behaviors, it is helpful to provide caregivers with guidelines that will assist them in systematically evaluating the behaviors and deciding on interventions. The following items provide a scale of common behaviors (with examples of comments made by caregivers) to help family members and caregivers classify the behaviors of patients with Alzheimer disease.

- **Positive behaviors.** “I like it when mother helps out. She seems to enjoy helping me do the dishes and weed the flower garden, and those times are precious to me.”
- **Neutral behaviors.** “Dad seems to enjoy looking out the window.”
- **Annoying but ultimately trivial behaviors.** “He keeps asking me the same questions over and over.”
- **Annoying behaviors that interfere with care.** “He is constantly irritable and swears at me.”
- **Risky behaviors.** “She wandered over to the neighbors, and they had to help her get back home.”
- **Dangerous behaviors.** “This is the second time that dad has caused a driving accident.”

After a patient’s behaviors are classified and rated according to this scale, caregivers can attempt to alter the patient’s environment and change their interactions with the patient in ways that promote more positive behaviors and minimize annoying ones. Risky and dangerous behaviors require immediate and definitive interventions. For example, frequent wandering can be controlled with effective barriers, such as locked doors, or easily installed alarm systems that alert caregivers when boundaries are crossed.

Patients with Alzheimer disease will eventually reach a point at which they will not be able to drive safely. Many states have “reporting laws” and manda-

tory periodic driver's tests for elderly people to monitor their capabilities. Patients with mild cognitive impairment or early-stage Alzheimer disease should be referred to and enrolled in regular driver-testing programs. Some patients will strongly resist giving up driving because it represents a major milestone in their progressive loss of independence and autonomy. In such circumstances, confrontation with the patient may be necessary, because continued driving poses a public health risk as well as a risk to the patient.

Physicians can help caregivers rate and respond to specific problematic patient behaviors. First, the target behavior needs to be clarified. For example, it is more helpful for the caregiver to report that "she [the patient] strikes out at me when I try to help her get dressed" than to simply say "she's having problems with aggression." Then, the caregiver needs to describe how troubling he or she finds the problematic behavior, such as by noting "it really bothers me when she does this [striking out], and it makes the whole day more stressful." Next, the physician should teach the caregivers the PPQRST assessment for pain—except this assessment should be applied to problematic behaviors, as in the following examples of questions asked by the physician to the caregiver:

- **Palliation.** "What have you done so far that seems to help control her [the patient] from striking out at you?"
- **Provocation.** "What is happening immediately prior to her striking out that seems to trigger this behavior or might make it worse?"
- **Quality.** "Does her striking out seem like nondirected flailing or well-aimed blows?"
- **Radiation.** "Does her striking out spread or escalate to other combative behaviors, such as kicking or biting?"
- **Scale.** "From 1 to 10, rate this behavior according to its effects on you and its interference with you being able to care for her."
- **Temporal profile.** "When, and under what circumstances, does this behavior usually occur?"

Eventually, patients with Alzheimer disease will become unable to clearly express themselves or to provide reasons for problematic behaviors. In these circumstances, a checklist for caregivers can be helpful in assessing the situation and in deciding on the most effective intervention. The following items are examples of the types of issues that can be addressed by a checklist:

■ **Physical discomfort experienced by patient**

- ☐ too hot
- ☐ too cold
- ☐ thirsty
- ☐ hungry
- ☐ pain
- ☐ full bladder
- ☐ constipation

■ **Environmental conditions of patient**

- ☐ overstimulation
- ☐ understimulation
- ☐ unfamiliar people or surroundings (eg, hospital admission)
- ☐ change in daily schedule or routine

■ **Sudden change in patient's health**

- ☐ medication adverse effect
- ☐ drug-drug interaction
- ☐ missed dose(s)
- ☐ urinary tract infection
- ☐ fecal impaction
- ☐ change in chronic illness (eg, arthritic flare-up, diabetes mellitus, emphysema, hypertension)

■ **Nature of caregiver problem**

- ☐ simple temporary frustration
- ☐ nonsophistication
- ☐ inattention
- ☐ demoralization
- ☐ burn-out
- ☐ abuse

