

# **GUIDELINE WATCH (OCTOBER 2014): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE AND OTHER DEMENTIAS**

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## ACRONYMS:

- **ADCS-ADL** Alzheimer's Disease Cooperative Study—Activities of Daily Living
- **ADAS-Cog** Alzheimer's Disease Assessment Scale—Cognitive Subscale
- **BADLS** Bristol Activities of Daily Living Scale
- **CADASIL** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
- **CATIE-AD** Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease
- **CIBIC+** Clinician Interview-Based Impression of Change Plus
- **CitAD** Citalopram for Agitation in Alzheimer Disease Study
- **DART-AD** Dementia Antipsychotic Withdrawal Trial—Alzheimer's Disease
- **DOMINO trial** Donepezil and Memantine in Moderate to Severe Alzheimer's Disease trial

## ABBREVIATIONS:

- **APA** American Psychiatric Association
- **CI** Confidence interval
- **CGI** Clinical Global Impression
- **CMAI** Cohen-Mansfield Agitation Inventory
- **DLB** Dementia with Lewy bodies
- **FDA** Food and Drug Administration
- **FTD** Frontotemporal dementia
- **MMSE** Mini-Mental State Examination
- **NPI** Neuropsychiatric Inventory
- **NSAIDs** Nonsteroidal anti-inflammatory drugs
- **PDD** Parkinson's disease dementia
- **RSG XR** Extended-release rosiglitazone
- **SD** Standard deviation
- **sMMSE** Standardized Mini-Mental State Examination

## INTRODUCTION

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This guideline watch summarizes new evidence and developments since the 2007 publication of APA's "Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias" (American Psychiatric Association, 2007). The authors of this watch participated in the work group that developed the 2007 guideline. Data from new studies have changed the strength of evidence supporting some of the recommendations in the 2007 guideline; however, in our opinion the recommendations remain substantially correct and current. New information highlighted in this watch includes the following.

### PHARMACOLOGICAL TREATMENTS

#### Cognitive Symptoms

- Available evidence remains modest for the efficacy of the cholinesterase inhibitors for mild to severe Alzheimer's disease and of memantine for moderate to severe Alzheimer's disease.
- A higher-dose oral formulation of donepezil and a patch formulation of rivastigmine are now available. Evidence does not show clinically meaningful advantages to administering higher doses of donepezil; higher doses of the rivastigmine patch may be associated with greater benefit.
- Three new trials of memantine for mild to moderate Alzheimer's disease showed no benefit. In addition, a sustained-release formulation of memantine is avail-

able but has not been studied in comparison with the immediate-release formulation of the drug.

- New randomized controlled trials show effects that are, at best, slight or of unclear clinical significance when memantine is added to cholinesterase inhibitors. Evidence for the sustained benefit of either cholinesterase inhibitors or memantine is unclear.
- Additional evidence has clarified the adverse effects of cholinesterase inhibitors when these agents are used on a long-term basis. Such effects include anorexia, weight loss, falls, hip fractures, syncope, bradycardia, and increased use of cardiac pacemakers.
- No new evidence supports the use of other pharmacological agents to prevent or treat cognitive symptoms.

#### Behavioral Symptoms

- New evidence indicates that antipsychotics provide weak benefits for the treatment of psychosis and agitation in patients with dementia. Adverse effects of antipsychotics reported in new studies include sedation, metabolic effects, and cognitive impairment.
- New evidence from a single trial suggests benefits for citalopram in the treatment of agitation in patients with Alzheimer's disease, but treatment may be constrained by cognitive and cardiac side effects.
- New evidence indicates that for many patients with Alzheimer's disease, antipsychotics can be tapered and discontinued without significant signs of withdrawal or return of behavioral symptoms.

- New studies indicate that cholinesterase inhibitors and memantine have no clinically significant effects on disruptive behaviors.

### Depression

- There continues to be mixed evidence for the efficacy of antidepressants to treat depression in patients with dementia.

### Apathy

- New evidence shows inconsistent effects of psychostimulants in treating severe apathy in patients with dementia.

## PSYCHOSOCIAL INTERVENTIONS

- Available research does not conclusively show which psychosocial intervention works best for which service setting, specific behavior, disease stage, or caregiver and patient profile.
- Additional evidence suggests the value of psychosocial interventions to improve or maintain cognition, function, adaptive behavior, and quality of life but does not

demonstrate whether any specific psychosocial intervention is more effective than another.

- Support programs for caregivers and patients with dementia significantly decreased the odds of institutionalization and improved caregiver well-being.

## ALTERNATIVE TREATMENTS

- There is not enough definitive new evidence to warrant a change to the 2007 guideline statement that alternative agents are not generally recommended because of uncertain efficacy and safety.

With the publication of the fifth edition of APA's *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 2013), there has been a shift in nomenclature to "major neurocognitive disorder" and "mild neurocognitive disorder" instead of the terms "dementia" and "mild cognitive impairment," respectively. For the purpose of this guideline watch, we have continued to use the terms "dementia" and "minimal cognitive impairment" because DSM-IV diagnoses were used in the studies described herein. Aspects of diagnosis, such as diagnostic criteria and use of imaging or laboratory studies for diagnostic purposes, are outside the scope of this guideline watch.

## METHODS

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The systematic literature review for the 2007 guideline ended in 2004, although some publications from 2005, 2006, and 2007 were included. For this guideline watch, we searched the Cochrane database and MEDLINE, using PubMed, for meta-analyses, systematic reviews, randomized trials, and other controlled trials on humans and adults published in English from 2002 through January 2012. In PubMed, we searched using the MeSH terms "Alzheimer Disease," "Creutzfeldt-Jakob Syndrome," "Dementia," "Dementia, Multi-Infarct," "Dementia, Vascular," "Lewy Body Disease," "Pick Disease of the Brain," and "Cognition Disorders" as well as the following title and abstract words or phrases: "Alzheimer," "Alzheimer's," "CADASIL," "cortical dementia," "cortical dementias," "dementia with lewy bodies," "dementia," "dementias," "frontotemporal dementia," "lewy body dementia," "mild cognitive impairment," "Parkinson's dementia," "subcortical dementia," "subcortical dementias," "vascular dementia," "vascular dementias," "cognitive disorder," "cognitive

disorders," "cognitive impairment," or "cognitive impairments." Titles, abstracts, and keywords in the Cochrane database were searched for the words "dementia," "dementias," and "cognitive." After duplicate citations were eliminated, these search strategies yielded 5,956 articles, which were screened by two separate raters for relevance to the treatment of patients with dementia: 5,228 articles were excluded as not relevant to treatment (e.g., the study population was not human; the study population did not include individuals with dementia; the study did not include an intervention intended to treat dementia or dementia symptoms), and 728 articles were retained and reviewed by the authors. A separate search of "memantine," "donepezil," "galantamine," or "rivastigmine," using the same term limits described above, was conducted for the year 2012. This search yielded an additional 984 articles, of which 22 were retained and reviewed by the authors. Other articles were identified and included during draft development and review.

# PHARMACOLOGICAL TREATMENTS FOR COGNITIVE SYMPTOMS

## CHOLINESTERASE INHIBITORS AND MEMANTINE

Since 2007, new randomized controlled trials of the cholinesterase inhibitors and memantine have been conducted to treat cognitive symptoms of dementia. The following sections review these new trials in patients with specific dementias (i.e., Alzheimer's disease, vascular dementia, and other dementias).

New systematic reviews and meta-analyses are also available, but most of these were not comprehensive, or they focused on a narrow question (e.g., a pooled analysis of selected outcomes from selected trials). Similarly, analyses of partial clinical samples are available but cannot be considered reliable. One thorough, well-designed systematic review by the McMaster University Evidence-Based Practice Center evaluated 92 publications representing 59 studies of pharmacological agents for dementias. The authors concluded, "Treatment of dementia with cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia" (Raina et al. 2008, p. 379).

New information is also available on adverse effects of cholinesterase inhibitors when these agents are used on a long-term basis. Such effects include anorexia, weight loss, syncope (Kim et al. 2011), bradycardia (Hernandez et al. 2009), falls, hip fractures, and increased need for a cardiac pacemaker (Gill et al. 2009).

### Alzheimer's Disease

The 2007 guideline identifies three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—that have been approved by the U.S. Food and Drug Administration (FDA) for treatment of mild to moderate Alzheimer's disease. The guideline notes that donepezil has been approved for severe Alzheimer's disease. Memantine is approved by the FDA for treatment of moderate to severe Alzheimer's disease. Available evidence for these medications remains modest.

