Annals of Internal Medicine | Clinical Guidelines

Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline

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Background: The effectiveness of the 5 U.S. Food and Drug Administration–approved pharmacologic therapies for dementias in achieving clinically relevant improvements is unclear.

Purpose: To review the evidence for the effectiveness of cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine) and the neuropeptide-modifying agent memantine in achieving clinically relevant improvements, primarily in cognition, global function, behavior, and quality of life, for patients with dementia.

Data Sources: Cochrane Central Register of Controlled Trials, MEDLINE, PREMEDLINE, EMBASE, Allied and Complementary Medicine Database, CINAHL, AgeLine, and PsycINFO from January 1986 through November 2006.

Study Selection: English-language randomized, controlled trials were included in the review if they evaluated pharmacologic agents for adults with a diagnosis of dementia, did not use a crossover design, and had a quality score of at least 3 on the Jadad scale.

Data Extraction: Data were extracted on study characteristics and outcomes, including adverse events. Effect sizes were calculated and data were combined when appropriate.

Data Synthesis: 96 publications representing 59 unique studies were eligible for this review. Both cholinesterase inhibitors and memantine had consistent effects in the domains of cognition and global assessment, but summary estimates showed small effect sizes. Outcomes in the domains of behavior and quality of life were evaluated less frequently and showed less consistent effects. Most studies were of short duration (6 months), which limited their ability to detect delay in onset or progression of dementia. Three studies directly compared different cholinesterase inhibitors and found no differences in cognition and behavior.

Limitations: Limitations of available studies included short duration, inclusion of only patients with mild to moderate Alzheimer disease, poor reporting of adverse events, lack of clear definitions for statistical significance, limited evaluation of behavior and quality-of-life outcomes, and limited direct comparison of different treatments.

Conclusions: 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.

Ann Intern Med. 2008;148:379-397. www.annals.org
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Dementias have become a major public health concern because of their increasing prevalence, chronicity, caregiver burden, and high personal and financial costs of care. Currently, there are no cures for most dementias. For the most common types (Alzheimer disease, vascular dementia, and mixed dementias), clinicians often prescribe pharmacotherapy to alleviate symptoms and delay disease progression. The pharmacotherapeutic agents available to treat problems associated with dementias (for example, psychosis) have varying levels of evidence to support their efficacy and have been reviewed elsewhere (1). Some drugs, although not approved, are being used in populations with mild cognitive impairment; in such patients, the rate of conversion to dementias is 0.3 to 2.3 per 100 person-years (2). Currently, 5 drugs have U.S. Food and Drug Administration (FDA) approval for managing dementias. The cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine) degrade acetylcholinesterase, allowing levels of acetylcholine (a neurotransmitter critical to the neurons involved in cognition) to increase. Memantine partially blocks the *N*-methyl-D-aspartic acid receptor and prevents excess stimulation of the glutamate system, which influences memory and learning. Although FDA approval specifies use of these 5 drugs for Alzheimer disease, in clinical practice the drugs are also prescribed for other dementias.

This review systematically evaluates the evidence for the effectiveness of these 5 drugs in improving outcomes in cognition, global function, behavior, and quality of life among patients with dementia.

Methods

Search and Selection

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, PREMEDLINE, EMBASE,

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Allied and Complementary Medicine Database, CINAHL, AgeLine, and PsycINFO for relevant evidence published in English from January 1986 through November 2006. We also reviewed the bibliographies of retrieved papers.

All populations with major dementias (including Alzheimer disease, vascular dementia, and Parkinson dementia) and mild cognitive impairment were included. Only parallel randomized, controlled trials that compared a cholinesterase inhibitor or memantine with placebo or another drug were eligible. We excluded crossover trials because of potential bias due to period effects or period-by-treatment interaction. Our content-expert panel reached consensus and established that eligible studies also had to have a minimum modified Jadad score of 3 of 5 (original scale), indicating moderate study quality. Study outcomes primarily encompassed 4 broad domains: cognition, global function, behavior, and quality of life (including activities of daily living [ADLs] and caregiver burden). We classified most clinical outcomes within these 4 domains; other outcomes were rate of institutionalization, mortality, or adverse events. Two independent reviewers evaluated each study for eligibility. **Appendix Table 1** (available at www.annals.org) describes the eligibility criteria in detail.

This systematic review was done in the context of an Agency for Healthcare Research and Quality–funded review that evaluated 92 pharmacologic agents for dementias (1).

Data Abstraction and Quality Assessment

Two independent reviewers abstracted data from and assessed the quality of all studies that met the eligibility criteria. The modified Jadad scale (which includes additional domains that concern collection of adverse events, description of statistical analysis, and reporting of eligibility criteria) (3) and a checklist for the quality of reporting of adverse events were used to evaluate methodological quality; the latter measures included questions on frequency of reporting harms, withdrawals, and method of collection (1).

Data Synthesis and Statistical Analysis

Evaluation of benefit was based on reported changes in the principal outcome within the domains of interest. Although we did not restrict studies by the type of outcome, we did anticipate that some outcomes would be more commonly used in these drug studies. We searched the literature to establish the magnitude of change considered to be clinically important in key outcomes.

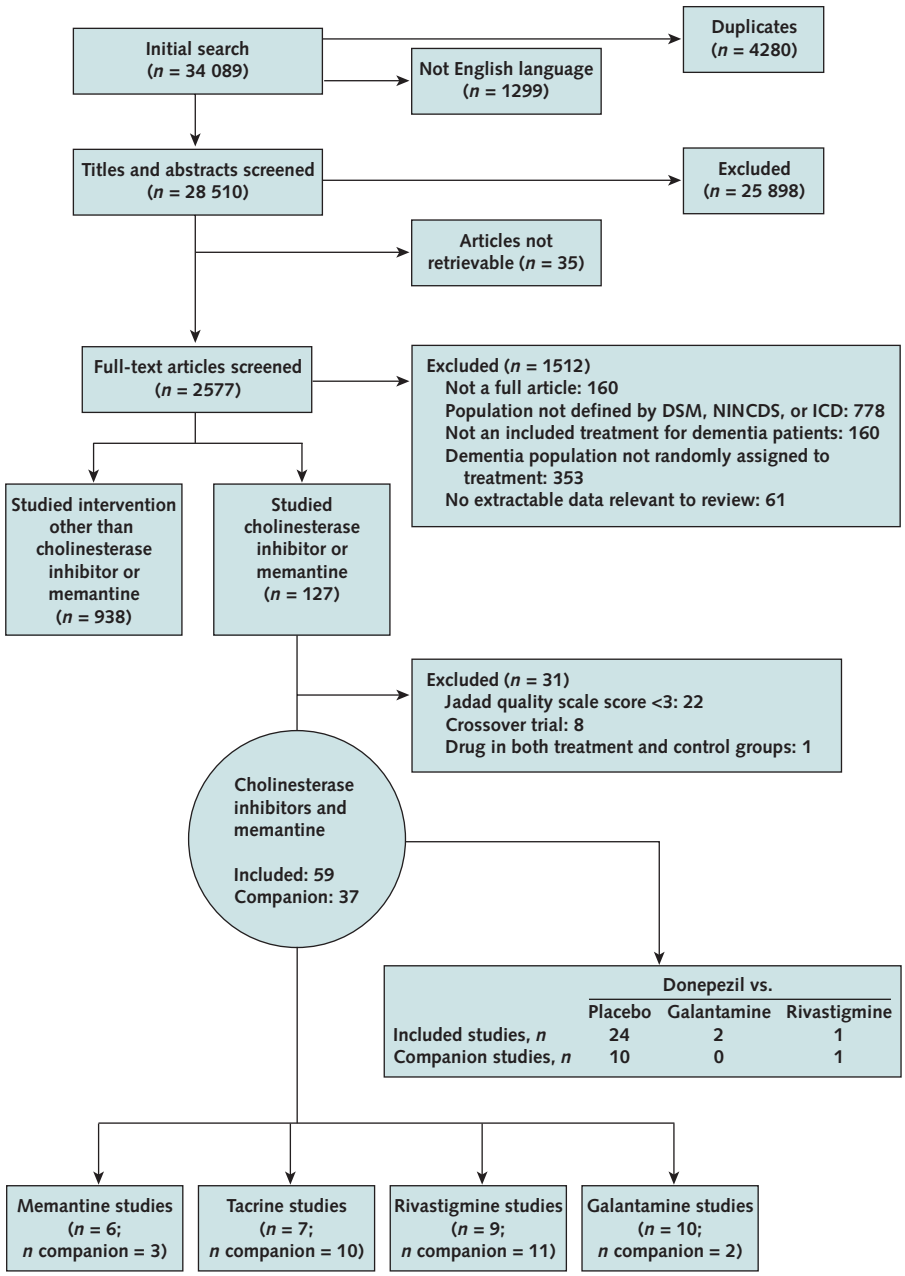
Specifically, within the domain of cognition, we considered the Alzheimer's Disease Assessment Scale (ADAS)—consisting of the cognitive subscale (ADAS-cog), noncognitive subscale (ADAS-noncog), and total ADAS score (ADAS-tot)—the Mini-Mental State Examination (MMSE) (or the standardized MMSE version), and the Severe Impairment Battery (SIB) to be commonly used measures that have established properties and are scored by a trained evaluator or clinician. The ADAS-cog is a validated psychometric assessment scale for the domains of attention, memory, orientation, language ability, and praxis in Alzheimer disease (4). Scores range from 0 to 70, with higher scores indicating greater impairment. A change of 4 points is considered clinically significant for patients with mild to moderate dementia, but the ADAS-cog is not uniformly sensitive to change over the course of the disease (5). The ADAS-noncog evaluates behavioral changes. The MMSE is a widely used measure of cognitive function validated in dementia populations (6). Scores range from 0 to 30, with lower scores indicating greater impairment. The MMSE measures orientation, attention, recall, and language, but it does not evaluate mood or disordered forms of thinking. The SIB is a validated measure of cognitive function for moderate to severe dementias in the areas of orientation, attention, language, and praxis (7). Scores on the SIB range from 0 to 100, with lower scores indicating greater deficits. There are no established clinically important differences for the MMSE or SIB.

