Treatment of Alzheimer's disease across the spectrum of severity

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia affecting nearly 18 million people around the world and 4.5 million in the US. It is a progressive neurodegenerative condition that is estimated to dramatically increase in prevalence as the elderly population continues to grow. As the cognitive and neuropsychiatric signs and symptoms of AD progresses in severity over time, affected individuals become increasingly dependent on others for assistance in performing all activities of daily living. The burden of caring for someone affected by the disorder is great and has substantial impact on a family's emotional, social and financial well-being. In the US, the currently approved medications for the treatment of mild to moderate stages of AD are the cholinesterase inhibitors (ChEIs). Cholinesterase inhibitors have shown modest efficacy in terms of symptomatic improvement and stabilization for periods generally ranging from 6 to 12 months. There are additional data that have emerged, which suggest longer-term benefits. For the moderate to severe stages of AD, memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist is in widespread use and has shown modest benefit as monotherapy and in combination with ChEIs. The cost effectiveness of the currently available therapeutic agents for AD has undergone great scrutiny and remains controversial, especially outside the US. Neuropsychiatric symptoms such as agitation and psychosis are common in AD. Unfortunately, in the US there are no Food and Drug Administration (FDA)-approved agents for the treatment of these symptoms, although atypical antipsychotics have shown some efficacy and have been widely used. However, the use of these agents has recently warranted special caution due to reports of associated adverse effects such as weight gain, hyperlipidemia, glucose intolerance, cerebrovascular events, and an increased risk for death. Alternative agents used to treat neuropsychiatric symptoms include serotonergic antidepressants, benzodiazepines, and anticonvulsant medications.

Keywords: cognitive enhancers, cholinesterase inhibitors, memantine, atypical antipsychotics

Introduction

Alzheimer's disease (AD) is an acquired neurodegenerative disease that causes persistent and progressively severe memory loss accompanied by other cognitive deficits that include aphasia, apraxia, agnosia, dyscalculia, executive function impairment, and changes in behavior. These clinical features have a major impact on the affected individual's ability to perform the activities of daily living. As AD progresses in severity across its different clinical stages, the affected patient becomes increasingly more dependent on others for care. As the most common cause of dementia, AD exerts a substantial toll on an aging population worldwide and is of great public health interest. The neuropathological hallmarks of AD include amyloid plaques, neurofibrillary tangles, inflammation, neuronal loss, and depletion of neurochemicals such as acetylcholine (Whitehouse et al 1982). Alterations in other neurotransmitter systems such as the glutamatergic system have also been identified as contributory to the pathogenesis of the disease.

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There is no cure for AD. Current treatment of the disorder involves the use of medications to obtain symptomatic cognitive, behavioral, and functional improvement or stabilization. In addition, individualization of the treatment plan to address medical co-morbidities, the social and financial impact of the disease on the family, and caregiver well-being is vital to achieving successful outcomes throughout all clinical stages of AD.

Treatment of cognition and function

Mild cognitive impairment

Alzheimer disease is a gradually progressive neurodegenerative disorder whose neuropathological alterations may precede the onset of clinical symptoms by decades. Mild cognitive impairment (MCI) is considered by some to represent the earliest clinical manifestations of impending dementia. In MCI, the affected individual subjectively complains of memory problems but has generally normal cognitive and daily functioning despite a demonstrable decrease in memory performance on testing (Peterson et al 2001). Mild cognitive impairment has been described as a transitional state between healthy cognitive aging and overt dementia caused by AD, vascular dementia, or other causes of progressive cognitive decline in the elderly. Approximately 10% to 15% of individuals with MCI progress to diagnosed AD each year. There is no treatment approved for MCI. Peterson and colleagues (2005) have reported on the use of donepezil and vitamin E in patients with MCI in a randomized double-blind, placebo-controlled study. They found that compared with placebo, at 18 months donepezil delayed the onset of AD by 6 months, however, donepezil had no beneficial effects in preventing the onset of AD by the end of the 36 month trial. Vitamin E was not shown to be of significant benefit.

Mild to moderate AD

Cholinesterase inhibitors

Available consensus treatment guidelines and practice parameters, including those of the American Academy of Neurology (AAN) recommend the use of cholinesterase inhibitors (ChEIs) as standard therapy for mild to moderate AD based on evidence accumulated from several 3- to 6-month, randomized, double-blind, placebo-controlled clinical trials (Doody et al 2001). These studies suggest a modest therapeutic effect of this class of medications on the symptoms of AD. The primary outcome measures used across these studies most often include the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) (Rosen et al 1984) and the clinician's interview-based impression of change plus caregiver input (CIBIC-Plus) (Schneider et al 1997). The ADAS-cog is a highly sensitive scale that measures multiple cognitive outcomes. Scores range from 0 to 70 (high to low cognitive functioning). Untreated patients with mild to moderate AD typically progress by a 3 to 4 point increase over 6 months. Patients with moderate to severe AD have an increase of 4 to 6 points over 6 months if untreated. The CIBIC-Plus is a tool that assesses patient functioning via a subjective examination of the patient and an interview with a caregiver (range of scores 1 to 7; score of 1 indicating substantial improvement and 7 indicating marked deterioration). The pivotal 12 to 24 week duration clinical trials examining the efficacy of ChEIs in AD have shown improvement in study subjects on the ADAS-cog of 2.5 to 3.5 points and on the CIBIC-Plus of 0.3 to 0.5 points as compared with deterioration in placebo-treated subjects (Cummings 2004).