Several new studies of galantamine are available. In a trial by Burns and colleagues (2009) of patients with severe Alzheimer's disease and a mean age of 84 years in a nursing home setting, galantamine was found to have minimal clinical benefit. In this study, participants were randomly assigned to receive galantamine titrated to 24 mg/day ( $n=207$ ) or placebo ( $n=200$ ); 168 and 161 individuals completed the study, respectively. The patients who received galantamine had improved cognitive function as measured by the Severe Impairment Battery but no benefit on their

ability to undertake normal daily activities. Efficacy of galantamine was also not found for patients with mild cognitive impairment without dementia in two 24-month randomized double-blind studies (Winblad et al. 2008). The first study had 990 subjects, the second 1,058.

Since publication of the 2007 guideline, a 23 mg/day formulation of donepezil, a rivastigmine transdermal patch, and a sustained-release formulation of memantine have become available.

In a randomized, double-blind, multisite study that included 1,371 patients with moderate to severe Alzheimer's disease (Farlow et al. 2010), the use of 23 mg/day donepezil did not result in a statistically significant difference from the 10 mg/day dosage on the Clinician Interview-Based Impression of Change Plus (CIBIC+) scale. The higher dose of donepezil was associated with a higher proportion of subjects dropping out of treatment as well as a substantial increase in the rate of adverse events compared with 10 mg/day of donepezil. Thus, in clinical use, the potential cognitive effects of the higher dose of donepezil are unlikely to outweigh the increase in adverse effects. In a subsequent subgroup analysis (Doody et al. 2012), outcomes in patients already taking memantine were compared with outcomes in patients not taking concomitant memantine. Although donepezil at 23 mg/day was found to provide cognitive benefits over the lower dose of donepezil at week 24, memantine had no additional effect.

A study in patients with severe Alzheimer's disease assessed the effects of two doses of rivastigmine transdermal patch in a 24-week prospective, randomized, double-blind trial (Farlow et al. 2013) and investigated the efficacy, safety, and tolerability of 13.3 mg/24 hour dosage as compared with 4.6 mg/24 hour dosage of a rivastigmine patch. Individuals who were randomly assigned to receive 13.3 mg/24 hours ( $n=356$ ) showed superior effects on cognition and function at weeks 16 and 24 as compared with individuals who were assigned to receive a 4.6 mg/24 hour patch ( $n=360$ ). Overall, rates of completion and rates of adverse effects were similar in the two groups, although treatment discontinuation (except for skin irritation) and most side effects occurred more frequently in the higher-dose group. An additional randomized, double-blind, parallel-group study (Cummings et al. 2012) examined the effects, tolerability, and safety of the rivastigmine transdermal patch at two different doses in 567 patients with Alzheimer's disease who exhibited cognitive and functional decline following 24–48 weeks of open-label treatment with 9.5 mg/24 hour rivastigmine patch. There was no cognitive benefit from the change to a 13.3 mg/day dosage of the rivastigmine

patch, but there was a statistically significant improvement in the Instrumental Activities of Daily Living domain of the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) in patients receiving 13.3 mg/day as compared with 9.5 mg/24 hours at all study time points. Adverse events occurred in a larger fraction of patients who received the 13.3 mg/24 hour rivastigmine patch as compared with the 9.5 mg/24 hour rivastigmine patch.

The 2007 guideline notes that “currently available data suggest that the combination of a cholinesterase inhibitor plus memantine is more likely to delay symptom progression than a cholinesterase inhibitor alone.” The DOMINO trial conducted by Howard and colleagues (2012) provides additional information on this issue, but interpretation of the findings is limited by important differences among the groups at baseline and high numbers of dropouts, with different dropout rates among the treatment groups. The study was designed to follow a community sample of 800 patients, but only 295 were enrolled, and many of these participants were excluded from the analyses because of poor treatment adherence. At the end of the study, sample sizes ranged from 20 to 38 per group. Study patients had moderate to severe Alzheimer's disease and had been treated with donepezil for at least 3 months. They were randomly assigned to continue donepezil, switch to placebo, switch to placebo plus memantine, or continue donepezil and start memantine. Patients for whom donepezil was discontinued showed worsening on the standardized Mini-Mental Examination (sMMSE) and the Bristol Activities of Daily Living Scale (BADLS) compared with patients who continued on donepezil: sMMSE  $-1.9$  points; BADLS  $+3.0$  points. These differences were statistically significant. Patients who received memantine had less pronounced worsening than patients who received placebo: sMMSE  $+1.2$  points and BADLS  $-1.5$  points, values that were also statistically significant. In individuals who continued on donepezil, there was no additional benefit of adding memantine.

In addition, there are two systematic reviews that show at best slight effects or unclear clinical significance of memantine added to cholinesterase inhibitors (Farrimond et al. 2012; Muayqil and Camicioli 2012). These reviews did not include the two trials and subanalyses above. Muayqil and Camicioli (2012) pooled data from 13 studies with a total of 971 patients. Small but statistically significant effect sizes were seen in favor of combination therapy among patients with moderate to severe Alzheimer's disease on scales of cognition, scales of functional outcomes, and the NPI. The authors noted heterogeneity in scales and patient characteristics and concluded that the clinical significance of their findings is uncertain (Muayqil and Camicioli 2012). Farrimond et al. (2012) pooled data from three

randomized controlled trials with a total of 1,317 patients. They found that adding memantine to a cholinesterase inhibitor had a small impact on patients' Clinical Global Impression (CGI) score but no benefit on function. They concluded that clinical relevance of adding memantine “is not robustly demonstrated” (Farrimond et al. 2012).

A clinical trial cited in the 2007 guideline suggested modest efficacy of memantine for patients with mild to moderate Alzheimer's disease (Peskind et al. 2006); however, the guideline notes that “this result is not conclusive and additional trials should be performed.” In more recent studies, memantine was not effective in patients with mild to moderate Alzheimer's disease. In a 24-week double-blind study, Bakchine and Loft (2008) randomly assigned 470 patients with mild to moderate Alzheimer's disease to receive either 20 mg/day memantine ( $n=318$ ) or placebo ( $n=152$ ); 85% and 91%, respectively, completed the study. After 24 weeks, patients treated with memantine showed numerically significant but clinically insignificant improvement relative to placebo on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the CIBIC+. Memantine showed no advantage over placebo in a similar trial by Porsteinsson and colleagues (2008) in which 433 patients with mild to moderate Alzheimer's disease were randomly assigned to receive placebo or memantine (20 mg/day) for 24 weeks. Primary outcomes were changes from baseline on the ADAS-Cog and CIBIC+ scores. Similarly, no effect for memantine was found in a randomized placebo-controlled trial of memantine and vitamin E in 613 patients with mild to moderate Alzheimer's disease (Dysken et al. 2014), as described in more detail in the section “Alternative Treatments.”

Taken together, the bulk of the evidence on the efficacy and effectiveness of cholinesterase inhibitors and memantine in individuals with Alzheimer's disease consists of trials of individual medications rather than head-to-head comparator trials. On the basis of the available evidence, one could justify using both memantine and a cholinesterase inhibitor, using memantine alone, or using a cholinesterase inhibitor alone in treating an individual with Alzheimer's disease.

### Vascular Dementia

Because of inconclusive evidence, the 2007 guideline does not specifically recommend cholinesterase inhibitors for patients with vascular dementia; however, it notes that individual patients may benefit from this class of medications. The guideline states that evidence does not support the use of memantine in such patients.

New trials of the cholinesterase inhibitors in patients with vascular dementia have not found them to be effective. For example, a 24-week double-blind, randomized, placebo-

controlled study of 710 patients with probable vascular dementia showed no effect of rivastigmine (Ballard et al. 2008b). Similarly, in a multinational, double-blind, parallel-group clinical trial, 788 patients with probable vascular dementia were randomly assigned to receive galantamine or placebo (Auchus et al. 2007). Galantamine showed no clear effect on activities of daily living or global functioning.

Kavirajan and Schneider (2007) conducted a meta-analysis of randomized controlled trials of cholinesterase inhibitors and memantine in vascular dementia. Three donepezil, two galantamine, one rivastigmine, and two memantine trials, comprising 3,093 patients taking the study drugs and 2,090 patients taking placebo, met selection criteria. Overall, the donepezil trials showed questionable, not clinically significant, or not statistically significant effects on cognition. This meta-analysis concluded that available evidence does not support use of galantamine, rivastigmine, donepezil, or memantine in vascular dementia.

Dichgans and colleagues (2008) conducted a multicenter, 18-week, placebo-controlled, double-blind, randomized parallel-group trial to determine whether donepezil improves cognition in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL;  $N=168$ ). The primary endpoint was change from baseline in the score on the vascular ADAS-Cog. Donepezil showed no effect in subcortical vascular cognitive impairment.

