ACP Clinical Practice
American College of Physicians
GUIDELINES

Current Pharmacologic Treatment of Dementia: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians

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Description: The American College of Physicians and American Academy of Family Physicians developed this guideline to present the available evidence on current pharmacologic treatment of dementia.

Methods: The targeted literature search included evidence related to the effectiveness of 5 U.S. Food and Drug Administration–approved pharmacologic therapies for dementia for outcomes in the domains of cognition, global function, behavior/mood, and quality of life/activities of daily living.

Recommendation 1: Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. (Grade: weak recommendation, moderate-quality evidence.)

Recommendation 2: Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. (Grade: weak recommendation, low-quality evidence.)

Recommendation 3: There is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia.

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Dementia is a syndrome of acquired cognitive defects sufficient to interfere with social or occupational functioning that results from various central neurodegenerative and ischemic processes (1). With the aging population in the United States, dementia has become an important public health problem. The prevalence of Alzheimer disease is projected to quadruple in the next 50 years to 1 in 45 Americans. In addition, the long duration, caregiver burden, and costs associated with providing care contribute to making dementia a major health care problem.

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The most common types of dementia include Alzheimer disease, vascular dementia, Lewy body dementia, and mixed dementia. At present, there is no cure for dementia. Current pharmacologic interventions are used primarily to delay progression of the syndrome and improve its symptoms. In most cases, dementia affects cognition, behavior, functional activities, and caregiver burden; these are key targets for the therapeutic interventions.

This guideline presents the available evidence on the effectiveness of 5 U.S. Food and Drug Administration (FDA)–approved pharmacologic therapies for dementia for outcomes in the domains of cognition, global function, behavior/mood, and quality of life/activities of daily living. The major types of dementia covered in this guideline include dementia related to Alzheimer disease and vascular dementia. The target audience for this guideline is all clinicians, and the target patient population is all adults with a diagnosis of dementia. These recommendations are based on the systematic evidence review by Raina and colleagues in this issue (2) and the Agency for Healthcare Research and Quality–sponsored McMaster University Evidence-based Practice Center evidence report (1).

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Methods

The literature search was done by the McMaster Evidence-based Practice Center by using electronic resources, including the Cochrane Central Register of Controlled Trials, MEDLINE, PREMEDLINE, EMBASE, Allied and Complementary Medicine Database, CINAHL, AgeLine, and PsycINFO from 1986 to November 2006. In addition to electronic databases, bibliographies of retrieved papers were reviewed for additional papers. Eligible literature included study outcomes in 4 broad domains: cognitive function, global function, behavior, and quality of life (including functional performance and caregiver burden). Other outcomes were rate of institutionalization, mortality, and adverse events. Eligibility criteria for studies were 1) patients with dementia who were 18 years of age or older; 2) diagnosis of dementia using International Classification of Diseases, Ninth or Tenth Revision, and Diagnostic and Statistical Manual of Mental Disorders III, III-R, or IV and various other criteria; 3) interventions restricted to pharmacologic agents, including food supplements administered at least once daily; 4) parallel randomized, controlled trials in English of any sample size; and 5) a score of 3 or greater on the modified Jadad scale. Details about inclusion and exclusion criteria are available in the evidence review (2).

Two independent reviewers completed data abstraction and quality assessment for all included studies. They used the modified Jadad score and adverse event quality checklist to evaluate the methodological quality of eligible studies. Standard meta-analytic techniques were used for data analysis except where they were not suitable to evaluate all outcomes or interventions. The primary scales used to measure the domain of cognition deficits were the Alzheimer's Disease Assessment Scale (ADAS) cognitive subscale (ADAS-cog), noncognitive subscale (ADAS-noncog), and total score (ADAS-tot); Mini-Mental State Examination (MMSE) or standardized MMSE; and the Severe Impairment Battery (SIB). For the domain of global assessment, the primary scale used was clinician-based impression of change (CIBIC) (with caregiver input [CIBIC-plus] and other modified versions).