Donepezil

Donepezil is a rapidly reversible inhibitor of acetylcholinesterase. Subjects treated with a daily dose of donepezil 5–10 mg, in several 12 to 24 week placebo-controlled trials of patients with mild to moderate probable AD (n=1759), demonstrated statistically significant differences on the ADAS-cog and the CIBIC-Plus scales favoring the active drug (Rogers, Doody, et al 1998; Rogers, Farlow, et al 1998; Burns et al 1999). During single-blind, 6 week placebo washout periods, ADAS-cog and CIBIC-Plus scores in the donepezil-treated groups reverted to levels similar to those in the placebo group (Rogers et al 1998; Burns et al 1999). This has been interpreted to suggest that donepezil treatment for 6 months has a symptomatic effect, but not a "disease modifying" effect.

Two double-blind, 12 month placebo-controlled trials of donepezil with 10 mg daily have been completed in patients with mild to moderate AD (Winblad et al 2001; Mohs et al 2001). Winblad and colleagues reported a difference in favor of donepezil over placebo using the Gottfries-Brane-Steen scale (GBS) (Brane et al 2001) as the primary outcome measure. The GBS scale is a measure of global functioning. This scale assesses patient function in four general areas using a semi-structured interview by a clinician with a patient and caregiver. It measures changes in the symptoms of dementia over a specified amount of time. Overall, GBS scale scores for subjects (observed cases)

in the active treatment group showed a decline half as large as that reported for patients in the placebo group. Mohs and colleagues reported that the median amount of time to clinically evident functional decline as determined by several measures of activities of daily living was delayed by 5 months in the donepezil treated group compared with the placebo group (Table 1).

In a Cochrane Library review of the efficacy of donepezil for mild to moderate AD, 4 studies were included covering treatment of 12 or 24 weeks duration in highly selected patients. The authors concluded that in selected patients with mild to moderate AD treated for 12 or 24 weeks, donepezil produced modest improvements in cognitive function and no improvements were noted on patient self-assessed quality of life. In addition, the authors noted significantly higher number of withdrawals before the end of treatment from the 10 mg/day donepezil group compared with placebo, which could have potentially resulted in overestimation of the beneficial effects at 10 mg/day, as last available measures were used in the analyses. It is not known whether these gains translate into gains for the caregiver or in substantial changes in the life of the patient (Birks et al 2000). A recent study on the long-term use of donepezil has attempted to address the controversies regarding the practical effectiveness of the agent from a cost–benefit analysis. Courtney and co-workers (Courtney et al 2004) studied 565 community residing subjects with mild to moderate AD. The subjects were referred from memory clinics and clinically diagnosed with AD with or without cerebrovascular disease. They were initially randomly assigned to treatment with donepezil 5 mg/day or placebo during a 12-week run-in period to assess initial effects. 486 subjects who completed this phase of the study were then re-randomized to receive either donepezil or placebo, with double blind treatment continuing for as long as "judged appropriate". At the end of 48 weeks of treatment, a 6 week washout period was commenced. Patients could then subsequently choose to continue with the same double-blinded treatment that they had been on for a further 48 weeks. At the end of every 48 week treatment period a further 4-week washout occurred, after which patients could again continue on for another 48 weeks. Primary endpoints were entry to institutionalized care and progression of disability in activities of daily living. The Mini-Mental State Examination (MMSE) (Folstein et al 1975), a widely used screening test for cognitive impairment in older adults was also used in this study as an outcome measure. The donepezil-treated group improved from baseline by 0.9 MMSE points during the first 12 weeks, however, no change was seen in the placebo group. After the 12th week, both groups declined at similar rates. Over the first two years, donepezil-treated subjects showed some advantage over placebo-treated subjects in MMSE scores (0.8 points) and functional ability. At three years, no significant difference was noted between the donepezil-treated group and the placebo-treated group in rates of institutionalization or progression of disability. The study also did not detect any significant difference between donepezil and placebo on the treatment of behavioral symptoms. There were no significant differences between donepezil and placebo in caregiver well-being, time of caregiving, and costs of care. However, the study confirmed the same degree of modest efficacy of donepezil in treating cognition as did the pivotal trials of shorter duration. The authors concluded that donepezil is not a cost effective treatment for AD.

Relkin and colleagues (2003) conducted an open-label trial of donepezil in a large community-based population. They included 1035 patients with mild to moderate AD, out of which 894 completed the trial. Nearly all patients had at least one co-morbid medical condition or were taking a minimum of one concomitant medication. Efficacy was measured using the standardized MMSE (sMMSE) (Molloy

Table 1 Summary of major clinical trials of donepezil

Study	Sample size, n	Study duration	Baseline MMSE	Cognitive measures	Global measures
Rogers, Farlow, et al 1998	473	24 weeks	10–26	ADAS-cog, MMSE	CIBIC-Plus; CDR-SB
Rogers, Doody, et al 1998	468	12 weeks	10–26	ADAS-cog, MMSE	CIBIC-Plus; CDR-SB
Burns et al 1999	818	24 weeks	10–26	ADAS-cog	CIBIC-Plus, CDR-SB
Mohs et al 2001	431	1 year	12–20	MMSE	CDR, CDR-SB
Winblad et al 2001	286	1 year	10–26	GBS, MMSE	GDS
Feldman et al 2001	290	24 weeks	5–17	sMMSE	CIBIC-Plus