For the domain of global function, a commonly used outcome is the clinician-based impression of change (CIBIC), with caregiver input (CIBIC-plus) and other modified versions (New York University–CIBIC-plus, clinician's global impression of change [CGIC], Alzheimer's Disease Cooperative Study CGIC, and clinician interview–based impression). The CIBIC-plus is a validated measure of change that requires a clinician to judge global patient function in 4 areas: general, cognitive, behavioral, and ADLs (8). This measure is scored on a 7-point scale, with 1 reflecting marked improvement, 4 indicating no change, and 7 denoting marked worsening. Because the CIBIC-plus is a global rating by clinicians, any change in score is considered clinically significant. Most other measures commonly used in clinical settings do not have established effect sizes that reflect clinically important differences.

To evaluate adverse effects, we used a standardized instrument that assessed rates of withdrawals due to adverse effects, the method (active vs. passive and standardized vs. nonstandardized approaches) and frequency of collection of harms, and the definition and collection of serious and severe harms. A priori, we selected specific events (nausea, diarrhea, dizziness, accidental injury, agitation, urinary disorder, serious adverse events) and expressed these as a percentage for each study. Where 2 or more studies provided sufficient information, we calculated the summary estimate for the specific adverse event evaluated.

We used standard meta-analytic techniques to estimate effect sizes for each drug in studies with the same outcomes. The effect measure selected varied according to the manner in which the outcome was reported and included change scores or, for dichotomous data, relative risks (RRs). Reasonableness of pooling was assessed on clinical and biological grounds in terms of clinical heterogeneity (drugs, similarity of populations, and outcomes); therefore, meta-analysis was not appropriate for all outcomes. We did not include summary estimates when studies provided only end point scores. Similarly, we excluded studies that did

Figure 1. **Study flow diagram.**



The term *companion* refers to multiple reports from a single study. The authors considered the first published study as the main paper and referred to all associated reports as "companion papers." DSM = *Diagnostic and Statistical Manual of Mental Disorders*; ICD = International Classification of Diseases; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke.

not provide a measure of variance for outcomes when computing summary estimates.

When meta-analyses were undertaken, the weighted mean difference (WMD) was selected as the pooled estimate instead of the standardized mean difference. When only the proportions of patients whose condition improved or worsened were reported, the RR was used as a measure of the summary effect size. In all meta-analyses, a random-effects model was used; tests for statistical heterogeneity were based on the chi-square statistic and the I^2 statistic. In some cases (9–12), estimates of mean changes in the study outcomes used for the meta-analyses were based on best estimates derived from figures in the citations.

RESULTS

Figure 1 shows the process of study selection. Of the papers in the larger review, 127 evaluated donepezil, galantamine, rivastigmine, tacrine, and memantine. We ex-

cluded 22 of these that scored less than 3 on the Jadad scale, 8 that were crossover trials, and 1 that administered tacrine to both study groups. The **Appendix** (available at www.annals.org) lists all excluded studies. The remaining 96 reports included 59 unique study cohorts. Seventy-five different outcomes were measured across the domains of interest. Cognition and global function were the domains from which efficacy was most frequently determined.

Donepezil versus Placebo

Twenty-four unique studies (9, 10, 12–33) from 34 different reports evaluating donepezil versus placebo (or vitamin E) were eligible for this systematic review. Three additional studies (4 reports) directly compared donepezil with galantamine (34, 35) and rivastigmine (36, 37) and are discussed in the section on comparative effectiveness. **Appendix Tables 2**, **3**, and **4** (available at www.annals.org) describe study characteristics and outcome effect sizes, the frequencies of a priori–selected harms, and all reported adverse events. A total of 7556 participants (sample size, 12 to 818 participants) were randomly assigned in these placebo-controlled trials. Most studies addressed Alzheimer disease, with fewer focusing on vascular dementia (22, 23), Parkinson dementia (28), dementia in patients with the Down syndrome (12), or patients with mild cognitive impairment (21, 32). Dementia severity was described as "probable" or mild to moderate in most studies, moderate to severe in 2 studies (14, 16), and severe in 1 study (33). Many studies inaccurately used the term *probable* to describe severity rather than a measure of diagnostic certainty. Most studies evaluated daily doses of 10 mg (10, 12–16, 20, 21, 25–30, 32, 33), whereas 2 studies used 5 mg or less daily (19, 31). Five studies compared 5-mg and 10-mg doses (9, 17, 18, 22, 23), and 1 study (24) presented combined data. The duration of the drug intervention (including titration) was 12 to 16 weeks (18, 19, 26), 18 weeks (28) to 23 or 24 weeks (9, 10, 12, 14, 16, 17, 20–23, 25, 27, 29–31, 33), 52 to 54 weeks (13, 15), or 156 weeks (32). One long-term study (33) reported 2-year follow-up, but participants did not receive donepezil continuously.

All studies that compared donepezil with placebo evaluated some form of cognitive outcome, and all but 3 of these studies (12, 16, 29) showed a positive effect in at least 1 measure used in this domain. Four trials (20, 21, 28, 31) evaluated more than 1 outcome in the cognition domain, and results varied. **Figure 2** shows summary estimates of effect sizes for the ADAS-cog at the highest dosage (10 mg/d) and across all levels of disease severity. The summary effect sizes were largest in patients with Alzheimer disease, next largest in those with vascular dementia, and smallest in those with mild cognitive impairment; no group achieved a change of 4 points (the change considered clinically significant) (5). The meta-analysis (**Figure 2**) shows a consistent and statistically significant treatment effect for improvement in the ADAS-cog; the exception is patients with mild cognitive impairment, in whom the effect was nonsignificant ($P = 0.31$). However, tests for heterogeneity were also significant for this group ($I^2 = 75.5\%$; $P = 0.043$). The length of these two trials differed appreciably (from 6 months to 3 years), as did their criteria for mild cognitive impairment.

Table 1 shows summary effect sizes for the MMSE and the SIB among patients with Alzheimer disease and vascular dementia. Consistent statistically but not clinically significant effects were observed.

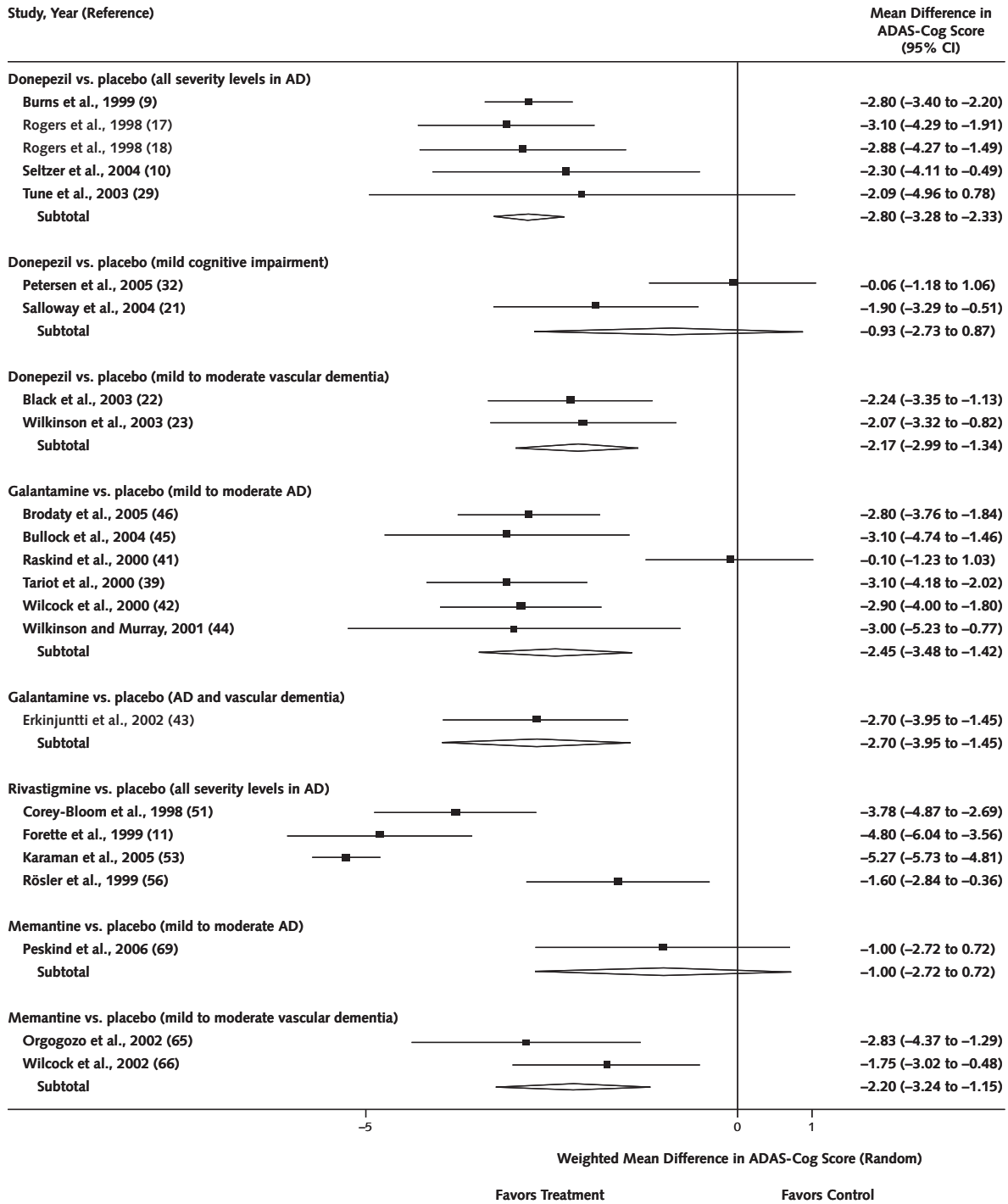
All but 8 studies (15, 20, 24–27, 29, 30) used some measure of global function assessment. All but 4 trials (10, 12, 21, 28) showed a statistically significant difference in this domain. One study (32) evaluating a population with mild cognitive impairment showed significant differences at 18 but not 36 months. On the basis of 3 studies that provided sufficient information, the summary RR for improvement (CIBIC score, 1 to 3) relative to baseline for the CIBIC-plus (**Figure 3**) in patients with Alzheimer disease indicates a significant improvement (RR, 2.01 [95% CI, 1.58 to 2.57]). The magnitude of the effect decreased in 1 study that dichotomized the CIBIC-plus score as improved or stabilized (CIBIC score, 1 to 4) and deteriorated (CIBIC score, 5 to 7). The summary RR estimate for improvement or stabilization of vascular dementia was not statistically significant and showed moderate heterogeneity; however, this estimate was based on only 2 trials. **Table 1** shows the summary estimate (WMD) for 4 studies that provided the mean change scores for the CIBIC-plus; this estimate also showed statistical significance. In addition, **Table 1** shows improvement in the WMD for the Clinical Dementia Rating scale, another measure of global function; however, the tests for heterogeneity were significant.