### Other Dementias

The 2007 guideline states that cholinesterase inhibitors should be considered for patients with mild to moderate Parkinson's disease dementia (PDD). Supporting evidence, however, remains weak. The guideline describes a single trial of rivastigmine, leading to an FDA indication for this condition. Donepezil was subsequently studied for PDD in a randomized double-blind trial (Dubois et al. 2012). In this 24-week study in 550 patients, donepezil had no effect on activities of daily living or behavior. There was also no effect on the protocol-specified analyses of cognition, although post hoc analyses found benefit on some measures of cognitive function.

The 2007 guideline suggests that cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies (DLB) and describes two randomized controlled trials, one of rivastigmine and one of donepezil. An additional trial is now available: Mori and Kosaka (2012) randomly assigned 140 patients with DLB to receive donepezil or placebo for 12 weeks. Donepezil at 5 and 10 mg/day was superior to placebo on measures of cognitive function and behavior.

The 2007 guideline noted little evidence overall to support the use of any particular agent for frontotemporal

dementia (FTD), except for two small trials and two case series showing that either trazodone or one of a variety of selective serotonin reuptake inhibitors may be beneficial in decreasing problematic behaviors or agitation. In a more recent study, 36 patients with behavioral variety FTD and primary progressive aphasia were treated in an open-label fashion with galantamine for 18 weeks and then were randomly assigned to receive an additional 8 weeks of either galantamine or placebo (Kertesz et al. 2008). Galantamine showed no effect on behavior or language.

Similarly, memantine did not improve cognition in randomized placebo-controlled trials of patients with DLB or PDD (Aarsland et al. 2009; Emre et al. 2010). In the study by Aarsland and colleagues (2009), 72 patients with PDD or DLB were randomly assigned to receive memantine ( $n=34$ ) or placebo ( $n=38$ ). Sixteen patients did not complete the study because of adverse events (the proportion of withdrawals was similar in both groups). In the study by Emre and colleagues (2010), 199 patients were randomly assigned to treatment; 34 with DLB and 62 with PDD were given memantine, and 41 with DLB and 58 with PDD were given placebo. The study was completed by 159 (80%) patients: 80 in the memantine group and 79 in the placebo group.

In two randomized, double-blind, placebo-controlled trials, memantine was not found to be effective for FTD (Boxer et al. 2013; Vercelletto et al. 2011). In the trial by Vercelletto and colleagues (2011), no significant differences were found between patients who received memantine ( $n=23$ ) and those who received placebo ( $n=26$ ) on the CIBIC+ or on secondary measures of cognitive function or illness burden. In the trial by Boxer and colleagues (2013), patients with FTD and patients with aphasias were randomly assigned to treatment with memantine ( $n=33$  and 8) or placebo ( $n=31$  and 8). After 26 weeks, there were no statistically significant differences between the groups on measures of cognitive function or clinical global impression.

A randomized, double-blind, placebo-controlled trial by Hanney and colleagues (2012) found that memantine is not effective for adults over 40 years of age who have Down's syndrome and dementia. In this study, 88 patients received memantine and 85 received placebo for 52 weeks. Both groups declined in cognition and function, with no differences between the groups for any outcomes.

## OTHER PHARMACOLOGICAL TREATMENTS FOR COGNITIVE SYMPTOMS

In addition to cholinesterase inhibitors and memantine, the 2007 guideline reviews other medications used to delay the progression of cognitive symptoms in dementia,

including statins, nonsteroidal anti-inflammatory drugs (NSAIDs), estrogen supplements, and other marketed and experimental agents. Since 2007, a number of studies have examined whether reducing risk factors for cerebrovascular disease, primarily with antihypertensive drugs, might delay or prevent development of dementia or slow its progression (McGuinness et al. 2009, 2010; Peters et al. 2008; Shah et al. 2009). The results have been inconclusive, and there is no new basis for recommending these types of treatments solely in the context of dementia treatment or prevention.

### Statins

The 2007 guideline recommends against the use of statins for dementia because of a lack of efficacy in the prevention or treatment of cognitive decline; subsequent evidence is consistent with this conclusion. A large randomized controlled trial on the use of pravastatin in 5,804 at-risk elderly patients found no difference between statins and placebo in the prevention of cognitive decline after a mean follow-up period of 42 months (Trompet et al. 2010). Last, two randomized controlled trials found no benefit of statins in the treatment of Alzheimer's disease, as measured by scales of cognition (ADAS-Cog) and global function (Feldman et al. 2010; Sano et al. 2011). Several systematic reviews (Beri et al. 2009; Muangpaisan and Brayne 2010) and a meta-analysis (Zhou et al. 2007) of statins have also noted that data for the use of statins in dementia is inconclusive.

### Nonsteroidal Anti-Inflammatory Drugs

The 2007 guideline also recommends against the use of NSAIDs, and subsequent evidence supports this. There have been numerous studies since 2007 on the potential of NSAIDs to delay or prevent emergence of mild cognitive impairment or dementia in cognitively normal older persons, delay or prevent conversion of mild cognitive impairment to dementia, or slow progression of dementia (Aisen et al. 2008b; Breitner et al. 2011; De Jong et al. 2008; Martin et al. 2008; Pasqualetti et al. 2009; Salpeter et al. 2006; Soinen et al. 2007; Soni et al. 2009). Overall, no clinically meaningful benefit has been seen, with mixed evidence regarding excess toxicity.

### Estrogen Supplements

Hormone replacement therapy is also not recommended in the 2007 guideline. A number of small studies since 2007 continue to show mixed results of estrogen treatment in women with Alzheimer's disease (Valen-Sendstad et al. 2010; Wharton et al. 2011) or to slow or prevent cognitive decline in older women (Tierney et al. 2009). Wharton

and colleagues (2011) conducted a placebo-controlled, double-blind, parallel-group study of the effect of transdermal estradiol in postmenopausal women with mild to moderate Alzheimer's disease. Forty-three postmenopausal women with Alzheimer's disease were assessed over 12 months; there was a 49% dropout rate during this period. Results showed favorable effects of hormone therapy on visual memory and semantic memory. A 12-month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone on 65 female outpatients with probable Alzheimer's disease by Valen-Sendstad and colleagues (2010) found that women without an apolipoprotein E  $\epsilon 4$  allele may show better mood and cognition with hormone therapy. Tierney and colleagues (2009) conducted a 2-year double-blind placebo-controlled trial of 142 women randomly assigned to receive low-dose estradiol and norethindrone or a placebo. On the basis of scores on the short-delay verbal recall tasks of the California Verbal Learning Test, the study results suggested that the benefits of estrogen exposure may be limited to those women with average to above average performance.

An additional study of magnetic resonance imaging (MRI) in 1,403 women (Espeland et al. 2009) suggested that treatment with conjugated equine estrogens was associated with brain volume loss and that hippocampal and total brain volumes were smaller in women who had been prescribed conjugated equine estrogen and developed cognitive impairment. However, the clinical significance of these findings is unclear.

Given the lack of benefit on cognitive outcome measures and the adverse vascular and cancer risks, the 2007 guideline recommendation against the use of hormone replacement therapy is unchanged.

### Other Agents

Since publication of the 2007 guideline, several other agents have been studied for their effects in dementia. None of these agents are considered appropriate for clinical use at present, and more research is necessary.

Lithium was previously studied for its potential to reduce psychopathological features of dementia, and since 2007 its neuroprotective potential has been investigated. Two studies have examined lithium's effects on biomarkers relevant to Alzheimer's disease (Forlenza et al. 2011; Hampel et al. 2009). In one study comparing random assignment to receive lithium or placebo in 71 individuals with mild Alzheimer's disease, there were no effects of lithium at serum levels of 0.5–0.8 mmol/L in terms of global cognitive performance, depressive symptoms, or cerebrospinal fluid biomarkers (Hampel et al. 2009) with 6 weeks of dose titration followed by 4 weeks of treatment

at therapeutic levels. In another relatively small study of low-dose lithium (with serum levels of 0.25–0.5 mmol/L), individuals with mild amnesic cognitive impairment showed a decrease in cerebrospinal fluid concentrations of p-tau and some improvement in performance on cognitive and attentional tasks with a year of treatment. Given the small sample sizes and varying duration of these studies, as well as the known side effects and potential toxicity of lithium, particularly in older individuals, use of lithium to treat or prevent dementia is not recommended. However, further study of lithium's potential neuroprotective effects may be warranted. A small ( $N=92$ ), 6-month trial of atomoxetine (Mohs et al. 2009) failed to show clinically significant benefit in patients with Alzheimer's disease measured on the ADAS-Cog, although there were hints of possible benefit in secondary measures. A 6-month double-blind pilot study of transdermal nicotine in people ( $N=74$ ) with mild cognitive impairment indicated possible cognitive benefit (Newhouse et al. 2012), with primary outcome variables being attentional improvement as assessed with the Connors' Continuous Performance Test and clinical improvement as measured by CGI. Safety and tolerability were noted to be excellent.

