New Paradigms in the Treatment of Alzheimer's Disease

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the series of planning teleconferences "New Paradigms in the Treatment of Alzheimer's Disease," which were held in June, July, and August 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Forest Laboratories, Inc.*

The teleconferences were chaired by ***Pierre N. Tariot****, M.D., Memory Disorders Clinic, Banner Alzheimer's Institute, Phoenix, Ariz. The faculty were* ***Jeffrey L. Cummings****, M.D., Alzheimer's Disease Center, Deane F. Johnson Center for Neurotherapeutics, David Geffen School of Medicine at University of California, Los Angeles;* ***M. Saleem Ismail****, M.D., Department of Psychiatry, University of Rochester Medical Center, Monroe Community Hospital, Rochester, N.Y.; and* ***Constantine Lyketsos****, M.D., M.H.S., Department of Psychiatry, Johns Hopkins Bayview, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Baltimore, Md.*

Faculty disclosure appears at the end of the article.

Alzheimer's Disease: The Challenge

Alzheimer's disease (AD) was the eighth overall leading cause of death in the United States in 2003 and the fifth leading cause among people 65 years and older.[1] Estimates indicate that the prevalence of AD will quadruple in the next 40 years.[2] Although cognitive impairment is the core feature of the disease, other psychological and psychiatric conditions can interfere with diagnosis and treatment. New treatments that specifically delay cognitive decline are available but are underused, as is combination pharmacotherapy. Here, experts in the field offer their insights on recognizing and managing this insidious disorder.

Variability in the Clinical Presentation of Alzheimer's Disease

Alzheimer's Disease is a heterogeneous illness with variability in clinical presentation that challenges timely and accurate diagnosis, according to M. Saleem Ismail, M.D. In the absence of a diagnostic or confirmatory test for this disease, special attention must be paid to clinical diagnosis, which has both prognostic and management implications.

Factors Influencing Clinical Presentation

Dr. Ismail described several factors that influence the clinical presentation of AD.

Age at onset. Younger individuals are more likely to have reversible causes of dementia than people over the age of 65 years,[3] and although AD is less common in younger individuals, the course of illness in these patients may show more rapid progression than in older adults. Genetic factors can influence the age at which AD develops, account for some variations in clinical presentation,[4,5] and play a greater role in early-onset AD.[6,7] In younger patients, non-Alzheimer's dementias may be relatively more common, so it is important to exclude causes such as frontal-temporal lobe dementia, human immunodeficiency virus (HIV), traumatic brain injury, toxins, alcohol, and vascular dementia.[3,8] Assessments such as magnetic resonance imaging (MRI), computed tomography (CT) scans, electroencephalogram (EEG), cerebrospinal fluid (CSF), and psychometric evaluations are of particular importance in excluding non-Alzheimer's dementias in younger adults.[8] The pattern of cognitive decline may vary based on age at onset of AD. Such variation is probably due to differences in the brain regions involved.[6]

Dr. Ismail noted that younger patients require a different management strategy compared with those who develop dementia later in life.[6,7] The economic and emotional toll of early AD can be worse than in late-onset AD. Emotional burden can be enormous when small children are involved. Similarly, job losses, economic hardship, and relationship issues can be a manifestation or a result of early-onset AD. Management plans for younger patients may require specialized services, day care, and care homes. However, for older patients, the medical burden, caregiver issues, and living arrangements are a more important part of the treatment plan.[7]

Stage of illness. Stage of illness also affects presentation. Dr. Ismail described 3 stages of AD: mild, moderate, and severe. At each stage, patients with the disease show variability in activities of daily living (ADL), behavior, and cognition,[9,10] and each patient may experience unique effects in these 3 areas. In the early mild stage, effects may include social isolation or avoidance, decreased participation in complex activities, some symptoms of depression, and memory loss. In the moderate stage, patients may exhibit loss of basic ADL and neuropsychiatric symptoms such as paranoia and agitation. In the severe stage, medical morbidities, complex medical conditions, and issues of safety, placement, and comfort care occur. A typical AD case study is shown in Table 1. The

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Table 1. Case Study 1: Typical Alzheimer's Disease

History
80-year-old man; retired insurance agent
12 years of school
2-year history of progressive decline in memory
Cognitive
Mini-Mental State Examination score = 23/30 (recall 0/3)
Medical
Pacemaker, hypertension, constipation, prostate carcinoma s/p radiation therapy with incontinence
Oxybutynin, aspirin, lisinopril
Nonfocal neurologic examination

Abbreviation: S/p = status post.

patient became increasingly dependent on caregivers and developed mild neuropsychiatric symptoms such as frustration and irritability with repetitive tasks. The neurologic examination was nonfocal, and imaging and blood work excluded reversible causes. The management plan needs to encompass all of the patient's medications and medical conditions as well as caregiving issues.

Comorbidities. Dr. Ismail stated that medical comorbidities influence diagnosis and management of AD. More than 60% of AD patients have been found to have 3 or more medical conditions.[11] The most prevalent comorbidities are musculoskeletal, genitourinary, and ear, nose, and throat disorders. Greater medical comorbidity means greater likelihood of complications, more emergency department visits, more complex medication regimens, greater mortality, and a higher impact on cognition (which increases the risk of delirium). Diagnostic evaluation and treatment plans need to address these issues.

Cardiovascular disease can also influence the presentation of AD. Patients may present with memory complaints following myocardial infarction or coronary bypass graft.[12] No relationship between coronary artery disease and the onset of AD has been established,[13] but Dr. Ismail speculated that the relationship could be connected with changes in white matter in the brain. However, patients with cardiovascular disease do have vascular risk factors that have been shown to be associated with cognitive disorder.[14,15] Dr. Ismail noted that the presence of vascular risk factors such as hypertension, diabetes, hyperlipidemia, obesity, and smoking does not automatically mean that an individual has vascular dementia.

Diabetes is also a common medical comorbidity with AD and evidence suggests that diabetes is a risk factor for AD, independent of vascular risk factors.[16] Distinguishing AD from vascular dementia is important since the diagnosis has prognostic and treatment implications.

