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Pharmacological Treatment of Dementia

Summary

Introduction

The focus of this review is the pharmacological treatment of dementia. Pharmacotherapy is often the central intervention used to improve symptoms or delay the progression of dementia syndromes. The available agents vary with respect to their therapeutic actions, and are supported by varying levels of evidence for efficacy. This report is a systematic evaluation of the evidence for pharmacological interventions for the treatment of dementia in the domains of cognition, global function, behavior/mood, quality of life/activities of daily living (ADL) and caregiver burden.

Many medications have been studied in dementia patients. These agents can be classified into three broad categories:

1. Cholinergic neurotransmitter modifying agents, such as acetylcholinesterase inhibitors.
2. Non-cholinergic neurotransmitters/ neuropeptide modifying agents.
3. Other pharmacological agents.

Although only five agents have been approved by the Food and Drug Administration (FDA) for the treatment of dementia, many other pharmacological agents have been evaluated in trials and may be prescribed in off-label use.

Given the range of pharmacological agents that have been tested in dementia, a systematic review of these interventions (using a consistent methodology) provides a meaningful contribution in this area. The key questions addressed in this systematic review are as follows:

1. Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?
2. Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?
3. Are certain drugs, including alternative medicines (non-pharmaceutical), more effective than others?
4. Do certain patient populations benefit more from pharmacotherapy than others?
5. What is the evidence base for the treatment of ischemic vascular dementia (VaD)?

This review considers different types of dementia populations (not just Alzheimer's Disease [AD]) in subjects from both community and institutional settings. The studies eligible in this systematic review were restricted to parallel RCTs of high methodological quality.

Methods

A team of content specialists was assembled from both international and local experts. The purpose of the expert panel was to assist in the topic assessment and refinement process; in addition, complex methodological issues were evaluated by this expert panel.

Search Strategy

Search strategies were developed and undertaken in the electronic databases including Cochrane Central, MEDLINE®, PreMEDLINE®, EMBASE, AMED, CINAHL®, AgeLine, and PsycINFO. In addition to the electronic databases, the bibliographies of retrieved papers were reviewed.

Eligibility Criteria:

Studies were included that met the following criteria:

- Populations included dementia patients who were 18 years or older in age.
- Diagnosis of dementia using criteria of International Classification of Diseases (ICD) 9 or 10, Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R or IV, National Institute of Neurological and Communication Disorders and Stroke (NINCDS), Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), or Neurological and Communication Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN).
- Potential populations at high risk of dementia conversion in order to address the issue of delay in onset. These populations included: Mild Cognitive Impairment (MCI), Cognitive Impairment not Dementia (CIND), Cognitive Loss No Dementia (CLoND).
- Interventions were restricted to pharmacological agents, including food supplements (as defined by the FDA) administered for at least 1 day.
- Parallel design randomized control trials (RCT) in the English language of any sample size.
- Score of 3 or greater on the modified Jadad quality scale.

All types of instruments were considered for this review within the outcome domains.

Populations of dementias caused by toxic agents (e.g., alcohol) and temporary dementia (e.g., side effect of anesthesia) were excluded.

Data Collection and Reliability of Study Selection

All studies meeting eligibility criteria were reviewed to assess quality and data abstracted according to predetermined criteria. The articles were grouped according to the pharmacological agent used in the intervention. A team of study assistants were trained in the criteria for eligibility and quality for the purposes of this systematic review. Standardized forms and a guide explaining the criteria were developed from previous templates.

Study outcomes were classified into the following domains:

1. General cognitive function.
2. Specific cognitive function.
3. Global clinical assessment.
4. Behavior/mood.
5. Quality of life/ADL.
6. Effects on primary caregiver (also referred to as caregiver burden).
7. Safety as measured by the incidence of adverse effects (particularly serious events).
8. Acceptability of treatment as measured by withdrawal rate from trial due to side effects of the medication.

Measurement of Benefits and Harms

Evaluation of efficacy is based upon reported changes for outcomes in the principal domains of interest. Evaluation of the potential for harm is considered within three main areas: 1) the most frequently reported adverse events across studies for a specific drug, 2) the overall withdrawal rate due to adverse events for both the control and treatment groups, and 3) the range of frequencies reported for a subset of specific symptoms (nausea, diarrhea, dizziness, agitation, eating disorder) selected *a priori* and evaluated for all pharmacological interventions.

Measure of Effect Size and Meta-analysis

Effect sizes (ES) for trials were conducted for those pharmacological interventions with the same outcomes. In studies with multiple dosage groups and where sufficient data were provided, each dose level had an ES estimated separately relative to placebo. Before calculating a pooled effect size measure, the reasonableness of pooling was assessed on clinical and biological grounds, in terms of clinical homogeneity and therefore statistical meta-analysis was not appropriate for all outcomes or interventions.

Results

Question 1: Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?

Seventy-two studies examined cholinergic neurotransmitter modifying agents, 61 studies examined non-cholinergic neurotransmitter/neuropeptide modifying agents and 76 trials evaluated other agents used to treat dementia. Table 1 lists all the pharmacological agents and the number of trials (in brackets) eligible for review in this study. Twenty of these agents are detailed in this summary. All drug agents are detailed in the full report.

Summary of Cholinergic Neurotransmitter Modifying Agents

Carnitine. Six trials[1-6] evaluated carnitine in 925 subjects with mild to moderate severity, recruited predominately from the community. A dose of 2 to 3 g was compared to placebo for either 24 or 52 weeks.

Evidence of benefit is conflicting for the domains of general or specific cognition. Results were not statistically significant in any study but the lack of sufficient power may have influenced

these results. Similarly, no statistically significant differences were found in the domains of global assessment, behavior/mood, and quality of life/ADL. Statistical power could not be evaluated for the most of these outcomes.

Four of the six studies scored 3 for quality on reporting adverse events. Withdrawal rates due to adverse events varied from 0-3 percent (excluding results from one outlier trial[7]), and gastrointestinal symptoms were the most frequently reported types of adverse events.

Donepezil. Ten trials[8-17] in 3239 subjects evaluated the efficacy of donepezil compared to placebo, and one trial18 compared donepezil with vitamin E. Eight of the studies evaluated AD patients, for which at least half were recruited from the community (other studies did not specify). The subjects had predominately mild to moderate disease and doses of 5 or 10 mg were used with study duration from 12 to 56 weeks.

There is consistent evidence of benefit in the domains of general cognitive function and global assessment; the combined effect sizes for the Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-cog) and the Clinician's Interview-Based Impression of Change (CIBIC) were estimated. Based on the three studies that evaluated two different doses (5 and 10 mg), there was no consistent dose response relationship as the benefit was of similar magnitude for global assessment outcomes. Two of the three studies that evaluated behavior/mood outcomes, using the Neuropsychiatric Inventory (NPI), showed no statistically significant changes relative to placebo but these trials lacked sufficient power to detect a difference. There is evidence of benefit in ADL outcomes, although this outcome was evaluated by a variety of instruments. Caregiver burden outcomes were measured in a single study that did not report the findings for this domain.

Adverse events quality scores were 3 or greater for the majority of studies (n=7). Four trials provided evidence of a dose response for adverse events. One study showed a statistical difference for balance-related problems and asthenia (neurological fatigue) between placebo and treatment groups. Withdrawal due to adverse events ranged from 0–18 percent for treatment groups and 0–11 percent for placebo. Four out of 6 studies testing for differences between groups were statistically significant for diarrhea, nausea and vomiting.

Galantamine. Six trials1[9-24] in 3530 subjects compared the efficacy of galantamine with placebo. Doses of 24 and 32 mg were evaluated in half of these studies. Five studies evaluated only AD patients and there was limited information regarding the subjects' residence (community or institutional settings). All studies recruited subjects with mild to moderate disease and the drug was administered from 3 to 6 months duration.