All interventions for patients with Alzheimer disease require monitoring to assess efficacy. Regularly scheduled visits provide the opportunity to review all of the complex levels of care involved in Alzheimer disease. Attention to the stress level of caregivers cannot be overemphasized, because excessive stress can affect caregiver health. In addition, patients are at risk for abuse if caretakers experience burn-out as a result of insufficient support.¹⁶

Useful Rating Instruments for Physicians

Rating scales are essential for both initial diagnosis of Alzheimer disease and monitoring of effectiveness of interventions and progression of the illness. For cognition, the most helpful scale used in the United States is the Mini-Mental State Examination (MMSE).¹⁷ A recent study of rating instruments, however, recommends use of the General Practitioner Assessment of Cognition (GPCOG), which is more commonly used in Australia and Canada.¹⁸ The authors of that study¹⁸ argue that the GPCOG retains all the features of other cognitive screening tests, and it can be administered in half the time that it takes to administer the MMSE. The study¹⁸ strongly emphasizes routine screening for all elderly patients. With both the MMSE and GPCOG, the physician may change some of the items to guard against effects of learning if assessments are made at short intervals.

Neuropsychiatric symptoms (NPS) require careful objective measurement to make judgments about the effectiveness of psychosocial/behavioral interventions and to assess the preintervention and postintervention effectiveness of pharmacotherapies. The Neuropsychiatric Inventory provides a multidimensional profile of behavioral problems associated with Alzheimer disease based on responses from caregivers.¹⁹ For mood disorders, the Beck Depression Inventory (BDI) can be used.²⁰ The BDI is a 21-item instrument that is generally self-administered if the patient is capable of doing so. If the patient is unable to independently complete the BDI, a caretaker may assist with little risk of invalidating the result. The BDI is especially helpful for uncovering the presence of depression and for rating its intensity and severity.²⁰

The overall functioning of patients with Alzheimer disease must be monitored, and the Quality of Life-Alzheimer's Disease (QOL-AD) scale is one of the most specific and useful tools for this purpose in the primary care setting.²¹ This scale provides for important distinctions between self-assessment and ratings made by caregivers. It consists of a straight-forward questionnaire cov-

ering the areas of chores, energy, family, friends, fun, life-as-a-whole, living situation, marriage, memory, money, mood, physical health, and self. Each item on the QOL-AD is rated on a 4-point Likert scale (1=poor to 4=excellent).²¹

Ultimately, rating instruments may not be sufficient to capture all of the distinctions that are clinically significant. Many critics of clinical studies argue that the objective ratings used in the studies are not sensitive enough to uncover subtle changes in symptoms. Furthermore, meta-analyses are rendered more difficult when studies use different rating instruments. Referral of patients for neuropsychological testing—though expensive—can be helpful in making the earliest possible diagnosis, in discerning subtle symptomatic changes, and in monitoring illness progression.

FDA-Approved Medications for Alzheimer Disease

The first medications to receive FDA approval for symptomatic treatment of patients with Alzheimer disease were the acetylcholinesterase inhibitors (AChEIs). Cholinergic-mediated neural pathways involved in memory function and cognition become increasingly damaged and eventually die as Alzheimer disease progresses. Expedient treatment with AChEIs can diminish the rate of cognitive decline and other associated disabling symptoms. In some cases, a period of cognitive stability can be achieved soon after the diagnosis is made. Acetylcholinesterase inhibitors exert their therapeutic effects by slowing the degradation of acetylcholine in non-affected neurons, compensating for those neurons that are injured or lost as the illness progresses.²²⁻²³

The first acetylcholinesterase inhibitor to receive FDA approval in 1993 was tacrine hydrochloride (Cognex; Shionogi Inc, Florham Park, New Jersey). Physicians and patients welcomed this novel treatment. However, because of the complicated dosage schedule, troubling adverse effects, and risk of hepatotoxicity, the use of tacrine has been eclipsed by newer and safer medications.²⁴

Donepezil hydrochloride (Aricept; Eisai Inc, Woodcliff Lake, New Jersey); rivastigmine tartrate (Exelon; Novartis