Clinically Important Improvement versus Statistical Significance

Whereas most studies reported on the statistical significance of changes in scale scores, such as those mentioned, patients with dementia, caregivers, and clinicians are concerned with clinically important improvement. Thus, in addition to evaluating statistically significant changes in scale scores, the guideline panel assessed clinically important effects of treatment regimens. Several studies have used a change of 4 points or more on the ADAS-cog scale to define a clinically important improvement for mild to moderate dementia (2). For the MMSE, a change of 3 points or more is considered clinically important. Any change in score on the CIBIC-plus scale is considered clinical improvement; however, results depend on an individual physician's perception. Details of the methods used for the systematic evidence review are found in the background paper by Raina and colleagues in this issue (2).

Table 1. **The American College of Physicians' Guideline Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I-recommendation	

* Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

This guideline grades its recommendations and evidence by using a system adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup (**Table 1**). The objective for this guideline is to analyze the evidence for the following questions:

1. Does pharmacologic treatment of dementia with any of the 5 FDA-approved drugs improve cognitive symptoms and outcomes?

2. What is the evidence for efficacy of the cholinergic neurotransmitter–modifying agents, such as cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine) and the noncholinergic neurotransmitter– or neuropeptide-modifying agent (memantine) in the treatment of dementia?

Cholinesterase Inhibitors

Donepezil

High-quality evidence was drawn from 24 studies (from 34 publications) that evaluated donepezil compared with placebo or vitamin E (3–27). Most focused on Alzheimer disease, and some focused on vascular dementia (15, 16), Parkinson disease dementia (22), Down syndrome and dementia (3), or mild cognitive impairment (14, 25). In most studies, the severity of dementia was described as probable or mild to moderate, except for 2 studies in which it was moderate to severe (6, 7). Dosages evaluated in the studies ranged from 10 mg/d (3–6, 9, 14, 15, 18–22, 24, 27) to 5 mg/d in 2 studies (12, 26), and 5 studies compared 5-mg and 10-mg dose groups (8–10, 15, 16). The total duration of drug intervention, including titration, varied from 12 to 16 weeks (10, 12, 20), 18 weeks (22), 23 to 24 weeks (3, 6–9, 13–16, 18, 19, 21, 23,

24, 26, 27), 52 to 54 weeks (4, 5), 156 weeks (25), and 2 years with interrupted use of donepezil (17).

All except 3 studies (3, 7, 23) showed a positive effect in at least 1 measure of cognition. Good-quality data showed a statistically significant treatment effect as measured by overall improvement in the ADAS-cog score in individuals with Alzheimer disease and vascular dementia; however, the average change in the ADAS-cog score did not reach a clinically significant level (change ≥4 points). In addition to the statistically significant overall CIBIC-plus score for mild to moderate Alzheimer disease, other measures of global assessment showed improvement in some studies (5–10, 12, 15, 16, 26, 27). Summary estimates for Neuropsychiatric Inventory were not significant in patients with Alzheimer disease (3, 5–7, 18, 22, 27–30). Eight studies showed statistically significant differences for outcomes assessing activities of daily living (4–6, 8, 10, 15, 17, 27); 1 found statistically significant changes in the Bristol Activities of Daily Living Scale, but the changes were not clinically important (17).

Nine of the 24 studies also reported the proportion of patients who achieved a clinically important improvement with donepezil or placebo. These findings are important because although the average improvement in cognition as assessed by the ADAS-cog did not reach statistical significance, a subset of patients may have clinical improvement. Although a larger proportion of patients had a clinically important improvement with donepezil in many of these studies (**Table 2**), whether these differences also reached statistical significance was only reported in 1 trial. In that trial (7), a larger proportion of patients achieved clinically important improvements in cognition as measured by the MMSE (**Table 2**). In addition, 6 of 10 studies also reported that a higher proportion of patients had clinical improvement in global assessment by the CIBIC-plus scale but did not report statistical significance of these differences (**Table 2**).