Evidence of benefit is consistent in the domains of general cognitive function, global assessment and quality of life/ADL. Two of the three studies that evaluated behavior/ mood found statistically significant differences in favor of galantamine. A dose effect was evident in the ADL domain when comparing the pooled estimates of the Disability Assessment for Dementia (DAD); no dose effect was observed for outcomes in the global assessment domain, and this could not be evaluated for the general cognition domain. Caregiver burden was not evaluated in any trial.

Five of the six trials scored 3 out of 5 on our quality scale for rating adverse events. Withdrawal rates due to adverse events ranged from 4–9 percent for placebo and 8–27 percent for the treatment group. One study showed a dose response for adverse events. Although four trials did not report significance testing for differences between groups, two trials did report a statistically significant difference in weight loss between the placebo and treatment group. The most common adverse events were gastrointestinal symptoms (nausea and vomiting, diarrhea), eating disorders/weight loss, and dizziness.

Metrifonate. Nine studies[25-33] compared metrifonate to placebo in 2759 subjects with mild to moderate AD (the majority of studies did not specify community settings). Metrifonate doses from 50 to 80 mg were given for 21 days to 26 weeks duration.

All but one study showed metrifonate to have a consistent positive effect on measures of general cognitive function; none of the studies evaluated specific cognitive function measures. Effects on global assessment were less consistent but suggested a positive effect in four of the eight studies. Evidence for effect in the domains of behavior/mood and quality of life/ADL were not statistically significant in the majority of studies that evaluated these domains; however these were primarily evaluated as secondary outcomes and likely lacked sufficient power.

With the exception of a single study, quality scores for reporting adverse events were greater than 3. However, only one trial tested for differences between groups and found nausea and vomiting, diarrhea, and muscle and joint disorder to have statistically significantly differences. Withdrawal due to adverse events varied from 0–9 percent for placebo and 0–12 percent for the treatment group. It was difficult to determine which types of reported adverse events had the potential to cause serious harm. This is noteworthy as metrifonate has been withdrawn from use in North America, and Bayer has suspended Phase III trials,[34] because some patients in clinical

trials have experienced serious muscle weakness. This decision was based on the results of an experimental study showing risk of respiratory paralysis with the use of metrifonate. Other adverse events of concern included severe leg cramps, dyspepsia, and bradycardia. None of the studies that we reviewed indicated that if present, these events differed with statistical significance between groups. It is not clear if this inconsistency is a function of the methods used to collect and report adverse events, or a limitation of RCTs as a source of detecting serious adverse events when the incidence is low.

Nicergoline. Four trials[35-38] in 705 subjects compared nicergoline to placebo and one trial[39] compared it to a second drug (antagonic-stress) in mixed populations that included AD, Multi-Infarct Dementia (MID), Progressive Degenerative Dementia (PDD), Vascular Dementia (VaD), mixed dementia, and Senile Dementia of the Alzheimer's Type (SDAT), which were classified as mild to moderate in severity.

All placebo-controlled trials found a positive effect for general cognitive outcomes, but half the results were based on observed case (OC) analyses. The evidence for benefit was mixed in the domain of global assessments. No statistically significant differences were found for behavior/mood, nor quality of life/ADL outcomes but these were evaluated in few studies and as secondary outcomes (suggesting that sufficient power was an issue).

Quality scores for reporting adverse events varied from 2 to 5 for these four trials, and none tested for differences between groups. Withdrawal due to adverse events varied from 0–8 percent for placebo and 0–9 percent for the treatment group. With the exception of headache, which was reported in all four trials, it was difficult to determine which types of adverse events most characterized exposure to this pharmacological agent.

Physostigmine. Four studies[40-43] in 1198 subjects with mild to moderate AD evaluated physostigmine administered in patch and oral form (30 to 60 mg dose) from 6 to 24 weeks duration. All subjects were recruited from the community.

There is evidence that physostigmine has a statistically significant positive effect on general cognitive function, as three of the four studies showed improvement. Evidence for an effect on global function was mixed with no consistent effect. Similarly, for quality of life/ADL outcomes, all three studies that evaluated this domain showed no statistically significant difference but these were secondary outcomes and may reflect a lack of power. Behavior/ mood and caregiver burden outcomes were not tested.

The quality scores for reporting adverse events were generally low, scoring 1 or 2 out of 5. Withdrawal rates due to adverse events varied from 1–5 percent for placebo and 12–55 percent in the treatment group, with one study not reporting rates. The high withdrawal rates were in studies with sample sizes that varied from181 to 475 subjects. A single study tested for differences between groups, and found that dizziness, tremor, weight loss, asthenia, confusion, delirium, and respiratory problems (not detailed) were significantly different statistically. The cluster of reported types of adverse events suggests that gastrointestinal problems (abdominal pain, diarrhea, nausea and vomiting and eating disorder) were most frequently reported.

Posatirelin. Four trials[44-47] evaluated posatirelin in 931 subjects in a variety of mild to moderate dementia populations (AD, PDD, VaD) using 10 mg per day dose for 3 months duration.

Three of the four trials showed statistically significant improvement in general cognitive function and quality of life/ADL (as measured by Gottfries-Brane-Steen (GBS) subscales for these domains). The evidence remains inconsistent for benefit in global assessment (evaluated in only one trial) and behavior/mood (mixed results). Caregiver burden and specific cognitive function were not evaluated.

Quality scores for reporting adverse events varied from 2 to 4. Withdrawal rates due to adverse events ranged from 0–3 percent in placebo and 0–4 percent in the treatment group. None of the studies tested for statistically significant differences between groups for adverse events. At least three studies reported arrhythmia, nausea/vomiting, headache, rash/skin disorder, and sleep disorder.

Rivastigmine. Six studies[48-53] evaluated 2071 subjects with three of these studies limited to AD patients. Doses of rivastigmine varied from 1 to 12 mg, given for 14 to 26 weeks and only one study specified a community sample.

Evidence shows that general cognitive function improves with rivastigmine at dose of 12 mg but there are mixed results for efficacy at lower doses. Two trials evaluated specific cognitive function but the results were not consistent within studies (between general and specific measures); similarly, the results were not consistent for general and specific cognition between studies. There is consistent evidence of benefit for global function but the dosage at which this occurs has statistically significant variation among studies. In the domains of behavior/mood, quality of life/ADL, the findings were neither statistically significant nor consistent; most of these analyses were not based on intention to treat analysis and lack of sufficient power cannot be ruled out. Caregiver burden outcomes were not evaluated.

Quality scores for reporting adverse events varied from 2 to 5. Withdrawal rates due to adverse events ranged from 4–11

percent in the placebo and 11–27 percent in the treatment group. Two trials demonstrated a dose response; however, one of these trials showed statistically significant differences for nausea and vomiting only, and the other trial showed statistically significant differences for all the adverse events reported. The majority of studies reported dizziness, nausea and vomiting, eating disorder/weight loss, and headache. It should be noted that one study allowed intentional prescribed anti-emetic drugs to increase the tolerance of subjects taking rivastigmine.

Tacrine. Six studies[54-59] evaluated tacrine in 994 subjects predominately with mild to moderate AD at doses of 80 to 160 mg lasting from either 12/13 or 30/36 weeks in duration. Two other studies[60,61] involving 425 patients were non-placebo controlled studies. The majority of studies recruited community-based subjects.

A single trial showed benefit for general cognitive function. The small effect size was based on a series of related publications. The five trials showing no benefit for general cognitive function comprised small sample sizes and much shorter study duration. Thus, the evidence for benefit in general cognitive function is limited to a single trial. There is evidence for benefit in global function in two of the three trials. Changes in behavior/mood, quality of life/ADL domains, specific cognitive function, and caregiver burden were all not statistically significant, but lack of sufficient power cannot be ruled out.

The quality scores for reporting adverse events varied from 1 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0–12 percent for placebo and 0– 55 percent in the treatment group. The higher rates of withdrawal were associated with higher doses. Elevated alanine transaminase (ALT) or hepatic abnormality (placebo=4–13 percent, all doses tacrine=7–67 percent) was reported in six studies, raising concerns for the potential for serious liver damage. None of these trials tested for differences between treatment and placebo with respect to adverse events. Five studies reported nausea and vomiting, gastrointestinal problems, and dizziness. There is evidence for potentially serious adverse events associated with liver dysfunction in six trials.