Of the 9 studies that evaluated behavior, all but 1 used the Neuropsychiatric Inventory (10). Summary estimates for this outcome were not significant in patients with Alzheimer disease (**Table 1**).

Eight (9, 13–15, 18, 22, 24, 33) of 12 studies showed statistically significant improvement in the various outcomes assessing ADLs. However, only 2 studies used the same outcome to allow computation of a summary estimate. **Table 1** shows the summary estimate for the Alzheimer's Disease Functional Assessment and Change Scale. The effect size is small and of borderline statistical significance ($P = 0.053$) for patients with vascular dementia. With the exception of 3 studies (9, 24, 33), ADLs were evaluated as a secondary quality-of-life outcome. Courtney and colleagues (24) found statistically significant changes in the Bristol Activities of Daily Living score, but this difference was not clinically significant (a threshold had been set a priori as an absolute change of 3 points).

One large trial (24) measured rate of institutionalization as the primary outcome but did not show statistically significant differences. This study had the longest duration (2 years) of any trial, but there were anomalies in the design. After initial randomization, patients in the donepezil group had treatment interruptions (described as washout

Figure 2. **Summary estimates for the change in Alzheimer's Disease Assessment Scale–cognitive subscale (*ADAS-cog*) scores.**



For donepezil (10 mg/d) versus placebo (Alzheimer disease [*AD*], all severity levels), the estimate was statistically significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 0.0\%$; $P = 0.94$). For donepezil (10 mg/d) versus placebo (mild cognitive impairment), the estimate was not significant ($P = 0.31$) and tests for heterogeneity were significant ($I^2 = 75.5\%$; $P = 0.043$). For donepezil (10 mg/d) versus placebo (mild to moderate vascular dementia), the estimate was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 0.0\%$; $P = 0.84$). For galantamine (24 mg) versus placebo (mild to moderate AD), the estimate was significant ($P < 0.001$) and tests for heterogeneity were significant ($I^2 = 75.5\%$; $P = 0.001$). For galantamine (24 mg) versus placebo (mild to moderate AD and vascular dementia), the estimate was significant ($P < 0.001$). For rivastigmine (6 mg and 12 mg) versus placebo (AD, all severity levels), the estimate was significant ($P < 0.001$) and tests for heterogeneity were significant ($I^2 = 90.8\%$; $P < 0.001$). For memantine (20 mg) versus placebo (mild to moderate AD), the estimate was not significant ($P = 0.25$). For memantine (20 mg) versus placebo (mild to moderate vascular dementia), the estimate was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 11.4\%$; $P = 0.29$).

Table 1. **Summary Effect Sizes for Outcomes of Benefit Computed for Donepezil in at Least 2 Studies**

Outcome Measures	Studies, *n* (Reference)	Limitations	Consistency of Effects
Donepezil vs. placebo for Alzheimer disease, all severity levels			
Outcomes of benefit			
ADAS-cog	10 (9, 10, 17–20, 26, 27, 29, 30)	No serious limitations	No important inconsistency (I^2 = 0.0%)
MMSE	14 (10, 13–20, 24, 25, 28, 31, 33)	No serious limitations	High inconsistency (I^2= 55.6%)
CIBIC-plus	4 (9, 14, 17, 18)	No serious limitations	No important inconsistency (I^2 = 0.0%)
SIB	3 (12, 14, 33)	No serious limitations	No important inconsistency (I^2 = 0.0%)
CDR-SB	6 (9, 10, 16–19)	No serious limitations	High inconsistency (I^2 = 58.0%)
NPI	9 (12, 13, 14, 16, 24, 25, 28, 29, 33)	No serious limitations	Moderate inconsistency (I^2 = 50.2%)
Outcomes of harm			
Anorexia	6 (9, 12, 15–18)	Some limitations	No important inconsistency (I^2 = 0.0%)
Asthenia	6 (10, 13–16, 33)	Some limitations	No important inconsistency (I^2 = 2.0%)
Diarrhea	11 (9, 10, 12, 13–19, 33)	Some limitations	No important inconsistency (I^2 = 15.6%)
Dizziness	9 (9, 10, 12, 13, 14, 16–19)	Some limitations	No important inconsistency (I^2 = 0.0%)
Fatigue	3 (12, 17, 18)	Some limitations	No important inconsistency (I^2 = 4.4%)
Insomnia	6 (9, 10, 12, Fuschillo et al., Homma et al., Kim et al.)†	Some limitations	No important inconsistency (I^2 = 0.0%)
Nausea	11 (9, 10, 12, 13–18, 20, 33)	Some limitations	No important inconsistency (I^2 = 0.0%)
Vomiting	7 (9, 12, 14, 16–18, 20)	Some limitations	Moderate inconsistency (I^2 = 50.4%)
Weight loss	4 (14–16, 18)	Some limitations	No important inconsistency (I^2 = 0.0%)
Donepezil vs. placebo for mild cognitive impairment			
Outcomes of benefit			
ADAS-cog	2 (21, 32)	No serious limitations	High inconsistency (I^2 = 75.6%)
Outcomes of harm			
Abnormal dreams	2 (21, 32)	Some limitations	No important inconsistency (I^2 = 0.0%)
Diarrhea	2 (21, 32)	Some limitations	No important inconsistency (I^2 = 0.0%)
Insomnia	2 (21, 32)	Some limitations	High inconsistency (I^2 = 56.3%)
Muscle cramps and leg cramps	2 (21, 32)	Some limitations	No important inconsistency (I^2 = 0.0%)
Nausea	2 (21, 32)	Some limitations	No important inconsistency (I^2 = 1.7%)
Donepezil vs. placebo for vascular dementia			
Outcomes of benefit			
ADAS-cog	2 (22, 23)	No serious limitations	No important inconsistency (I^2 = 0.0%)
MMSE	2	No serious limitations	No important inconsistency (I^2 = 0.0%)
CDR-SB	2	No serious limitations	No important inconsistency (I^2 = 0.0%)
ADFACS	2	No serious limitations	No important inconsistency (I^2 = 0.0%)
Outcomes of harm			
Abnormal dreams	2 (22, 23)	No serious limitations	No important inconsistency (I^2 = 0.0%)
Diarrhea	2 (22, 23)	No serious limitations	No important inconsistency (I^2 = 0.0%)
Muscle cramps and leg cramps	2 (22, 23)	No serious limitations	No important inconsistency (I^2 = 0.0%)
Nausea	2 (22, 23)	No serious limitations	No important inconsistency (I^2 = 0.0%)

* Outcomes of harms are those with significant effect size. All others evaluated are shown in **Appendix Table 4** (available at www.annals.org). ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADFACS = Alzheimer's Disease Functional Assessment and Change Scale; CDR-SB = Clinical Dementia Rating Sum of the Boxes; CIBIC-plus = clinician-based impression of change, with caregiver input; MMSE = Mini-Mental State Examination; NA = not available; NPI = Neuropsychiatric Inventory; RR = relative risk; SIB = Severe Impairment Battery; WMD = weighted mean difference.
† For full citations of studies by Fuschillo et al., Homma et al., and Kim et al., see the **Appendix** (available at www.annals.org).

periods) and were randomly assigned twice during the trial. The purpose of discontinuation of drug therapy was not clearly specified. A study evaluating patients with mild cognitive impairment showed statistically significant differences in the rate of conversion to Alzheimer disease at 12 months but not at 36 months. Another study (30) showed some statistical differences in certain sleep variables.