Depression is a comorbidity that has an atypical presentation in patients who have AD and therefore can be challenging to diagnose.[17] Symptoms may include delusions, intraday variations in mood and vital sense, and brief and highly recurrent mood disturbances, with irritability, worry, anxiety, and fear being more prominent in patients with AD than in those with typical geriatric depression. Apathy and loss of motivation are common in patients with AD and comorbid depression, along with lack of ability to sustain activities and sleep disturbances. Depression can be a prodrome of AD or it can coexist with AD.

Delirium is frequently underrecognized in patients with preexisting dementia.[18,19] Delirium may be the first manifestation of underlying dementia in newly admitted inpatients. If delirium is hypoactive, it may be mistaken for depression. Recognition of delirium has implications for both treatment and prognosis and should always be part of the differential diagnosis of dementia. According to Dr. Ismail, an episode of delirium in an older adult should prompt a dementia evaluation once the delirium is resolved.

Primary sleep disturbances can mimic a cognitive disorder or affect dementia evaluations.[20] Sleep disturbances, such as increased nocturnal awakenings, daytime napping, reversal of day/night sleep, and sundowning, occur in AD, but it is important to distinguish between primary sleep disorders, such as sleep apnea, and the effects of sleep disturbance on cognitive impairment.[21,22]

Table 2. Case Study 2: Mild Cognitive Impairment

History
57-year-old woman; recently switched jobs
13 years of school
6- to 12-month history of decreased attention, short-term memory, and ability to recall names
Grandmother admitted to nursing home
Cognitive
Mini-Mental State Examination score = 28/30 (recall 2/3)
Medical
No history of psychiatric illness or drug or alcohol use
Uneventful medical history, uses ibuprofen as needed

Challenges in Clinical Presentation

Dr. Ismail next described 3 particularly challenging clinical presentations encountered in clinical evaluation of AD: mild cognitive impairment, mixed dementia, and parkinsonism.

Mild cognitive impairment. Differentiating between mild cognitive impairment and AD is difficult, reported Dr. Ismail. Patients may present with subjective sense of memory loss and/or deficits in other cognitive functions but may not have associated impairment in daily functioning; that is, they may not yet meet criteria for dementia.[23,24] Recognizing this group is important since these patients have a higher risk of progression to AD. Research[25] found that patients with amnesic-type mild cognitive impairment showed early pathologic changes similar to those of AD. Also, progression from mild cognitive impairment to AD was suggested by the presence of increased neurofibrillary tangles, which were more prominent than β-amyloid peptide deposition. Most experts believe that mild cognitive impairment is actually early AD and that the difference between the 2 is quantitative rather than qualitative.[24–26] Dr. Ismail presented a case study of a patient whose neuropsychiatric testing results were consistent with mild cognitive impairment (Table 2), and he stressed that patients like this who exhibit early symptoms may be progressing toward AD.

Mixed dementia. A typical patient with mixed dementia has insidious onset and progressive cognitive decline but presents with cerebrovascular events and cerebrovascular risk factors and may also have focal neurologic findings or changes on neuroimaging.[27,28] Mixed dementia seems to be on a continuum between AD and vascular dementia. Dr. Ismail suggested that a careful assessment of the patient's history may be the most important tool in differentiating between AD and mixed dementia. The course of mixed dementia is suggestive of AD but has a faster onset, more stepwise deterioration, a fluctuating course, focal signs and symptoms, patchy cognitive deficits, early gait abnormalities, seizures, and radiographic features such as stroke and white matter changes.[27]

Parkinsonism. When parkinsonism coexists with features of AD, a question of dementia with Lewy bodies is raised. Dementia with Lewy bodies can present as a complex condition with additional challenges for treatment and prognosis, and the condition requires care in treatment selection.[29–31] Dr. Ismail emphasized that the presence of parkinsonian symptoms does not exclude a diagnosis of AD. Patients with AD commonly have parkinsonian symptoms,[29,31] and some reports[28] suggest that up to 50% of cases of dementia with Lewy bodies are associated with AD pathology. Tremors, rigidity, and myoclonus at diagnosis generally predict a lower survival rate,[30] so it is important to look for these signs and symptoms.

Dr. Ismail concluded that variability in the clinical presentation of AD poses diagnostic challenges. Accurate and early clinical diagnosis is important to ensure that individual needs are addressed and long-term treatment effectiveness can be assessed. Although AD remains the most common form of dementia, it is not uncommon in clinical practice to see patients with AD who present with cerebrovascular disease, dementia with Lewy bodies, Parkinson's disease, and other medical conditions.

Treatment Initiation in Alzheimer's Disease

Basic principles of patient-focused care, treatment initiation in both mild-to-moderate and moderate-to-severe AD, tangible benefits of available therapies, and new antidementia therapies being developed were the topics presented by Pierre N. Tariot, M.D.

Treatment Principles

Dr. Tariot introduced 3 principles of patient-focused care.[32–34] The first principle stresses that diagnosis is crucial because management recommendations are determined by which form of dementia the patient has. Necessary details include how and when the dementia began, what changes have occurred over time, which domains are affected, and what the effects of prior therapy were. Another principle of patient-focused care is that some help can be offered at all stages of the illness. The third principle is that patients' residual strengths should be identified in order to maximize autonomy, quality of life, and dignity. Every attempt should be made to understand feelings and needs that patients have at all stages of AD but may not be able to express clearly. The ability to transmit and receive emotions accurately is often preserved even in the late stage of AD.

Patient-focused care also emphasizes the importance of maintaining daily activities and lifestyle; optimizing physical, emotional, and intellectual stimulation; eating a healthy diet; and avoiding isolation.[32,33] Promoting mobility as long as possible is vital because people who are mobility-impaired are at greater risk for complications such as pneumonia, pressure sores, and urinary tract infection. They also are at greater risk for social isolation. Safety concerns regarding wandering, driving, and use of tools need to be monitored, and emotional and psychological states need to be assessed regularly. Medical illnesses can influence the manifestations of dementia and can raise concerns such as nutrition and polypharmacy.

On the basis of available evidence[32,33] and his own experience,[34] Dr. Tariot advocated the use of standard antidementia therapies that are now available. On average, these agents can slow the decline in cognition and daily functioning that occur in patients with AD. The U.S. Food and Drug Administration (FDA) has approved cholinesterase inhibitors for treatment of mild-to-moderate AD and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine for treatment of moderate-to-severe AD. More recently, the FDA has approved the use of donepezil for treatment of severe AD as well. The cholinesterase inhibitors currently approved by the FDA include donepezil, galantamine, and rivastigmine. Antidementia therapies may also reduce some neuropsychiatric symptoms and delay their emergence in some people with AD. If this proved to be true, it would offer substantial benefit to patients, reduce caregiver burden, and have favorable public health repercussions. If antidementia therapies prove to have no impact on psychopathology, then psychotropic medication, used judiciously, can have beneficial effects at least in some AD patients.