Velnacrine. Three studies[62-64] evaluated the effects of velnacrine in 774 AD patients with a probable severity classification. Doses between 75 mg twice daily and 225 mg were given for 15 to 24 weeks duration. Location of recruitment was not specified.

Statistically significant positive effects were observed for general cognitive function, and global assessment in the two studies with sample sizes over 300 subjects. Behavior/mood and caregiver burden showed some benefit in one trial[62] at the highest dose only. Quality of life/ADL was tested as a secondary outcome and showed mixed findings.

Quality scores for reporting adverse events were 3 for all studies. Withdrawal rates varied from 0–22 percent for the placebo group and 5–33 percent for the treatment group. None of the studies reported a dose response. None of the studies tested for statistical differences between the placebo and treatment groups. Two studies reported aberrant hematology and hepatic abnormality[62,64]; for these two studies the rates of occurrence were 2–21 percent for placebo, and 32–40 percent for all doses. The potential for serious effects is not well specified in these trials. All studies reported diarrhea and nausea and vomiting.

Summary of Non-cholinergic Neurotransmitter/Neuropeptide Modifying Agents

Haloperidol. Five studies[65-69] evaluated the effect of haloperidol relative to placebo in a total of 622 subjects with mild to moderate disease that included AD patients and mixed populations (MID/VaD/ PDD). One trial had only 15 patients, and one trial[65] lasted only 3 weeks. Two studies recruited subjects from institutions; one from the community; and, two did not specify.

Mixed results were observed for improvement in global assessment. In three of the trials there was benefit in the domain of behavior/mood which reached statistical significance. Two trials evaluated caregiver burden and found no statistically significant differences but lack of sufficient power cannot be ruled out. Few studies evaluated outcomes in quality of life/ADL. Haloperidol did not affect general cognitive function in two trials and was not evaluated in the other studies.

The quality scores for reporting adverse events varied from 1 to 5 and only three of five studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 5–17 percent for placebo and 17–33 percent in the treatment group. One trial showed a dose-response effect but the study lasted only 3 weeks. Three trials tested for differences between treatment and placebo with respect to extra-pyramidal symptoms (placebo=17–32 percent, all doses=34–97 percent), and two found statistically significant differences.[65,66] One study[66] found statistically significant differences between groups for balance-related problems.

Memantine. Three trials[70-72] evaluated memantine in 1066 patients, primarily with VaD, with 10 or 20 mg doses for durations of 12 or 28 weeks. Disease severity was moderate to severe in a single study[70] and mild to moderate in the remaining two studies.[71,72] One study included patients that were

institutionalized; one study included community subjects; and the other study did not report the source of patients.

Consistent evidence of benefit in general cognitive function was demonstrated in the two studies that evaluated this domain. Findings for global assessment are mixed. The only trial that evaluated mixed dementia populations (including some VaD) with moderate to severe dementia found statistically significant improvements in global function, behavior/mood, and quality of life/ADL outcomes, but did not evaluate general cognitive function. It should be noted that this trial with mixed populations used half the dose of memantine for half the study duration in patients with greater disease severity, and had approximately half the sample size of the other two trials evaluated in this systematic review. Despite a lower dose, a smaller number of more severely affected patients and a shorter duration, a statistically significant difference was found.

The quality scores for reporting adverse events varied from 3 to 4. Only two of three studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 3–7 percent for placebo and 9–12 percent in the treatment group. A single trial tested for differences between treatment and placebo, and none of the comparisons were significantly different statistically.

Selegiline. Six trials[73-78] evaluated selegiline in 733 patients with AD, PDD, and dementia Alzheimer's type (DA) with 10 mg per day and study duration of 60 days or 2 years.

All but one trial that evaluated general cognition showed no statistically significant changes. A single trial found statistical improvements in specific cognitive tests (Sternberg Memory tests); this trial also showed statistically significant improvements in global assessment and behavior/mood. Only this trial, which had the highest quality score (7), showed consistently positive findings across all domains tested. Three of the five trials that evaluated part or all of these domains had very small sample sizes and were likely underpowered, possibly accounting for the inconsistent findings. Based on a single trial there is evidence that selegiline and selegiline combined with vitamin E, delays the time to important functional decline milestones.

The quality scores for reporting adverse events varied from 0 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0–4 percent for placebo and 0–9 percent in the treatment group. Only one trial tested for differences between the treatment and placebo groups and showed that balance and falls were statistically significantly different (worse) between groups (particularly the group with selegiline combined with vitamin E [22 percent] versus placebo [5 percent]). However, when adjusted for multiple comparisons, these were no longer statistically significant.

Summary of Other Pharmacological Agents

Cerebrolysin. Six studies[79-84] evaluated the effect of cerebrolysin in a total of 819 subjects All but one of the trials included only AD patients with mild to moderate disease. All of the studies used the same dose of cerebrolysin, 30 ml per day for 5 days per week for 4 to 24 weeks duration. Location of recruitment was not specified.

Cerebrolysin showed a statistically significant improvement in cognition in four of five studies that evaluated this domain. Although a pooled estimate for the ADAS-cog was calculated, the model was positive for heterogeneity and the overall estimate was not statistically significant. The results for specific cognitive tests for the three trials that evaluated this domain were inconsistent. Global assessment measures showed a statistically significant effect in five of the trials. A summary estimate for the Clinical Global Impression (CGI) was presented; this model was also positive for heterogeneity but statistically significant for an overall effect. Two out of three studies showed an effect for behavior/ mood, but none of the six studies showed an effect on quality of life/ADL. No study measured caregiver burden.

Two of the six trials scored 5 out of 5 on our quality scale for rating adverse events, but did not report any adverse events. Two studies scored 4, and the other two trials scored 3 and 2. All the studies with scores equal to 4 or less tested for statistical differences in adverse events between placebo and treatment groups. Withdrawals due to adverse events were not reported in one study, and were 1 percent in two studies and none withdrew in three studies. A statistically significant difference between treatment and control group was reported in one study for weight change, anxiety, and headache.

Estrogen. Five studies[85-89] evaluated estrogens for dementia in 247 patients with primarily mild to moderate AD from the community, with the exception of one study that included moderate to severe dementia patients who were all institutionalized. One of the studies with AD patients provided 0.10 mg per day by skin patch for 8 weeks and the others used 1.25 mg per day for 12 to 52 weeks duration. The study including severe subjects used 2.5 mg per day for 4 weeks.

Three trials evaluated general cognitive function and all showed statistically non-significant findings; two trials lacked sufficient power to show changes on the ADAS-cog. Two other trials evaluated specific cognitive function but results were mixed. Most of the outcomes evaluated in the domains of global assessment, behavior/mood, and quality of life/ADL

were secondary outcomes and none showed statistically significant differences (but lack of power could be a factor).

One of the five trials scored 5 out of 5 on our quality scale for rating adverse events, but did not report any adverse event. Withdrawal rates due to adverse events ranged from 0–5 percent for placebo and 0–14 percent for the treatment group. The most frequently reported adverse event was vaginal bleeding and a single trial reported a statistically significant difference between placebo and treatment group for this symptom. It was not clear from the descriptions provided in the study if they had ascertained whether vaginal bleeding was present prior to the trial commencement.

Ginkgo biloba. Three trials[90-92] evaluated Ginkgo biloba, 120 to 240 mg per day for 3 to 12 months, in a total of 563 subjects with mixed dementias of mild to moderate severity. All were recruited from the community.

The largest trial had the longest treatment duration but the lowest daily dosage and reported a statistically significant impact for general cognitive function but had mixed findings for global assessment. A second large trial found positive changes for neuropsychological tests, global assessment, and behavior/mood outcomes with double the dosage of the previously described trial and half the treatment interval. In this RCT, clinical efficacy was assessed by using a responder analysis, with therapy response being defined as response in at least two of the three variables: CGI—global function, Syndrome Kurz test (SKT)—special cognitive function, and Nurnberger-Alters-Beobachtungs-Skala (NAB)—ADL. A single trial evaluated behavior/mood and the result was not statistically significant. No trial evaluated caregiver burden or quality of life/ADL.