Rosiglitazone failed to show benefit in three large phase III trials after showing possible benefit in a phase II trial (Risner et al. 2006), which measured the effects of 2, 4, or 8 mg of extended-release rosiglitazone (RSG XR) using the ADAS-Cog and the CIBIC+. In one of these phase III trials, Gold and colleagues (2010) conducted a double-blind placebo-controlled study in which 693 subjects were randomly assigned to receive a once-daily placebo, 2 mg

RSG XR, 8 mg RSG XR, or 10 mg donepezil as an active comparator. Co-primary endpoints were change from baseline to week 24 on the ADAS-Cog and CIBIC+. RSG XR showed no effect in either dose. Harrington and colleagues (2011) conducted two double-blind, placebo-controlled phase III studies in which subjects with mild to moderate probable Alzheimer's disease were randomly assigned to receive once-daily placebo, 2 mg RSG XR, or 8 mg RSG XR for 48 weeks. No statistically or clinically significant effect was detected for either dose, using the ADAS-Cog subscale and Clinical Dementia Rating–Sum of Boxes scores. A randomized, double-blind, placebo-controlled pilot study of intranasal insulin—with primary measures consisting of delayed story recall score and the Dementia Severity Rating Scale score and secondary measures including the ADAS-Cog score and the ADCS-ADL scale—suggested benefit in patients with mild cognitive impairment or Alzheimer's disease (Craft et al. 2012). A well-designed trial is under way to test efficacy.

A large number of experimental agents, many targeting the amyloid pathway such as bapineuzumab, tarenflurbil, and tramiprosate, have failed to show benefit (Aisen et al. 2007, 2011; Gauthier et al. 2009; Green et al. 2009; Sallo-way et al. 2009; Saumier et al. 2009; Sperling et al. 2012). In a phase III trial of solanezumab in patients with mild to moderate severity of Alzheimer's disease, no benefits were seen on primary outcomes; however, secondary analyses showed trends for improvement in participants with mild Alzheimer's disease (Doody et al. 2014). Intravenous immunoglobulin showed possible benefit in pilot studies but not in more definitive studies (Relkin et al. 2009).

## PHARMACOLOGICAL TREATMENTS FOR AGITATION AND PSYCHOSIS

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### ANTIPSYCHOTIC MEDICATIONS

The 2007 guideline recommends with moderate clinical confidence the use of antipsychotic medications for the treatment of psychosis in patients with dementia and for the treatment of agitation but only after addressing potential underlying causes and after trying environmental measures, including reassurance and redirection. The guideline also states that antipsychotics must be used with caution and at the lowest effective dosage because they are associated with severe adverse events. As noted in the 2007 guideline, all second-generation (“atypical”) antipsychotics carry a black box warning about increased risk of mortality in elderly patients. In 2008, the FDA extended this warning to all first-generation agents.

Since 2007, new randomized controlled trials of antipsychotics have been published. Although some of these trials involved large samples, few trials included head-to-head comparisons of antipsychotic agents that would inform the choice of a specific medication for an individual patient. Additional limitations in the newer trials affecting their external validity and potential for translation into practice included rates of attrition and variability in eligibility criteria, outcome measures, treatment protocols, control conditions, and masking procedures.

Unpublished summaries of some of the new trials were reviewed during development of the 2007 guideline, specifically two aripiprazole trials (Mintzer et al. 2007; Streim et al. 2008). In addition, results from a quetiapine trial



(Zhong et al. 2007) were reviewed as the guideline was being finalized for publication. Since the publication of the 2007 guideline, a small ( $N=40$ ) 6-week randomized placebo-controlled trial of quetiapine at a median dosage of 200 mg/day has been completed (Paleacu et al. 2008). No consistent differences were found in behavioral or psychological symptoms of dementia for patients treated with quetiapine as compared with placebo. Together with the large 10-week double-blind fixed-dose study of Zhong and colleagues (2007) and other small quetiapine trials (Ballard et al. 2005), which were already described in the 2007 guideline, available evidence suggests weak efficacy of quetiapine with increases in sedation at dosages above 200–300 mg/day.

Several small randomized controlled trials comparing two antipsychotics or an antipsychotic with an antidepressant showed no differences between the drugs. However, none of these studies included a placebo control group. Among these studies were comparisons between olanzapine and haloperidol (Verhey et al. 2006), quetiapine and risperidone (Rainer et al. 2007), risperidone and citalopram (Pollock et al. 2007), and risperidone and escitalopram (Barak et al. 2011). The latter two trials showed fewer adverse events and dropouts with the antidepressant. Because the trials were not placebo controlled, they provide no evidence that either drug in the trial was actually superior to placebo; however, they do provide evidence that there is little to distinguish between the drugs in terms of efficacy, although adverse events appear to be different.

Additional analyses of data from the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD), a comparison of olanzapine, quetiapine, and risperidone, showed modest effects on symptom scales that were similar to effects observed in other trials (Sultzer et al. 2008). As in the primary analysis of the CATIE-AD data, however, the small advantages were offset by adverse events. In terms of effectiveness, placebo treatment in CATIE-AD was associated with lower health care costs (Rosenheck et al. 2007); further cognitive impairment was associated with antipsychotics (Vigen et al. 2011); and the antipsychotics were associated with “weight gain in women, with olanzapine and quetiapine in particular, and with unfavorable change in HDL cholesterol and girth with olanzapine” (Zheng et al. 2009, p. 583).

Post hoc pooled analysis of trials of risperidone suggests improvement in a number of behavioral symptoms but not individual items on hallucinations or delusions (Rabinowitz et al. 2007). Another meta-analysis suggested that benefits of risperidone may be more notable in patients with more severe behavioral symptoms (Katz et al. 2007). However, meta-analyses also indicated that increased adverse effects with antipsychotic treatment may offset any

potential benefit of treatment (Katz et al. 2007; Kryzhanovskaya et al. 2006).

In summary, new trials and studies better define adverse effects, but they do not strengthen the evidence for efficacy of antipsychotic drugs in treating psychosis or agitation. Rather, they demonstrate minimal or no efficacy with strong placebo effects as well as variations in response with trial duration. These findings strengthen the support for using nonpharmacological interventions and environmental measures to attempt to reduce psychosis and agitation prior to initiation of medications.

### Discontinuation Trials

In a long-term, randomized, placebo-controlled discontinuation trial, Dementia Antipsychotic Withdrawal Trial–Alzheimer's Disease (DART-AD), 165 patients were randomly assigned to continue or discontinue their antipsychotic medications. This trial showed a continuing increase in the risk for death among patients who continued to take antipsychotics compared with patients for whom antipsychotics were tapered and changed to placebo (Ballard et al. 2009). There was a reduction in survival in the patients who continued to receive antipsychotics. When compared with individuals who received placebo, those who continued to receive antipsychotics showed a reduction in survival that was apparent at 12 months of follow-up, with a strong and persistent effect for up to 4 years. Because the majority of patients were initially treated with risperidone (67%) or haloperidol (26%), the results apply primarily to these drugs. The results support the concern that an increased risk for death continues if patients remain on antipsychotic medications and is not just a short-term effect seen for 10–12 weeks after initiation of antipsychotic medication (Schneider et al. 2005).

Another objective of this discontinuation trial was to assess clinical change associated with withdrawal of antipsychotic medication (Ballard et al. 2008a). Here, results over the 1-year follow-up period showed that there were no detrimental effects of antipsychotic discontinuation on either cognition or behavioral measures. However, there was evidence to suggest that patients with higher levels of behavioral symptoms prior to randomized discontinuation may have had some benefits from continued treatment with antipsychotics, which were mainly risperidone and haloperidol.

In a randomized discontinuation trial in Norway, 55 patients taking risperidone, olanzapine, or haloperidol were randomly assigned to continue or discontinue medication (Ruths et al. 2008). At 4 weeks follow-up, 23 of the 27 patients (85%) who were assigned to discontinue the antipsychotic remained off medication. No differences in NPI scores were found between the group who continued

treatment and the group who discontinued antipsychotics, with scores generally remaining stable or improving. Patients who exhibited worsening of behavioral symptoms with cessation of the antipsychotic were receiving daily drug doses at baseline that were higher than average.