Abbreviations: ADAS-cog, Alzheimer's disease assessment scale – cognitive subscale; CDR, clinical dementia rating; CDR-SB, clinical dementia rating – sum of the boxes; GBS, Gottfried-Brane-Steen scale; GDS, global deterioration scale; MMSE, mini-mental state exam; sMMSE, standardized mini-mental state exam; CIBIC-Plus, clinician interview-based impression of change incorporating caregiver information.

et al 1991). The goal of the sMMSE is to impose clear and explicit guidelines for administration and scoring to improve the reliability of the instrument. The sMMSE has significantly better inter-rater and intra-rater reliability compared with the MMSE. Over the initial 12 week study period the sMMSE increased by 1.54 points over baseline. Donepezil was shown to be well-tolerated with the occurrence of adverse events significantly lower after a dose increase at 4 weeks as compared with a dose increase after 1 week as in previous trials. In addition, the investigators found that concomitant medication use such as aspirin or nonsteroidal antiinflammatory drugs did not increase the risk of gastrointestinal side effects with use of donepezil. Concomitant medications such as digoxin, calcium channel blockers, or beta blockers did not increase the risk of bradycardia, a potential side-effect of cholinergic medications.

Seltzer and colleagues (2004) studied the efficacy of donepezil in mild AD in subjects with MMSE scores of 21 to 26. In a double blind fashion, subjects were randomized to receive either donepezil or placebo in a 2:1 ratio for 24 weeks. Donepezil-treated subjects performed better than placebo-treated subjects on the ADAS-cog and MMSE at all time points studied.

None of the ChEIs have been approved for treatment of the severe stages of AD. However, in a 6 month placebo-controlled trial of donepezil in moderate to severe AD, donepezil was shown to be of benefit (Feldman et al 2001). At 6 months, 63% of moderate to severely affected patients in the donepezil-treated group versus 42% of the placebo-treated group showed improvement or no change in CIBIC-Plus scores.

Based on the results from the pivotal double-blind, randomized, placebo-controlled clinical trials in patients with mild to moderate AD, the US Food and Drug Administration (FDA) has approved use of donepezil at doses of 5 mg to 10 mg once daily. The starting dose of donepezil is 5 mg once daily, with an increase to 10 mg recommended at 4 to 6 weeks.

Rivastigmine

Rivastigmine inhibits acetylcholinesterase and butyryl-cholinesterase (Ballard 2002). In two 26-week trials involving patients with mild to moderate AD (n=1424), patients receiving a daily dose of 6 mg to 12 mg of rivastigmine demonstrated favorable and significant differences in ADAS-cog and CIBIC-Plus scores as compared with the placebo-treated group (Corey-Bloom et al 1998; Rosler et al 1999) (Table 2).

Sustained benefits of rivastigmine have been reported for over a 1-year period by Farlow and colleagues (2000). After receiving double-blind placebo or rivastigmine at daily doses of 1 mg to 4 mg or 6 mg to 12 mg for 26 weeks, patients were eligible to enter an open label extension phase. The withdrawal rate for subjects treated with rivastigmine 6 mg to 12 mg with more rapid dose titration in the initial double-blind phase of the study was 35% (Corey-Bloom et al 1998). For the open label extension phase, dose titration was more flexible and the rate of withdrawal was decreased to 19% (Farlow et al 2000). At 52 weeks, a large difference (5.7 points) was seen in ADAS-cog scores favoring the rivastigmine-treated group over the placebo group (Farlow et al 2000). Although impairment advanced in both groups, subjects originally receiving placebo for the initial 6 months of the study did not show the same amount of benefit as subjects treated with effective doses of rivastigmine for the entire 52 weeks. This observation suggests the benefit of starting rivastigmine treatment early in the course of the illness.

There is some evidence from a retrospective analysis of rivastigmine therapy that it might have beneficial effects in moderately severe AD (Burns et al 2004). Data were pooled

Table 2 Summary of major clinical trials of rivastigmine

Study	Sample size, n	Duration	Baseline MMSE	Cognitive measures	Global measures
Corey-Bloom et al 1998	699	26 weeks	10–6	ADAS-cog	CIBIC-Plus
Rosler et al 1999	725	26 weeks	10–26	ADAS-cog, MMSE	CIBIC-Plus
Farlow et al 2000	533	26 week open label extension of a 26 week placebo-controlled study	10–26	ADAS-cog	CIBIC-Plus
Burns et al 2004	112	Retrospective analysis from 3 trials	10–12	ADAS-cog, MMSE	PDS, BEHAVE-AD

Abbreviations: ADAS-cog, Alzheimer's disease assessment scale – cognitive subscale; BEHAVE-AD: behavior pathology in AD rating scale; CIBIC-Plus, clinician interview-based impression of change incorporating caregiver information; MMSE, mini-mental state exam; PDS: progressive deterioration scale.

from three 6-month randomized, placebo-controlled, double-blind trials. Patients with severe cognitive impairment were identified if they had MMSE scores of 10 to 12. 112 patients met the inclusion criteria and had received placebo or daily rivastigmine, 6 mg to 12 mg. After 6 months, subjects in the rivastigmine group showed a 0.2 point decrease in mean ADAS-cog scores (decreased impairment) compared with baseline, whereas placebo group subjects had an increase of 6.3 points (increased impairment) ($p<0.001$). Clinical improvement was also observed with the MMSE, Progressive Deterioration Scale (PDS), and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).