All three trials scored 3 or greater on the quality scale for rating adverse events. Two studies had no withdrawals due to adverse events, and one trial had a withdrawal rate of 6 percent for both placebo and treatment groups. Two studies reported no adverse events. One study reported a statistically significant difference between the treatment and the placebo group for skin disorders. The same study reported gastrointestinal and headache adverse effects, but did not test for statistical differences between the placebo and the treatment group.

Idebenone. Four studies[93-96] evaluated the drug idebenone in 1153 subjects of mixed dementia populations of mild to moderate severity; one of these trials evaluated idebenone relative to tacrine. Doses varied from 30 mg per day to 360 mg per day, and the treatment interval ranged from 90 days to 60 weeks.

There was evidence of benefit in general cognitive function and global assessment. Several studies evaluated behavior/mood and quality of life/ADL and these outcomes were found to be statistically different. None of the trials evaluated caregiver burden.

Quality scores for reporting adverse events varied from 1 to 5. Rates of withdrawal due to adverse events varied from 0–5 percent for the placebo group and 0–5 percent in the treatment group; a single trial did not report withdrawal rates. Two trials tested for statistical differences between groups and found none. Although no clear pattern emerges, three studies identified at least one balance-related adverse event.

Oxiracetam. Five studies[97-101] evaluated oxiracetam in 554 subjects with different dementia syndromes of mild to moderate severity. All studies used 1600 mg daily, with one exception where the dose ranged between 1600-2400 mg per day. The treatment interval ranged from 90 days to 26 weeks duration.

All outcomes shown to be positive for this drug were based on Observed Cases (OC) evaluation. The two trials that evaluated general cognitive function showed benefit. The findings for specific cognitive function were mixed. A single trial evaluated global assessment and showed statistically significant change. Behavior/mood and quality of life/ADL outcomes showed mixed results. No study evaluated caregiver burden.

The quality scores for reporting adverse events varied from 2 to 5. The proportion of withdrawals due to adverse events varied from 0–9 percent for the placebo group and 0–6 percent for the treatment group. No clear pattern for adverse events is evident, but three of the five studies reported gastrointestinal related problems, primarily abdominal pain.

Pentoxifylline. Three placebo-controlled studies[102-104] evaluated pentoxifylline and one study compared pentoxifylline to sulodexide, with a total of 482 subjects with predominately MID. The dose administered in all studies was 1200 mg per day but varied between once or three times daily. The treatment intervals ranged from 12 to 36 weeks.

All three placebo trials showed statistically non-significant findings for any primary outcome evaluated on all subjects in the study. Two of these trials had very small sample sizes (n=38, n=28) and employed Observed Cases (OC) analyses; this suggests that the trials lacked sufficient power to evaluate multiple outcomes. The remaining trial had a large sample size (n=289) and employed an Intention to Treat (ITT) analysis; all primary outcomes evaluated were not statistically significant.

The quality scores for reporting adverse events were generally low, varying from 1 to 3. Withdrawal rates due to adverse events varied from 0–25 percent in the placebo group and 0–22 percent in the treatment group. The two studies that

reported adverse events indicated the presence of gastrointestinal disturbances, including abdominal pain and nausea and vomiting.

Propentofylline. Four trials[105-108] using propentofylline in 510 patients with AD and VaD were included. A dose of 900 mg per day was consistent across all studies, and the treatment duration ranged from 3 to 12 months.

Two studies with small sample sizes (n=30) showed no statistically significant results for any outcome evaluated but likely lacked power. There were two trials that found benefit in general cognitive function based on the Mini-Mental Status Exam (MMSE). The results for specific cognitive function as measured by the Digit Symbol Substitution Test (DSST) were mixed, as were those for global assessment. Behavior/mood outcomes were evaluated in a single trial and showed no statistically significant difference; this same trial evaluated quality of life/ADL and showed no statistically significant difference. No trial evaluated caregiver burden.

The quality scores for reporting adverse events varied from 1 to 4. The percentage of withdrawals varied from 0–13 percent for the placebo group and 0–12 percent for the treatment group. None of the trials tested for differences between groups. Three of the trials reported gastrointestinal events that included abdominal pain, constipation, and nausea and vomiting.

Question 2: Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?

Delay of Onset of Dementia

The concept of "delay onset" was operationalized to imply conversion from a state of cognitive impairment, classified as MCI, CLoND or CIND, to a true dementia state. No studies with this population met the final eligibility criteria, although four trials[109-112] advanced to the full text screening stage. The lack of studies eligible for evaluation in this systematic review points to a gap in the literature for pharmacological interventions (attempting to demonstrate a delay in disease onset) in MCI-type populations.

Delay of Progression of Dementia

The need for good evaluation of disease progression in trials was also identified. In general, few studies evaluated subjects in more severe states of the disease. This suggests that a bias exists towards evaluating mild to moderate disease in the trials eligible in this systematic review; this may reflect an underlying assumption that the less severe groups are most likely to benefit from drug trials. Since so few studies have evaluated the more severe groups, this assumption may require some empirical justification in future research. A consensus is required regarding the diagnostic criteria to be used to establish levels of severity.

Three studies evaluating cerebrolysin, selegiline and vitamin E, and donepezil have shown statistically significant effects in delaying disease progress in mild to moderate and moderately severe disease in patients with AD. This delay in progress was expressed in terms of delay in days to primary event or statistical differences between placebo at a specified time interval. Although these trials coincidentally evaluated dementia patients over the longest time interval, their protocol did not withdraw the drug at the end of the study. Theoretically, conclusive evidence of disease delay would be demonstrated if the treatment groups did not return to the level of the placebo. Thus, distinguishing between symptomatic and disease modifying effects is not possible unless the drug is withdrawn and the treatment groups are observed for these changes.

When studies attempted to evaluate disease progression, long-term (1 year or greater) trials continued in an "open-label fashion," where blinding was no longer maintained. This limits the confidence that bias did not affect the subsequent changes in the outcomes. It was observed that increasing levels of dropout (for a variety of reasons) also plagued these open-label phases of evaluation. From a practical perspective, maintaining adherence in longer-term trials in dementia patients is challenging, particularly for those in the placebo arm or for those with interventions that have a high proportion of adverse events. Although this practical challenge exists, the findings of this review suggest that there is a gap in the literature showing delay of the disease process of dementia related disorders.

Question 3: Are certain drugs, including alternative medicines (non-pharmaceutical) more effective than others?

Head to head comparisons of drugs in the treatment of dementia

A total of 26 [18,39,47,60,61,65,66,68,69,73,113-128] studies compared efficacy of the two or more pharmacological agents relative to each other. In general, few drugs showed statistically significant differences relative to each other. Those that did include (listed in declining order of performance):

1. Sulphomucopolysaccharides versus CDP-choline:[117] Statistically significant differences were seen in favor of sulphomucopolysaccharides in measures of behavior and global assessment in 30 institutionalized patients with mild to moderate MID.

2. Donepezil and vitamin E:[18] Statistically significant differences were seen in favor of donepezil in general cognitive function 54 patients with mild AD.
3. Antagonic stress versus nicergoline:[39] Statistically significant differences were seen in favor of antagonic stress in cognition as well as a global assessments in 62 subjects with mild to moderate AD.
4. Antagonic stress versus meclofenate:[124] Statistically significant differences were seen in favor of antagonic stress in measures of cognition and global assessment in 63 patients with mild to moderate AD.
5. Posatirelin versus citicoline:[47] Statistically significant differences were seen in favor of posatirelin in general cognitive measure and mood in 222 community living patients with mild to moderate AD.
6. Pyritinol versus hydergine:[125] A significant difference in favor of pyritinol in a global assessment measure in 102 Hispanic patients with mild to moderate AD.
7. Idebenone[61] versus tacrine: Mixed results were observed; the Efficacy Index Score showing a statistically significant benefit over tacrine, while the global assessment showed no difference in 203 individuals with AD, 44 of whom completed the study.