A recently published discontinuation trial (Devanand et al. 2012) treated 180 patients with risperidone for 16 weeks in an open-label design. Next, 110 individuals who responded to treatment were randomly assigned to continuation of risperidone or to withdrawal of risperidone and administration of placebo. Sixteen weeks later, some of the patients who continued on risperidone were randomly assigned to receive placebo while others continued to receive risperidone for another 16 weeks. The primary outcome was time to relapse, defined by the investigators as a minimum of a 5-point or 30% increase in the NPI psychosis and agitation score. Patients who continued to take risperidone were less likely to relapse than those whose risperidone was changed to placebo, with relapse rates of 33% on risperidone as compared with 60% with placebo for the initial randomization and 15% and 48%, respectively, for those changed to placebo at 16 weeks. Nevertheless, a large proportion of patients who met the investigators' definition of response in the initial 16 weeks and who continued to receive risperidone in the double-blind, randomized, placebo-controlled phase had a relapse or dropped out of the study. The rates of discontinuation of risperidone treatment were 38% in the 16-week initial open phase, 68% in one randomized risperidone group during 32 weeks of follow-up, and 29% in the second risperidone group during 16 weeks of risperidone and 16 weeks of placebo. Indeed, only 10 of 32 patients (31%) assigned to continue risperidone for 32 weeks completed the study as compared with 10 of 40 patients (25%) assigned to 16 weeks of placebo. There were no differences in adverse events and ratings, cognitive function, or behavior rating scales between the patients assigned to 16 weeks of continuing risperidone and those assigned to 16 weeks of withdrawal from risperidone followed by placebo. Thus, there was a sizeable rate of treatment dropout or symptom relapse in individuals who were maintained on risperidone, but the risk of symptomatic relapse was even higher when risperidone was discontinued.

Taken together, these trials suggest that many patients with Alzheimer's disease who are receiving antipsychotics can have these medications tapered and discontinued without return of behavioral symptoms. A small minority of patients may show increased behavioral symptoms when antipsychotics are withdrawn, and the physician will need to decide whether or not to restart medications. These observations further strengthen the recommendation of the

2007 guideline to discontinue antipsychotic medications when possible and particularly when the physician is uncertain that a patient is benefiting from treatment.

### **Cognitive Impairment**

Several randomized trials clearly indicate that antipsychotic medications can worsen cognition. Deberdt et al. (2008) combined data from three trials of olanzapine in elderly patients with behavioral and psychiatric symptoms associated with dementia. For the olanzapine group as a whole there was a trend for worsening on the MMSE, which was significant in the subgroup of subjects with lower MMSE scores. In an additional study of olanzapine, Kennedy et al. (2005) reported a 2.6 point difference in ADAS-Cog score compared with placebo and a 1.5 point difference on the MMSE over 6 months. With quetiapine, Ballard et al. (2005) reported substantial worsening on the Severe Impairment Battery compared with placebo over 26 weeks. With second-generation antipsychotics overall, Vigen et al. (2011) reported a worsening of scores on the MMSE and ADAS-Cog compared with placebo.

### **ANTIDEPRESSANTS**

The 2007 guideline notes that antidepressants have not been well studied for symptoms other than depression in patients with dementia. The Citalopram for Agitation in Alzheimer Disease (CitAD) study was a randomized, placebo-controlled, double-blind, multisite trial of citalopram for agitation in patients with probable Alzheimer's disease (Porsteinsson et al. 2014). Participants received a psychosocial intervention plus either citalopram ( $n=94$ ) or placebo ( $n=92$ ) for 9 weeks. Citalopram was initiated at a dosage of 10 mg/day with planned titration to 30 mg/day over 3 weeks on the basis of response and tolerability. Participants who received citalopram showed significant improvement compared with those who received placebo on the Neurobehavioral Rating Scale Agitation Subscale and on the modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change. Caregiver distress was also reduced. As noted by the study authors, cognitive and cardiac adverse effects of citalopram may limit its use at the dosage of 30 mg/day.

### **CHOLINESTERASE INHIBITORS AND MEMANTINE**

Pharmacological alternatives to antipsychotics are lacking for the treatment of agitation in individuals with dementia. Since the 2007 guideline, the evidence is clearer that cholinesterase inhibitors and memantine do not have benefits in reducing agitation, although they may have benefits on other clinically relevant behaviors.

Since 2007, two trials in patients with Alzheimer's disease have addressed this issue. In patients with Alzheimer's disease who had clinically significant agitation and no response to a brief psychosocial treatment program, 272 subjects were randomly assigned to receive 10 mg/day of donepezil (128 patients) or placebo (131 patients) (Howard et al. 2007). After 12 weeks, the two groups showed no significant differences on the Cohen-Mansfield Agitation Inventory (CMAI) or other agitation scales. Furthermore, adverse effects of donepezil include agitation and insomnia.

In a similar trial of memantine, Fox et al. (2012) randomly assigned 149 patients with moderate to severe Alzheimer's disease and clinically significant agitation to receive memantine or placebo. After 6 weeks, improvement in cognition was observed, but the two groups showed no significant differences on the CMAI or other agitation scales. The efficacy of memantine for behavioral symptoms was examined in a 2008 meta-analysis that included five of six available trials that reported NPI outcomes (Maidment et al. 2008). Patients had mild to severe Alzheimer's disease without significant agitation or psychosis and were being treated with memantine to improve cognition, not behavior. The authors found a small effect size but questioned whether the 1.99 point difference ( $p=0.041$ ) on the NPI was clinically beneficial, especially in light of the sixth trial, which was not included in the meta-analysis but showed no significant benefit of memantine.

## BENZODIAZEPINES

There are no new studies since 2007 to augment the modest data demonstrating benefit of benzodiazepines.

## ANTICONVULSANTS

The 2007 guideline notes that there is some evidence for modest benefit of low doses of carbamazepine in patients with dementia who have agitation. There are no new data since 2007 regarding carbamazepine. As described in the 2007 guideline, carbamazepine is not recommended for routine use for agitation in patients with dementia because of weak evidence and known risks such as drug-drug interactions and poor tolerability with long-term use.

Oxcarbazepine was studied in an 8-week multicenter randomized controlled trial in 103 patients with Alzheimer's disease with agitation and aggression (Sommer et al. 2009). The investigators found no differences between oxcarbazepine and placebo.

The 2007 guideline also recommends against routine use of valproate in any formulation to treat behavioral symptoms in dementia on the basis of inconsistent results from several randomized controlled trials. Since 2007, the

use of valproate to delay or prevent behavioral symptoms has also been studied. In a 2-year multicenter trial, 313 individuals with moderate Alzheimer's disease who had not yet experienced agitation or psychosis were randomly assigned to receive valproate treatment or placebo; there was no difference between groups in time to emergence of agitation or psychosis (Tariot et al. 2011). The study also found no attenuation of cognitive or functional decline, and valproate was associated with significant toxic effects. Additionally, 89 of the 313 patients in the study received MRI scans at baseline and 12 months; there was greater hippocampal and whole brain volume loss after 1 year of treatment with divalproex versus placebo (Fleisher et al. 2011).

## OTHER AGENTS

A number of medications have been used to manage pain in individuals with dementia, with the goal of reducing agitation and other behavioral symptoms. The 2007 guideline also notes that new or worsening agitation can be a sign of untreated or undertreated pain, among other underlying medical conditions. Importantly, a randomized controlled trial showed positive effects of adequate pain management on behavioral symptoms in 352 Norwegian nursing home residents with moderate to severe dementia and significant behavioral disturbances (Husebo et al. 2011). A study of 3,000 mg acetaminophen daily that had multiple outcomes, including behavior, social engagement, and emotion, reported benefit on social behavior (Chibnall et al. 2005). In contrast, other adequately designed trials of acetaminophen (Buffum et al. 2004) and vitamin D (Bjorkman et al. 2008) for pain showed no benefit. A meta-analysis of studies of procaine as a treatment for dementia found clear evidence of adverse effects and weaker evidence for benefits, suggesting that the harm of some pain-related interventions may outweigh the benefits (Szatmari and Bereczki 2008).

No evidence for prazosin was available to inform recommendations in the 2007 guideline. A pilot study of prazosin has now been published (Wang et al. 2009). Twenty-two patients with probable or possible Alzheimer's disease and with agitation or aggression were randomly assigned to receive placebo or prazosin titrated to an average dosage of about 6 mg/day. Although prazosin had some benefit, available evidence was not sufficient to support use. A larger trial is planned by the Alzheimer's Disease Cooperative Study.

Other agents reviewed in the 2007 guideline for the treatment of agitation and psychosis in dementia include trazodone, buspirone, lithium carbonate, hormonal agents, and beta-blockers. There is no new evidence since 2007 to support the benefit of these agents.