Pharmaceuticals Corp, Basel, Switzerland); and galantamine hydrobromide (Razadyne [formerly Reminyl]; Janssen Pharmaceutica NV, Beerse, Belgium) are all AChEIs that represent distinct improvements over tacrine in ease of dosing and safety profile (*Table 1*).^{25,26} They are all most effective when initiated soon after diagnosis of Alzheimer disease has been established, and they all show nearly equal efficacy with respect to slowing the rate of decline in memory and cognition. These AChEIs also show mild efficacy in preserving daily functioning and slowing the progression of behavioral problems. With AChEI use, patients may experience a period of cognitive improvement or stability lasting as long as 12 months.^{25,26}

Each of these AChEIs is started at a low initial dose and tapered according to the patient's trajectory of improvement and toleration of adverse effects over a period of 1 to 6 months. No therapeutic effects are generally seen within the first month of treatment, but adverse effects can be immediate. The adverse effect profiles of these AChEIs are similar and primarily gastrointestinal (eg, anorexia, nausea, vomiting, weight loss, increased frequency of bowel movements) in nature. Common neurologic adverse effects include dizziness, drowsiness during daytime, headache, insomnia, and muscle cramping.^{25,26}

Memantine hydrochloride (Namenda; Forest Pharmaceuticals Inc, New York, New York) is the most recent FDA-approved medication for the treatment of patients with Alzheimer disease (*Table 1*). Memantine is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, one of two receptors that bind glutamate.²⁷ Glutamate, the primary excitatory neurotransmitter in the central nervous system, is implicated in the excitotoxicity involved in Alzheimer disease. Injured and dying neurons release excessive amounts of glutamate into their synaptic clefts. This release creates overstimulation and progressive damage to downstream neurons. The excessive levels of glutamate also increase NMDA receptor activity, thereby flooding the cell with calcium and causing progressive cell damage and death.^{28,29}

Memantine exerts its therapeutic effects by blocking NMDA receptors, providing neurons with a time-limited protective mechanism against the excess glutamate. Memantine has not shown statistically significant efficacy for treatment in the early course of Alzheimer disease, but it is approved for both monotherapy and adjunctive therapy with an AChEI in middle and late stages of the disease. The most common strategy involving memantine is to initiate treatment with an AChEI and to add memantine as the patient begins to show further decline in cognition. Memantine's most common adverse effects are constipation, dizziness, and headache.²⁷

Each of the FDA-approved medications for Alzheimer disease can be dosed once a day. Galantamine is available in an extended release form, and rivastigmine is available in a transdermal patch.^{25,26}

Pharmacotherapy for Associated Neuropsychiatric Symptoms

Physicians and caretakers must anticipate and manage the complicating noncognitive symptoms that will inevitably occur in patients with Alzheimer disease. Behavioral symptoms can generally be recognized as being beyond the former "in-character" nature of the person with Alzheimer disease, and these symptoms can be disturbing and frightening to caretakers and family members.

Behavioral problems typically begin with subtle personality changes and progress to increasing lapses in manners and social propriety. These behavioral problems, which can seriously compromise care, include aggression, agitation, aimless wandering, repetitive speech, restlessness, and sleep-wake cycle disruption. Patients are also increasingly at risk of having hallucinations and delusions. Most patients will eventually have mood disturbances, including affective blunting, anxiety, apathy, and depression.^{30,31}

The severity of mood and behavioral disturbances fluctuates as Alzheimer disease progresses. Neuropsychiatric symptoms may actually diminish as the illness reaches the final stages. This feature of Alzheimer disease progression

Table 1
Food and Drug Administration–Approved Medications for Patients With Alzheimer Disease

Generic Name (Trade Name), Year Approved	Dosage	Common Adverse Effects	Indications
■ Donepezil hydrochloride (Aricept), 1996	5 mg daily at bedtime with or without food for 4 to 6 weeks; 10 mg daily thereafter as tolerated	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia, vivid dreams	All stages of Alzheimer disease
■ Galantamine hydrobromide (Razadyne), 2001	8 mg daily split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks as tolerated, with a maximum daily dose of 16–24 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue	Mild to moderate Alzheimer disease
■ Memantine hydrochloride (Namenda), 2003	5 mg daily with or without food; dose increased by 5 mg every week, with a daily dose of 20 mg	Constipation, dizziness, headache, pain (nonspecific)	Moderate to severe Alzheimer disease
■ Rivastigmine tartrate (Exelon), 1998	3 mg daily split into morning and evening doses with meals; dose increased by 3 mg every 4 weeks as tolerated, with a maximum daily dose of 12 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness	Mild to moderate Alzheimer disease

highlights the importance of regular monitoring of symptoms and possible discontinuation of some medications as symptoms change. Unless the changing symptoms can be expeditiously controlled, they will predictably result in earlier caretaker burn-out, more frequent hospitalizations for the patient, increased length of inpatient stays, and earlier extended-care placement.^{32–34}