Withdrawal rates because of adverse events associated with donepezil ranged from 0% to 57% in the treatment groups (0% to 20% in placebo groups). No study showed a statistically significant difference between the treatment and placebo groups for serious adverse events except for the expected side effects of cholinesterase inhibitors (diarrhea, nausea, and vomiting). Six studies reported a dose–response effect with increasing frequency of adverse events as dosage increased (8–10, 15, 16). Nine adverse events had statistically significant effect sizes in patients with Alzheimer disease; diarrhea (relative risk, 2.57) and nausea (relative risk, 2.54) were reported most frequently. For patients with vascular dementia, abnormal dreams, diarrhea, nausea, and muscle and leg cramps were statistically significant; muscle cramps had the largest effect size (relative risk, 9.62), and nausea had the smallest (relative risk, 2.21). The effect sizes for the mild cognitively impaired group were similar to findings in those with vascular dementia, with the addition of insomnia; muscle and leg cramps had the largest effect size (relative risk, 7.73), and nausea had the smallest (relative risk, 2.92). The overall quality of reporting harms was moderate to low.

In summary, the average change in cognitive score (using ADAS-cog, MMSE, and SIB) with donepezil treatment was statistically significant but not clinically important. A subset of 9 studies also reported the proportion of patients who achieved clinically important change. Although these studies suggested that a modestly higher proportion of patients had clinically important improvement in cognition with donepezil, they generally did not report whether these findings were statistically significant. Thus, evidence is insufficient to determine whether a subgroup of patients has a clinically important improvement in cognition with donepezil. Most studies found statistically significant improvements on global assessments, but the clinical importance of these changes is uncertain. Some, but not all, studies found improvements in activities of daily living scores for patients with Alzheimer disease and vascular dementia and no severe adverse effects. Of note, the duration of all but 1 trial was less than 1 year, so the long-term effect of donepezil is unknown.

Galantamine

Ten high-quality studies (from 12 publications) evaluated galantamine (31–40) compared with placebo. Seven studies included only patients with Alzheimer disease, whereas 2 enrolled patients with Alzheimer disease and cerebrovascular disease (31, 32, 35–40). All studies classified individuals as having mild to moderate dementia with a final treatment dose of either 24 mg/d or 32 to 36 mg/d. The length of trials varied from 12 to 16 weeks (34, 36, 39), 20 weeks (37), 24 to 26 weeks (31, 33, 35, 38), and 48 months (40).

For general cognitive function, pooled evidence showed a statistically significant benefit of galantamine on the ADAS-cog (Figure 2 in the evidence report) (2, 31–38); the pooled estimate of improvement did not meet the clinically important threshold of a 4-point change on the ADAS-cog. One trial showed a dose-related effect with statistically significant improvement in ADAS-cog score at 24 mg but not at 32 mg (39). In addition, 6 studies did global assessments with the CIBIC-plus and showed statistically significant improvements. The summary estimate from these studies indicated that improvement in global assessment was more likely (relative risk, 1.23) in patients treated with galantamine (see Figure 4 in the evidence review) (2). Although the magnitude of improvement is difficult to assess, improvements on the CIBIC-plus are generally considered to be clinically important. Evidence for behavior was mixed, with 2 of 5 studies showing statistically significant benefit by using the Neuropsychiatric Inventory; however, the summary estimate (based on 2 studies) was statistically significant. All but 1 study evaluated quality of life; measures on both the Disability Assessment Dementia Scale and the Alzheimer disease Cooperative

Table 2. **Studies That Reported the Proportion of Patients Who Achieved a Clinically Significant Change on 2 Domains of Dementia***