Current drugs approved in the United States for the treatment of dementia

What may be most relevant to clinicians are head to head comparison of the cholinergic modifying neurotransmitter pharmacological agents, particularly those currently approved for the treatment of dementia (tacrine, rivastigmine, galantamine, donepezil) in the United States. The evidence for each of these drugs has been extensively detailed, and the relative merits and handicaps of each are outlined in the results section of the full report (Chapter 3). Relative effectiveness as demonstrated by effect sizes for the ADAS-cog and the CIBIC are also compared in Chapter 3. Although, the psychometric properties of these two outcomes are commonly accepted, comparison across the populations in these pooled estimates may not lend themselves to direct comparison across these four different specific drugs; populations may be different and reporting of adverse events is not consistent. Thus, inferences about the relative efficacy of these four medications specific for the treatment of dementia should be made cautiously as head to head comparisons were not undertaken.

Question 4: Do certain patient populations benefit more from pharmacotherapy than others?

In general, very few trials examined the efficacy of dementia drugs across different populations or described the population characteristics in sufficient detail. From the 15 studies [2,3,8,10-12,23,24,61,84,93,129-132] that reported stratified analyses, eight different variables were identified, which included age, gender, Apolipoprotein E gene (APOE) genotype, disease type, disease severity (as determined by MMSE/ ADAS-cog threshold levels), treatment center, care dependence, and presence of depression. Additionally, three trials were identified that evaluated efficacy in 1) patients with Down's syndrome and dementia, 2) different races as a function of treatment center of a multicenter trial, and 3) depressed patients. Given the relatively small number of trials evaluating these variables within different populations and different pharmacological interventions, the findings of this review are inconclusive with respect to these variables. A significant gap in the literature has been identified.

Question 5: What is the evidence-base for the treatment of ischemic vascular dementia?

A total of 20 pharmacological interventions in 29 studies [17,36,38,44,46,70-72,81,92,96,98,102-104,106,107,117,126,128,133-141] were applied specifically to VaD classified dementias. The majority of these pharmacological interventions (n=14) were represented by single trials, limiting the ability to judge the evidence; these interventions included ateroid, buflomedil, cerebrolysin, sulphomucopolysaccharides (CDP choline), citalopram, donepezil, Ginkgo biloba, idebenone, minaprine, nimodipine, oxiracetam, 5-THF (trazodone), vincamine, and xantinolnicotinate. Six interventions had more than a single trial, and these included Choto-san (n=2), memantine (n=3), nicergoline (n=2), pentoxifylline (n=4), posatirelin (n=2), and propentofylline (n=2). In general, when the drug interventions were shown to be effective, it was in the domains of cognitive function (both general and specific) and global assessment. Other domains were less frequently evaluated. Several trials attempted to test for differences between VaD groups and other dementia types.

Discussion

The findings of this report suggest several important areas for future research using pharmacological treatments for dementia and these include:

Analytic framework of the intended aim of the therapy on the disease

- Better conceptualization and research design to capture "delay in progression."
- Clearer consensus on defining efficacy (benefits and clinically important change).
- Longer term studies (> 12 months).

Potential for bias

- Clarification of the role of industry sponsorship; one recommendation should be that all studies are required to disclose such information in future, including who analyzed the results.
- More concerted effort to incorporate unpublished studies and negative trials in future reviews.

Population

- Inclusion of the spectrum of severity in the patient populations (nothing to suggest that severe patients may not benefit from pharmacotherapy aimed at cognitive function improvement).
- The need for validation of trials and testing processes within cultures other than the traditional white population.
- Examining the efficacy of interventions in different sub-populations (age, disease severity levels, etc.).
- Better measurement and reporting of important patient characteristics (including baseline cognition scores, co-morbid conditions, the use of other medications, etc.).
- Inclusion of MCI type groups of subjects to evaluate "delay of onset" (studies in progress).

Outcomes

- Expansion of outcomes collected to include more than just cognitive function, and especially include caregiver burden and quality of life/ADL.
- Clear operational definitions for determining critical outcomes (delay to onset, delay to progression, important effect size, etc.).
- Understanding of how therapies are addressed and what outcomes are produced in different cultures.
- Production of other testing tools to detect both onset and responses to therapies across varied cultural groups.
- Improvement in the reporting of adverse events to evaluate harm and risk vs. benefit.
- Improvement in detailing adverse events associated with the duration period and those occurring following this period.

Analysis

- Appropriate analytical strategies that take into account intention to treat (ITT)/ last observation carried forward (LOCF) analyses; where possible both observed case and ITT/LOCF analyses should be presented.
- Sufficient data to estimate effect size, taking into account variability in both treated and control populations on the primary measures.
- Reporting the power of the study when findings are statistically non-significant.

Intervention

- Undertake more studies with direct comparison of drugs to determine the relative efficacy of agents.
- Improved description of the titration process.
- Improved collection of adverse events undertaken in a systematic fashion with standardized instruments.

Table 1. Pharmacological interventions and the number of trials (#) evaluated in this systematic review.

Cholinergic neurotransmitter modifying agents	
Antagonic Stress (2)	Metrifonate (9)
Acetyl-L-Carnitine (6)	Nicergoline (5)
Donepezil (11)	Physostigmine (4)
Eptastigmine (2)	Posatirelin (4)
Galantamine (6)	Rivastigmine (6)
Huperzine-A (2)	Sabeluzole (1)
Linopirdine (2)	Tacrine (8)
Mexofenoxate (1)	Velnacrine (3)
Non-cholinergic neurotransmitter/neuropeptide modifying agents	
Alaproclate (1)	Memantine (3)
Alprazolam (1	Mianserin (1)
Anapsos (1)	Minaprine (1)
BMY (Nootropic) (1	Moclobemide (1)
Carbamazepine (2)	Naftidrofuryl (1)
Citalopram (2)	Olanzapine (2)
Diphenhydramine (1)	Oxazepam (1)
Divalproex (2)	Paroxetine (1)
Fluoxetine (2)	Perphenazine (1)
Fluvoxamine (1)	Phosphatidylserine (2)
Haloperidol (8)	Risperidone (2)
Imipramine (1)	Selegiline (6)
Lisuride (1)	Sertraline (2)
Lorazepam (2)	Thioridazine (1)
Loxapine (2)	Tiapride (2)
Lu25-109 (1)	Trazodone (2)
Maprotiline (1)	Xanomeline (1)
Melperone (1)	
Other agents	
5'-MTHF (1)	Misoprostol (1)
Aniracetam (1)	Monosialotetrahexosylganglioside (GM-1) (1)
Amitriptyline (1)	N-Acetylcysteine (1)
Ateroid (1)	Nimesulide (1)
Buflomedil (1)	Nimodipine (2)
Cerebrolysin (6)	Nizatidine (1)
Choro-San (1)	Nootropic (1)
Choto-San (1)	ORG 2766 (2)
Citicoline (2)	Oxiracetam (5)
Cyclandelate (2)	Pentoxifylline (4)
Denbufylline (1)	Piracetam (1)
Desferrioxamine (1)	Prednisone (1)
Diclofenac (1)	Propentofylline (4)
Ergokryptine (CMB 36-733) (1)	Pyritinol (1)
Ergokryptine (Dek) (1)	Silymarin + Tacrine (1)
Estrogens (5)	Simvastatin (1)
Ginkgo Biloba (3)	Sulphomucopolysaccharides (1)
Glycosaminoglycan Polysulfate (1)	Sulodexide (1)
Guanfacine (1)	Thiamine (1)
Hydergine (1)	Vasopressin (DDAVP) (1)
Hydroxychloroquine (1)	Vincamine (1)
Idebenone (5)	Vitamin E (2)
Indomethacin (1)	Xantinolnicotinate (1)