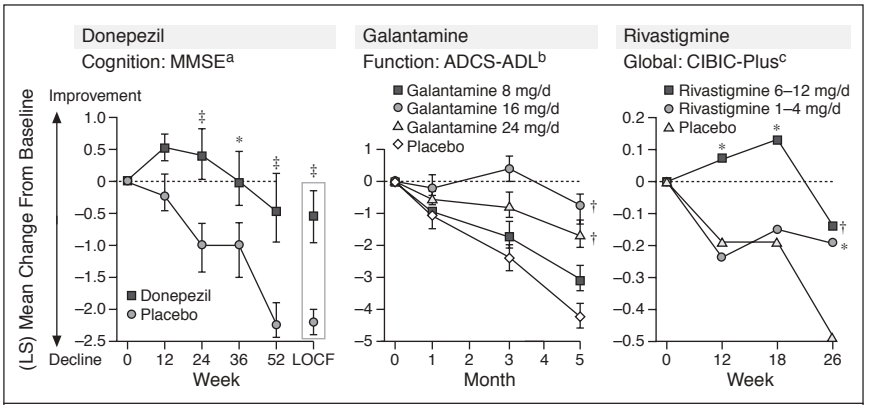
Treatment Initiation in Mild-to-Moderate AD

Clinical trials of cholinesterase inhibitors have shown that, compared with placebo or low-dose therapy, full dose therapy of donepezil, galantamine, and rivastigmine slowed cognitive decline, functional decline, and the decline of global estimates of clinical condition (Figure 1).[35–37] Cholinesterase inhibitors are safe. The package insert for galantamine[38] mentions a small imbalance in death rates, and a single trial (data on file, Eisai Inc., Teaneck, N.J.) of donepezil in vascular dementia showed a potential death signal. This unproven possible signal is not seen when data are aggregated and was seen only in studies with atypically low mortality rates in the placebo arms.

Well-understood adverse events are associated with cholinesterase inhibitors.[39] The chief side effects are gastrointestinal (GI) and include nausea, vomiting, diarrhea, and abdominal pain, which may result in anorexia and weight loss. Depending on the particular drug and study design, frequency rates for GI adverse effects range from the low teens to 30% or higher.[39] Bradycardia and fatigue occur at low rates. Donepezil is associated with a low rate of muscle cramps and occasional rhinorrhea, and some cholinesterase inhibitors are associated with sleep disturbance.

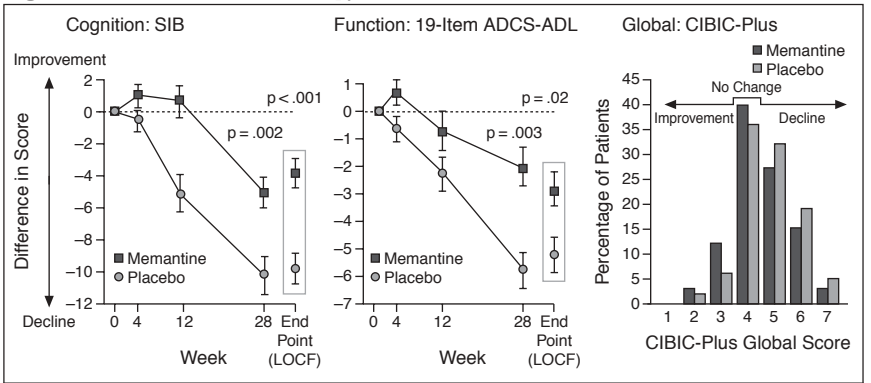
Dr. Tariot reported that cholinesterase inhibitors have limited rates of drug-drug and drug-disease interactions.[39] Cholinesterase inhibitors combined with digoxin and β-blockers may exert exaggerated vagotonic effects on cardiac conduction. During anesthesia, cholinesterase inhibitors may exaggerate succinylcholine-type muscle relaxation, and there may be interactions with either anticholinergic or procholinergic drugs. Donepezil and galantamine are partially metabolized by cytochrome P450 isoenzymes, and galantamine clearance is decreased in renal insufficiency.

Figure 1. Cholinesterase Inhibitor Monotherapy in Mild-to-Moderate Alzheimer's Disease[a,b,c]



[a]Adapted with permission from Winblad et al.[35]
[b]Adapted with permission from Tariot et al.[36]
[c]Adapted with permission from Corey-Bloom et al.[37]
*p < .05, †p < .01, ‡p ≤ .001.
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living inventory, CIBIC-Plus = Clinician's Interview-Based Impression of Change With Caregiver Input, LOCF = last observation carried forward, LS = least squares, MMSE = Mini-Mental State Examination.

Figure 2. Memantine Monotherapy in Moderate-to-Severe Alzheimer's Disease[a]



[a]Adapted with permission from Reisberg et al.[41]
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living inventory, CIBIC-Plus = Clinician's Interview-Based Impression of Change With Caregiver Input, LOCF = last observation carried forward, SIB = Severe Impairment Battery.