Five (9, 15, 17, 18, 32) of 7 studies showed statistically significant differences between groups for diarrhea, nausea, and vomiting, which are consistent with expected effects of cholinesterase inhibitors. Six studies (9, 17, 18, 22, 23, 38) reported a dose–response effect, with increasing frequency of adverse events as dose increased. The summary effect size could be computed for 29 different harms

Table 1—**Continued**

Patients				Magnitude of Effect (95% CI or Reference)	Clinically Significant Difference
Randomly Assigned, *n*	Completed Trial, *n*	Receiving Donepezil, *n/n (%)*	Receiving Placebo, *n/n (%)*		
				$P < 0.001$	
2275	1845	–	–	WMD, −2.83 (−3.29 to −2.37); $P < 0.001$ (9, 10, 17–19, 29)	>4-point change
3532	2439	–	–	WMD, 1.14 (0.76 to 1.53); $P < 0.001$ (10, 13, 14, 16–19, 25, 31, 33)	>3-point change
2049	1658	–	–	WMD, −0.45 (−0.54 to −0.36); $P = 0.000$	Any change
570	468	–	–	WMD, 5.39 (3.26 to 7.52); $P < 0.001$ (14, 33)	NA
2281	1830	–	–	WMD, −0.44 (−0.65 to −0.23); $P = 0.000$	NA
1769	1231	–	–	WMD, −3.99 (−6.85 to −1.12); $P = 0.006$ (14, 25, 29, 33)	NA
–	–	67/921 (7.3)	19/925 (2.1)	RR, 3.21 (1.94 to 5.33)	NA
–	–	65/827 (7.9)	37/789 (4.7)	RR, 1.65 (1.09 to 2.48)	NA
–	–	213/1470 (14.5)	76/1432 (5.3)	RR, 2.57 (1.93 to 3.41)	NA
–	–	91/1128 (8.1)	59/1095 (5.4)	RR, 1.47 (1.06 to 2.03)	NA
–	–	31/331 (9.4)	13/329 (4.0)	RR, 2.24 (1.17 to 4.30)	NA
–	–	89/899 (9.9)	38/859 (4.4)	RR, 2.19 (1.51 to 3.17)	NA
–	–	204/1451 (14.1)	76/1412 (5.4)	RR, 2.54 (1.97 to 3.29)	NA
–	–	98/871 (11.3)	41/874 (4.7)	RR, 2.25 (1.26 to 4.03)	NA
–	–	51/619 (8.2)	28/621 (4.5)	RR, 1.83 (1.18 to 2.86)	NA
1060	973	–	–	WMD, −0.93 (−2.73 to 0.87); $P = 0.31$	>4-point change
–	–	47/385 (12.2)	9/396 (2.3)	RR, 5.36 (2.67 to 10.76)	NA
–	–	78/385 (20.3)	27/396 (6.8)	RR, 2.96 (1.95 to 4.48)	NA
–	–	41/385 (10.6)	12/396 (3.0)	RR, 3.34 (1.27 to 8.80)	NA
–	–	53/385 (13.8)	7/396 (1.8)	RR, 7.73 (3.56 to 16.8)	NA
–	–	41/385 (10.6)	14/396 (3.5)	RR, 2.92 (1.61 to 5.31)	NA
1219	969	–	–	WMD, −2.16 (−3.00 to −1.34); $P < 0.001$	>4-point change
1219	969	–	–	WMD, 1.10 (0.64 to 1.55); $P < 0.001$	>3-point change
1219	969	–	–	WMD, −0.39 (−0.64 to −0.15); $P = 0.002$	NA
1219	969	–	–	WMD, −0.78 (−1.58 to 0.01); $P = 0.053$	NA
–	–	24/421 (5.7)	–	RR, 4.07 (1.54 to 10.74)	NA
–	–	70/421 (16.6)	–	RR, 1.62 (1.13 to 2.34)	NA
–	–	41/421 (9.7)	–	RR, 9.62 (3.48 to 26.58)	NA
–	–	69/421 (16.4)	–	RR, 2.21 (1.47 to 3.34)	NA

in studies of Alzheimer disease, 11 for vascular dementia, and 6 for mild cognitive impairment; these effect sizes were based on 2 studies for these latter 2 patient populations but a variable number of studies for the patients with Alzheimer disease. Many of the effect sizes were not statistically significant (**Appendix Table 4**). Of the 29 different adverse effects examined in patients with Alzheimer dementia, 9 had statistically significant effect sizes. Diarrhea (RR, 2.57 [CI, 1.93 to 3.41]) and nausea (RR, 2.54 [CI, 1.97 to 3.29]) were reported most frequently. Anorexia had the largest effect size (RR, 3.21 [CI, 1.94 to 5.33]) and dizziness the smallest (RR, 1.47 [CI, 1.06 to 2.03]). The pooled estimate for vomiting was moderately heterogeneous. For patients with vascular dementia, abnormal dreams, diarrhea, nausea, and muscle and leg cramps were statistically more frequent with donepezil; muscle cramps had the highest RR (9.62 [CI, 3.48 to 26.58]). The effect sizes for the group with mild cognitive impairment were similar to those for patients with vascular dementia, with the addition of insomnia.

Rates of withdrawal due to adverse events ranged from 0% to 57% in treatment groups and 0% to 20% in placebo groups (**Appendix Table 2**). In general, the quality of reporting harms was low to moderate in all but 2 trials (22, 23) evaluating vascular dementia. The methods of recording harms varied; 10 trials did not specify the mode (13, 20, 21, 23, 26, 29–33), and a minority used standardized instruments (12, 16, 17, 19, 27, 28). Six trials specified an operational definition of serious adverse events (14, 16, 17, 19, 23, 33); however, no serious harms were attributed to donepezil in any study.

Galantamine

We included 10 studies (12 reports) of galantamine (39–48) that evaluated 3997 patients total (sample size range, 182 to 978 patients). All but 3 of the studies (43, 45, 47) included only patients with Alzheimer disease. Two studies enrolled patients with Alzheimer disease and cerebrovascular disease, and 1 included only patients with mild cognitive impairment (47). All studies aimed for a final treatment dose of 24 mg or 32 or 36 mg/d (1 study used 32 mg/d and 1 used 36 mg/d). One study (46) compared extended-release galantamine with the usual formulation. Trials lasted 12 to 16 weeks (40, 44, 47), 20 weeks (39), and 24 to 26 weeks (41–43, 45, 46) (**Appendix Table 2**). One trial (48) evaluated the difference between a 3-day and a 7-day washout period when patients were switched from donepezil to galantamine; the subsequent follow-up lasted 48 months.

Eight trials (39–43, 45–47) showed significant improvement in cognitive function. One trial (44) reported mixed effects—improvement on the ADAS-cog with 24 mg but not with 32 mg. Another study (48) of the length of 2 washout periods showed no difference between groups, suggesting that the washout period had no effect on cognition. **Figure 2** shows the summary estimate for improvement on the ADAS-cog with 24 mg (currently the maximum dose recommended by the manufacturers); this finding was statistically significant, but so were tests for heterogeneity. One small study (47) evaluated patients with mild cognitive impairment and found significant changes after 4 months.

Of the 6 studies that evaluated global function with the CIBIC-plus, all but 1 (46) showed significant changes relative to placebo (**Table 2**). **Figure 3** shows the summary estimates for the CIBIC-plus with 24 mg, and the summary RR for improvement or stabilization from baseline was 1.22 (CI, 1.12 to 1.33), a statistically significant finding with minimal heterogeneity.

Five studies (39, 40, 43, 45, 46) measured behavior using the Neuropsychiatric Inventory. The summary estimate of improvement based on the 2 studies that reported sufficient data was significant (**Table 2**) and shows no important inconsistency.

Five studies (40–43, 45) used the Disability Assessment for Dementia to measure ADLs. Only 2 were included in the summary estimate; this improvement was statistically significant. Two studies used the Alzheimer's Disease Cooperative Study–ADL subscale, and the summary effect was also statistically significant (**Table 2**).

The most common harms reported in galantamine studies were gastrointestinal symptoms (nausea and vomiting, diarrhea), eating disorders or weight loss, and dizziness (**Appendix Table 3**). **Table 2** shows that the effect sizes for all these harms were significant, with anorexia having the largest effect (RR, 3.41 [CI, 2.36 to 4.93]) and dizziness the smallest (RR, 1.90 [CI, 1.43 to 2.51]). One study (49) evaluated a subgroup of patients who reported nausea or vomiting and found that women and patients with lower body weight at baseline were more likely to report these adverse events. Most trials did not report statistical testing of adverse events for differences between groups, but 2 trials (41, 42) reported a statistically significantly greater weight loss in the treatment groups. Some studies (40, 42, 43, 46) showed a dose–response relationship for adverse events during titration.

Rates of withdrawal due to adverse events ranged from 4% to 17% for placebo and 8% to 54% for active treatment. Although not consistently reported for half the studies, no important differences emerged in the rates of serious adverse events between the placebo and galantamine groups. Most studies did not report using a standardized instrument to collect harms, but some (39, 41, 42, 45) used standardized coding to classify adverse events.