Placebo-controlled trials of the efficacy of pharmacotherapy for NPS in patients with Alzheimer disease clearly demonstrate that expectations should be modest for both prescribers and caregivers, and that the risks to patients are considerable.³⁵ Nonpharmacologic measures must be tried before, and concomitantly with, pharmacologic efforts to promote maximum benefit to patients. No firm and specific treatment rules exist for Alzheimer disease. Therefore, physicians must do their best to practice within the realm of expert consensus, “common-sense” anticipatory guidance, and cautious, systematic “trial-and-error” measures.^{36,37}

The more comorbid illnesses that a

patient with Alzheimer disease has, the higher is the likelihood of NPS development. Many elderly patients have longstanding chronic illnesses, especially diabetes mellitus and cardiovascular disease—thus increasing their risk of dementia from causes other than Alzheimer disease. Before further complicating the clinical picture with yet another medication, physicians should seek to get concurrent illnesses under the best possible control.

Pharmacotherapy for NPS must be customized for each patient, and it must be symptom-specific and time-limited. Medication doses should be started low and then titrated upward or downward gradually, with a predetermined time for discontinuation and reevaluation of the target symptoms.

Psychosis, Agitation, and Aggression

Antipsychotic agents are most helpful in the control of such “classic” symptoms as hallucinations and delusional thinking—rather than for agitation or attenuating aggression—in patients with Alzheimer

disease. Newer, atypical antipsychotic medications are generally preferable, because they have fewer untoward adverse effects than older medications. However, physicians must still be prepared for low therapeutic yield and high risk with these newer agents.

The more common atypical antipsychotic agents include aripiprazole (Abilify; Bristol-Myers Squibb, New York, New York); clozapine (Clozaril; Novartis, East Hanover, New Jersey); olanzapine (Zyprexa; Eli Lilly and Co, Indianapolis, Indiana); paliperidone (Invega; Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, New Jersey); quetiapine fumarate (Seroquel; AstraZeneca, Wilmington, Delaware); risperidone (Risperdal; Ortho-McNeil-Janssen Pharmaceuticals, Inc, Titusville, New Jersey); and ziprasidone (Geodon; Pfizer Inc, New York, New York) (Table 2). None of these atypical antipsychotic agents show clinical superiority over any other in the management of NPS in patients with Alzheimer disease, and all of them carry FDA “black box” warnings about increased risk of mortality in

elderly patients with dementia-related psychoses.

Patients with dementia are at higher risk for untoward events and adverse effects, including metabolic syndrome, neuroleptic malignant syndrome, tardive dyskinesia, and a range of extrapyramidal symptoms. Patients are also at risk for injury from drowsiness and falls. Increased mortality—especially from cardiac events and pneumonia within the first 3 months of treatment—has been demonstrated in a number of studies.³⁸

The newest atypical antipsychotic medication is asenapine (Saphris; NV Organon, Roseland, New Jersey). Asenapine shows promise in the management of NPS related to Alzheimer disease, perhaps because of reported minimal cardiovascular and anticholinergic adverse effects, as well as minimal weight gain. Like other atypical antipsychotic medications, asenapine does not have an FDA-approved indication for NPS of dementia, and it also carries the “black box” warning previously mentioned. No studies have been completed to test its safety and efficacy in an Alzheimer disease patient population compared with other atypical antipsychotic agents.

Mood Disturbance and Depression

Depression is common in patients with Alzheimer disease and has many etiologic considerations. Most obvious is the emotional reaction of fear, dread, and despondency as patients anticipate and experience their cognitive decline and impending loss of independent functioning. Signs and symptoms of depression are difficult to distinguish from those of Alzheimer disease itself—especially apathy, irritability, lassitude, and increasing social and interpersonal withdrawal. Even more classic “neurovegetative” symptoms of major depression—such as anhedonia, anorexia, insomnia, and weight loss—are common presentations of Alzheimer disease.