## PHARMACOLOGICAL TREATMENTS FOR DEPRESSION

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There have been additional clinical trials of antidepressants in dementia since 2007, but the evidence for efficacy remains mixed. For example, a review and meta-analysis of seven trials with 330 subjects found that the odds ratio for treatment response was 2.12 (95% CI 0.95–4.70;  $p=0.07$ ) (Nelson and Devanand 2011). Most of the new evidence comes from two relatively large trials. One trial was conducted in 326 people with Alzheimer's disease and depression and failed to show benefit of either sertraline (at a target dosage of 150 mg/day) or mirtazapine (at a target dosage of 45 mg/day) in comparison with placebo (Banerjee et al. 2011). The other trial included 135 people with Alzheimer's disease and depression and also failed to show benefit of sertraline (at a target dosage of 100 mg/day) in comparison with placebo (Rosenberg et al. 2010). In both

studies, there were more adverse effects associated with active treatment than placebo.

Overall, the evidence for the efficacy of antidepressant pharmacotherapy for people with depression and dementia is weak, mostly because trials were underpowered and confounded by variability in presenting symptoms, trial methods, and presence of comorbid conditions and differences among treatments and doses used. However, as noted in the 2007 guideline, clinical consensus still supports undertaking one or more trials of an antidepressant to treat clinically significant and persistent depressed mood in patients with dementia because of the increased rates of disability, impaired quality of life, and greater mortality associated with depression.

## PHARMACOLOGICAL TREATMENTS FOR APATHY

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The 2007 guideline describes a small amount of evidence that psychostimulants may aid in the treatment of severe apathy in patients with dementia. Further support is provided by a 6-week, randomized, double-blind, placebo-controlled multicenter trial by Rosenberg et al. (2013), in which 60 patients with Alzheimer's disease and apathy were assigned to receive methylphenidate 20 mg/day or placebo. Methylphenidate treatment was associated with sig-

nificant improvement in two of three efficacy outcomes and a trend toward improved global cognition with minimal adverse events. In contrast, modafinil was not associated with reductions in apathy or improvements in activities of daily living in a randomized, double-blind, placebo-controlled trial of 23 subjects who were also receiving stable doses of a cholinesterase inhibitor (Frakey et al. 2012).

## PSYCHOSOCIAL INTERVENTIONS

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Since 2007, publication of a number of high-quality meta-analyses, systematic reviews, and randomized controlled trials has increased the overall quality of evidence that psychosocial interventions improve or maintain cognition, function, adaptive behavior, and quality of life. The available research does not conclusively determine whether any one intervention is more effective than another or which intervention works best for which service setting, specific behavior, disease stage, or caregiver and patient profile. With the exception of possible frustration in patients who receive cognition-oriented therapies, there are no plausible harms associated with these interventions. Thus, despite limitations in supporting research, common sense continues to support their use in the care of all persons with dementia, as recommended in the 2007 guideline.

Principles of rehabilitation, clinical practice, and research studies also support the use of psychosocial inter-

ventions to optimize the cognitive, affective, behavioral, and functional capacities of persons with dementia. These interventions, which include caregiver education and skills training (Gitlin 2012), can be delivered in the home and in institutional settings and constitute the foundation of treatment for persons with Alzheimer's disease and other dementias. Although in actual practice clinicians and caregivers use a wide array of overlapping psychosocial interventions, the 2007 guideline characterizes psychosocial interventions as behavior-oriented, emotion-oriented, cognition-oriented, and stimulation-oriented. The guideline recommends behavior-, emotion-, and stimulation-oriented approaches with moderate confidence and cognition-oriented approaches with less confidence. Limitations of the research reviewed in the guideline included small samples; attrition; variability in eligibility criteria, outcome measures, treatment protocols, control condi-

tions, and masking procedures; and uncertainty about long-term benefits and the potential for translating these approaches into practice.

## BEHAVIOR-ORIENTED INTERVENTIONS

The 2007 guideline notes that behavioral interventions have not been shown to improve the overall functioning of patients with dementia, although there is some evidence that they can lessen or eliminate specific problem behaviors or be somewhat beneficial for improving mood and disruptive behavior. Still, “with some exceptions, the limited available follow-up data have suggested that the benefits do not persist beyond the duration of interventions” (American Psychiatric Association, 2007). Since the 2007 guideline was issued, O'Connor and colleagues (2009a) conducted two systematic reviews of studies of behavior-oriented psychosocial treatments to reduce behavioral disturbances in dementia and, in a separate analysis (O'Connor et al. 2009b), to reduce psychological symptoms such as anxiety and depression. All studies met quality research standards (e.g., control for attention). Treatments with moderate or large effect sizes for behavioral symptoms included caregiver education, aromatherapy, muscle relaxation training, and preferred music. Treatments for psychological symptoms with moderate effect sizes included music and recreational therapies. Maintenance effects were brief, suggesting that treatment works best in specific, time-limited situations and when tailored to individuals' preferences.

Brody and Arasaratnam (2012) conducted a meta-analysis of studies evaluating the efficacy of interventions delivered by family caregivers to reduce neuropsychiatric symptoms. The studies represented 3,279 caregiver-recipient dyads and tested a variety of interventions, often in combination, including skills training for caregivers (e.g., managing behavioral symptoms, improving communication), activity planning, home modifications, and increasing care recipients' participation in meaningful activities. The interventions were effective in reducing behavioral and psychological symptoms, with an overall effect size of 0.34 (95% CI=0.20–0.48;  $p<0.01$ ), as well as in improving caregiver reactions to these behaviors, with an overall effect size of 0.15 (95% CI=0.04–0.26;  $p=0.006$ ). A notable randomized controlled trial of an in-home tailored activity program showed positive results in 60 patient-caregiver dyads (Gitlin et al. 2008). The eight-session occupational therapy intervention customized activities to match participants' cognitive and physical capabilities and enabled caregivers to support these activities. At 4 months, compared with wait-list controls, intervention participants had, according to caregiver reports, reduced frequency of problem behaviors (e.g., shadowing and repetitive ques-

tioning), higher levels of care recipients' activity engagement, and enhanced caregiver skills and self-efficacy, although this benefit did not persist after 9 months.

A nursing home-based clinical trial evaluated the effectiveness of a staff education intervention to reduce behavior disorders (Deudon et al. 2009). The education and training program, involving 16 nursing homes and 306 patients with a diagnosis of dementia, included personalized staff training, advice, and feedback as well as easily carried cards with “how-to” instructions for dealing with behavioral symptoms. Compared with the usual-care control treatment, the active intervention significantly reduced global CMAI scores and the CMAI subscale scores for physically nonaggressive and verbally nonaggressive behaviors at 8 weeks postbaseline. This positive effect was sustained 3 months after the end of the program.

## EMOTION-ORIENTED INTERVENTIONS

Emotion-oriented treatments (e.g., supportive psychotherapy, reminiscence therapy) aim to improve mood, cognition, and quality of life. Logsdon et al. (2010) conducted a large randomized controlled trial testing the efficacy of a support group program for persons with early-stage dementia and their caregivers (142 dyads). Compared with a wait-list control condition, treated persons had improved quality of life, mood, and family communication. Small clinical trials of reminiscence groups report positive effects on these outcomes as well (Haslam et al. 2010; Wang et al. 2007). A meta-analysis of studies on the efficacy of simulated presence (i.e., a personalized videotape of family and friends) yielded limited support (Zetteler 2008). No systematic reviews, however, have been conducted to support or demonstrate the efficacy or risks of emotion-oriented treatments.

## COGNITION-ORIENTED INTERVENTIONS

Cognition-oriented treatments include reality orientation and cognitive stimulation, training, and rehabilitation. The 2007 guideline described modest improvements with some of these cognition-oriented treatments but concluded that transient benefits may not justify the cost of treatment or the risk of adverse effects, such as increased frustration in some patients. New evidence remains consistent with that recommendation.

Kurz et al. (2011) conducted a systematic review of randomized controlled trials evaluating cognition-focused interventions in participants with mild cognitive impairment or dementia and used meta-analytic strategies to calculate effect sizes. Cognition-focused interventions conferred small and inconsistent effects on trained cognitive skills, which, in some studies, translated into gains on gen-

eral cognitive ability. However, convincing evidence of clinical significance (i.e., mild short-term improvements in selected cognitive domains) was observed only in single trials with small sample sizes. In a single community-based randomized controlled trial, Clare et al. (2010) compared the efficacy of cognitive rehabilitation with relaxation therapy or no treatment in 69 persons with early-stage Alzheimer's disease. The eight weekly cognitive rehabilitation sessions consisted of personalized interventions to achieve participants' goals using practical aids and strategies, techniques for learning new information, practice in maintaining attention and concentration, and techniques for stress management. Cognitive rehabilitation produced improvement in goal performance and satisfaction, whereas the control treatments were not associated with any gains. In a nursing home-based randomized controlled trial, Graessel et al. (2011) tested the efficacy of a group intervention comprising motor stimulation, practice in activities of daily living, and cognitive stimulation on cognition and function. At 12 months, compared with usual-care, the 98 intervention participants remained stable in cognitive and functional capacities, whereas controls declined. A literature review and meta-analysis of cognitive stimulation therapy for individuals with mild to moderate dementia found only a trend toward delayed cognitive decline (Yuill and Hollis 2011).