Treatment Initiation in Moderate-to-Severe AD

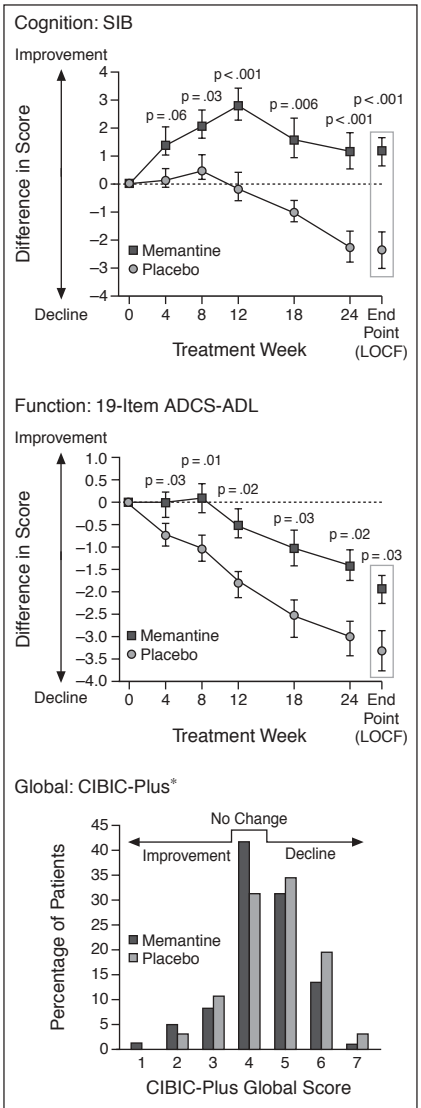
Since Dr. Tariot's presentation, the FDA has approved donepezil for treatment of severe AD, based on randomized controlled studies[40] showing more favorable outcomes with donepezil versus placebo in patients with advanced disease. Principles of best practice based on these welcome new findings remain to be established.

At the time of his presentation, the only type of drug approved for treatment of moderate-to severe AD was an NMDA receptor antagonist. Dr. Tariot presented results from a study[41] of monotherapy with memantine in outpatients with moderate-to-severe AD that showed a slowing of progression in deterioration of cognition, function, and overall dementia severity (Figure 2).[41] As discussed later by Dr. Lyketsos, adding memantine to ongoing donepezil therapy in outpatients with moderate-to-severe AD also produced a relative slowing of functional decline and globally assessed deterioration, and cognitive performance showed a preservation or even improvement of function (Figure 3).[42] Therefore, both memantine monotherapy and memantine plus donepezil benefit patients with moderate-to-severe AD.

Memantine was well-tolerated in placebo-controlled trials.[43] Low rates of drug-placebo differences were found in dizziness, worsening of confusion, headaches, and constipation. However, Dr. Tariot cautioned that, as with any new medication used in a vulnerable population, clinicians should be alert to side effects not seen in clinical trials.

Several drug-drug and drug-disease interactions can occur with memantine.[43,44] People with mild-to-moderate renal disease should be treated with standard doses of memantine, but patients with severe renal disease should be treated with halved doses. The bioavailability of drugs that undergo tubular secretion, such as hydro-

Figure 3. Efficacy of Memantine and Ongoing Donepezil in Patients With Alzheimer's Disease[a]



[a]Adapted with permission from Tariot et al.[42]
*p = .03.
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, CIBC-Plus = Clinician's Interview-Based Impression of Change With Caregiver Input, LOCF = last observation carried forward, SIB = Severe Impairment Battery.

chlorothiazide, has been shown to decrease in these patients. Low plasma binding means that minimal to no interactions occur with drugs that are highly protein-bound, such as warfarin. Memantine should not be used with other NMDA antagonists such as ketamine or amantadine, but cholinesterase inhibitors can be used.

Tangible Benefits of AD Treatment

Dr. Tariot said that, although not yet proven by extensive clinical trials, early treatment appears to be beneficial to AD patients,[45] and the maximum tolerated dose may be important.[46] Data from a study[45] with galantamine showed that patients who received galantamine for a year, initially in a blinded fashion for 6 months and then openly, exhibited modest cognitive improvement and relative cognitive stabilization. Data such as these suggest, but do not prove, that earlier treatment might confer better outcome. In a study[46] of rivastigmine versus placebo that measured cognitive function in patients with mild to moderately severe AD, the best clinical outcomes appeared to be conferred by the highest tolerated dose.

Treatment with cholinesterase inhibitors other than donepezil in patients with advanced AD is considered to be an "off-label" use, since they are not approved by the FDA. In addition to the data from severe AD above, data from a study[47] of patients with moderate-to-severe AD showed functional benefit as well as benefit in global change from treatment with donepezil. Conversely, 2 of 3 studies (reference 48 and data on file, Forest, Jersey City, N.J.) of memantine versus placebo in patients with mild-to-moderate AD showed no benefit. New information may emerge, and whether either of these new approaches will receive FDA approval remains to be seen. Some evidence suggests the hope that treatment with cholinesterase inhibitors[49] and with memantine therapy[50] may delay nursing home placement in people with AD, while the largest prospective study[51] addressing this question found no such effect.

Newer Therapies

The knowledge that oxidative burden occurs in AD and aging led to the hope that antioxidants might confer benefit, but Dr. Tariot reported that only slim evidence is available from clinical trials.[52] The inflammatory hypothesis of AD has created interest in anti-inflammatory drugs, but trials have been null or have shown adverse effects.[53] Currently, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) is studying anti-inflammatory drugs in people who are at risk for AD, but results are not yet available. The results of hormonal therapy trials[54] have also been negative or null. An emerging area of interest is statins, and evidence[55] suggests they may have a therapeutic role in AD. A pilot study[56] of statins produced positive results, although the study was too small to suggest the use of this class of medication; however, several large trials are now taking place and future trial results may be of interest. According to Dr. Tariot, elevated homocysteine levels appear to be a risk factor for brain diseases including stroke and AD, and an Alzheimer's Disease Cooperative study (ADCS) is investigating whether lowering homocysteine levels will confer therapeutic benefit.

Dr. Tariot expressed excitement about current research into antiamyloid therapies, including immunization techniques, secretase inhibitors, secretase activity promoters, antifibrillization techniques, and amyloid clearance techniques. These therapies attack aspects of the mishandling of the amyloid precursor protein in AD but have not yet been proven to confer clinical benefit. Some new ideas about normalizing the processing of the tau protein are being studied through the ADCS, and some strategies involving nerve growth factors are in early development.

Summary

Dr. Tariot concluded that many aspects of the pathobiology of AD have been understood and have led to promising therapeutic targets. In the future, some novel therapeutics could further attack the biology of the illness. The use of cholinesterase inhibitors may broaden to include both more severe and milder AD. For the present, however, available treatments are cholinesterase inhibitors, which have a well-established rationale for use in mild-to-moderate AD, and the only

available NMDA receptor antagonist memantine, for which there is a well-established rationale for use in patients with moderate-to-severe AD. Dr. Tariot reiterated his support for early treatment, beginning at diagnosis, with its benefits in preserving cognition, daily functioning, and global measures of performance. He stressed that stimulation, healthy diet, and active lifestyle are important for people who are at risk for cognitive impairment because they may confer some degree of protection against AD. He advocated use of the current guidelines articulated by the American Academy of Neurology,[26] namely that treatment should be afforded to people at all stages of AD.