If these symptoms of mood disturbance are present and affecting quality of life, nonpharmacologic treatments should be tried before, and concurrent with, prescribing antidepressant medications. Evidence-based social and environmental interventions that are effective include

Table 2
Atypical Antipsychotic Agents Used in Patients With Alzheimer Disease

Generic Name (Trade Name)	Daily Dosage Range, mg
Aripiprazole (Abilify)	5-15
Asenapine (Saphris)	5-10
Clozapine (Clozaril)	200-600
Olanzapine (Zyprexa)	5-30
Paliperidone (Invega)	6-12
Quetiapine fumarate (Seroquel)	200-500
Risperidone (Risperdal)	2-6
Ziprasidone (Geodon)	10-40

increasing socialization with pets and friends, increasing known enjoyable activities, reducing activities known to be frustrating, redirecting perseverative speech and behaviors, and attending to the needs of caregivers.^{39,40}

Even with these measures, the use of antidepressant medications may be warranted. Selective serotonin reuptake inhibitors (SSRIs) generally represent the best first choice in such cases because of their milder adverse-effect profiles, compared with other antidepressant classes (Table 3). Tricyclic and tetracyclic antidepressants are rarely a first choice because

of their anticholinergic, histaminergic, and alpha-adrenergic blocking properties—which limit their use in geriatric patients with dementia. Choices of medications generally involve matching the corollary features of the particular medication with the clinical condition and target symptoms of the patient.

Citalopram (Celexa; Forest Pharmaceuticals, New York, New York); escitalopram oxalate (Lexapro; Forest Pharmaceuticals); and sertraline hydrochloride (Zoloft; Pfizer Inc, New York, New York) are three SSRIs that have been systematically studied and show reasonable safety (Table 3). Fluoxetine hydrochloride (Prozac; Eli Lilly and Co, Indianapolis, Indiana) is less desirable because of its long half-life, and paroxetine (Paxil; GlaxoSmithKline, Brentford, England) is rarely used because of its potential interactions with other medications metabolized by the cytochrome P-450 enzyme system.⁴¹ Most adverse effects of SSRIs are gastrointestinal in nature and can be managed by beginning the medications at low doses and tapering upward or downward gradually.

Pharmacologic treatment for depression should last between 6 and 12 months, with reevaluation on at least a monthly basis.³⁷

Table 3
Medications by Category for Depression in Patients With Alzheimer Disease

Generic Name (Trade Name)	Daily Dosage Range, mg
■ Monoamine Oxidase Inhibitor	
□ Selegiline (EMSAM)	8-12*
■ Psychostimulant	
□ Methylphenidate (Ritalin and others)	5-20
■ Serotonin and Norepinephrine Reuptake Inhibitor	
□ Desvenlafaxine (Pristiq)	50
□ Duloxetine hydrochloride (Cymbalta)	40-60
□ Venlafaxine hydrochloride (Effexor)	75-350
■ Selective Serotonin Reuptake Inhibitor	
□ Citalopram (Celexa)	10-60
□ Escitalopram oxalate (Lexapro)	10-30
□ Sertraline hydrochloride (Zoloft)	50-200
■ Tetracyclic	
□ Mirtazapine (Remeron)	15-45

*In transdermal patch.

Special Circumstances for Antidepressants

Mirtazapine (Remeron; Schering-Plough Corp, Kenilworth, New Jersey), a tetracyclic antidepressant, may be helpful in patients with Alzheimer disease who show signs of depression accompanied by poor sleep, poor appetite, and weight loss (Table 3). It may also be helpful in patients with Parkinson disease or in patients who experience tremors or bradykinesia with SSRIs. Mirtazapine would be a poor choice for patients who are overweight or at risk for metabolic syndrome or who have diabetes mellitus.⁴¹

Venlafaxine hydrochloride (Effexor; Pfizer Inc, New York, New York); desvenlafaxine (Pristiq; Pfizer Inc); and duloxetine hydrochloride (Cymbalta; Eli Lilly and Co, Indianapolis, Indiana) are serotonin and norepinephrine reuptake inhibitors (SNRIs) that may be helpful in depressed patients with Alzheimer disease who are also being treated for problems with pain, especially arthritis. These medications should be avoided in patients with hypertension, and they may also aggravate insomnia.⁴²