Domain	Donepezil			Galantamine			Rivastigmine		
	Reference	Criterion for Clinically Significant Change in Cognition	Patients Who Experienced a Clinically Significant Change, %	Reference	Criterion for Clinically Significant Change in Cognition	Patients Who Experienced a Clinically Significant Change, %	Reference	Criterion for Clinically Significant Change in Cognition	Patients Who Experienced a Clinically Significant Change, %
Cognition	10	ADAS-cog: ≥4-point change	10 mg: 60 Placebo: 30	33	ADAS-cog: ≥4-point change	24 mg: 35.3 ($P = 0.005$) Placebo: 22.2	50	ADAS-cog: 4-point change	High dose: 24 Low dose: 15 Placebo: 16
Cognition	9	ADAS-cog: ≥4-point change	5 mg: 37.8 10 mg: 53.5 Placebo: 26.8	36	ADAS-cog: 4-point change	24.2–32 mg: 28.3 Placebo: 22			
Cognition	9	ADAS-cog ≥7-point change	5 mg: 15.4 10 mg: 25.2 Placebo: 7.8	37	ADAS-cog: ≥7-point change	16 mg: 15.9 ($P < 0.001$) 24 mg: 22.3 ($P < 0.001$) Placebo: 7.6			
Cognition	7	MMSE: ≥3-point change	Intervention†: 51 Placebo: 36	38	ADAS-cog: ≥4-point change	24 mg: 29 ($P < 0.001$) 32 mg: 32 ($P < 0.001$) Placebo: 15			
Cognition	14	ADAS-cog: ≥4-point change	5–10 mg: 50 Placebo: 31.8						
Cognition	14	ADAS-cog: ≥7-point change	5–10 mg: 22.3 Placebo: 12.1						
Global assessment	15	CIBIC-plus: 1-point change	5 mg: 2 10 mg: 1.5 Placebo: 1	35	CIBIC-plus: 1-point change	24 mg: 1.6 32 mg: 1.2 Placebo: 0.5	46	CIBIC-plus: ≤3-point change	bid: 57 ($P < 0.027$) tid: 36 Placebo: 16
Global assessment	15	CIBIC-plus: 2-point change	5 mg: 6.6 10 mg: 7.7 Placebo: 9.8	35	CIBIC-plus: 2-point change	24 mg: 3.2 32 mg: 2.3 Placebo: 3.6	50	CIBIC-plus: ≤3-point change	High dose: 37 Low dose: 30 Placebo: 20
Global assessment	15	CIBIC-plus: 3-point change	5 mg: 27 10 mg: 19 Placebo: 19.1	35	CIBIC-plus: 3-point change	24 mg: 15.1 32 mg: 12.3 Placebo: 9.7			
Global assessment	11	CIBIC-plus: ≤3-point change	5 mg: 46 10 mg: 36 Placebo: 32	36	CIBIC-plus: 1 point change	24–32 mg: 0.4 Placebo: 0			
Global assessment	16	CIBIC-plus: ≤3-point change	5 mg: 39 10 mg: 32 Placebo: 25	36	CIBIC-plus: 2 point change	24–32 mg: 2.8 Placebo: 0.8			
Global assessment	8	CIBIC-plus: ≤3-point change	5 mg: 43 10 mg: 37 Placebo: 14	36	CIBIC-plus: 3 point change	24–32 mg: 22.6 Placebo: 18.5			
Global assessment	10	CIBIC-plus: ≤3-point change	5 mg: 32 10 mg: 38 Placebo: 18	38	CIBIC-plus: 2 point change	24 mg: 3 32 mg: 5 Placebo: 0.5			
Global assessment	9	CIBIC-plus: ≤3-point change	5 mg: 26 10 mg: 25 Placebo: 11	38	CIBIC-plus: 3 point change	24 mg: 14 32 mg: 20 Placebo: 16			

* ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; bid = twice daily; CIBIC-plus = clinician-based impression of change with caregiver input; MMSE = Mini-Mental State Examination; tid = three times daily.
† Information on dosage was not available.

Study–Activities of Daily Living Scale met criteria for statistical significance.