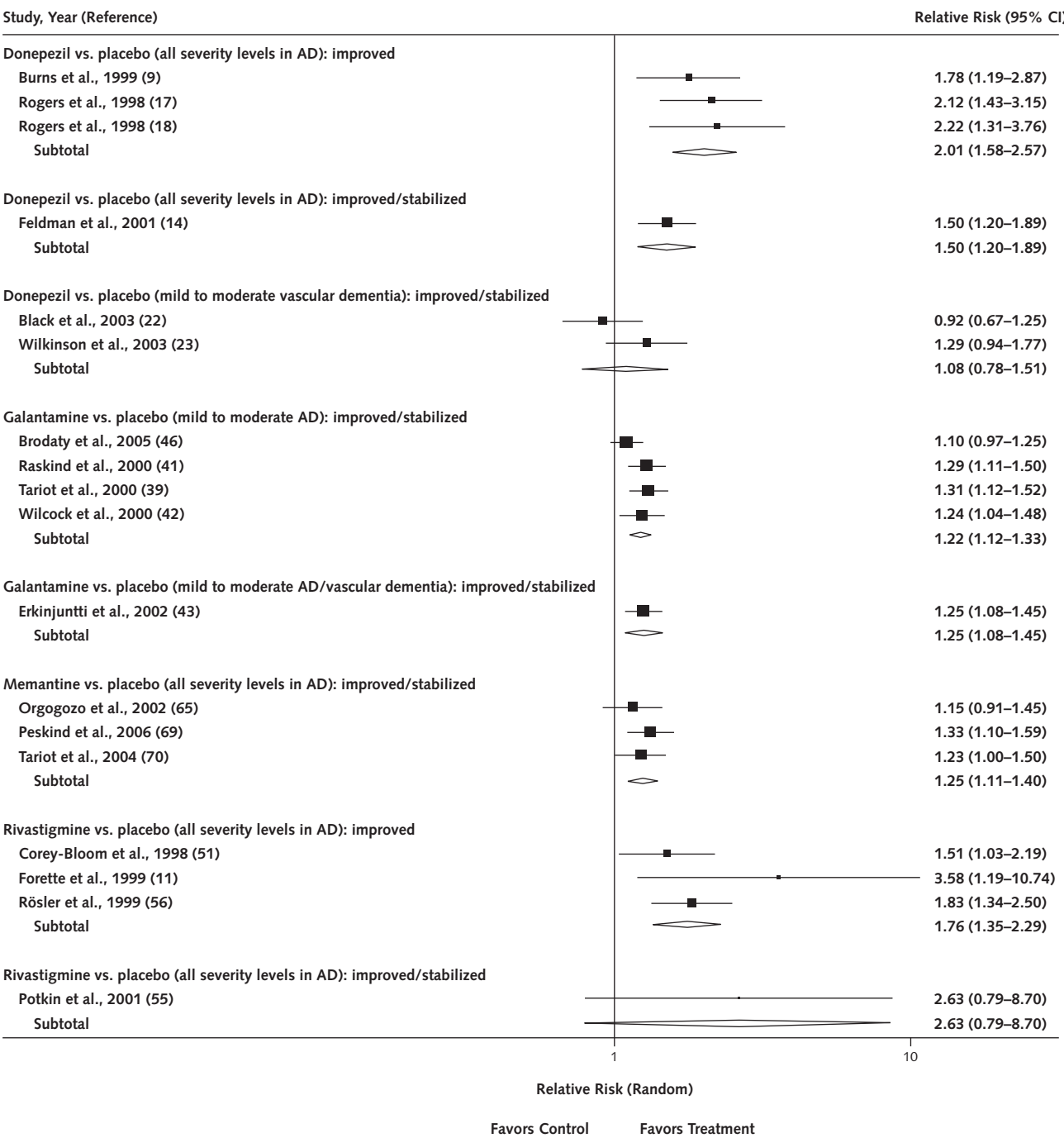
Rivastigmine

Nine eligible studies (11, 50–57) (11 reports) compared rivastigmine with placebo. These studies evaluated 2164 patients, with sample sizes ranging from 27 to 725. One trial (52) evaluated dementia associated with Parkinson disease, 1 study (54) evaluated Lewy body dementia, and the remainder evaluated Alzheimer disease. These studies included all levels of severity. Daily rivastigmine doses ranged from 1 mg (51) to 12 mg (11, 52–54, 56), and treatment lasted 14 to 52 weeks.

Eight studies evaluated general cognitive function. Those using the ADAS-cog (11, 51–53, 56) showed statistically significant improvement, whereas those using other measures (SIB, specific neuropsychological tests) did not. Two studies (51, 56) (1 North American and 1 European site) of the same protocol had different findings: one (51) found improvements with both higher (6 to 12 mg) and lower (1 to 4 mg) doses, but the other (56) failed to show significance for the lower doses. **Figure 2** shows the summary estimate for trials that provided sufficient data on the ADAS-cog for all levels of severity and mixed doses. The effect was statistically significant and larger, but with significant heterogeneity. **Table 3** shows the summary estimate for the MMSE, which was not significant and showed a high level of heterogeneity.

For global changes, 7 (11, 50–53, 55, 56) of 8 studies showed significant improvements, but 3 studies used the

Figure 3. **Summary relative risks for improvement or stabilization from baseline on the clinician-based impression of change scale, with caregiver input.**



For donepezil versus placebo (Alzheimer disease [*AD*], all severity levels), the relative risk (RR) for improvement was statistically significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 0.0\%$; $P = 0.762$). For donepezil versus placebo (AD, all severity levels), the RR for improvement or stabilization was significant ($P < 0.001$). For donepezil versus placebo (mild to moderate vascular dementia), the RR for improvement or stabilization was not significant ($P = 0.633$) and tests for heterogeneity were not significant ($I^2 = 55.1\%$; $P = 0.136$). For galantamine versus placebo (mild to moderate AD), the RR for improvement or stabilization was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 19.9\%$; $P > 0.20$). For galantamine versus placebo (mild to moderate AD and vascular dementia), the RR for improvement or stabilization was significant ($P = 0.002$). For memantine versus placebo (AD, all severity levels), the RR for improvement was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 0.0\%$; $P > 0.20$). For memantine versus placebo (AD, all severity levels), the RR for improvement or stabilization was significant ($P < 0.001$) and tests for heterogeneity were not significant ($I^2 = 13.8\%$; $P > 0.20$). For rivastigmine versus placebo (AD, all severity levels), the RR for improvement or stabilization was not significant ($P = 0.114$).

Table 2. **Summary Effect Sizes for Outcomes of Benefit and Harm Computed for Galantamine in at Least 2 Studies***

Outcome Measures	Studies, *n* (Reference): Galantamine vs. Placebo for Alzheimer Disease	Limitations	Consistency of Effects
Outcomes of benefit			
ADAS-cog	8 (39, 40, 41, 42, 44–46, 48)	No serious limitations	High inconsistency (I^2 = 75.2%)
CIBIC-plus	5 (39, 40, 41, 42, 46)	No serious limitations	No important inconsistency (I^2 = 0.0%)
NPI	3 (39, 40, 46)	No serious limitations	No important inconsistency (I^2 = 0.0%)
ADCS-ADL	2 (39, 46)	No serious limitations	No important inconsistency (I^2 = 0.0%)
DAD	2 (39, 40, 42)	No serious limitations	No important inconsistency (I^2 = 0.0%)
Outcomes of harm			
Anorexia	6 (39, 40, 41, 42, 45, 46)	Some limitations	No important inconsistency (I^2 = 0.0%)
Dizziness	6 (40, 41, 42, 44–46)	Some limitations	No important inconsistency (I^2 = 0.0%)
Nausea	7 (39, 40, 41, 42, 44–46)	Some limitations	High inconsistency (I^2 = 83.7%)
Vomiting	7 (39, 40, 41, 42, 44–46)	Some limitations	Moderate inconsistency (I^2 = 49.3%)
Weight loss	3 (41, 42, 46)	Some limitations	No important inconsistency (I^2 = 18.8%)

* Outcomes of harms are those with significant effect size; all others evaluated are shown in **Appendix Table 4** (available at www.annals.org). ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study subscale for activities of daily living; CIBIC-plus = clinician-based impression of change scale, with caregiver input; DAD = Disability Assessment for Dementia; NA = not available; NPI = Neuropsychiatric Inventory; RR = relative risk; WMD = weighted mean difference.

higher dose only. One of these 3 (50) defined the higher dosage as 6 mg/d, which was the minimum dosage for the other 2 studies. **Figure 3** shows the summary estimate of the RR for improving from baseline (RR, 1.76 [CI, 1.35 to 2.29]) for CIBIC-plus in 3 studies that provided sufficient information. **Table 3** shows that the CIBIC-plus summary estimate (WMD, −0.36), based on 5 studies, was statistically significant and consistent across studies.

Two studies (11, 50) evaluated behavior using the Nurses Observation Scale for Geriatric Assessment–Mood subscale. Although there were no consistently significant changes in individual trials, the summary effect size estimate (**Table 3**) was significant but showed moderate heterogeneity across studies. The Neuropsychiatric Inventory was used to evaluate patients with different dementias (Parkinson dementia [52] and dementia with Lewy bodies [54]); statistically significant differences between the treatment and placebo groups were found. Three studies (51, 53, 56) that evaluated ADL in patients with Alzheimer disease using the Progressive Deterioration Scale failed to show a significant summary effect size and found moderate heterogeneity (**Table 3**). One study (52) of patients with Parkinson dementia found significant improvement as measured with the Alzheimer's Disease Clinical Scale.