Selegiline (Eldepryl; sanofi-aventis, Bridgewater, New Jersey) is a selective monoamine oxidase inhibitor (MAOI) used for the treatment of patients with Parkinson disease. This neurodegenerative disorder is associated with both depression and dementia, and it severely complicates diagnosis and treatment of concurrent Alzheimer disease. A transdermal form of selegiline (EMSAM; Somerset Pharmaceuticals Inc, Tampa, Florida) is used for the treatment of patients with depression. Transdermal delivery obviates the need for dietary restrictions in the lowest dosage that would be recommended for elderly patients with Alzheimer disease.⁴³

Although not antidepressant medications, psychostimulants may be used as adjuncts in patients with Alzheimer disease who show signs of depression. Methylphenidate (Ritalin; Novartis Pharmaceuticals Corp, Basel, Switzerland) and similar products in low doses represent

the best first choice within the psychostimulant class (Table 3).⁴⁴ Methylphenidate is commonly used in palliative care as an off-label choice to manage signs and symptoms of depression.⁴⁴ Patients exhibiting anorexia, dysphoria, and lethargy show expeditious response to methylphenidate, tending to “perk up” and become more capable of cooperating with their care and interacting with family members and caregivers. When using this drug, extra care must be taken to monitor patients who have hypertension and cardiac disease.

Mania and Mood Lability

If patients with Alzheimer disease show symptoms of mania or severe mood fluctuations, mood-stabilizing medications are indicated—but extra caution must be taken to monitor patients for adverse reactions. The mood stabilizers that have been most studied are divalproex sodium (Depakote; Abbott Laboratories, Abbott Park, Illinois) and carbamazepine (Tegretol; Novartis Pharmaceuticals Corp, Basel, Switzerland) (Table 4).⁴⁵⁻⁴⁷

Divalproex sodium places patients at risk for weight gain, hyperglycemia, and hyperlipidemia. It is further associated with orthostasis, sedation, and worsening cognitive functioning. Carbamazepine has been demonstrated to decrease aggression in a nursing home population. However, its use requires vigilant monitoring of liver and hematologic functions. Carbamazepine is difficult to dose because it alters the

metabolism of many other medications, as well as the metabolism of itself.⁴⁵⁻⁴⁷

Sleep Problems

Behavioral interventions are generally more effective than pharmacologic ones in cases of insomnia in patients with Alzheimer disease. Caregivers must be educated in the principles of sleep hygiene and coping with common behaviors, such as patients’ daytime napping and drinking of caffeinated beverages, that can disrupt evening sleep. Caregivers should also encourage such helpful behaviors in patients as establishing a sleep-wake routine, performing daytime activities rather than daytime napping, and maintaining a regular activity/exercise schedule as tolerated.^{48,49}

Medications may be helpful for improving sleep in patients with Alzheimer disease (Table 5), but such drugs should be used in the context of concurrent sleep hygiene measures. Trazodone hydrochloride (Desyrel; Bristol-Myers Squibb, New York, New York) is an antidepressant medication that is highly sedative and can be used safely in low doses (50-100 mg) to improve sleep.⁵⁰ Ramelteon (Rozerem; Takeda Pharmaceuticals North America, Deerfield, Illinois) is the only noncontrolled drug (ie, with little potential for abuse or addiction) available for insomnia. It is a melatonin receptor agonist with no significant effect on other neurotransmission systems. It has few interactions with

Table 4
Mood Stabilizing Medications Used in Patients With Alzheimer Disease

Generic Name (Trade Name)	Daily Dosage Range, mg	Precautions
Carbamazepine (Tegretol; Equetro[extended release])	300-1600	Rash, incoordination, dizziness, drowsiness, ataxia, tremors, slurred speech, leucopenia, induction of its own metabolism and that of other drugs. Serum levels recommended.
Divalproex sodium (Depakote)	700-3000	Nausea, vomiting, weight gain, possible insulin resistance, hyperlipidemia, asymptomatic elevation of transaminase and serum ammonia, sedation, cognitive blunting

other medications commonly taken by older people with chronic illness.⁵¹

Benzodiazepines

The use of benzodiazepines in the management of NPS in patients with Alzheimer disease is generally not recommended because of many untoward outcomes. Adverse effects of this medication include aggravation of memory impairment, ataxia, disinhibition, and drowsiness. These adverse effects can create more problems for the patient and caregivers than any therapeutic benefit of reduced anxiety or improved sleep.