Of 10 eligible studies of galantamine, 5 reported some information about the proportion of participants who had a clinically important response. Three of the 5 studies also reported statistical significance of these differences in proportions. In each of the 3 studies, treatment with galantamine led to a statistically significant and clinically important improvement (2); 3 reported improvements in cognition with the ADAS-cog, and 1 reported improvement in global assessment with the CIBIC-plus (**Table 2**).

Withdrawal for adverse events for galantamine ranged from 8% to 54% in the treatment group (4% to 17% in the placebo group). Four studies showed a dose–response relationship for adverse events during titration (31, 33, 36, 38). Although most trials did not report statistical analysis of adverse effects, 2 studies reported statistically significant weight loss in the treatment group (35, 38). Commonly

reported adverse effects included gastrointestinal symptoms (nausea, vomiting, and diarrhea), eating disorders/weight loss, and dizziness. The largest effect was for anorexia (relative risk, 3.29), and the least was for dizziness (relative risk, 1.90). Overall, the quality of reporting harms was moderate.

In summary, although the pooled evidence for patients treated with galantamine showed a statistically significant average improvement (pooled estimate) in cognition as measured by the ADAS-cog, this change did not reach the level of clinical importance. However, 3 studies suggested that a subgroup of patients do have a clinically important benefit. This finding should be interpreted cautiously because not all trials reported this outcome and because it was a secondary outcome in the trials that did report it. The duration of trials was less than 1 year; therefore, the long-term outcomes of treatment are unknown.

Rivastigmine

Evidence included 9 high-quality studies (from 11 publications), and all compared rivastigmine with placebo (41–49). Most studies evaluated Alzheimer disease, 1 included dementia associated with Parkinson disease (44), and 1 included Lewy body dementia (47). All levels of severity were analyzed, and dosages ranged from 1 mg/d (43) to 12 mg/d (30, 44, 45, 47, 49) or greater than 18 mg/d (42). The duration of treatment ranged from 14 to 52 weeks.

Rivastigmine had a statistically significant beneficial effect on cognitive function in some individual trials. However, when calculating the overall summary effect for trials that provided sufficient data on the ADAS-cog, the change score at 6 mg and 12 mg for all severity levels in Alzheimer disease was statistically significant but highly inconsistent. Evidence from global assessment by using the CIBIC-plus showed statistically significant and clinically important benefit (41, 43, 44, 46, 48, 49), although 3 studies evaluated only the higher doses. The effect on behavior and quality of life was not statistically significant in any study that evaluated these outcomes.

Five of the 9 studies reported information about the proportion of patients whose improved response to treatment was clinically important. Of the 5 studies, 3 reported the statistical significance of the differences in proportion of responders between placebo and rivastigmine. Each of these 3 studies reported that a statistically significantly higher proportion of patients improved in global assessment as measured by the CIBIC-plus; these changes were considered clinically important (**Table 2**).

Withdrawal rates related to adverse events ranged from 12% to 29% in the treatment group (0% to 11% in the placebo group). The frequency of adverse events between treatment and control groups did not differ. However, 2 studies showed a dose–response relationship for adverse events (43, 49). The types of adverse events were consistent with those related to cholinesterase inhibitor use and included dizziness, nausea, vomiting, eating disorder/weight loss, and headache. The harm with the greatest effect size was vomiting (relative risk, 6.06); that with the smallest effect size was dizziness (relative risk, 2.24).

In summary, use of rivastigmine did not improve cognition as measured by the ADAS-cog but did result in clinically important improvements as measured by global assessment with the CIBIC-plus. Behavior and quality-of-life outcomes did not significantly improve. Because the duration of trials was less than 7 months, the long-term effects of treatment with rivastigmine are not known.

Tacrine

Evidence from 7 moderate-quality studies (from 17 publications) was used to evaluate tacrine (50–56): 6 compared tacrine with placebo (50–55), and 1 compared tacrine with idebenone (56). One trial assessed patients with primary degenerative dementia and Alzheimer disease; the rest included individuals with Alzheimer disease. Severity of dementia varied from mild to moderate, with treatment dosages varying from 80 mg/d to 160 mg/d. Duration of treatment was 12 to 13 weeks (52, 43, 55), 30 to 36 weeks (50, 51, 54), or 60 weeks (56).