All the summary adverse effect sizes presented in **Appendix Table 4** are statistically significant, except diarrhea. **Table 3** demonstrates that vomiting had the greatest effect size (RR, 6.06 [CI, 3.88 to 9.45]) and that dizziness had the smallest (RR, 2.24 [CI, 1.45 to 3.46]). This finding is consistent with data for the other cholinesterase inhibitors evaluated. Two trials demonstrated a dose response; 1 (56) showed significant differences for rates of nausea and vomiting only, whereas the other (51) found significant differences for all reported adverse events.

Rates of withdrawal due to adverse events ranged from 0% to 11% in the placebo groups and from 12% to 29% in the treatment groups. One trial (55) did not report the withdrawal rates or the types of adverse events observed. One study (11) prescribed antiemetics to increase the tolerance of patients taking rivastigmine. Only 3 trials (50, 51, 56) provided an operational definition of serious adverse events, but overall the frequency of severe adverse events did not differ between the treatment and placebo groups. The quality of reporting for harms varied widely.

Tacrine

Seven studies (17 reports) evaluating tacrine were eligible for this review. Tacrine was compared with placebo in 6 trials (58–63) and with idebenone in 1 (64). The placebo-controlled studies evaluated a total of 1203 randomly assigned patients (range, 13 to 663 patients) (**Appendix Table 2**). All but 1 study (64) included patients with Alzheimer disease; the exception included patients with "primary degenerative dementia" and those with Alzheimer disease. All studies enrolled participants with dementias of mild to moderate severity or specified as "probable" disease. Daily doses ranged from 80 mg/d (60) to 160 mg/d (58). Treatment duration varied from 12 to 13 weeks (60, 61, 63) and 30 to 36 weeks (58, 59, 62) for all placebo-controlled studies, whereas the trial with idebenone (64) treatment lasted 60 weeks.

No summary effect size could be computed for tacrine

Table 2—**Continued**

Patients				Magnitude of Effect (95% CI or Reference)	Clinically Significant Difference
Randomly Assigned, *n*	Completed Trial, *n*	Receiving Galantamine, *n/n (%)*	Receiving Placebo, *n/n (%)*		
4479	3138	–	–	WMD, −2.46 (−3.47 to −1.44); $P < 0.001$ (39, 41, 42, 44–46)	>4-point change
3624	2488	–	–	RR improved or stabilized, 1.22 (1.12 to 1.33) (39, 41, 42, 46)	Any change
2335	1735	–	–	WMD, −1.72 (−3.12 to −0.33); $P = 0.015$ (39, 46)	NA
1949	1447	–	–	WMD, 1.84 (0.68 to 3.00); $P = 0.002$	NA
1036	813	–	–	WMD, 4.20 (2.18 to 6.22); $P = 0.000$	NA
–	–	154/1441 (10.7)	34/1245 (2.7)	RR, 3.41 (2.36 to 4.93)	NA
–	–	158/1222 (12.9)	66/1046 (6.3)	RR, 1.90 (1.43 to 2.51)	NA
–	–	407/1495 (27.2)	124/1332 (9.3)	RR, 2.84 (1.76 to 4.61)	NA
–	–	209/1495 (14.0)	54/1332 (4.1)	RR, 3.27 (2.13 to 5.01)	NA
–	–	51/755 (6.8)	15/748 (2.0)	RR, 3.29 (1.66 to 6.53)	NA

trials because insufficient information was provided or different outcomes were evaluated.

Of the 6 placebo-controlled studies, only 1 (58) that used the ADAS-cog showed statistically significant improvement. Three doses (80, 120, and 160 mg) were compared in 1 trial (58), and only the 120- and 160-mg doses were shown to be statistically significantly better than placebo (mean change in ADAS-cog score, approximately 2 points). The remaining studies used other measures of cognition and showed no difference or inconsistent results; these trials had small sample sizes (12 to 32 participants). One trial (63) that found no statistical difference for general cognitive function was short (12 weeks) and used 80 mg/d, a dosage that another trial showed to be ineffective (58). Three placebo-controlled studies (58, 62, 63) evaluated global function; 2 (58, 63) showed statistically significant improvement. The trial that found no benefit (62) also had inconclusive findings for general cognitive function. Five trials evaluated behavior, and 4 (58–60, 63) showed no difference between groups. Two trials (58, 61) that used different outcomes for quality of life failed to show significant improvement (**Appendix Table 2**). Two studies (59, 61) evaluated caregiver burden and showed no benefit from tacrine.

Appendix Table 3 shows the frequencies of various harms. No studies provided sufficient information on any of these harms to allow us to compute summary effect sizes. Elevated alanine aminotransferase levels or other hepatic abnormality (4% to 13% in the placebo groups; 7% to 67% in the treatment groups [all doses]) was reported in 6 studies, suggesting the potential for serious liver damage. No trial tested for differences in adverse events between treatment and placebo groups. Five of the studies reported nausea and vomiting, gastrointestinal problems, and dizziness; these findings are consistent with other effects of cholinesterase inhibitors.

The proportion of patients withdrawing because of adverse events ranged from 0% to 12% in the placebo groups and 0% to 55% in the treatment groups. Rates of withdrawal were greater with higher doses. In general, the quality of procedures used to collect harms was moderate to low across studies (**Appendix Table 3**). Only 1 study (58) reported methods for reporting adverse events, only half reported the frequency of collection, and no study provided an operational definition of a serious event.

Memantine

Five eligible studies (65–69) (6 reports) compared memantine with placebo (**Appendix Table 2**). In 1 study (70) (3 reports), all participants also received donepezil for at least 6 months before randomization to memantine or placebo. Sample sizes ranged from 166 to 579 (1944 patients total). The study populations included vascular dementia (65, 66), mixed groups (67), and Alzheimer disease (68–70). Half of the studies evaluated mild to moderate disease, and the rest evaluated moderate to severe disease. All but 1 study (68) used a final dosage of 20 mg/d; this study had the shortest duration (12 weeks) compared with the other trials (range, 24 to 28 weeks).

Two studies (65, 66) in patients with mild to moderate vascular dementia showed significant improvement on the ADAS-cog. The summary estimate was also significant (**Table 4**). Two studies (68, 70) found changes on the SIB to be significantly different in patients with moderate to severe Alzheimer disease. In 1 of these trials, patients also received donepezil; the summary effect size was significant but also positive for heterogeneity. Two studies (65, 66), both evaluating vascular dementia, showed varied results

Table 3. **Summary Effect Sizes for Outcomes of Benefit and Harm Computed for Rivastigmine in at Least 2 Studies***

Outcome Measures	Studies, *n* (Reference): Rivastigmine vs. Placebo for Alzheimer Disease, All Severity Levels	Limitations of Studies	Consistency of Effects
Outcomes of benefit			
ADAS-cog	4 (11, 51, 53, 56)	No serious limitations	High inconsistency (I^2 = 90.8%)
CIBIC-plus	5 (11, 51, 53, 55, 56)	No serious limitations	No important inconsistency (I^2 = 0.0%)
MMSE	3 (50, 53, 56)	No serious limitations	High inconsistency (I^2 = 94.6%)
GDS	3 (51, 53, 56)	No serious limitations	No important inconsistency (I^2 = 0.0%)
PDS	3 (51, 53, 56)	No serious limitations	Moderate inconsistency (I^2 = 42.6%)
NOSGER-Mood	2 (11, 50)	No serious limitations	Moderate inconsistency (I^2 = 36.5%)
Outcomes of harm			
Abdominal pain	2 (53, 56)	Some limitations	No important inconsistency (I^2 = 17.6%)
Anorexia	4 (11, 51, 53, 56)	Some limitations	Moderate inconsistency (I^2 = 38.9%)
Dizziness	5 (11, 50, 51, 53, 56)	Some limitations	Moderate inconsistency (I^2 = 39.1%)
Fatigue	2 (51, 56)	Some limitations	No important inconsistency (I^2 = 0.0%)
Headache	4 (11, 50, 53, 56)	Some limitations	No important inconsistency (I^2 = 0.0%)
Malaise	2 (51, 56)	Some limitations	No important inconsistency (I^2 = 0.0%)
Nausea	5 (11, 50, 51, 53, 56)	Some limitations	High inconsistency (I^2 = 91.2%)
Vomiting	5 (11, 50, 50, 51, 53, 56)	Some limitations	No important inconsistency (I^2 = 14.1%)

* Outcomes of harms are those with significant effect size; all others evaluated are shown in **Appendix Table 4** (available at www.annals.org). ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; CIBIC-plus = clinician-based impression of change scale, with caregiver input; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; NA = not available; NOSGER = Nurses' Observation Scale for Geriatric Patients; PDS = progressive deterioration scale; RR = relative risk; WMD = weighted mean difference.

for the MMSE. A single study (68) in patients with Alzheimer disease found no difference in MMSE scores. Another (69) showed significant differences on the ADAS-cog. The summary estimate was not significant (**Table 4**) but was positive for heterogeneity. **Figure 2** shows that in studies that used the ADAS-cog to evaluate patients with vascular dementia, the summary estimate was significant.

Two trials (65, 66) that evaluated patients with vascular dementia did not show significant differences on the CIBIC-plus, and a summary effect size could not be computed. In studies that enrolled patients with Alzheimer disease, the summary effect size was statistically significant (**Table 4**). In 1 of these trials, all patients received donepezil concurrently. **Figure 3** shows that the summary effect size for the CIBIC-plus was statistically significant. This meta-analysis combines patients with Alzheimer disease and those with vascular dementia. Sensitivity analyses showed no change in the summary effect size when the studies were stratified according to the types of dementia.