Neuropsychiatric Symptoms and Comorbidity in Alzheimer's Disease: Preventing Emergence and Decreasing Severity

Neuropsychiatric Symptoms in AD

Jeffrey L. Cummings, M.D., began by stating that studies[57,58] show that in excess of 90% of patients with AD have some neuropsychiatric symptoms. These symptoms tend to be heterogeneous; some patients exhibit more agitation, psychosis, or mood symptoms than other patients or have prominent apathy, whereas other patients have relatively few neuropsychiatric phenomena. It is common for a patient to be agitated, psychotic, and depressed simultaneously. A challenge for the clinician is to choose which symptom is the most urgent target for treatment.

Neuropsychiatric symptoms may be present throughout the course of AD; they are already present in some patients with mild cognitive impairment and tend to worsen throughout the course of the illness. Once present, neuropsychiatric symptoms are highly recurrent and tend to be a part of that patient's clinical syndrome for several years. As AD progresses, psychosis and agitation become systematically more common and occur in a greater proportion of patients with AD.

A cross-sectional study[58] examined the extent of neuropsychiatric symptoms in patients with mild, moderate, or severe AD. As shown in Figure 4,[58] delusions were more common in patients with moderate and severe AD, hallucinations emerged in severe AD, agitation became systematically more common across the course of the disease, depressive symptoms were present throughout and tended to change little, and anxiety symptoms tended to emerge in the final phase of the illness. Dr. Cummings drew attention to the frequency of symptoms; agitation, for example, was present in more than 80% of individuals toward the end of the illness. The study also showed that disinhibition and irritability continued throughout the course of the illness with relatively similar frequencies. Elation, usually a relatively rare phenomenon, was infrequently present in this study but increased throughout the course of the illness, as did apathy. Walking, wandering, rummaging, and other purposeless motor activities also increased throughout the course of AD.

Dr. Cummings asserted that several generalizations have emerged from the study of the neuropsychiatry of AD. Cognitive decline is more rapid when neuropsychiatric symptoms are present.[58] Agitation, psychosis, and depression all exaggerate the rate of cognitive decline. Neuropsychiatric symptoms do not, however, appear to shorten the illness; patients die at about the same time after onset, whether or not these symptoms are present. Neuropsychiatric symptoms correlate primarily with executive dysfunction and impairment of ADL, while a weaker correlation is found between neuropsychiatric symptoms and cognition.[58] Dr. Cummings observed that executive dysfunction, neuropsychiatric symptoms, and impairment of ADL reflect impairment of the frontal cortex.

Neuropsychiatric symptoms cause distress and reduce quality of life for both the patient and the caregiver. Neuropsychiatric symptoms can also precipitate institutionalization. Dr. Cummings remarked that families do not institutionalize a family member for repeatedly asking the same question, but they cannot tolerate agitation, psychosis, and severe depression.[59] One study[59] found that patients with behavioral disturbances were institutionalized within about 1000 days or 3 years, whereas patients who had few behavioral disturbances continued in the community for over 1600 days or about 5 years. Neuropsychiatric symptoms substantially increase the cost of management of AD, since institutionalization represents much of the cost.

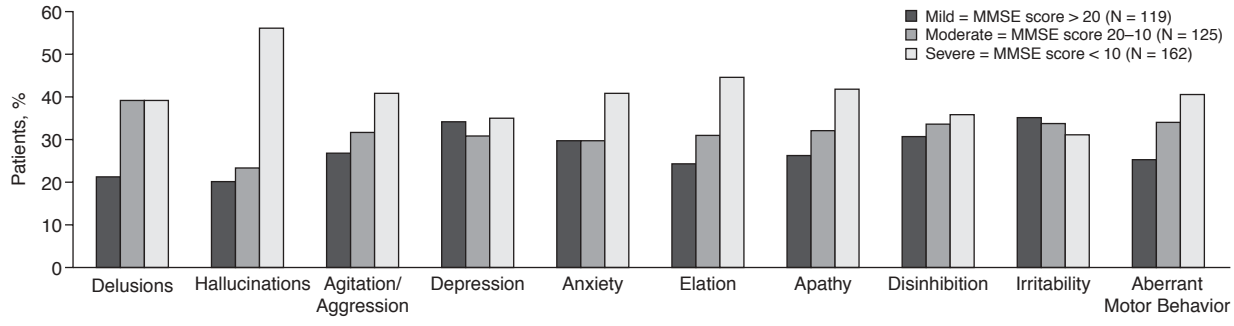
Neurobiology of Neuropsychiatric Symptoms in AD

Dr. Cummings stated that a variety of methodologies have been applied to determine why some patients develop neuropsychiatric symptoms and others do not. Neuroimaging, such as single photon emission computed tomography (SPECT) scans and positron emission tomography (PET) scans, shows disproportionate frontal and temporal lobe dysfunction in patients with neuropsychiatric symptoms.[60] Neuropathologic evidence[61] from deceased patients on whom autopsies have been performed revealed that those who exhibited psychosis or agitation in the course of their illness had a greater abundance of neurofibrillary tangles than those who did not. In patients with agitation, neurofibrillary tangles were disproportionately present in the frontal cortex; however, no difference was found in the amyloid burden or in the number of Lewy bodies in the cortical neurons.[62]

Dr. Cummings explained that transmitter changes in the cholinergic system with a deficiency in choline acetyltransferase, or an increase in muscarinic receptors, were found to be associated with neuropsychiatric symptoms.[63] Muscarinic M_2 binding in patients with AD was also greater in patients with both hallucinations and delusions compared with those who did not have psychosis.[63]

Dr. Cummings then reported that molecular genetics is beginning to pro-

Figure 4. Neuropsychiatric Symptoms in Patients With Mild, Moderate, or Severe Alzheimer's Disease[a]



[a]Data from Craig et al.[58]
Abbreviation: MMSE = Mini-Mental State Examination.

vide some insight into the neuropsychiatry of AD, and serotonin receptor or transmitter gene polymorphisms have been associated with a variety of neuropsychiatric symptoms in AD.[64]

Treatment of Neuropsychiatric Symptoms in AD

Depression. Depression in AD is treated with selective serotonin reuptake inhibitors (SSRIs) including escitalopram, citalopram, sertraline, fluoxetine, and paroxetine because they have few side effects in elderly individuals. Patients unresponsive to these agents can be considered for treatment with a tricyclic antidepressant such as nortriptyline that has few anticholinergic side effects. Combined serotonin and noradrenergic reuptake inhibitors, for example venlafaxine, can also be used to treat depression in AD. These therapeutic recommendations are based primarily on the treatment of idiopathic depression in the elderly, not specifically in patients with AD. However, in a study by Lyketsos and colleagues,[65] outpatients (N = 22) with AD who received sertraline showed a decrease in depression compared with patients who received placebo. Measures of ADL revealed that patients treated with sertraline had no change over the 9 weeks of therapy, whereas patients who received placebo had a further decline in their ability to perform ADL. Compared with placebo, sertraline both reduced depression and maintained ADL.