Evidence was insufficient to support a beneficial effect of tacrine on various measures of cognition; only 1 trial showed a statistically significant difference when using the ADAS-cog (50). In addition, no effect on behavior (50–52, 54, 55) or quality of life (50, 53) was observed. Two of 3 trials showed a statistically significant effect on global function, by using various assessment instruments (50, 55).

Two of 7 studies reported information about a proportion of patients who had a clinically important response to treatment, but neither trial reported whether these results were statistically significant.

The withdrawal rate related to adverse events ranged from 0% to 55% in the treatment group (0% to 12% in the placebo group). The evidence showed that adverse events related to tacrine were serious and increased with higher doses. Elevated alanine aminotransferase level and other hepatic abnormalities were reported in 6 of 7 studies. Nausea, vomiting, gastrointestinal problems, and dizziness were reported in addition to the serious liver abnormalities. In general, the quality of collecting harms was moderate to low across studies.

In summary, evidence was insufficient to substantiate beneficial effects of tacrine on various measures of cognition or behavior, with the exception of global assessment in 2 of 3 trials. Evidence also showed serious adverse effects related to tacrine, including liver damage. Duration of trials was less than 1 year.

Neuropeptide-Modifying Agent: Memantine

Evidence from 5 high-quality studies (from 6 publications) was included to evaluate memantine, and all compared memantine with placebo (57–61). In 1 study, individuals also received donepezil for at least 6 months before

random allocation to memantine (62). Studies evaluated Alzheimer disease (60–62), vascular dementia (57, 58), and mixed dementia (59), and severity of dementia ranged from moderate to severe. Duration of trials varied from 24 to 28 weeks, with a dosage of 20 mg/d (57, 58, 60–62). One study (61) lasted for 12 weeks.

A pooled estimate from 3 trials showed that memantine resulted in statistically significant, but not clinically important, improvement on the ADAS-cog scale in cognition for individuals with mild to moderate vascular dementia (57, 58) and mild to moderate Alzheimer disease (61). In addition, patients with moderate to severe Alzheimer disease statistically significantly improved on the SIB scale (60, 62). However, patients with mixed dementia had no difference (59). Summary estimates demonstrated statistically significant change on the CIBIC-plus scale for patients with all levels of severity of Alzheimer disease and vascular dementia with the 20-mg dose. One of 4 studies in which patients were also taking donepezil showed statistically significant improvement in behavior (62). Three of 4 studies that evaluated quality of life found statistically significant improvements, and the summary estimate was statistically significant (59, 60, 62). Two trials evaluated caregiver burden and resource utilization and found statistically significant improvements.

Two of the 6 eligible studies reported information on the proportion of patients who had a clinically important improvement. Only 1 of these trials reported statistical significance, and that trial did not find a statistically significant change.

The withdrawal rates related to adverse effects varied from 9% to 12% in the treatment group (7% to 13% in the placebo group), including nausea, dizziness, diarrhea, and agitation.

In summary, memantine showed statistically significant, but not clinically important, improvement in cognition scores for moderate to severe Alzheimer disease, as well as all levels of severity for Alzheimer disease and vascular dementia, as measured by the ADAS-cog. Summary estimates of global assessment with the CIBIC-plus were statistically significant. Limited evidence shows improvement in quality of life, caregiver burden, and resource utilization.