The FDA has approved rivastigmine (like all other available ChEIs) for mild to moderate AD. The dose of rivastigmine increases from 1.5 mg twice daily to 3 mg twice daily, then to 4.5 mg twice daily, and to a maximum of 6 mg twice daily. Dose increments are recommended at 1 to 4 week intervals; fewer side effects emerge when the intervals are longer.

Galantamine

Galantamine has been proposed to both inhibit acetylcholinesterase and to act as an allosteric potentiating ligand on nicotinic acetylcholine receptors (Maelicke et al 2001). Several large 5- to 6-month placebo-controlled trials for patients with mild to moderate AD (n= 2267) have found beneficial drug effects on the ADAS-cog and CIBIC-Plus scales for patients treated with galantamine, 16 mg to 24 mg per day versus placebo (Table 3).

There is some evidence of longer-term benefits of galantamine in 12-month open label extension studies (Raskind et al 2000). After 12 months of therapy, patients who received 24 mg per day of galantamine had ADAS-cog scores that remained stable relative to baseline measures. Comparatively, the placebo group had increased impairment in ADAS-cog scores (increase of 4 to 5 points). The group that received galantamine throughout the 12-month study period had better ADAS-cog outcomes at endpoint than did patients who received placebo during the first 6 months of the study and were then switched to galantamine. All findings were observed case (OC) analyses which were confirmed with intent to treat analyses (ITT) using the last observation carried forward method (LOCF). Lyketsos and colleagues (2004) assessed the long-term efficacy as well as tolerability of galantamine. The authors conducted a 12-month open-label extension of an earlier 5-month, double-blind, placebo-controlled trial with a 6-week withdrawal phase. The authors concluded that patients treated with galantamine continuously throughout the double-blind and open-label phases (n=288) showed sustained cognitive benefits at 18.5 months. In addition, the safety and tolerability of galantamine was comparable with other large studies of the drug.

Blesa and colleagues (2003) investigated the benefits of galantamine in patients with more severe disease by performing a post-hoc analysis using data collected from two long-term galantamine studies. Patients included in this study were those with MMSE scores <14, or ADAS-cog subscale scores of >30. The authors concluded that galantamine offered both cognitive and functional benefit in this population. Galantamine is approved by the FDA for mild to moderate AD. It is initiated at a dose of 4 mg twice daily for 1 month. The dose is increased to 8 mg twice daily and if desired, up to 12 mg twice daily. Longer intervals between dosage increases are associated with a lower incidence of gastrointestinal side effects. Recently, galantamine was introduced in an extended release form for

Table 3 Summary of major clinical trials of galantamine

Study	Sample size, n	Duration	Baseline MMSE	Cognitive measures	Global measures
Tariot et al 2000	978	5 months	10–22	ADAS-cog	CIBIC-Plus
Raskind et al 2000	636	6 months	11–24	ADAS-cog	CIBIC-Plus
Wilcock et al 2000	653	6 months	11–24	ADAS-cog	CIBIC-Plus
Lyketsos et al 2004	699	18.5 months (12 month open label extension of earlier 5 month study)	10–22	ADAS-cog	ADCS–ADL, NPI
Blesa et al 2003	72 165	12 months	<14 ADAS-cog >30	ADAS-cog	DAD

Abbreviations: ADAS-cog, Alzheimer's disease assessment scale – cognitive subscale; ADCS–ADL, Alzheimer's disease cooperative study – activities of daily living scale ; BEHAVE-AD: behavior pathology in AD rating scale; CIBIC-Plus, clinician interview-based impression of change incorporating caregiver information; DAD, disability assessment for dementia scale (Gelinas et al 1999); MMSE, mini-mental state exam; NPI, neuropsychiatric inventory (Cummings et al 1994).

once per day dosing. The starting dose is 8 mg per day for one month followed by titration up to 16 mg or 24 mg per day.

Despite the postulated differences in mechanisms of action of the ChEIs, all three drugs (donepezil, rivastigmine, and galantamine) have similar degrees of efficacy. This was demonstrated by Ritchie and colleagues (2004) who conducted a meta-analysis of randomized trials of the efficacy and safety of these three agents. The authors conducted regression analyses to compare the effect of dose on clinical outcomes and completion rates, analyzing ten donepezil, six galantamine, and five rivastigmine studies. All three drugs showed beneficial effects on cognitive tests, as compared with placebo. For donepezil and rivastigmine, larger doses were associated with larger symptomatic effects as assessed by the ADAS-cog. Clinical global improvement was shown to be superior for each drug over placebo with no dose effects noted.

The optimal duration of treatment with ChEIs is uncertain. The duration of most blinded trials has been 6 months. Trials lasting one year have shown a sustained difference in efficacy between actively treated groups of patients and patients receiving placebo (Raskind et al 2000; Winblad et al 2001). In addition, studies in which the rate of deterioration in the placebo group was extrapolated and compared with the level of function of patients continuing treatment with a ChEI suggest that patients continue to derive modest benefit from treatment for two to three years (Rogers et al 2000).