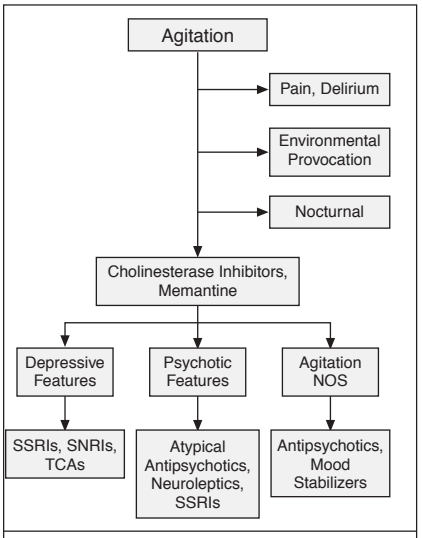
Psychosis. The agents of choice for treating psychosis are the atypical antipsychotics, including risperidone, olanzapine, and quetiapine. In patients resistant to these agents, conventional neuroleptics such as haloperidol can be used, and patients may also respond to SSRIs or to antidementia agents. In a study[66] of 625 patients with dementia and psychosis, daily treatment with 1 mg or 2 mg of risperidone was shown to be superior to placebo. However, 30% of patients who received placebo had a reduction in delusions, possibly an effect of the additional attention given to patients in trials.

The use of antipsychotics in AD is particularly problematic since recent reviews[67] by the FDA revealed that risperidone and olanzapine are associated with an increased risk of stroke, and all antipsychotics are associated with an increased risk of death in the elderly. Thus, the use of these drugs should be minimized in elderly individuals with AD; if possible, patients should be treated with antidementia agents or SSRIs before turning to antipsychotics. Dr. Cummings stressed that when antipsychotics are used, informed consent must be obtained from both the patient and the caregiver and documented in the patient's chart.

Agitation. Dr. Cummings stated that one of the most common and difficult-to-treat phenomena of AD is agitation. Atypical antipsychotics and conventional neuroleptics can be used with the precautions articulated above. Anticonvulsants and mood stabilizers have also been used with some success, particularly in patients who have impulsive disorders as part of their agitation syndrome. Treatment with SSRIs can be considered, especially in those patients who have evidence of depression with agitation. Trazodone has a role in the treatment of nocturnal agitation, and buspirone in patients who have anxiety symptoms as part of their agitation disorder. When agitation has not responded to other treatments, β-blockers can be used. A trial[68] showed that olanzapine at both 5-mg and 10-mg doses substantially reduced agitation among nursing home residents with AD. Dr. Cummings commented that a relatively robust placebo effect was again apparent.

Dr. Cummings presented an algorithm for the treatment of agitation (Figure 5). Clinicians should begin by examining agitated patients for causes such as pain, delirium from drug intoxication, or electrolyte imbalance. The next step is to determine whether there is any environmental provocation, such as a bothersome roommate, excessive stimulation, or too much noise, and to attempt to intervene to reduce these. Then, find out whether the agitation is nocturnal, with sundowning and confusion; this may respond to better sleep management. After these steps, ensure that patients are treated appropriately with antidementia agents such as a cholinesterase inhibitor or memantine. Many patients have reduced agitation when their dementia is appropriately treated. If agitation persists, for those with depressive features, Dr. Cummings

Figure 5. Algorithm for Agitation Management in Patients With Alzheimer's Disease



Abbreviations: NOS = not otherwise specified, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

recommended trying antidepressants as discussed above, and for those with psychotic features, atypical antipsychotics, neuroleptics, or SSRIs. For patients with agitation and no particularly predominant symptom, try antipsychotics and mood stabilizers.

Use of Antidementia Therapies for Neuropsychiatric Symptoms

Available antidementia therapies have behavioral effects. Dr. Cummings reviewed results from a trial[69] that examined the efficacy of donepezil on behavioral symptoms in patients with moderate-to-severe AD. Patients treated with donepezil had substantial reductions in psychosis, agitation, and mood symptoms. However, no effect was found on frontal lobe symptoms including disinhibition and irritability. Another study[36] revealed stabilization of behavior in patients receiving galantamine compared with patients who received placebo. Similarly, treatment with rivastigmine appears to reduce behavioral disturbances.[70] Nursing home patients receiving rivastigmine showed substantial reductions in most behavioral symptoms including delusions, hallucinations, anxiety, disinhibition, irritability, and aberrant motor behavior.

Memantine has also been associated with an improvement in behavioral problems.[71] Patients who received memantine had reduced levels of agitation, aggression, apathy, and indifference, and they also experienced better nighttime behavior than patients who received placebo. Patients who were asymptomatic at baseline and received memantine had lower rates of emergence of agitation and aggression compared with patients who received placebo.

Summary

Dr. Cummings concluded that behavioral disturbances affect nearly all patients with AD, cause distress and deterioration in quality of life for patients and carers, and may hasten institutionalization. Condition-specific neurobiological changes have been revealed via brain imaging and other methods that begin to explain why only some patients exhibit neuropsychiatric symptoms. Psychotropic agents are effective in some cases, although there are few randomized, controlled studies of drugs for neuropsychiatric symptoms in AD. Caution must be exercised in using these psychotropic agents in elderly patients, particularly the atypical and typical antipsychotics. Finally, cholinesterase inhibitors and memantine may reduce behavioral disturbances in patients with AD.