Of the 5 studies that evaluated behavior, only 2 showed statistically significant differences. However, the summary estimate (**Table 4**) showed a significant effect size for both the Nurses Observation Scale for Geriatric Patients in patients with vascular dementia and the Neuropsychiatric Inventory in patients with Alzheimer disease. One study (70), in which all participants were also taking donepezil, showed improvements in the Neuropsychiatric Inventory caregiver distress subscale at 12 weeks (P = 0.006) but not 24 weeks (P = 0.059).

Three (67, 68, 70) of the 4 studies that evaluated ADLs showed statistically significant differences; the summary effect size for the Alzheimer's Disease Clinical Scale–ADL subscale was also statistically significant (**Table 4**). Two trials (68, 70) evaluated caregiver burden and resource utilization and found statistically significant improvements in patients with moderate to severe Alzheimer disease.

Appendix Table 3 reports the frequencies of various harms. Reported adverse events included nausea, dizziness, diarrhea, and agitation (8% to 32% in the placebo groups; 4% to 18% in the treatment groups [all doses]), and none reported eating disorders. In all but 1 study (69) that evaluated agitation as a potential adverse event, the treatment group experienced less agitation; the pooled estimate was not significant, but memantine showed a protective effect for agitation (**Appendix Table 4**). One trial (65) tested and found no significant differences between the treatment and placebo groups. None of the summary effect size estimates for different harms reported for memantine was statistically significant (**Appendix Table 4**).

All but 1 study (67) reported withdrawal rates; the proportion of patients withdrawing because of any adverse events varied from 5% to 17% in the placebo groups and 8% to 13% in the treatment groups. The quality of methods used to collect and report harms was moderate to high (**Appendix Table 3**); however, no study provided an operational definition of serious events or indicated that a standardized instrument for collection was used.

Studies of Comparative Effectiveness: Donepezil versus Galantamine or Rivastigmine

Two studies (34, 35) compared donepezil (10 mg/d) with galantamine in 251 patients. One study (35) was a pilot undertaken primarily to evaluate the potential of riv-

Table 3—**Continued**

Patients				Magnitude of Effect (95% CI)	Clinically Significant Difference
Randomly Assigned, *n*	Completed Trial, *n*	Receiving Rivastigmine, *n/n (%)*	Receiving Placebo, *n/n (%)*		
1582	1252	–	–	WMD, −3.91 (−5.48 to −2.34); $P < 0.001$	>4-point change
1609	1279	–	–	WMD, −0.36 (−0.45 to −0.27); $P < 0.001$	Any change
1171	979	–	–	WMD, −0.04 (−1.28 to 1.20); $P = 0.95$	NA
1468	1167	–	–	WMD, 0.22 (0.15 to 0.28); $P < 0.001$	NA
1468	1167	–	–	WMD, 0.35 (−0.78 to 1.47); $P = 0.56$	NA
516	442	–	–	WMD, 3.75 (2.66 to 4.85); $P < 0.001$	NA
–	–	30/267 (11.2)	8/259 (3.1)	RR, 3.19 (1.03 to 9.83)	NA
–	–	90/543 (16.6)	13/518 (2.5)	RR, 5.34 (2.30 to 12.42)	NA
–	–	143/676 (21.2)	60/651 (9.2)	RR, 2.24 (1.45 to 3.46)	NA
–	–	46/474 (9.7)	15/474 (3.2)	RR, 3.04 (1.72 to 5.38)	NA
–	–	71/445 (16.0)	27/416 (6.5)	RR, 2.43 (1.60 to 3.70)	NA
	–	30/474 (6.3)	7/474 (1.5)	RR, 4.24 (1.88 to 9.55)	NA
–	–	303/676 (44.8)	74/651 (11.4)	RR, 2.79 (1.26 to 6.19)	NA
–	–	188/676 (27.8)	28/651 (4.3)	RR, 6.06 (3.88 to 9.45)	NA

astigmine to affect sleep in patients with mild to moderate Alzheimer disease and lasted only 8 weeks. It was insufficiently powered because of the small sample size. The second study (34) showed no statistical differences in the primary outcome of function (measured with the Bristol Activities of Daily Living Scale) in patients with Alzheimer disease over 52 weeks. Changes in secondary outcomes of cognition (measured with the ADAS-cog and MMSE) showed statistical differences favoring galantamine only in a subgroup of patients with MMSE scores between 12 and 18. One study (34) showed differences favoring galantamine over donepezil in scores on the Screen for Caregiver Burden. However, many caregivers were missing from the analysis, and the results were presented in a limited manner. In this trial, the adverse events most frequently reported were nausea, agitation, vomiting, headache, and falls. Although not statistically evaluated, the rates for all these harms were marginally higher with galantamine. Galantamine and donepezil did not differ with respect to serious adverse events.

One large trial (36, 37) compared donepezil (up to 10 mg/d) with rivastigmine (up to 12 mg/d) in patients with moderately severe Alzheimer disease over 2 years. Measures of cognition (SIB and MMSE) and behavior (Neuropsychiatric Inventory) did not significantly differ. However, statistically significant differences in global function (Global Deterioration Scale) and function (Alzheimer's Disease Cooperative Study–ADL subscale) favored rivastigmine. A subgroup analysis of patients age 75 years or older showed statistical differences favoring rivastigmine in some measures of behavior and function compared with younger patients. The collection of harms was well reported (maximum quality score) and showed higher frequency of nausea for rivastigmine than donepezil during the titration phases. This finding was attributed to the faster escalation rate with rivastigmine. In general, patients receiving rivastigmine reported more adverse events than those receiving donepezil, but serious events did not differ.

Clinical Effectiveness of Approved Drugs

Data on clinically significant changes for the ADAS-cog, MMSE, and CIBIC-plus were noted during data extraction. For donepezil, only 10 of 27 studies reported on the percentage of patients with a clinically significant change in at least 1 of these outcomes; 1 study (34) compared donepezil with galantamine. Six of 10 studies on galantamine, 5 of 9 studies on rivastigmine, and 3 of 6 studies on memantine reported this information. For tacrine, 2 studies reported the proportion of change for the treatment group or placebo group but not both. When data were presented on patients with clinically significant changes on the ADAS-cog, MMSE, or CIBIC-plus, they suggest that a small proportion of patients may respond to the drug therapy. However, the characteristics of these responders were not adequately detailed within the studies.

Discussion

For each drug except tacrine, the evidence consisted of 1 or more well-designed and well-executed randomized, controlled trials yielding consistent, directly applicable results for most of the outcomes. However, most trials were of less than 1 year's duration. For tacrine, the evidence reviewed was of moderate quality because it was obtained from randomized, controlled trials with important limitations. These included great variation in the tacrine doses used in the studies and the fact that few studies selected the ADAS-cog or CIBIC-plus as outcomes; this limited comparability across studies and with other drugs used to manage dementias.

Methodological caveats that may affect the interpreta-

Table 4. **Summary Effect Sizes for Outcomes of Benefit Computed for Memantine in at Least 2 Studies**

Outcome Measures	Studies, *n* (Reference)	Limitations	Consistency of Effects
Memantine vs. placebo for Alzheimer disease, all severity levels			
Outcomes of benefit†			
SIB	2 (68, 70)	No serious limitations	High inconsistency (I^2 = 52.8%)
CIBIC-plus	3 (68–70)	No serious limitations	No important inconsistency (I^2 = 0.0%)
NPI	3	No serious limitations	No important inconsistency (I^2 = 0.0%)
ADCS-ADL	3	No serious limitations	No important inconsistency (I^2 = 5.1%)
Memantine vs. placebo for vascular dementia, all severity levels			
Outcomes of benefit†			
ADAS-cog	2 (65, 66)	No serious limitations	No important inconsistency (I^2 = 14.6%)
MMSE	2	No serious limitations	High inconsistency (I^2 = 81.1%)
GBS	2	No serious limitations	No important inconsistency (I^2 = 22.0%)
NOSGER	2	No serious limitations	No important inconsistency (I^2 = 0.00%)

* Outcomes of harms are those with significant effect size; all others evaluated are shown in **Appendix Table 4** (available at www.annals.org). ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study subscale for activities of daily living; CIBIC-plus = clinician-based impression of change scale, with caregiver input; GBS = Gottfries–Brane–Steen scale; MMSE = Mini-Mental State Examination; NA = not available; NOSGER = Nurses' Observation Scale for Geriatric Patients; NPI = Neuropsychiatric Inventory; SIB = Severe Impairment Battery; WMD = weighted mean difference.
† For outcomes of harms, no findings were significant.

tion of systematic reviews in this areas of research centered on 3 main areas: 1) classification of dementias and severity levels, 2) capture of adverse events, and 3) definition of clinically meaningful changes in outcome measures.

Classification systems used for diagnosing the various types of dementias and other forms of cognitive impairment are not interchangeable. Moreover, concerns about the accuracy of these criteria remain (71). Defining severity in patients with dementia raises another concern, and a variety of methods were used across studies. Although popular, the MMSE may not best capture severity levels, and the categories (mild, moderate, and severe) may not always reflect cognitive and functional differences in a clinically meaningful manner. These factors may contribute to heterogeneity and limit the inferences that can be drawn across studies. Trials were inconsistent in classifying serious events or the severity of typical events. Capturing information on the basis of self-report from individuals with cognitive decline can be problematic even if done by a caregiver. Most of the trials in this systematic review were of relatively short duration and included relatively healthy individuals with mild to moderate dementias. Patients with dementia seen in practice often have more complex medical illnesses and are at greater risk for side effects and pharmacologic interactions. Published rates of adverse events in controlled trials may underestimate the rates seen in clinical practice.