Although the ChEIs as a class are generally well tolerated, the commonest adverse effects noted in the pivotal trials include nausea, vomiting, diarrhea, loss of appetite, loss of weight, muscle cramps, and insomnia. The dosing recommendation provided with these agents is to have them administered with a meal to lower the risk of side effects. As a class, ChEIs are contraindicated in the presence of cardiac conduction abnormalities such as left bundle branch block and sick sinus syndrome as well as gastric ulcer disease in which bleeding has occurred. From a comparative tolerability perspective, data from the pivotal clinical trials of all three agents suggest that rivastigmine is associated with the greatest risk of gastrointestinal side-effects (nausea, emesis, diarrhea) followed by galantamine and then donepezil. A more gradual dose titration of rivastigmine than initially recommended with the use of this agent appears to attenuate the frequency of these symptoms. Donepezil has been more often associated with muscles cramps and sleep disturbance than the other two agents in the class.

Moderate to severe AD

Memantine

Memantine was approved by the FDA in October 2003 for the treatment of moderate to severe AD having been previously widely available in Germany for several years. Memantine is an N-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist that is proposed to lessen the neurotoxic effects of excessive excitatory glutamatergic neurotransmission that occurs in AD. To assess the impact of treatment, pivotal trials of memantine for moderate to severe AD have used the Severe Impairment Battery (SIB) to evaluate abilities to perform basic cognitive tasks (Panisset et al 1994), the Alzheimer's disease cooperative study –

Table 4 Summary of major clinical trials of memantine

Study	Sample size, n	Duration MMSE	Baseline	Dose	Outcome: last observation carried forward analyses at end point compared with placebo
Reisberg et al 2003	252	28 week	3–14	20 mg	SIB: -4.0 vs 10.1, p<0.001); CIBIC-Plus: 4.5 vs 4.8, p=0.06; ADCS-ADL: -3.1 vs -5.2, p=0.02
Tariot et al 2004 (patients already receiving donepezil for at least 6 months)	404	24 weeks	5–14	20 mg memantine/ donepezil vs donepezil/placebo	SIB: 0.9 vs –2.5 p<0.001; CIBIC-Plus: 4.41 vs 4.66, p=0.03; ADCS-ADL: -3.4 vs –2.0, p=0.03
Winblad and Poritis 1999	166	12 weeks	<10	5 mg/day (first week) and 10 mg/day (next 11 weeks) vs placebo	CGI-C: (ITT): 73% positive response (memantine 10 mg/day) vs 45% (placebo). p<0.001; BGP: (ITT): 3.1 points improvement with memantine, 1.1 points with placebo. p=0.016)

Abbreviations: ADCS-ADL, Alzheimer's disease cooperative study – activities of daily living scale ; CIBIC-Plus, clinician interview-based impression of change incorporating caregiver information; GCI-C, clinical global impression of change (NIMH 1986); BGP, behavioral rating scale for geriatric patients (van de Kam et al 1971); ITT, intent to treat analyses; SIB, severe impairment battery.

activities of daily living scale (ADCS–ADL) (Galasko et al 1997); and the CIBIC-Plus scale (Table 4).

As noted in Table 4, results from the trial by Reisberg and colleagues indicated benefit of memantine treatment on cognitive and functional measures. As measured by the SIB, cognition was stable for the first 12 weeks and the extent of impairment in the memantine-treated group at end point was significantly less than that in the placebo treated group (–4.0 vs –10.1). Memantine treatment also delayed decline in functional ability versus placebo (ADCS–ADL scores: –3.1 with memantine vs –5.2 with placebo).

Tariot and colleagues (2004) reports results from a double-blind combination study in which moderate to severely impaired AD subjects were randomized to receive donepezil plus placebo (monotherapy) or donepezil plus memantine. The investigators reported that combination therapy with donepezil and memantine had a greater influence on cognitive improvement, reduced decline in activities of daily living, and a reduced frequency of new behavioral symptoms versus the donepezil monotherapy group.

In another study conducted by Winblad and Poritis (1999), patients with severe dementia living in a nursing home setting or a single psychiatric hospital were recruited to assess the clinical efficacy and safety of memantine during a 12 week trial. Patients with AD or vascular dementia with a MMSE score of less than 10 were included. It was a double-blind, parallel-group comparison study utilizing memantine 5 mg/day during the first week and 10 mg/day during the next 11 weeks or placebo. Notably, this dosing is in contrast to 10 mg twice per day utilized in the pivotal trials reported by Reisberg and colleagues and Tariot and colleagues. Outcome scales used in this study included the Clinical Global Impression of change (GCI-C) (NIMH 1986) and the Behavioral Rating scale for Geriatric Patients (BGP) subscore 'care dependence', (van de Kam et al 1971). The GCI-C is a 7-point global rating scale related to the CIBIC-Plus. The BGP is an observer-rated scale for the assessment of functional and behavioral disturbances in geriatric patients. The investigators reported that a positive response was seen in 73% of the memantine-treated subjects versus 45% of the placebo-treated patients on the CGI-C. As measured by the BGP, memantine treatment improved functioning and behavioral symptoms to a statistically significant greater extent than placebo

Adverse effects with memantine are uncommon, however, they include headache, sedation, fatigue, constipation, increased confusion, irritability, and agitation. The recommended starting dose is 5 mg once daily, with a gradual dose titration that increases the daily dose in 5 mg increments each week to reach a maximum dose of 10 mg twice daily. Although memantine is approved for use in moderate to severe AD, there is preliminary published evidence to suggest that memantine may be effective for mild to moderate AD (Peskind et al 2004). Peskind and colleagues studied memantine in a 24 week placebo-controlled, randomized trial (n= 403, baseline MMSE score of 10 to 22) and noted significant improvement in cognition and observed function. Two additional unpublished studies of memantine in mild to moderate AD, a monotherapy study conducted in Europe and a combination study with a ChEI conducted in the US, failed to show statistically significant benefits over placebo in the primary outcome measures. Despite the one positive study cited above, the FDA recently denied a supplemental new drug application to broaden the agent's indication to mild to moderate AD.