Individualizing Alzheimer's Disease Therapy Over the Disease Course

Constantine Lyketsos, M.D., M.H.S., divided his presentation into 2 parts. First, he reviewed the 4 principles of dementia care articulated recently in a publication by the American Association of Geriatric Psychiatry (AAGP)[72] and elsewhere.[73] These principles are disease treatment, symptom treatment, supportive care for the patient, and supportive care for the family or caregiver. Second, he addressed 4 common quandaries faced by clinicians when treating patients with AD: using combination dementia therapies,[72,73] switching cholinesterase inhibitors,[73] evaluating patient response,[73] and stopping dementia therapy.[73]

Four Principles of Dementia Care

Dr. Lyketsos noted that once dementia has been properly diagnosed as either AD, vascular, or another type of dementia, appropriate care can be initiated. Currently, dementia treatment is underpinned by 4 principles of care.[73] Treatment for these 4 areas of care is assembled into a unified collection of interventions that is typically managed by psychiatrists or neurologists who aim to take care of people with dementia over the long term (Table 3).[72] Dr. Lyketsos highlighted some components of unified dementia care.

Disease treatment. In AD and other types of dementia, disease treatment focuses on factors known to be responsible for the ongoing progression of brain degeneration in patients who have risk factors. Therapies are currently available for vascular risk and glutamate excitotoxicity. Vascular risk can be managed with blood pressure control and appropriate use of low-dose aspirin. Evidence[74] shows that systolic blood pressure above 140 mm Hg accelerates the progression of dementia and that antihypertensive treatment with β-blockers and diuretics slows the progression of dementia. Glutamate excitoxicity can be inhibited by treatment with memantine.[41,75]

Symptom treatment. Dementia has 3 groups of symptoms: cognitive, neuropsychiatric, and functional. Although no proven therapy is available for functional symptoms, cognitive symptoms can be treated with cholinesterase inhibitors, and pharmacologic and nonpharmacologic treatments are available for neuropsychiatric symptoms, as discussed by Dr. Cummings.

Supportive care for the patient. Dr. Lyketsos emphasized that supportive care for patients and caregivers is a critical aspect of dementia care because

Table 3. Four Principles of Dementia Care[a]

Disease Treatment	Symptom Treatment	Supportive Care for Patient	Supportive Care for Family/Caregiver
Vascular risk	Cognitive symptoms	Comfort and emotional support	Emotional support and comfort
Blood pressure control	Cholinesterase inhibitors	Safety and supervision	Education
Low-dose aspirin	Neuropsychiatric symptoms	Proper approach and communication	Instruction in the skills of caregiving
Glutamate excitotoxicity	Pharmacologic and	Maximizing function and abilities	Problem solving and crisis intervention
Memantine	nonpharmacologic	Nutrition and sleep hygiene	Respite
	treatments	Activity and stimulation	Substitute decision making
		Planning/assistance with decision making	Attention to personal needs and wants
		Good nursing care in advanced stages	

[a]Based on Lyketsos et al.[72] and Rabins et al.[73]

it improves quality of life, reduces emotional distress, and may help patients stay in their home environments longer. Dealing with safety and supervision is important; this includes, for example, ensuring that patients stop driving, that medication administration is supervised, and that fall risks are dealt with in later stages of disease. Providing activity and stimulation to patients and structuring day-to-day life are other critical interventions that can involve prescribing exercise, physical therapy, or adult day care. Patients with dementia need to identify an appropriate person to help with planning and decision making in all areas of their life, and may need help making health care decisions and finding good nursing care in later stages of AD.

Supportive care for the family and caregiver. In addition to emotional support, comfort, and education, caregivers need instruction in the skills of caregiving and help in problem-solving. Clinicians should make themselves available for crisis intervention; simply making available to home-based caregivers a 24-hour phone number for the caregiver to call seems to be an important component of dementia care. Respite is also very important for caregivers and should be delivered in the form of patient day care or regular breaks from the caregiving situation.

Four Quandaries in the Treatment of AD

Dr. Lyketsos discussed whether to combine antidementia therapies, whether to switch cholinesterase inhibitors, how to evaluate response to treatment, and whether to stop antidementia medications. He reminded his audience that these 4 quandaries should be seen in the broader context of delivering the whole package of dementia care, as outlined in Table 3.

Combining antidementia therapies. Dr. Lyketsos explained the rationale for combining antidementia therapies.[73] First, the cause of AD pathology is likely to be heterogeneous, and multiple agents may be needed to maximize treatment. Second, management of a range of symptoms may also require several agents, each targeting a different group of symptoms or different aspects of the condition. Third, AD is a progressive, degenerative disease, so treatment interventions may be stage-specific. Last, cholinesterase inhibitors and memantine work by diverse mechanisms, raising the possibility for synergistic effects in using them together, as recommended in the AAGP position statement.[72]

In Tariot and colleagues' study[42] of patients with moderate-to-severe AD who received donepezil plus placebo or donepezil plus memantine, those who received donepezil plus memantine showed a statistically significant benefit of memantine versus placebo on several measures (see Figure 3). Dr. Lyketsos cautioned that adding medications can cause tolerability problems. In this case, the main side effect appeared to be that confusion, typically transient during titration, was more common with the combination therapy. Diarrhea and fecal incontinence were more common in the donepezil monotherapy, but other adverse events were comparable. Dr. Lyketsos noted that the combination of memantine and rivastigmine led to improved cognition in an open study of mild-to-moderate AD.[76]

Switching cholinesterase inhibitors. According to Dr. Lyketsos, in the literature, strategies for the use of cholinesterase inhibitors vary, but generally, experts suggest that a patient starts on a particular cholinesterase inhibitor and remains on that medication long-term. Dr. Lyketsos pointed out that the strategy that he and his colleagues propose[73] is slightly different because they found that switching patients to a second, and in some cases, a third, cholinesterase inhibitor can produce additional benefits for patients. The rationale for this strategy is that the average duration of treatment with a cholinesterase inhibitor is less than 200 days, suggesting that clinicians in practice are not totally satisfied with the response they obtain from an individual cholinesterase inhibitor. The pharmacologic profiles of cholinesterase inhibitors differ, and many patients respond to a second cholinesterase inhibitor even if they did not respond to the first one. A review by Gauthier and colleagues[77] suggested that about 50% of patients switched from donepezil responded to treatment with rivastigmine.