Consensus is lacking about which outcomes best reflect clinical importance in the domains we evaluated. For most studies in this review, cognition and global assessment (measured with >40 different instruments) were the domains from which efficacy was determined; the emphasis on these 2 domains reflects the "dual efficacy" recommended by the FDA for dementia drugs. European guidelines emphasize the importance of functional and behavioral outcomes to evaluate efficacy of drugs (72). A clinically relevant treatment can be defined as one in which the change is both relevant and important to the patient or caregiver and to clinicians. In contrast, a statistically significant difference, which is associated with probabilities of events, does not always reflect clinically meaningful changes. The magnitude of a clinically relevant change may vary depending on whether importance is defined by the patient, caregiver, or clinician. Moreover, the goals for treatment vary with disease stage. In early stages, the aim is to improve cognition and slow progression of disease. In the mid-stages of the disease, the emphasis is on preserving function (that is, ADLs), maintaining safety, and delaying institutionalization; support in the home becomes increasingly important. In the late stages, the emphasis moves toward management of difficult behaviors, which can be addressed with both pharmacotherapy and manipulation of the physical and social environment. Ultimately, clinical significance is a complex issue; its definition can vary among individuals and clinicians as well as with the stage of disease.

Despite these methodological caveats, the literature evaluated in this systematic review can be used to guide the development of practice guidelines. The strength of the evidence considers the methodological quality, consistency, and directness of the findings and the relevance to populations likely to be prescribed the drug.

Donepezil versus Placebo

On the basis of 34 reports (from 24 distinct studies), there is consistent evidence that donepezil, at both 5 and

Table 4—Continued

Patients, *n*		Magnitude of Effect (95% CI)	Clinically Significant Difference
Randomly Assigned	Completed Trial		
656	463	WMD, 4.46 (1.87 to 7.04); $P = 0.001$	NA
1059	857	WMD, −0.27 (−0.43 to −0.10); $P = 0.002$	Any change
1059	857	WMD, −3.19 (−5.09 to −1.29); $P = 0.001$	NA
1059	857	WMD, 1.39 (0.39 to 2.39); $P = 0.006$	
900	698	WMD, −2.21 (−3.27 to −1.15); $P = 0.000$	>4-point change
900	698	WMD, 0.45 (−1.02 to 1.92); $P = 0.55$	>3-point change
900	698	WMD, −1.93 (−4.69 to 0.84); $P = 0.172$	NA
900	698	WMD, −0.93 (−2.90 to 1.05); $P = 0.36$	NA

10 mg, improves cognition and global function assessment for patients with Alzheimer disease and vascular dementia. The summary estimates for the ADAS-cog and the CIBIC-plus suggest that these effects are small; the exception is for patients with mild cognitive impairment, in whom no benefit occurred. Clinically significant changes are demonstrated with the CIBIC-plus but not the ADAS-cog. Improvement in behavioral symptoms and quality of life were not evaluated as extensively or with consistent outcomes. Adverse events are primarily associated with gastrointestinal problems consistent with this class of drugs and are dose related. Most studies evaluated patients with mild to moderate Alzheimer disease for relatively short periods. Although differences in cognition and global assessment were maintained between treatment and placebo groups during the studies, short study durations prevent us from drawing conclusions about the potential of donepezil to delay the progression of the disease or about longer-term use (>6 months) in those already given a diagnosis. For patients with mild cognitive impairment, donepezil reduced rates of conversion to Alzheimer disease in the short term, but differences relative to placebo disappeared by 36 months.

In a previous review, Passmore and colleagues (73) pooled individual-patient data from 4 trials and concluded that donepezil affected cognition and global function in both Alzheimer disease and vascular dementia. Similarly, Whitehead and colleagues (74) pooled individual-patient data across 11 trials for Alzheimer disease and showed differences between the 5-mg and the 10-mg doses in terms of cognition and global assessment (the only 2 outcomes considered). Two Cochrane reviews (75, 76) evaluating donepezil in Alzheimer disease and vascular dementia also highlight the limited number of studies that evaluated other important outcomes (such as behavior and caregiver burden). The major findings from these previous reviews are consistent with those in this systematic review.

Galantamine versus Placebo

In the 10 studies (12 reports) evaluated, consistent evidence indicates that galantamine positively affects cognition and global assessment, as measured by the ADAS-cog and CIBIC-plus; only the latter achieved clinical significance. The evidence is inconsistent with respect to change in ADLs. The single study evaluating caregiver burden demonstrated positive results. Adverse events were primarily gastrointestinal problems. All of these studies evaluated patients with mild to moderate Alzheimer disease and vascular dementia for up to 6 months. The short duration of these studies and the open-label design of the single longer study (1 year) limit interpretation of the findings for use of the drug beyond 6 months.

Wilkinson and colleagues (77) pooled individual-patient data from 4 phase III trials (24 and 32 mg) in patients with moderate Alzheimer disease. Changes in cognition (ADAS-cog) and global assessment (CIBIC-plus) in trials of up to 6 months' duration were evaluated. The findings show statistical and clinical (change >4 points) significance for the ADAS-cog in a subgroup with a baseline ADAS-cog score greater than 30 and an MMSE score greater than 12. Their data also suggest that galantamine may delay deterioration on the Neuropsychiatric Inventory scores compared with placebo. A Cochrane review (78) concluded that galantamine improved cognition (ADAS-cog) and global assessment (CIBIC-plus) in the trials evaluated, with less consistent evidence for functional and behavior changes.

Rivastigmine versus Placebo

The 9 studies (11 reports) showed consistent results for the outcome of cognition and global assessment. However, the summary effect size for the ADAS-cog was not statistically significant. Although this effect was smaller rel-

ative to other cholinesterase inhibitors, fewer studies were combined; in addition, heterogeneity was present. In a Cochrane review, Birks and colleagues (79) reported an effect size of −2.09, which is similar to that estimated in our review. Efficacy in other domains has not been evaluated as extensively, but findings suggest some benefit in ADLs. Adverse events are primarily associated with gastrointestinal problems consistent with this class of drugs. Half of the studies evaluated patients with disease of all severity levels (1 study included patients with moderate to severe disease) for a duration of up to 6 months. One study with a small sample size maintained blinding for up to 12 months, suggesting that statistical differences between groups were maintained.

Tacrine versus Placebo

On the basis of the 6 trials that compared tacrine with placebo, the evidence is less consistent for a significant difference in cognition. In part, this may be due to the choice of outcome instruments, small sample sizes, low doses, and insufficient study duration. Two of 3 trials found benefit in global assessment. Benefit in other domains has not been evaluated as extensively. Adverse events were primarily associated with gastrointestinal problems. The high rates of withdrawal due to adverse events and the potential for liver damage suggest that this drug is less well tolerated by patients.

Cholinesterase Inhibitors versus Placebo

Many previous reviews have considered the class effects of cholinesterase inhibitors in patients with dementia. Trinh and colleagues (80) selected studies that used the Neuropsychiatric Inventory and instrumental ADLs. Their conclusions were based on various cholinesterase inhibitors (including velnacrine, physostigmine, eptastigmine, metrifonate, and those included in the present review) and noted only small changes in function and neuropsychiatric symptoms. A recent review by the Canadian Centre for Health Technology (81) on cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in mild to moderate Alzheimer disease also concluded that the long-term benefit of using these drugs was difficult to evaluate given the short duration of the trials. Comparisons between the cholinesterase inhibitors could not be made because of the paucity of head-to-head trials. Lanctôt and colleagues (82), in a review of 16 cholinesterase trials, also concluded that the mean proportion of global responders in excess of placebo was 9% (CI, 6% to 12%).

Memantine versus Placebo

On the basis of 6 distinct studies (from 9 reports), consistent evidence indicates that memantine improves cognition and global assessment, but the magnitude of the effect size for the ADAS-cog does not approximate those considered clinically significant. Outcomes of benefit in other domains are limited but suggest improvement in quality of life in patients with moderate to severe Alzheimer disease. Adverse events included gastrointestinal symptoms, dizziness, and headache; in most studies, agitation was less frequently reported in the treatment group than in the placebo group. Memantine was well tolerated as monotherapy and in conjunction with donepezil. The memantine trials evaluated populations with mild to moderate vascular dementia and moderate to severe Alzheimer disease. Although differences in cognition, global assessment, and quality of life were maintained throughout the study, the short study duration cannot inform use for more than 28 weeks. Other reviews on memantine (83, 84) concur with the findings of this systematic review.

Conclusion

For the treatment of dementias, cholinesterase inhibitors and memantine can improve symptoms, primarily in the domains of cognition and global function. Clinically important differences were not consistently evaluated or demonstrated in these 2 domains for all drugs. Direct comparisons among these drugs are limited and do not suggest important differences.

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Disclaimer: The authors are solely responsible for the content of this review. The opinions expressed herein do not necessarily reflect the opinions of the Agency for Healthcare Research and Quality, the Ontario Ministry of Health and Long-Term Care, or the McMaster Evidence-based Practice Center.

Grant Support: Parminder Raina holds a Canadian Institute of Health Research Investigator award and an Ontario Premier's Research Excellence award. The original systematic review was funded by the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services (contract no. 290-02-0020). The update to this review was funded by the Ontario Ministry of Health and Long-Term Care and the McMaster University Evidence-based Practice Center.

Potential Financial Conflicts of Interest: *Honoraria:* P. Santaguida (American College of Physicians).

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Appendix: Studies of Cholinesterase Inhibitors or Memantine That Were Excluded

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