## STIMULATION-ORIENTED INTERVENTIONS

Stimulation-oriented treatments (e.g., physical activity, music therapy, and multisensory stimulation) create opportunities for socialization; improve cognition and function; and aim to reduce behavior disorders, anxiety, and apathy. A meta-analysis of studies identified in the Cochrane database (Forbes et al. 2008) found insufficient evidence of effectiveness for physical activity to improve cognition, function, behavior, or depression. A more recent systematic review with meta-analysis (Potter et al.

2011) found that physical activity improved physical function (e.g., walking, timed get-up-and-go) but had uncertain effects on mood and quality of life. Some, but not all, clinical trials of music therapy (Cooke et al. 2010; Raglio et al. 2008; Sung et al. 2006) report positive outcomes (e.g., reduced agitation), but small samples, uncertain adherence to treatment protocols, and other limitations in research methods preclude strong recommendations. On the other hand, the lack of adverse effects supports their use. As in the 2007 guideline, studies of multisensory stimulation, including Snoezelen rooms, have shown mixed results, and there is not enough new evidence to make conclusions about efficacy (Klages et al. 2011; Milev et al. 2008).

## PSYCHOSOCIAL INTERVENTIONS FOR CARE DELIVERY AND END-OF-LIFE CARE

There is moderately strong evidence supporting interventions to improve different aspects of end-of-life care (Lorenz et al. 2008; Sampson et al. 2011), and as discussed in the 2007 guideline, a palliative care referral for patients with end-stage dementia should be considered. Case management and coordinated care have shown encouraging but not definitive results (Callahan et al. 2006; Duru et al. 2009; Lam et al. 2010; Pimouguet et al. 2010; Spijker et al. 2011). An integrated psychiatric nursing home program showed positive effects on behavior (Bakker et al. 2011), and implementing new nursing guidelines for depression showed benefit as well (Verkaik et al. 2011). High-calorie feeding helped maintain weight in individuals with advanced dementia, but there was no benefit of enteral tube feedings (Candy et al. 2009; Hanson et al. 2011). In the aggregate, these data support the use of interventions to improve coordination of care at all stages of illness and to integrate fundamental nursing precepts, particularly in more advanced stages of dementia.

## CAREGIVERS

### PSYCHOEDUCATION

Providing education to the patient and his or her family about dementia is an important aspect of care, as noted in the 2007 guideline. Patients differ in their ability and desire to understand their diagnosis, so it is important that the family understands the diagnosis and available treatment options.

Interventions have been designed to help informal caregivers manage neuropsychiatric problems in care recipients with dementia, with additional goals of reducing care-

givers' distress and burden. One such intervention, Project Care, teaches informal caregivers specific behavioral techniques to manage patients' neuropsychiatric symptoms in the home environment (Gonyea et al. 2006). In a randomized controlled trial involving 80 caregivers, five weekly sessions helped caregivers with the stress of managing neuropsychiatric symptoms in patients with dementia when compared with a control intervention but did not affect caregivers' overall burden. Other studies published since the 2007 guideline suggest that the benefits of psy-

choeducation and support for caregivers are seen across cultures. In India, a multidisciplinary intervention with counselors and psychiatrists focused on supporting the caregiver by providing information on dementia, helping with management of behavioral problems in the patient, and prescribing psychotropic medications if needed (81 families enrolled in the trial; 41 were randomly assigned to the intervention; 59 completed the trial; and 18 died during the trial). When compared with control subjects, scores on the General Health Questionnaire scale and Neuropsychiatric Inventory–Distress scale were significantly reduced in the caregivers who participated in the intervention (Dias et al. 2008). Likewise, in Hong Kong, a pilot intervention was developed with a treatment program consisting of 13 weekly sessions teaching cognitive-behavioral strategies to handle caregiver stress resulting from disruptive behaviors of the care recipients. Twenty-seven female primary caregivers were randomly assigned to the treatment group or wait-list control group. The caregivers in the intervention were significantly better able to use problem-focused and emotion-focused coping strategies to handle the disruptive behaviors of the care recipients (Au et al. 2010).

Psychoeducational approaches have also been developed to help families and patients cope with decisions related to driving. Although the 2007 guideline recommends that the risks of driving be discussed with patients with dementia and their families, restrictions on driving can produce significant stress. Family caregivers must frequently make the final decision to restrict a cognitively impaired loved one from driving. However, they are often reluctant to do so. Stern and colleagues (2008) developed a group intervention consisting of four 2-hour manualized educational support group meetings to assist caregivers in addressing patients' driving issues. Two months after the intervention was completed, a battery of self-report and interview-based questionnaires showed that caregivers in the intervention group ( $n = 31$ ) scored significantly higher on self-efficacy, communication, and preparedness than participants who were assigned to a control condition (31 participants received written materials only after a pretest; 12 participants received written materials after a posttest). This type of assistance for caregivers may reduce their stress in addressing issues related to their cognitively impaired loved one's driving, but the sample size was small and the intervention is not widely available.

## CAREGIVER DISTRESS

Educating the patient and family about dementia, the stages of progression of the illness, and the associated symptoms

that often accompany dementia is important, but there is limited evidence that education alone is adequate in decreasing caregiver distress and burden. Consequently, interventions that are specifically designed for the caregiver may be necessary. Distress is common in those caring for patients with dementia and may result from physical burdens, financial strain, or psychological issues such as anxiety and depression. The recommendation that clinicians be vigilant for distress remains unchanged from the 2007 guideline.

Interventions to address caregiver distress have been developed and can have positive effects on the well-being of caregivers. Thompson and colleagues (2007) systematically reviewed interventions designed to improve overall quality of life for people caring for someone with dementia. Unfortunately, they found little evidence that interventions aimed at supporting or providing information to caregivers individually were effective. However, they did find evidence that group-based supportive interventions influence psychological morbidity.

Selwood and colleagues (2007) systematically reviewed the effect of various psychological interventions on the psychological health of caregivers. They found that six or more sessions of behavioral management therapy improved the caregivers' psychological health. Cooper and colleagues (2007) systematically reviewed interventions designed to address anxiety in caregivers of people with dementia. They found a paucity of randomized controlled trials directly targeting anxiety. One of the few studies meeting inclusion criteria reported reduced anxiety in caregivers who received CBT and relaxation-based interventions.

Interventions designed to help family caregivers with care planning, such as Tailored Caregiver Assessment and Referral (Kwak et al. 2011), have been found to often have a positive effect on caregiver stress, burden, and depressive symptoms. Interventions directly targeting depression in caregivers have also been shown to be beneficial. One study assessed the efficacy of a 12-session cognitive-behavioral therapy-based program for improving caregivers' dysfunctional thoughts. This intervention improved both dysfunctional thoughts and depressive symptoms in the caregivers participating in the study (Losada et al. 2010; Marquez-Gonzalez et al. 2007). Technology-based psychoeducational interventions for family caregivers have also been found to reduce levels of depression in caregivers (Finkel et al. 2007).

In addition to affecting emotional health, caregiving has an impact on physical well-being and sleep. A randomized controlled trial by Hirano and colleagues (2011) assessed the influence of regular exercise, defined as three exercise sessions per week for 12 weeks, on subjective sense of burden and physical symptoms in a community-based

caregiver sample in 31 elderly caregivers. They found decreased caregiver burden and frequency of feeling fatigued as well as an improvement in self-reported quality of sleep. Elliott and colleagues (2010) developed a structured multicomponent skills training intervention, Resources for Enhancing Alzheimer Caregiver Health. In a randomized, multisite clinical trial involving 495 dementia caregiver and recipient dyads, caregivers reported improved self-rated health, quality of sleep, and both physical and emotional well-being.

Other research suggests that patients who are trained in a memory compensation strategy have greater independence and require less care. In a randomized trial, Greenaway et al. (2013) trained individuals with mild cognitive impairment and their care partners in the use of a notebook/calendar system to help compensate for their memory difficulties. At follow-up, the calendar training group ( $n=20$ ) demonstrated significantly improved function in memory-dependent daily activities compared with controls ( $n=20$ ). They also had improvement in memory self-efficacy. Moreover, mood improved for care partners of the notebook/calendar trainees, whereas caregiving burden worsened for control group partners over time.