Controversial Therapies

Because Alzheimer disease is such a devastating illness, many patients and their families are desperate for any approaches to treatment that carry claims of potential help. Many patients—especially elderly individuals—independently use complementary and alternative therapies.⁵² Physicians must be vigilant to take thorough medical histories of patients, including use of any complementary medications or “nutraceuticals.” Physicians should provide patients with the best common-sense and data-based advice on these substances. A comprehensive review of the range of complementary therapies is beyond the scope of the present article, but some of the more common agents are covered with a focus on safety.

Complementary and alternative treatments generally have not been subjected to the kind of scientific scrutiny that would permit FDA approval or strong clinical endorsement by physicians. However, many of these therapies are recommended by physicians and other clinicians for a number of chronic illnesses that are common in elderly individuals, especially cardiovascular disease and various forms of arthritis.⁵³

Aspirin and NSAIDs

Some epidemiologic studies indicated that aspirin and various nonsteroidal anti-inflammatory drugs (NSAIDs) might offer some protection against Alzheimer disease and other forms of dementia, and these studies created great excitement within the medical community.^{54,55} Likewise, some animal studies

Table 5 Medications for Insomnia for Patients With Alzheimer Disease	
Generic Name (Trade Name)	Bedtime Dosage Range, mg
Melatonin (Multiple OTC brands; some sublingual preparations)	0.3-3
Ramelteon (Rozerem)	8-16
Trazodone (Desyrel) hydrochloride	50-100
Abbreviation: OTC, over the counter.	

demonstrated β -amyloid suppression with the use of NSAIDs.⁵⁶ However, randomized controlled trials of NSAIDs in humans with dementia have been inconclusive.

Moreover, aspirin and NSAIDs carry risks of cardiotoxicity, gastrointestinal bleeding, and impairment of renal function. For these reasons—without further medical indication for their concomitant use (eg, low-dose daily aspirin for cerebrovascular disease)—aspirin and NSAIDs should not be recommended solely for the treatment of patients with Alzheimer disease.

Vitamin E

The discovery of the neurotoxicity of oxidative free radicals in Alzheimer disease led to a number of trials of antioxidant vitamins, which have had mixed and confusing results. Several studies using vitamin E in doses as high as 2000 IU daily failed to demonstrate improvement in cognition or overall function.⁵⁷ Recent evidence indicates that, at high doses, vitamin E may aggravate vitamin K-deficient coagulation disorders and increase all-cause mortality in elderly patients.⁵⁷

Thus, vitamin E can no longer be recommended for the treatment of patients with Alzheimer disease. If patients wish to take vitamin E for other reasons, physicians should recommend that the dose not exceed 400 IU daily.

Curcumin

More promising than vitamin E is the turmeric extract curcumin, which seems

to have low toxicity and potential to produce therapeutic effects in patients with Alzheimer disease. It is a combined polyphenolic antioxidant and a natural NSAID. Curcumin inhibits the expression of inflammatory cytokines and shows a number of anti-amyloid properties.⁵⁸

Besides demonstrating neuroprotective properties, curcumin has a wide margin of safety and is not expensive. If patients wish to add this substance to their treatment plan, they should be advised to begin at a dose of 400 mg twice daily and not exceed 2 grams daily.⁵⁹

Omega-3 Fatty Acids

The typical American diet has less than the recommended daily intake of docosahexaenoic acid (DHA). Like curcumin, DHA has been demonstrated to have neuroprotective properties at a number of metabolic sites. Omega-3 fatty acids are now recommended for a host of chronic conditions associated with aging, especially cardiovascular disease. In addition, they have an even stronger safety profile than curcumin.⁶⁰⁻⁶³

Fish oil capsules are inexpensive and widely available over the counter. A prescription pharmaceutical-grade preparation of omega-3 acid ethyl esters called Lovaza (GlaxoSmithKline, Brentford, England) is also available. The therapeutic dose of Lovaza that is used as adjunctive treatment for patients with hyperlipidemia is 4 grams daily in a divided dose. Omega-3 fatty acids should be strongly considered as a safe and potentially helpful adjunct in the prevention and management of Alzheimer disease, especially in patients with concurrent cardiovascular disease.⁶⁰⁻⁶³