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by McMaster University Evidence-based Practice Center under Contract No. 290-02-0020. It is expected to be available in April 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 97, *Pharmacological Treatment of Dementia*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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References

1. Thal LJ, Calvani M, Amato A, et al. A 1-year controlled trial of acetyl-l-carnitine in early-onset AD. Neurology 2000a; 55(6):805-10.
2. Thal LJ, Carta A, Clarke WR, et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 1996a; 47(3):705-11.
3. Sano M, Bell K, Cote L, et al. Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. Arch Neurol 1992 Nov; 49(11):1137-41.
4. Livingston GA, Sax KB, McClenahan Z, et al. Acetyl-l-carnitine in dementia. Int J Geriatr Psychiatry 1991; 6(12):853-60.
5. Spagnoli A, Lucca U, Menasce G, et al. Long-term acetyl-L-carnitine treatment in Alzheimer's disease. Neurology 1991 Nov; 41(11):1726-32.
6. Rai G, Wright G, Scott L, et al. Double-blind, placebo-controlled study of acetyl-l-carnitine in patients with Alzheimer's disease. Curr Med Res Opin 1990; 11(10):638-47.
7. Dunne MP, Hartley LR. Scopolamine and the control of attention in humans. Psychopharmacologia 1986; 89(1):94-7.
8. Prasher VP, Huxley A, Haque MS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease: Pilot study. Int J Geriatr Psychiatry 2002 Mar; 17(3):270-8.
9. Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001 Aug 14; 57(3):481-8.
10. Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001b; 57(3):489-95.
11. Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001 Aug 28; 57(4):613-20.
12. Tariot PN, Cummings JL, Katz IR, et al. A randomised, double-blind, placebo-controlled study of the efficacy and safety of Donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001a; 49(12):1590-9.
13. Burns A, Rossor M, Hecker J, et al. The effects of donepezil in Alzheimer's disease—results from a multinational trial. Dement Geriatr Cogn Disord 1999 May; 10(3):237-44.
14. Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998b; 50(1):136-45.
15. Rogers SL, Doody RS, Mohs RC, et al. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Arch Intern Med 1998a; 158(9):1021-31.
16. Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. The Donepezil Study Group. Dementia 1996 Nov; 7(6):293-303.
17. Pratt RD, Perdomo CA. Donepezil-treated patients with probable vascular dementia demonstrate cognitive benefits. Ann N Y Acad Sci 2002 Nov; 977:513-22.
18. Thomas A, Iacono D, Bonanni L, et al. Donepezil, rivastigmine, and vitamin E in Alzheimer disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months. Clin Neuropharmacol 2001 Jan; 24(1):31-42.
19. Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002 Apr 13; 359(9314):1283-90.
20. Rockwood K, Mintzer J, Truyen L, et al. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2001; 71(5):589-95.
21. Wilkinson D, Murray J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2001 Sep; 16(9):852-7.
22. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000 Jun 27; 54(12):2269-76.
23. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000 Dec 9; 321(7274):1445-9.
24. Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000 Jun 27; 54(12):2261-8.
25. Schulz R, O'Brien A, Czaja S, et al. Dementia caregiver intervention research: in search of clinical significance. Gerontologist 2002 Oct; 42(5):589-602.
26. Jann MW, Cyrus PA, Eisner LS, et al. Efficacy and safety of a loading-dose regimen versus a no-loading-dose regimen of metrifonate in the symptomatic treatment of Alzheimer's disease: a randomized, double-masked, placebo-controlled trial. Clin Ther 1999; 21(1):88-102.
27. Raskind MA, Cyrus PA, Ruzicka BB, et al. The effects of metrifonate on the cognitive, behavioral, and functional performance of Alzheimer's disease patients. J Clin Psychiatry 1999; 60(5):318-25.

28. Becker RE, Colliver JA, Markwell SJ, et al. Effects of metrifonate on cognitive decline in Alzheimer's disease: a double-blind, placebo-controlled, 6-month study. Alzheimer Dis Assoc Disord 1998 Mar; 12(1):54-7.
29. Morris JC, Cyrus PA, Orazem J, et al. Metrifonate benefits cognitive, behavioral, and global function in patients with Alzheimer's disease. Neurology 1998 May; 50(5):1222-30.
30. Cummings JL, Cyrus PA, Bieber F, et al. Metrifonate treatment of the cognitive deficits of Alzheimer's disease. Neurology 1998b; 50(5):1214-21.
31. Pettigrew LC, Bieber F, Lettieri J, et al. Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. J Clin Pharmacol 1998 Mar; 38(3):236-45.
32. Becker RE, Colliver JA, Markwell SJ, et al. Double-blind, placebo-controlled study of metrifonate, an acetylcholinesterase inhibitor, for Alzheimer's disease. Alzheimer Dis Assoc Disord 1996; 10(3):124-31.
33. Cummings J, Bieber F, Mas J, et al. Metrifonate in Alzheimer's disease: results of a dose finding study. Alzheimers Dis Biol Diagn Ther 1997:665-9.
34. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. Drug Saf 1998 Dec; 19(6):465-80.
35. Winblad B, Bonura ML, Rossini BM, et al. Nicergoline in the treatment of mild-to-moderate Alzheimer's disease: a European multicentre trial. Clin Drug Investig 2001a(9):621-32.
36. Herrmann WM, Stephan K, Gaede K, et al. A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. Dement Geriatr Cogn Disord 1997 Jan; 8(1):9-17.
37. Nappi G, Bono G, Merlo P, et al. Long-term nicergoline treatment of mild to moderate senile dementia. Results of a multicentre, double-blind, placebo-controlled study. Clin Drug Investig 1997(6):308-16.
38. Saletu B, Paulus E, Linzmayer L, et al. Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. Psychopharmacologia 1995 Feb; 117(4):385-95.
39. Schneider F, Popa R, Mihalas G, et al. Superiority of antagonic-stress composition versus nicergoline in gerontopsychiatry. Ann N Y Acad Sci 1994 Jun; 717:332-42.
40. Moller HJ, Hampel H, Hegerl U, et al. Double-blind, randomized, placebo-controlled clinical trial on the efficacy and tolerability of a physostigmine patch in patients with senile dementia of the Alzheimer type. Pharmacopsychiatry 1999 May; 32(3):99-106.
41. Thal LJ, Schwartz G, Sano M, et al. A multicenter double-blind study of controlled-release physostigmine for the treatment of symptoms secondary to Alzheimer's disease. Neurology 1996b; 47(6):1389-95.
42. Van Dyck CH, Newhouse P. Extended-release physostigmine in Alzheimer's disease: a multicenter, double-blind, 12-week study with dose enrichment. Arch Gen Psychiatry 2000; 57(2):157-64.
43. Thal LJ, Ferguson JM, Mintzer J, et al. A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. Neurology 1999 Apr 12; 52(6):1146-52.
44. Ferrari E, Cucinotta D, Albizatti MG, et al. Effectiveness and safety of posatirelin in the treatment of senile dementia: a multicenter, double-blind, placebo-controlled study. Arch Gerontol Geriatr 1998; 27(Suppl 6):163-74.
45. Gasbarrini G, Stefanini G, Addolorato G, et al. Posatirelin for the treatment of degenerative and vascular dementia: results of explanatory and pragmatic efficacy analyses. Arch Gerontol Geriatr 1997; 26(1):33-47.
46. Parnetti L, Ambrosoli L, Agliati G, et al. Posatirelin in the treatment of vascular dementia: a double-blind multicentre study vs placebo. Acta Neurol Scand 1996 Jun; 93(6):456-63.
47. Parnetti L, Ambrosoli L, Abate G, et al. Posatirelin for the treatment of late-onset Alzheimer's disease: a double-blind multicentre study vs citicoline and ascorbic acid. Acta Neurol Scand 1995 Aug; 92(2):135-40.
48. Potkin SG, Anand R, Fleming K, et al. Brain metabolic and clinical effects of rivastigmine in Alzheimer's disease. Int J Neuropsychopharmacol 2001 Sep; 4(3):223-30.
49. McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000 Dec 16; 356(9247):2031-6.
50. Forette F, Anand R, Gharabawi G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon registered). Eur J Neurol 1999; 6(4):423-9.
51. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999 Mar 6; 318(7184):633-8.
52. Agid Y, Dubois B, Anand R, et al. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp 1998; 59(12):837-45.
53. Corey-Bloom JR, Anand JV, Veach J, et al. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998; 1:55-65.
54. Knapp MJ, Knopman DS, Solomon PR, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994b; 271(13):985-91.
55. Maltby N, Broe GA, Creasey H, et al. Efficacy of tacrine and lecithin in mild to moderate Alzheimer's disease: double blind trial. BMJ 1994 Apr 2; 308(6933):879-83.
56. Prentice N, Van BM, Dougall NJ, et al. A double-blind, placebo-controlled study of tacrine in patients with Alzheimer's disease using SPET. J Psychopharmacol (Oxf) 1996; 10(3):175-81.
57. Weinstein HC, Teunisse S, Van Gool WA. Tetrahydroaminoacridine and lecithin in the treatment of Alzheimer's disease. Effect on cognition, functioning in daily life, behavioural disturbances and burden experienced by the carers. J Neurol 1991 Feb; 238(1):34-8.
58. Wong WJ, Liu HC, Fuh JL, et al. A double-blind, placebo-controlled study of tacrine in Chinese patients with Alzheimer's disease. Dement Geriatr Cogn Disord 1999 Jul; 10(4):289-94.
59. Wood PC, Castleden CM. A double-blind, placebo controlled, multicentre study of tacrine for Alzheimer's disease. Int J Geriatr Psychiatry 1994; 9(8):649-54.
60. Allain H, Schuck S, Lebreton S, et al. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. Dement Geriatr Cogn Disord 1999 May; 10(3):181-5.
61. Gutzmann H, Kuhl KP, Hadler D, et al. Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. Pharmacopsychiatry 2002 Jan; 35(1):12-8.
62. Antuono PG. Effectiveness and safety of velnacrine for the treatment of Alzheimer's disease. A double-blind, placebo-controlled study. Mentane Study Group. Arch Intern Med 1995 Sep 11; 155(16):1766-72.