## REFERRAL FOR CARE AND SUPPORT

Caring for a family member with dementia can be overwhelming; thus, the 2007 guideline recommends that clinicians refer family members to appropriate sources of care and support. There are a number of community-based support services for caregivers; however, a connection between these services and the professional medical services available is often lacking. Fortinsky and colleagues (2009) designed a process to improve collaboration between primary care physicians and community-based support services. Eighty-four caregivers participated in total, and randomization was based on the patient's primary care physician. Dementia care consultants located at an Alzheimer's Association chapter provided individualized counseling and support over a 12-month period to caregivers in the intervention group and sent copies of the care plans to the referring primary care physicians. Although no significant benefit to caregivers was reported in the intervention group as compared with controls, the caregivers did report a greater satisfaction with the intervention and felt more equipped to manage the patient's behavior. Only 27% of those in the intervention group reported discussing these care plans with their physicians, but nursing home placement was less likely for patients whose caregivers were in the intervention group.

## NURSING HOME PLACEMENT

Despite resources and programs available for caregivers managing loved ones with dementia at home, many caregivers are unable to prevent institutionalizing the patient. The 2007 guideline notes that psychiatrists can be a valuable resource in assisting patients and caregivers with decisions about nursing home placement, and some new research provides continuing support. In a randomized controlled trial, Gaugler and colleagues (2008) provided enhanced counseling and support to 406 spouse caregivers of persons with Alzheimer's disease during transition to a nursing home and followed the spouse caregivers for up to 16 years. After six supportive counseling group sessions followed by ongoing ad hoc telephone counseling, the burden and depressive symptoms in caregivers in the intervention program were significantly lower than those in a usual-care control group, both before and after institutionalization. Spijker et al. (2008) conducted a systematic review with meta-analysis of high-quality studies, with a total of 9,043 patients, on the impact of caregiver support programs on delaying institutionalization and found that these programs reduced the odds of institutionalization (odds ratio=0.60, 95% CI=0.43–0.85;  $p=0.004$ ). Compared with ineffective interventions, effective programs allowed greater caregiver involvement in choosing among treatment options for their family member.

Nursing home placement of a family member with dementia often leads to stress and guilt for the caregiver. Helping family caregivers adjust to the change and maintain a good working relationship with the nursing home staff is important. In a study by Davis and colleagues (2011) assessing a telephone-based psychosocial intervention, caregivers were randomly assigned to the group receiving 10 telephone contacts over 3 months ( $n=24$ ) or to a non-contact control group ( $n=22$ ). Those in the intervention group showed a reduction in feelings of guilt related to the nursing home placement and more positive perception of the nursing home staff compared with controls. In a randomized controlled trial, Robison and colleagues (2007) studied a nursing home-based intervention for 384 family members of residents with dementia and 384 staff members recruited from 20 nursing homes. Training sessions for improved communication and conflict resolution individually and jointly with families and staff resulted in positive outcomes. Both the families and the staff believed communication improved, families were more involved in the nursing home care, and nursing home staff experienced less depression and burnout compared with the control group.



## ALTERNATIVE TREATMENTS

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The past decade has seen widespread interest in dietary, nutraceutical, and alternative medication therapies for Alzheimer's disease and other dementias. Many of these studies lack rigor and are plagued by the lack of a specified primary a priori outcome, multiple outcomes (often across domains of cognition, behavior, and function), lack of power to exclude type 2 error, and lack of randomization or a placebo comparison group. There is not enough definitive new evidence to warrant a change to the 2007 guideline statement that alternative agents are not generally recommended because of uncertain efficacy and safety.

Although cohort and case control studies have found Mediterranean diet, elevated homocysteine, and greater intake of fish or fatty acids and folate to be associated with lower dementia incidence, no adequately designed prospective trial has demonstrated cognitive benefit in individuals with Alzheimer's disease or other dementias (Aisen et al. 2008a; Kwok et al. 2011). Dangour et al. (2010) stated that "the available evidence is insufficient to draw definitive conclusions on the association of B vitamins and fatty acids with cognitive decline or dementia" (p. 205). Other reviews of B vitamins and antioxidants (Jia et al. 2008), homocysteine-lowering B-vitamin supplementation (Balk et al. 2007; Ford and Almeida, 2012) and omega-3 fatty acids (Issa et al. 2006) have come to similar conclusions. A meta-analysis of trials of omega-3 fatty acids also found no effect on cognition in participants (Mazereeuw et al. 2012).

In the 2007 guideline, vitamin E was not recommended for the treatment of cognitive symptoms of dementia because of safety concerns and limited evidence for efficacy. Nevertheless, the guideline also noted that some physicians and their patients may elect to use vitamin E after considering its potential risks and benefits. More recently, possible benefit for vitamin E was found in a double-blind, placebo-controlled, randomized clinical trial involving 613 patients with mild to moderate Alzheimer's disease at 14 Veterans Affairs medical centers (Dysken et al. 2014). Participants received either 2,000 IU/day of alpha-tocopherol ( $n=152$ ), 20 mg/day of memantine ( $n=155$ ), the combination ( $n=154$ ), or placebo ( $n=152$ ). Data from 52 participants were excluded from analysis because of lack of follow-up. Among those patients with mild to moderate AD, 2,000 IU/day of alpha-tocopherol compared with placebo resulted in a slower functional decline of 6.2 months at mean follow-up of 2.27 years. Caregiver burden also decreased, but no significant differences were observed for other outcomes. Furthermore, there were no significant differences in any outcomes for the groups receiving memantine alone or memantine plus alpha-tocopherol in

comparison with the placebo group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of "infections or infestations," with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 31 participants) compared with the placebo group (13 events in 11 participants). Patients taking warfarin were excluded from the study.

Ginkgo biloba has been widely studied since publication of the guideline, with both positive (Ihl et al. 2010; Napryeyenko and Borzenko 2007) and negative (McCarney et al. 2008) findings. Two Cochrane reviews, one published in 2007 (Birks and Grimley Evans 2007) and an updated review in 2009 (Birks and Grimley Evans 2009), found the evidence for ginkgo biloba in individuals with cognitive impairment or dementia to be inconsistent and unreliable. Studies assessing whether ginkgo biloba prevents cognitive decline or dementia have also shown no benefit (DeKosky et al. 2008; Snitz et al. 2009; Vellas et al. 2012). A single, small randomized controlled trial of saffron (Akhondzadeh et al. 2010) showed benefit on the ADAS-Cog. One randomized controlled trial of soybean-derived phosphatidylserine in elderly patients with mild cognitive impairment showed some preliminary evidence for memory improvement, but more research is needed (Kato-Kataoka et al. 2010).

Trials of melatonin for cognitive and noncognitive symptoms have provided insufficient evidence of clinical efficacy and safety (De Jonghe et al. 2010; Jansen et al. 2006). Studies indicated that vitamin D<sub>2</sub> (Stein et al. 2011), oral copper (Kessler et al. 2008), docosahexaenoic acid (Quinn et al. 2010), and Huperzine A (Rafii et al. 2011; Xu et al. 2012) did not improve cognition. Reviews of selenium (Loef et al. 2011) and ginseng (Lee et al. 2009b) also found no evidence for efficacy.

Trials of multiple medical foods for cognition in dementia, including yamabushitake mushroom extract (Mori et al. 2009) and yi-gan san [*yokukan* in Japanese] (Iwasaki et al. 2005; Mizukami et al. 2009; Okahara et al. 2010), did not show cognitive benefits. No adverse effects were observed in these studies.

Since 2007, systematic reviews of available literature found no consistent benefit of shiatsu or acupuncture (Lee et al. 2009a; Robinson et al. 2011); of reflexology, despite some encouraging small studies (Burns et al. 2011; Ernst 2009; Ernst et al. 2011; Hodgson and Andersen 2008; Lin et al. 2007); of transcranial magnetic stimulation, despite some positive smaller studies (Ahmed et al. 2012; Cotelli et al. 2011; Freitas et al. 2011); of cranial electrical stimulation (Rose et al. 2009); or of peripheral electrical stimu-

lation (Scherder et al. 2007). However, a pilot study of a multimodal intervention consisting of Taiji exercises, cognitive-behavioral therapies, and support group participation showed encouraging results in patients with mild dementia (Burgener et al. 2008). In addition, a relatively large study of therapeutic touch showed positive results for rest-

lessness but not for aggression in nursing home patients with dementia (Hawranik et al. 2008; Woods et al. 2009).

Taken together, the evidence supporting most of these alternative management strategies is not sufficient to warrant their routine adoption, but future evidence could change this perspective.

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