Hormone Replacement Therapy

Initial evidence supported investigation of estrogen replacement therapy (ERT) as prevention and management of Alzheimer disease. Estrogen receptors are located throughout the brain in both women and men, especially in those regions that process memory. Estrogen has both anti-inflammatory and antioxidant properties and has been demonstrated to act as a trophic factor for cholinergic neurons.⁶⁴ Early promising

open-label and observational trials with estrogen showed selective improvement in cognition in women with Alzheimer disease. Several epidemiologic studies demonstrated that ERT lowered risk and delayed onset of Alzheimer disease in postmenopausal women.⁶⁴

Unfortunately, randomized controlled clinical trials of ERT for Alzheimer disease have been consistently disappointing. The Women's Health Initiative Memory Study (WHIMS)^{65,66} actually indicated deleterious effects of ERT in patients with Alzheimer disease or other forms of dementia. Critics point out that most of these trials used oral conjugated equine estrogens, and that smaller clinical trials using transdermal 17 β -estradiol showed selective improvement in attention and memory scores in patients with Alzheimer disease. Critics also point to the need to develop more sensitive instruments to tease out small but important changes in cognition.

On balance, evidence of the therapeutic value of ERT is too scant to recommend its general use in the treatment of patients with Alzheimer disease. However, ERT may be useful in improving overall quality of life in carefully selected and closely monitored individual patients.⁶⁷

Aging in men is associated with a decline in levels of total testosterone, bioavailable testosterone, and free testosterone. Clinically, this decline corresponds predictably to decreased muscle mass and strength, increased risk of osteoporosis, decreased libido, and alterations in mood and cognition.^{68,69} Testosterone levels are potentially related to Alzheimer disease in men, according to a number of clinical studies. The basic science literature demonstrates that testosterone reduces the formation of β -amyloid from amyloid precursor protein and decreases hyperphosphorylation of tau protein. Several small placebo-controlled studies have shown that testosterone replacement reversed the previously described age-related changes and improved both spatial cognition and working memory.

A recent, well-designed study used a wide variety of outcome measures to analyze the effects of transdermal testosterone in men with Alzheimer disease.⁷⁰

The results indicated minimal beneficial effects on cognition but statistically significant improvement in overall quality of life.⁷⁰ Like ERT for women, testosterone replacement for men may have some benefit in well-selected individuals, but it is not recommended for general use in the management of Alzheimer disease.

Statins

The wide use of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) for prevention of cardiovascular disease—and the association between high levels of cholesterol and Alzheimer disease—have generated great interest for the use of statins in both prevention and management of Alzheimer disease.⁷¹ Retrospective observational studies correlated the long-term use of statins with a decreased risk of Alzheimer disease. However, randomized controlled studies have dampened the early excitement.⁷² The outlook for statins in the prevention and treatment of Alzheimer disease shows promise, but presently these medications cannot be recommended outside the context of their FDA-approved indications.

Further Alternatives

An outstanding review of the use of alternative therapies in Alzheimer disease was written by Kelley and Knopman⁷³ in 2008. These authors stressed the importance of physicians being familiar with complementary therapies in order to provide meaningful recommendations to interested patients.⁷³

The use of complementary and alternative therapies is increasingly entering mainstream medical education, research, and practice. Using these therapies in the treatment of patients with Alzheimer disease requires careful discussion with patients and shared decision-making with the informed decision on use ultimately resting with the patient and caregivers.

Conclusion

For the foreseeable future, physicians will continue to see an increase in the number of Alzheimer disease cases in their practices. The intent of the present article is to emphasize that Alzheimer

disease has sweeping impact beyond the suffering of the individual patient and that effective care requires the coordinated efforts of professional and lay caregivers.

Treatment of patients consists of a combination of psychosocial, behavioral, and pharmacologic strategies aimed at slowing the process of Alzheimer disease and preserving quality of life for as long as possible. Attention to the health and welfare of caregivers is an essential component of treatment. The family physician continues to be the central and most appropriate figure to direct and coordinate this care. Until medical research discovers definitive disease-modifying treatments for patients with Alzheimer disease, we must continue to maximize all available resources to provide the best possible individualized patient-centered and family care.

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