63. Huff FJ, Antuono P, Murphy M, et al. Potential clinical use of an adrenergic/cholinergic agent (HP 128) in the treatment of Alzheimer's disease. Ann N Y Acad Sci 1991; 640:263-7.
64. Zemlan FP, Folks DG, Goldstein BJ, et al. Velnacrine for the treatment of Alzheimer's disease: a double-blind, placebo-controlled trial. J Neural Transm Gen Sect 1996; 103(8-9):1105-16.
65. Allain H, Dautzenberg PH, Maurer K, et al. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. Psychopharmacologia 2000 Mar; 148(4):361-6.
66. Teri L, Logsdon RG, Peskind E, et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. Neurology 2000 Nov 14; 55(9):1271-8.
67. Petrie WM, Ban TA, Berney S, et al. Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation. J Clin Psychopharmacol 1982 Apr; 2(2):122-6.
68. De Deyn PP, Rabheru K. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999 Sep 22; 53(5):946-55.
69. Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1997; 9(4):591-3.
70. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999 Feb; 14(2):135-46.
71. Orgogozo J, Rigaud AS, Stoffler A, et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia. Stroke 2002; 33:1834-9.
72. Wilcock G, Mobius HJ, Stoffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002; 17(6):297-305.
73. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336(17):1216-22.
74. Mangoni A, Grassi MP, Frattola L, et al. Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. Eur Neurol 1991; 31(2):100-7.
75. Agnoli A, Fabbrini G, Fioravanti M, et al. CBF and cognitive evaluation of Alzheimer type patients before and after IMAO-B treatment: a pilot study. Eur Neuropsychopharmacol 1992 Mar; 2(1):31-5.
76. Burke WJ, Roccaforte WH, Wengel SP, et al. L-deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. J Am Geriatr Soc 1993a; 41(11):1219-25.
77. Filip V, Kolibas E. Selegiline in the treatment of Alzheimer's disease: a long-term randomized placebo-controlled trial. Czech and Slovak Senile Dementia of Alzheimer Type Study Group. J Psychiatry Neurosci 1999 May; 24(3):234-43.
78. Freedman M, Rewilak D, Xerri T, et al. L-deprenyl in Alzheimer's disease: cognitive and behavioral effects. Neurology 1998; 50(3):660-8.
79. Ruether E, Ritter R, Apecechea M, et al. Efficacy of the peptidergic nootropic drug cerebrolysin in patients with senile dementia of the Alzheimer type (SDAT). Pharmacopsychiatry 1994 Jan; 27(1):32-40.
80. Bae CY, Cho CY, Cho K, et al. A double-blind, placebo-controlled, multicenter study of Cerebrolysin for Alzheimer's disease. J Am Geriatr Soc 2000 Dec; 48(12):1566-71.
81. Xiao S, Yan H, Yao P, et al. The efficacy of cerebrolysin in patients with vascular dementia: results of a Chinese multicentre, randomised, double-blind, placebo-controlled trial. Hong Kong Journal of Psychiatry 1999(2):13-9.
82. Xiao S, Yan H, Yao P, et al. Efficacy of FPF 1070 (cerebrolysin) in patients with Alzheimer's disease: a multicentre, randomised, double-blind, placebo-controlled trial. Clin Drug Investig 2000(1):43-53.
83. Ruether E, Husmann R, Kinzler E, et al. A 28-week, double-blind, placebo-controlled study with Cerebrolysin in patients with mild to moderate Alzheimer's disease. Int Clin Psychopharmacol 2001 Sep; 16(5):253-63.
84. Panisset M, Gauthier S, Moessler H, et al. Cerebrolysin in Alzheimer's disease: a randomized, double-blind, placebo-controlled trial with a neurotrophic agent. J Neural Transm Gen Sect 2002; 109(7-8):1089-104.
85. Asthana S, Baker LD, Craft S, et al. High-dose estradiol improves cognition for women with AD: results of a randomized study. Neurology 2001 Aug 28; 57(4):605-12.
86. Wang PN, Liao SQ, Liu RS, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. Neurology 2000 Jun 13; 54(11):2061-6.
87. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000 Jan 25; 54(2):295-301.
88. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. JAMA 2000(8):1007-15.
89. Kyomen HH, Satlin A, Hennen J, et al. Estrogen therapy and aggressive behavior in elderly patients with moderate-to-severe dementia: results from a short-term, randomized, double-blind trial. Am J Geriatr Psychiatry 1999; 7(4):339-48.
90. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. JAMA 1997(16):1327-32.
91. Maurer K, Ihl R, Dierks T, et al. Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. J Psychiatr Res 1997 Nov; 31(6):645-55.
92. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996 Mar; 29(2):47-56.
93. Weyer G, Babej-Dolle RM, Hadler D, et al. A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. Neuropsychobiology 1997; 36(2):73-82.
94. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. J Neural Transm Suppl 1998; 54:301-10.
95. Bergamasco B, Scarzella L, La Commare P. Idebenone, a new drug in the treatment of cognitive impairment in patients with dementia of the Alzheimer type. Funct Neurol 1994 May; 9(3):161-8.
96. Marigliano V, Abate G, Barbagallo-Sangiorgi G, et al. Randomized, double-blind, placebo controlled, multicentre study of idebenone in patients suffering from multi-infarct dementia. Arch Gerontol Geriatr 1992; 15(3):239-48.
97. Bottini G, Vallar G, Cappa S, et al. Oxiracetam in dementia: a double-blind, placebo-controlled study. Acta Neurol Scand 1992 Sep; 86(3):237-41.