The cost-effectiveness of AD treatments has been questioned. Specifically, the use of ChEIs has been recently challenged in the UK by the National Institute for Clinical Excellence (NICE). NICE proposed in their preliminary guideline to withdraw ChEIs and memantine from the UK National Health Service (NHS) (Kmietowicz 2005). The NICE assessment group has indicated that there is insufficient evidence that acetylcholinesterase inhibitors have measurable effects on quality of life and time to admission to nursing home care. This proposal has caused significant international concern. The NICE guideline does not adequately take into consideration the effect of treatment on caregivers who bear a significant care burden. In addition, the NICE recommendation does not consider the wishes of the individual patient and caregiver, denying them a chance to benefit from consistently proven effective therapies.

Treatment of neuropsychiatric symptoms

Neuropsychiatric symptoms associated with dementia are common and have been reported in more than 80% of subjects in most studies (Cummings 2004). These features of the disorder contribute to poor outcomes for patients and caregivers. There is some controversy about the frequency of these symptoms in patients with varying severity of dementia, although psychotic symptoms seem to be more common in advanced dementia (Lyketsos et al 2000). Lyketsos and colleagues (2000) reported findings from a study of 5092 community residents who represented 90% of the elderly population of Cache County in Utah, US.

Several disturbances (delusions, anxiety, apathy, irritability, elation, and disinhibition) were reported with similar severity at all stages of dementia. In contrast, aggression/agitation and aberrant motor behavior were more common at later stages of AD. The study also identified a slightly increased occurrence of depression and hallucinations in moderately severe dementia as compared with mild stage dementia. As behavior disturbances emerge in individuals with dementia, they should be managed initially by nonpharmacologic interventions to avoid the potential adverse effects of psychotropic agents (Cohen-Mansfield 2001). A wide spectrum of nonpharmacologic interventions have been studied for the treatment of behavior disturbances in Alzheimer's disease (Cohen-Mansfield 2001). These include music, videotapes of family members, audiotapes of the voices of caregivers, walking, exercise, and sensory stimulation.

In behaviorally disturbed demented patients, few studies of the psychotropic effects of the ChEIs and memantine have been published. However, in some of the pivotal trials of the ChEIs and memantine, the data suggest that treatment with active drug is associated with less behavioral deterioration over time than placebo treatment. Holmes and co-workers (2004) conducted a 12 week, randomized withdrawal study in 134 patients with donepezil. Patients with mild to moderate stage AD with neuropsychiatric symptoms as indicated by a baseline Neuropsychiatric Inventory (NPI) scale of more than 11 points were treated with donepezil 5 mg daily for 6 weeks, followed by 10 mg daily for a further 6 weeks. Patients were then randomized to either placebo or 10 mg donepezil daily. The patients were assessed using the NPI and NPI-caregiver distress (NPI-D) (Cummings et al 1994) scales at 6 weeks and then again at 12 weeks. The NPI is a caregiver-based interview to assess 10 behavioral disturbances: delusions, hallucinations, euphoria, anxiety, agitation, disinhibition, irritability, apathy, and aberrant motor behavior. Frequency is rated from 1 (occasional, less than once per week) to 4 (very frequent, daily or continuous). Severity is rated from 1 (mild) to 3 (severe). Total score ranges from 1 to 120 points. The NPI-D scale assesses the caregiver distress caused by the individual behaviors. Total scores range from 0 to 50 points. In the randomization phase as well as the open label phase of the study, there was improvement in the NPI and NPI-D scores in the donepezil-treated group. For patients who were on donepezil in the first 6 weeks and later randomized to placebo, there was a significant worsening of neuropsychiatric symptoms and caregiver distress at 6 and 12 weeks.

Olin and colleagues (2002) have reported in a Cochrane review on 2 randomized controlled trials of galantamine for AD that included the NPI as an outcome measure. In one trial, there was no benefit of galantamine 24 mg/day or 32 mg/day treatment on behavioral symptoms versus placebo treatment. In the second trial, the 16 mg/day dose was found to be significantly better than placebo. Two randomized-controlled trials with memantine for the treatment of moderate to severe stage AD have included neuropsychiatric symptom measures as outcomes. Reisberg and colleagues (2003) reported that the memantine-treated group was not significantly different than the placebo-treated group in terms of NPI scores. Tariot and colleagues (2004) reported a statistically significant difference in favor of the memantine/donepezil-treated group versus the donepezil/placebo-treated group in terms of the NPI scores. However, the magnitude of this difference was small.