Dr. Lyketsos summarized an approach for switching therapies in AD.[73,77] He stressed the importance of setting parameters to evaluate response to treatment with the first-line agent after 6 to 9 months. If there is a clear response, it is appropriate for the patient to continue taking the drug long-term. If there is no clear response and/or the patient continues to decline, even after maximizing the dose, then a switch should be considered. Tolerability is a common reason for switching,

and although clinicians worry that patients who do not tolerate their first-line agent may not tolerate a second-line or third-line agent, Dr. Lyketsos pointed out that in his clinical experience this is often not the case. Patients who have not tolerated a first-line agent can be switched to a different one if it is introduced at a lower dose and with slower titration. Dantoine and colleagues[78] found that 46.3% of patients who were switched from donepezil or galantamine responded to rivastigmine. Dr. Lyketsos emphasized that, in his clinical experience, switching from any cholinesterase inhibitor to any other cholinesterase inhibitor with which the patient was not treated previously produces benefits for many patients.

There is some debate whether switching should involve a washout period. A study[79] of tolerability in patients switched from donepezil to galantamine with either a 4-day or a 7-day washout period found that patients who switched within 4 days had fewer GI (the most common) adverse events. This research supports Dr. Lyketsos's belief that shorter washouts are preferred and that too long of a treatment break may lessen efficacy.

Dr. Lyketsos described one of his patients, who, over a period of 8 years since she was first diagnosed with AD, had been treated first with donepezil, then switched to huperzine, then rivastigmine, and lastly galantamine. Although the Mini-Mental State Examination (MMSE) score steadily declined, at the introduction of each medication, there was an improvement, showing that occasionally a patient will respond incrementally less but will still respond to a sequential cholinesterase inhibitor.

Patients and caregivers should be involved during a medication switch to develop realistic expectations of the new medication and to collaborate with the clinician in assessing symptom domains that demonstrate the response of the patient to the new medication.

Evaluating response to treatment. In deciding whether a patient is responding to treatment, 3 domains are important: cognition, function, and behavior.[73] Dr. Lyketsos emphasized that clinicians need to make decisions about each of these domains because patients will often respond only in one area or will respond to a small extent in 2 areas; only rarely will they respond in all 3 domains. Taking into account information from caregivers, the usual approach is to carefully assess patients at baseline and systematically evaluate cognition, functioning, and behavior. Then, clinicians should reevaluate patients 6 to 12 months after they reach a maximum tolerated dose. Assessment should include the patient's participation in and enjoyment of activities, his or her ability to do individual ADL, affect, level of interest in life, and neuropsychiatric symptoms. Clinicians should consider whether psychotropic medication usage can be reduced. Next, clinicians can consider a carefully planned and executed discontinuation of medication to decide whether the medication is helping the patient. Lack of response may be due to inadequate dose, nonadherence to medication, inadequate length of treatment, interference from other medications (particularly anticholinergic medication), the wrong diagnosis, or the patient being a nonresponder. Dr. Lyketsos stressed that all possible reasons for nonresponse should be considered before concluding that a patient is a nonresponder because that conclusion has implications for long-term use or nonuse of cholinesterase drug therapy.

Stopping dementia medications. Dr. Lyketsos then explained that when to stop medication is a common challenge that psychiatrists often encounter with AD patients who first come into their care when admitted to a nursing home or an assisted living facility. Evidence suggests that even patients with late-stage dementia will improve if cholinesterase inhibitors[80,81] or memantine[41] are used, and donepezil now has U.S. Food and Drug Administration (FDA) approval[40] for use in patients with severe Alzheimer's disease. There is no cutoff MMSE score at which treatment should be stopped, and continuous long-term treatment is often beneficial to those who responded initially.

The best strategy is a case-by-case approach in which the physician examines the patient's history to decide whether the individual was an initial responder to the medication. When evidence exists that a patient was a good responder at first, as is at times the case with cholinesterase inhibitors, Dr. Lyketsos recommended that he or she should be maintained on the medication long-term.

In very late stages, or terminal dementia, consideration should be given to discontinuing medication. This approach can be reasonable, but in making this decision, careful consideration should be given to advance directives. Family members and multidisciplinary teams in long-term care facilities should also be consulted. Clinicians should be forewarned that unrecoverable and precipitous declines in functioning may rarely occur. A typical case would be a patient with a MMSE score of 5 or 6, in a long-term care facility, who is still capable of some basic ADL functioning, for example, bathing, dressing, or feeding himself or herself. On discontinuing either memantine or a cholinesterase inhibitor, in rare cases, he or she could have a substantial decline in functioning over the ensuing few days and rapidly lose any remaining functional abilities. Restarting the medicine will often not stop the precipitous decline. This outcome is rare but can dramatically impair a patient's quality of life and should be part of the risk-benefit considerations.

Summary

Dr. Lyketsos concluded by stressing the importance of applying the whole package of dementia care from diagnosis to terminal stages, using appropriate combination therapies or medication switching strategies, evaluating patients' response, and making decisions about whether to stop therapy in later stages of the disease.

Drug names: amantadine (Symmetrel and others), buspirone (BuSpar and others), citalopram (Celexa and others), digoxin (Lanoxicaps, Lanoxin, and others), donepezil (Aricept), escitalopram (Lexapro and others), fluoxetine (Prozac and others), galantamine (Razadyne), haloperidol (Haldol and others), hydrochlorothiazide (Esidrix, Oretic, and others), ketamine (Ketalar and others), lisinopril (Zestril, Prinivil, and others), memantine (Namenda), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), oxybutynin (Ditropan and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), rivastigmine (Exelon), sertraline (Zoloft and others), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, buspirone, citalopram, escitalopram, fluoxetine, haloperidol, nortriptyline, olanzapine, paroxetine, quetiapine, risperidone, sertraline, venlafaxine, huperzine, and trazodone are not approved by the U.S. Food and Drug Administration for the treatment of dementia/Alzheimer's disease; donepezil is not approved for the treatment of vascular dementia or agitation in dementia, or for improving efficacy when switching; galantamine and rivastigmine are not approved for the treatment of agitation or severe Alzheimer's disease, or for improving efficacy when switching; and memantine is not approved for the treatment of mild-to-moderate Alzheimer's disease or agitation.

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