98. Maina G, Fiori L, Torta R, et al. Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. Neuropsychobiology 1989; 21(3):141-5.
99. Mangoni A, Perin C, Smirne S, et al. A double-blind, placebo-controlled study with oxiracetam in demented patients administered the Luria-Nebraska Neuropsychological Battery. Drug Dev Res 1988; 14(3-4):217-4.
100. Rozzini R, Zanetti O, Bianchetti A. Effectiveness of oxiracetam therapy in the treatment of cognitive deficiencies secondary to primary degenerative dementia. Acta Neurol (Napoli) 1992 Apr; 14(2):117-26.
101. Burgio LD, Reynolds CFI, Janosky JE, et al. A behavioral microanalysis of the effects of haloperidol and oxazepam in demented psychogeriatric inpatients. Int J Geriatr Psychiatry 1992; 7(4):253-62.
102. Ghose K. Oxpentifylline in dementia: a controlled study. Arch Gerontol Geriatr 1987 Apr; 6(1):19-26.
103. Black RS, Barclay LL, Nolan KA, et al. Pentoxifylline in cerebrovascular dementia. J Am Geriatr Soc 1992 Mar; 40(3):237-44.
104. Knezevic S. European Pentoxifylline Multi-Infarct Dementia Study. Eur Neurol 1996; 36(5):315-21.
105. Mielke R, Ghaemi M, Kessler J, et al. Propentofylline enhances cerebral metabolic response to auditory memory stimulation in Alzheimer's disease. JNS 1998 Jan 21; 154(1):76-82.
106. Mielke R, Kittner B, Ghaemi M, et al. Propentofylline improves regional cerebral glucose metabolism and neuropsychologic performance in vascular dementia. JNS 1996 Sep 15; 141(1-2):59-2.
107. Marcusson J, Rother M, Kittner B, et al. A 12-month, randomized placebo-controlled trial of propentofylline (HWA 285) in patients with dementia according to DSM III-R. Dement Geriatr Cogn Disord 1997; 8(5):320-8.
108. Saletu B, Moller HJ, Grunberger J, et al. Propentofylline in adult-onset cognitive disorders: double-blind, placebo-controlled, clinical, psychometric and brain mapping studies. Neuropsychobiology 1990 Sep; 24(4):173-84.
109. Convit A, de Asis J, de Leon MJ, et al. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. Neurobiol Aging 2000 Jan; 21(1):19-26.
110. Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging Ment Health 2002 Feb; 6(1):5-11.
111. Johnson SA, Simmon VF. Randomized, double-blind, placebo-controlled international clinical trial of the AMPAKINE CX516 in elderly participants with mild cognitive impairment. A progress report. J Mol Neurosci 2002; 19(1-2):197-200.
112. Sherwin BB. Estrogen and cognitive functioning in men with mild cognitive impairment. J Mol Neurosci 2002; 19(1-2):219-23.
113. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002 Apr; 26(4):494-504.
114. Carlyle W, Ancill RJ, Sheldon L. Aggression in the demented patient: a double-blind study of loxapine versus haloperidol. Int Clin Psychopharmacol 1993; 8(2):103-8.
115. Ancill RJ, Carlyle WW, Liang RA, et al. Agitation in the demented elderly: a role for benzodiazepines? Int Clin Psychopharmacol 1991; 6(3):141-6.
116. Coccaro EF, Kramer E, Zemishlany Z, et al. Pharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients. Am J Psychiatry 1990 Dec; 147(12):1640-5.
117. Cucinotta D, Romagnoli S, Godoli G, et al. Comparison of sulfomucopolysaccharides and cytidine diphosphocholine in the treatment of multi-infarct dementia: a randomized double-blind test. Curr Ther Res Clin Exp 1988; 43(1):12-20.
118. Karlsson I, Godderis J, Augusto De Mendonca LC, et al. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. Int J Geriatr Psychiatry 2000 Apr; 15(4):295-305.
119. Pollock BG, Mulsant BH, Rosen J, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry 2002; 159(3):460-5.
120. Barnes R, Veith R, Okimoto J. Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. Am J Psychiatry 1982; 139(9):1170-4.
121. Chan WC, Lam LC, Choy CN, et al. A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001 Dec; 16(12):1156-62.
122. Katona CL, Hunter BN, Bray J. A double-blind comparison of the efficacy and safely of paroxetine and imipramine in the treatment of depression with dementia. Int J Geriatr Psychiatry 1998 Feb; 13(2):100-8.
123. Taragano FE, Lyketsos CG, Mangone CA, et al. A double-blind, randomized, fixed-dose trial of fluoxetine vs. amitriptyline in the treatment of major depression complicating Alzheimer's disease. Psychosomatics 1997 May; 38(3):246-52.
124. Popa R, Schneider F, Mihalas G, et al. Antagonic-stress superiority versus meclofenoxate in gerontopsychiatry. Arch Gerontol Geriatr 1994; 18(Suppl 4):197-206.
125. Spilich GJ, Wannenmacher W, Duarte A, et al. Efficacy of pyritinol versus hydergine upon cognitive performance in patients with senile dementia of the Alzheimer's type: a double-blind multi-center trial. Alzheimers Res 1996(3):79-84.
126. Parnetti L, Mari D, Abate G, et al. Vascular dementia Italian sulodexide study (VA.D.I.S.S.). Clinical and biological results. Thromb Res 1997 Jul 15; 87(2):225-33.
127. Gutzmann H, Kuhl KP, Kanowski S, et al. Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. Pharmacopsychiatry 1997 Jan; 30(1):6-11.
128. Passeri M, Cucinotta D, Abate G, et al. Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. Aging (Milano) 1993 Feb; 5(Milano):63-71.
129. Alvarez XA, Pichel V, Perez P, et al. Double-blind, randomized, placebo-controlled pilot study with anapsos in senile dementia: effects on cognition, brain bioelectrical activity and cerebral hemodynamics. Methods Find Exp Clin Pharmacol 2000 Sep; 22(7):585-94.
130. Ruether E, Alvarez XA, Rainer M, et al. Sustained improvement of cognition and global function in patients with moderately severe Alzheimer's disease: a double-blind, placebo-controlled study with the neurotrophic agent Cerebrolysin. J Neural Transm Suppl 2002(62):265-75.
131. Schellenberg R, Todorova A, Wedekind W, et al. Pathophysiology and psychopharmacology of dementia: a new study design. Neuropsychobiology 1997; 35(3):132-42.

132. Reifler BV, Teri L, Raskind M, et al. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. Am J Psychiatry 1989 Jan; 146(1):45-9.
133. Ban TA, Morey LC, Santini V. Clinical investigations with ateroid in old-age dementias. Semin Thromb Hemost 1991b; 17(Suppl 2):161-3.
134. Cucinotta D, Aveni Casucci MA, Pedrazzi F, et al. Multicentre clinical placebo-controlled study with buflomedil in the treatment of mild dementia of vascular origin. J Int Med Res 1992 Apr; 20(2):136-49.
135. Shimada Y, Terasawa K, Yamamoto T, et al. A well-controlled study of Choto-san and placebo in the treatment of vascular dementia. J Tradit Med 1994; 11:246-55.
136. Terasawa K, Shimada Y, Kita T, et al. Choto-san in the treatment of vascular dementia: a double-blind, placebo-controlled study. Phytomedicine 1997; 4(1):15-22.
137. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. Br J Psychiatry 1990 Dec; 157:894-901.
138. Passeri M, Cucinotta D, de Mello M, et al. Comparison of minaprine and placebo in the treatment of Alzheimer's disease and multi-infarct dementia. Int J Geriatr Psychiatry 1987; 2(2):97-103.
139. Saletu B, Anderer P, Semlitsch HV. Relations between symptomatology and brain function in dementias: double-blind, placebo-controlled, clinical and EEG/ERP mapping studies with nicergoline. Dement Geriatr Cogn Disord 1997; Vol 8(Suppl 1):12-21.
140. Pantoni L, Rossi R, Inzitari D, et al. Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. JNS 2000b; 175(2):124-34.
141. Fischhof PK, Moslinger-Gehmayr R, Herrmann WM, et al. Therapeutic efficacy of vincamine in dementia. Neuropsychobiology 1996; 34(1):29-35.

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