Studies of Comparative Effectiveness

Donepezil versus Galantamine

Two studies compared donepezil (10 mg/d) with galantamine (28, 63). Both studies focused on Alzheimer disease, with 1 describing severity of dementia as mild to moderate (63). The duration of the studies were 8 weeks (63) and 52 weeks (28). The results from the longer study showed no statistical differences in the primary outcome of function (measured with the Bristol Activities of Daily Living Scale) (28). However, changes in secondary outcomes of cognition (measured with the ADAS-cog and MMSE) showed statistical differences favoring galantamine in patients with MMSE scores between 12 and 18 only. The most frequently reported adverse events were nausea, agitation, vomiting, headache, and falls (28). The rates for adverse events were marginally higher for galantamine but were not statistically evaluated. Serious adverse events did not differ between galantamine and donepezil.

Donepezil versus Rivastigmine

One large trial compared donepezil (up to 10 mg/d for 2 years) with rivastigmine (up to 12 mg/d for 2 years) and focused on patients with moderately severe Alzheimer disease for more than 2 years (29, 30). The results statistically significantly differed in global function (Global Deterioration Scale) and function (Alzheimer disease Co-operative Study–Activities of Daily Living Scale), favoring rivastigmine. A subgroup analysis of patients age 75 years or older versus those younger than 75 years showed statistical differences in some measures of behavior and function, favoring rivastigmine. Comparison of adverse events showed that rivastigmine had higher rates of nausea during titration and maintenance phases. In general, patients receiving rivastigmine reported more adverse events than those receiving donepezil, but no differences in serious events were observed.

Summary

Pharmacologic therapeutic interventions of the 5 FDA-approved drugs discussed in the review have shown statistically significant improvement in scores on various instruments to evaluate changes in patients with dementia. Most of these outcomes are not used in routine clinical practice, and interpretation of the clinical importance of improvements is challenging. Many of the improvements demonstrated in the trials, although statistically significant, were not clinically important or their relative importance cannot be determined at this time. Evidence of improvement on global assessment was available for donepezil, galantamine, rivastigmine, and memantine, although changes were generally modest. The evidence about effects on quality of life was mixed. Evidence for tacrine was less convincing, especially in the presence of serious adverse effects. Adverse events related to the other cholinesterase inhibitors were more tolerable. No convincing evidence demonstrates that one therapeutic treatment is more effective than another. The duration of trials in most cases was less than 1 year.

Recommendations

Recommendation 1: Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. (Grade: weak recommendation, moderate-quality evidence.)

The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. In particular, in more advanced dementia, family or other decision makers may not view stabilization or

slowing of decline as a desirable goal if quality of life is judged to be poor. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. However, limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvements. These findings should be interpreted cautiously because many trials did not report the proportion of patients who achieved clinically important improvements, and for trials that did, these outcomes were often not the primary end point of the trial. In addition, many trials that did report the proportion of patients who achieved clinically important improvements did not report the statistical significance of these findings. Currently, we have no way to predict which patients might have a clinically important response. Therefore, the evidence does not support prescribing these medications for every patient with dementia.

Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months on the basis of duration of trials. This effect could be an improvement or stabilization. In addition, no evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. However, if slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate.

Recommendation 2: Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. (Grade: weak recommendation, low-quality evidence.)

Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Therefore, tolerability, adverse effect profile, ease of use, and cost of medication are reasonable criteria to help select a treatment. For example, when the benefits and harms related to a drug are being evaluated, the severe side effects associated with tacrine make it an unreasonable choice.

Cholinesterase inhibitors discussed in this guideline are approved for treatment of mild to moderate dementia, and memantine is approved by the FDA for the treatment of moderate to severe Alzheimer disease. Patients with mild vascular dementia have shown mild benefit from memantine. However, memantine use in mild Alzheimer disease has not been well studied. Major contraindications of cholinesterase inhibitors and memantine include, but are not limited to, uncontrolled asthma, angle-closure glaucoma, the sick sinus syndrome, and left bundle-branch block.

Recommendation 3: There is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia.

Further research is needed to evaluate the effectiveness of pharmacologic therapy for dementia and to assess whether treatment affects outcomes, such as institutionalization. Evaluation of the appropriate duration of therapy and more head-to-head comparisons of agents are needed. Finally, assessment of the effectiveness of combination therapy is lacking.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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