THERAPEUTICS

Review: Pharmacotherapy improves cognitive symptoms in dementia

Santaguida P, Raina P, Booker L, et al. **Pharmacological treatment of dementia.** Evid Rep Technol Assess (Summ). 2004;Apr:1-16.

QUESTION

In patients with dementia, how effective is pharmacotherapy for improving cognitive symptoms?

METHODS

Data sources: Cochrane Central Trial Registry (containing MEDLINE and EMBASE/Excerpta Medica citations to 1998) (to 2003), MEDLINE (1998 to 2003 wk 4), EMBASE/Excerpta Medica (1998 to 2003 wk 5), AMED (1985 to February 2003), CINAHL (1982 to February 2003), Ageline (1978 to December 2002), and PsycINFO (1967 to December 2003); and references of retrieved articles.

Study selection and assessment: Studies were selected if they were English-language parallel-group randomized controlled trials (RCTs) of pharmacologic agents in patients ≥ 18 years of age with dementia. Study quality was assessed using the modified Jadad scale for RCTs.

Outcomes: Outcomes included changes in general and specific cognitive function, global assessment, behavior and mood, quality of life and activities of daily living, and caregiver burden.

MAIN RESULTS

186 RCTs evaluating 97 pharmacologic agents were included. The Table summarizes the placebo-controlled RCTs of agents showing statistically significant improvement in outcomes.

CONCLUSIONS

In patients with dementia, several agents improve cognitive function; some agents improve global assessment; and few improve behavior or mood or quality of life or activities of daily living. Caregiver burden is rarely evaluated.

Source of funding: Agency for Healthcare Research and Quality (AHRQ).

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Randomized placebo-controlled trials (RCTs) of pharmacologic agents for dementia*

Drug	Number of RCTs (*n*)	Number of RCTs showing significant improvement/total number of RCTs measuring outcome					
		GCF	SCF	GA	B/M	QOL/ADL	CB
CNMAs							
Carnitine	6 (925)	0/4	0/4	0/4	0/3	0/5	NT
Donepezil	10 (3239)	8/10	NT	8/9	0/4	5/8	0/1
Galantamine	6 (3530)	5/6	NT	5/6	2/3	4/6	NT
Metrifonate†	9 (2759)	8/9	NT	4/9	1/7	1/6	NT
Nicergoline	4 (705)	4/4	NT	2/4	0/2	0/1	NT
Physostigmine	4 (1198)	3/4	NT	2/4	0/1	0/3	NT
Posatirelin	4 (931)	2/4	NT	1/1	1/4	3/4	NT
Rivastigmine	6 (2071)	4/5	1/2	5/6	0/3	2/4	NT
Tacrine	6 (994)	1/6	0/1	2/3	0/4	0/2	0/2
Velnacrine	3 (774)	2/2	0/1	2/3	0/1	1/2	1/1
NCNMAs							
Haloperidol	5 (622)	0/3	NT	1/4	3/5	0/2	0/2
Memantine	3 (1066)	2/2	NT	1/3	1/1	1/1	NT
Selegiline	6 (733)	0/5	1/2	1/4	1/3	NT	NT
Other agents							
Cerebrolysin	6 (819)	4/5	2/4	5/6	1/3	0/6	NT
Estrogens	5 (247)	0/3	1/3	0/5	0/5	0/4	NT
Ginkgo biloba	3 (563)	1/2	2/2	1/3	0/2	NT	NT
Idebenone	4 (950)	3/3	0/1	3/3	1/1	2/2	NT
Oxiracetam	5 (554)	2/3	1/4	1/1	2/4	2/3	NT
Pentoxifylline	3 (389)	0/3	0/1	0/3	0/2	0/1	NT
Propentofylline	4 (510)	2/4	1/4	1/2	1/1	0/1	NT

*GCF = global cognitive function; SCF = specific cognitive function; GA = global assessment; B/M = behavior/mood; QOL/ADL = quality of life/activities of daily living; CB = caregiver burden; CNMAs = cholinergic neurotransmitter–modifying agents; NCNMAs = noncholinergic neurotransmitter/neuropeptide- modifying agents; NT = not tested.

†Withdrawn from use in North America.

COMMENTARY

Pharmacotherapy of dementia involves treatment aimed both at the underlying disease and associated behavioral problems that occur during the course of the dementia. The summary of the extensive AHRQ report by Santaguida and colleagues serves as a concise but already-outdated reference on the efficacy of individual medications, medication classes, and dietary supplements that have been evaluated for treatment of dementia and about which patients or families may seek advice. The full report contains tables and figures that can help the clinician critically compare trial designs and the effect size of different drugs on a given outcome measure. A print copy is recommended because the downloadable version is fragmented into hundreds of separate files.

Meta-analysis of the results from pooled trials suggests that donepezil, rivastigmine, and galantamine have similar, small effect sizes for short-term cognitive improvement in Alzheimer disease (AD). The failure of trials either to assess functional outcomes or to use the same functional outcome measure hinders a comparison of drug effects on functional decline. A lack of consensus exists on what constitutes a clinically meaningful benefit. One RCT of donepezil and 1 of memantine have shown clinically significant reductions in caregiver time devoted to activities of daily living in moderate-to-severe AD (1, 2).