Only a few placebo-controlled clinical trials have addressed the treatment of depression in patients with AD. The most abundant data exist for sertraline and citalopram in which the former agent has shown some efficacy for depressive symptoms and the latter, depression, agitation, and lability (Table 5).

Risperidone, olanzapine, and quetiapine are frequently used atypical antipsychotic agents for the treatment of psychosis and agitation in dementia. There are several open label trials reporting the efficacy of these agents and a limited number of placebo-controlled studies (Table 6).

Studies of the efficacy and tolerability of two of the newer atypical antipsychotics, aripiprazole and ziprazidone in dementia with behavior disturbance, have not yet appeared

Table 5 Summary of antidepressant trials in elderly dementia patients

Study	Sample size, n	Study duration	Medication	Outcome
Pollock et al 2002	52	17 days	Citalopram (20 mg/day)	Agitation and lability significantly improved
Lyketsos et al 2003	44	12 week	Sertraline (mean dose 95 mg)	Significant improvement in depression but not in agitation
Finkel et al 2004	245	12 week	Sertraline (mean dose 125 mg)	No significant improvement in depression

Table 6 Overview of placebo-controlled trials of atypical antipsychotics in dementia

Study	Medication	Study design	Sample size, n	Duration	Outcome
Katz et al 1999	Risperidone, doses of 0.5 mg, 1.0 mg, 2.0 mg	Double-blind	625	12 week	Significant (>50%) reductions in some psychotic symptoms and aggression with Risperidone 1 mg
DeDeyn et al 1999	Risperidone (mean dose 1. 1 mg) or haloperidol (mean dose 1.2 mg), versus placebo	Double-blind	344	13 week	Risperidone caused >30% reduction in some measures of aggression
Street et al 2000	Olanzapine (doses of 5 mg, 10 mg, 15 mg daily) versus placebo	Double-blind	206	6 week	5 mg and 10 mg and not 15 mg had a significant decrease in agitation, aggression, hallucinations, delusions
Tariot et al 2002	Quetiapine (mean dose 120 mg), haloperidol (mean dose 2 mg)	Randomized placebo controlled		10 week	Both treatment groups improved in severity of psychosis and agitation. Quetiapine was better tolerated than haloperidol

in the peer-reviewed literature. The available evidence suggests that overall, atypical antipsychotic agents are better tolerated than conventional neuroleptics and more efficacious than placebo in decreasing agitation in patients with dementia. Importantly, it has been recently reported that medications in this class may increase the risk of glucose intolerance and cerebrovascular adverse events. Clozapine is occasionally recommended for treatment refractory elderly patients with movement disorders such as Parkinsonism or tardive dyskinesia and psychosis. One of the major drawbacks with clozapine use is a significantly increased risk of agranulocytosis and the need for standardized blood monitoring (Kasckow et al 2004).

In April 2005, the FDA requested that all manufacturers of atypical antipsychotic medications add a "black box warning" to their prescribing information regarding the use of these medications in elderly patients with dementia-related psychosis (FDA 2005). According to the FDA, "analyses of seventeen placebo-controlled trials that enrolled 5106 elderly patients with dementia-related behavior disturbances revealed a risk of death in the drug-treated patients of 1.6 to 1.7 times that seen in placebo-treated patients". The data reviewed were gathered from dementia trials of olanzapine, aripiprazole, risperidone, and quetiapine. Over the course of these trials, averaging about 10 weeks, the rate of death in drug treated patients was about 4.5% compared with a rate of 2.6 % in the placebo group. The causes of death varied, appearing to be either cardiovascular or infectious in origin. The black box warning further goes on to state that the FDA has not approved aripiprazole, quetiapine, ziprazidone, risperidone, and olanzapine for the treatment of patients with dementia-related psychosis. Given the black box warning as well as increased cardiovascular risks (stroke), metabolic side effects such as weight gain, hyperlipidemia, insulin resistance, and diabetes, the clinician should very carefully consider the choice of pharmacological agent for the treatment of dementia-related psychosis and other neuropsychiatric symptoms. Before prescribing an atypical antipsychotic in dementia care, one should be able to identify target symptoms of psychosis such as delusional thinking and hallucinations. Only in the presence of sustained patient distress, danger to self or others, or impairment of functioning (resistance to care) is the use of atypical antipsychotic medications recommended.

In addition to the emergence of atypical antipsychotic agents as commonly used agents for the treatment of dementia-associated neuropsychiatric symptoms, the use of anticonvulsant medications such as carbamazepine and sodium valproate has commanded significant attention. One placebo-controlled study using an average dose of 300 mg per day of carbamazepine showed that the drug was well tolerated by patients and significantly decreased aggression and agitation (Tariot et al 1998). Potential side effects of carbamazepine include drowsiness, gastrointestinal distress, ataxia, rash, elevated hepatic enzymes, and drug interactions with other agents. This agent has also been associated with aplastic anemia and agranulocytosis.

Sodium valproate has been reportedly effective in the treatment of behavioral disturbances in dementia and has

fewer drug interactions than carbamazepine. Porsteinsson and colleagues (2001) reported on the use of sodium valproate in a randomized placebo-controlled six week study of 56 nursing home patients with dementia and agitation. The average dose of divalproex sodium used was 840 mg per day. The authors noted that their results suggested improvement in the agitation subscale of the Brief Psychiatric Rating Scale (BPRS). Potential side effects of this agent include nausea, vomiting, sedation, diarrhea, ataxia, and tremor. Hepatotoxicity and pancreatitis have been noted to be rare complications of the use of sodium valproate. When this medication is administered, complete blood counts, hepatic enzymes, and serum drug concentrations need to be monitored regularly to prevent toxicity.

Gabapentin, lamotrigine, and topiramate are newer anticonvulsants whose efficacy and tolerability have not been systematically evaluated for efficacy and tolerability in the treatment of dementia.

Benzodiazepines such as lorazepam and oxazepam are often used in the management of agitation, but their efficacy has not been comprehensively studied. These agents are generally safe when used in low doses, but with increasing doses, common side effects include over-sedation, ataxia, confusion, and paradoxical agitation. In addition, with long-term use, tolerance and dependence is likely. Zolpidem, a hypnotic, was shown to reduce nighttime wandering in two dementia patients (Shelton et al 1997).

The antianxiety agent buspirone has shown efficacy in case reports in reducing anxiety, aggression, and agitation in patients with dementia (Sakauye et al 1993). The drug is generally well-tolerated, however, if used in combination with selective serotonin reuptake inhibitors (SSRIs), the patient is at increased risk for the development of serotonin syndrome (confusion, tremors, hyperthermia, hypertension, and seizure).

In a recent review of the pharmacological treatment of neuropsychiatric symptoms of dementia, Sink and colleagues (2005) conducted a systematic review of English language articles published from 1996 to 2004. They utilized Medline, the Cochrane database of systematic reviews and a manual search of bibliographies for this review. Only double-blind, placebo-controlled, randomized control trials (RCT) or meta-analyses of dementia trials reporting effects on neuropsychiatric symptoms were included. Twenty-nine articles met inclusion criteria. Five trials of antidepressants were included. No efficacy was demonstrated for symptoms other than depression, except one study of citalopram. For mood stabilizers, three trials of sodium valproate showed no efficacy. Two trials of carbamazepine showed mixed results. Four studies of typical antipsychotics showed small benefit and no differences were shown among specific agents. Six trials of atypical antipsychotics were included. Results indicated modest, statistically significant, efficacy of olanzapine and risperidone. Two meta-analyses and six randomized clinical trials of ChEIs showed small, statistically significant, efficacy. Two randomized clinical trials of memantine had mixed results for the treatment of neuropsychiatric symptoms.

Prior to the recent FDA warning regarding the use of atypical antipsychotic agents in elderly patients with dementia, expert consensus guidelines were published to address the treatment of agitation in dementia (Alexopoulos et al 2005). The guidelines recommend initiating therapy with risperidone at low doses of 0.25 mg to 0.5 mg per day with an average maximum dose of 1 mg to 1.5 mg per day if there is evidence of psychosis. These guidelines also recommend the use of environmental interventions in addition to medication treatment. If agitation is due to depression and/or anxiety, an SSRI trial is the first recommended option. If insomnia is a contributing factor, trazodone use is indicated. Other consensus guidelines (AGS–AAGP 2003) recommend that nonpharmacological interventions alone are indicated if there is no threat to the patient or others, medical conditions are being addressed, and if no psychotic symptoms are evident.

At present, no psychotropic agent presently available within the US is FDA-approved for use in dementia. Atypical antipsychotics are the first line agents of choice for severe behavioral symptoms with psychosis. When medications are used to manage behavior disturbances, one must document the specific target symptoms being addressed. Combination therapy is indicated only after two different trials with two different classes of agents have proven unsuccessful. Taper or discontinuation of medications should be attempted and documented by six months following response and every six months, thereafter. There is no consensus on the choice of medication for nonpsychotic behavioral symptoms. There are no comparison studies between pharmacological and nonpharmacological interventions, which makes it difficult to prioritize a specific approach for most nonpsychotic behavioral symptoms (Table 7).

Conclusions

ChEIs are the mainstay of treatment for mild to moderate AD and memantine is indicated as therapy for moderate to severe AD. The degree of efficacy of these agents in

Table 7 Commonly prescribed drugs, dosage guidelines in the elderly

Drug	Starting daily dose	Maximum recommended daily dose
Divalproex	125 mg twice daily	1000 mg
Carbamazepine	50–100 mg	500–800 mg
Risperidone	0.25–0.5 mg	1 mg
Olanzapine	2.5 mg	5–10 mg
Quetiapine	25 mg	200–300 mg
Trazodone	25 mg	100–150 mg
Buspirone	5 mg twice daily	30–45 mg
Lorazepam	0.5 mg	2 mg
Zolpidem	5 mg	10 mg

improving or stabilizing cognition and function is modest, but has been consistently demonstrated across numerous clinical trials. Some controversy exists regarding whether the putative benefits of these agents outweigh their expense. As AD advances, neuropsychiatric symptoms contribute substantially to caregiver distress and are especially difficult to manage. Preliminary data suggest that memantine and ChEIs may reduce the severity or delay the emergence of neuropsychiatric symptoms. Despite their recent association with an increased risk of death, cerebrovascular adverse events, and metabolic alterations such as hyperglycemia and hyperlipidemia, atypical antipsychotics are widely used in treating psychosis and agitation. Although supporting data are limited, serotonergic antidepressants and anticonvulsant agents are frequently used for the treatment of neuropsychiatric symptoms such as depression, agitation, and aggression.

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