The AHRQ report highlights the paucity of data on long-term efficacy. AD2000, published after this report, randomized 565 patients

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Review: Limited evidence supports the use of atypical antipsychotic drugs in behavioral and psychological symptoms of dementia

Lee PE, Gill SS, Freedman M, et al. **Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review.** BMJ. 2004;329:75-9.

QUESTION

In patients with behavioral and psychological symptoms of dementia (BPSD), how effective and safe are atypical antipsychotic drugs (AADs)?

METHODS

Data sources: Studies were identified by searching MEDLINE (1966 to September 2003), EMBASE/Excerpta Medica (1980 to September 2003), and the Cochrane Library (issue 1, 2003); scanning reference lists of retrieved articles; and contacting experts in the field.

Study selection and assessment: Studies were selected if they were blinded, randomized controlled trials (RCTs) that evaluated the 4 oral AADs available in Canada, the United States, and the United Kingdom used to treat BPSD (clozapine, risperidone, olanzapine, and quetiapine). Methodological quality of the RCTs was assessed using the Jadad and Jüni scales, including randomization procedure, blinding, withdrawals and dropouts, concealment, and follow-up.

Outcomes: Efficacy was assessed by scores on the Behavior pathology in Alzheimer's Disease (BEHAVE-AD), Cohen-Mansfield Agitation Inventory (CMAI), and Neuropsychiatric Inventory-nursing home (NPI-NH) version scales. Adverse events, specifically extrapyramidal symptoms, were also assessed.

MAIN RESULTS

5 RCTs (n = 1570, mean age 82 y) met the selection criteria. Most patients had severe dementia (mean score on the Mini-Mental State Examination 6.8 out of 30). Follow-up was 12 weeks in 4 RCTs and 6 weeks in 1 RCT. 4 RCTs evaluated risperidone (3 were placebo-controlled) and 1 compared olanzapine with placebo. Study quality was generally high. Of the 4 placebo-controlled trials, risperidone was better than placebo in 2 of 3 RCTs and olanzapine was better than placebo in 1 RCT. Of 2 RCTs comparing risperidone with haloperidol, 1 showed no difference between groups on BEHAVE-AD total scores but did show superiority of risperidone on aggressiveness subscales of BEHAVE-AD and CMAI. 1 RCT showed no difference between groups on total or subscale scores. 1 RCT showed more extrapyramidal symptoms in patients receiving 2 mg/d of risperidone than in those receiving placebo. 2 RCTs showed more extrapyramidal symptoms with haloperidol than with risperidone.

CONCLUSION

In patients with behavioral and psychological symptoms of dementia, limited evidence supports the effectiveness of atypical antipsychotic drugs.

Source of funding: Canadian Institutes of Health Research.

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with AD, diagnosed by community physicians using the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, criteria, to donepezil or placebo (3). At 3 years, no significant difference existed between the placebo and treatment groups on the principal endpoints of institutionalization and the progression to predefined disability. AD2000 has raised doubts about the efficacy and cost-effectiveness of cholinesterase inhibitors in real-world clinical practice (4), although its study design, which incorporated periodic wash-outs of the study medication, may have biased the trial toward showing no difference.

For BPSD, AADs have largely replaced conventional antipsychotic drugs because of the lower incidence of cardiac and extrapyramidal side effects. Caregiver burden caused by BPSD exerts pressure on clinicians to prescribe AADs despite restrictions on their use in long-term care facilities in the United States. The 5 RCTs reviewed by Lee and colleagues show statistically significant improvements in BPSD, compared with placebo, with effects similar to those of haloperidol. The BEHAVE-AD and NPI-NH assess the frequency and severity of various behavioral disturbances; the CMAI focuses on agitation and aggression. Because the measures do not weigh harmful or dangerous behaviors more than others, the clinical significance of these small change scores is uncertain. The shorter CMAI and NPI-NH are a convenient way to assess disruptive behaviors and develop an intervention and monitor its effectiveness in individual patients. In the 3 trials with fixed endpoints, 33% to 47% of the placebo groups achieved the target reduction in BPSD, suggesting that the behavioral disturbances of many patients are trans-ient. It has been recommended that patients with new or changed behavior be assessed for reversible contributors, such as infection, and that they be reassessed for the continued need for antipsychotics at least once every 6 months (5).

With more muscarinic, α-adrenergic, and histaminic blockade than haloperidol, AADs may cause sedation and hypotension in susceptible patients. The concern that risperidone and olanzapine increase the risk for stroke has not been supported by a retrospective population-based cohort study of patients prescribed these medications (6). Cumulative data support an association between AADs, weight gain, and impaired glucose metabolism (7). Ultimately, the choice of antipsychotic should be based on a balance between unwanted and acceptable potential side effects.

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