Review

Pharmacological management of dementia: current evidence

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Introduction

Dementia is a clinical syndrome characterised by global cognitive impairment, with a decline from previous level of functioning. It is associated with impairment in functional abilities and in many cases with behavioural and psychiatric disturbances. 1-2% of 65 year olds, 10% to 15% of 80 year olds and 40% of 90 year olds have dementia. Pharmacotherapy is often the main intervention used to improve the symptoms as well as delay the progression of dementia syndromes.

Many medications have been tried in dementia patients and they can be classified into 3 broad categories: Cholinergic neurotransmitter modifying agents; non-cholinergic neurotransmitters/neuropeptide modifying agents and other pharmacological agents. Tacrine (1993), donepezil (1996), rivastigmine (2000), galantamine (2001 and memantine (2003) are the only five agents approved by the Food and Drug Administration (FDA) for the treatment of dementia. Other agents have been evaluated in trials and prescribed off-label. The various agents have different levels of evidence for efficacy.

This review focuses on the evidence for pharmacological treatment of dementia in the domains of cognition, global function, behaviour/mood and quality of life/activities of daily living. The main focus will be of the 5 drugs approved by the FDA.

Pharmacological management of Alzheimer disease

Of the five drugs approved for treatment of dementia tacrine, donepezil, rivastigmine and galantamine are cholinergic neurotransmitter modifying agents. Tacrine has been discontinued due to the side effects.

Cholinesterase inhibitors

Numerous trials have been carried out to evaluate the efficacy of the different drugs. Cholinesterase inhibitors are used based on the cholinergic hypothesis of memory impairment where cholinergic deficits were considered to be responsible for the cognitive and behavioural changes and augmentation of central cholinergic function was considered to improve cognitive function.

Donepezil

Donepezil is a long acting reversible acetylcholinesterase inhibitor approved by the FDA based on evidence of efficacy in 2 phase three clinical trials; additional randomized clinical trials of 6 to 12 months duration and trials carried out in severely impaired and nursing home patients. Of the trials that evaluated the efficacy of donepezil compared to placebo most evaluated Alzheimer disease of mild to moderate severity. Doses of 5 or 10 mg were used and the study duration varied from 12 to 56 weeks. These trials were reviewed in a Cochrane review[1]. A single placebo controlled trial followed patients over several years and showed modest cognitive effects over two years but no significant effects on loss of function, nursing home placement or health economics[2].

Rivastigmine

Rivastigmine is a pseudo-irreversible cholinesterase inhibitor selectively for acetylcholinesterase and butyrylcholinesterase. Two trials[3,4] evaluated rivastigmine in doses from 1 to 4 mg or 6 to 12 mg and the duration of therapy varied from 14 to 26 weeks. These studies showed that rivastigmine was efficacious. Due to dose decreases not being permitted there was less tolerability and more side effects. A trial[5] studied transdermal patches (17.4 mg and 9.5 mg patch vs 6 mg oral rivastigmine twice daily) in patients with moderately severe Alzheimer disease for 6 months and the patch was efficacious with fewer adverse reactions.

Galantamine

Galantamine is a reversible competitive acetylcholinesterase inhibitor with less butyrylcholinesterase inhibition compared to rivastigmine. A Cochrane review[6] showed that 4 trials of 3 to 6 months duration demonstrated the efficacy of galantamine at doses of 8 to 16 mg twice daily. Galantamine showed positive effects with no additional effects at doses over 16mg/d. The frequency of gastrointestinal adverse events was similar to cholinesterase inhibitors.

Adverse effects of cholinesterase inhibitors

Nausea, diarrhoea, vomiting, anorexia and weight loss are the most common adverse effects of the cholines-

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terase inhibitors. Muscle cramps are common with donepezil. The early cholinergic effects are dose related and temporary dose reduction and retritrating reduces re-emergence of adverse effects. Few trials compared adverse effect of cholinesterase inhibitors. Donepezil in doses of 23mg/d had more adverse effects than 10mg/d in a direct comparison[7] and fewer adverse events were noted with transdermal rivastigmine. Long term safety of cholinesterase inhibitors have not been systematically studied and warrant consideration in future studies.

Efficacy of cholinesterase inhibitors

Most trials have been carried out for 3 to 6 months in patients with mild to moderate Alzheimer disease. No evidence exists for difference in efficacy between the 3 cholinesterase inhibitors. In a Cochrane review[8] all drugs showed an overall positive effect over placebo on the Alzheimer Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) over 6 months. The trial design and modest therapeutic effect make it difficult to identify individual treatment responders.

Based on three 6-month, randomised placebo controlled clinical trials donepezil is the only cholinesterase inhibitor efficacious for severe Alzheimer disease. However the effects were modest.

Dosage of cholinesterase inhibitors

Donepezil is started at 5mg/d and can be increased up to 10mg/d after 4 weeks. Both doses were effective but the 10mg dose was more effective when the dosing groups were directly compared. Patients with moderate to severe Alzheimer disease can be treated with the sustained release 23mg/d donepezil if they have been treated with 10mg/d for at least 3 months[7].

Rivastigmine is commenced at 1.5mg twice a day with meals. It can be increased to 3mg twice daily after 2 weeks. Doses can be increased up to 6mg twice per day. Higher doses have better efficacy. The initial dose of the transdermal patch is 4.6mg per day and the maintenance dose vary from 4.6mg/d, 9.5mg/d or 13.3mg/d.

Galantamine is commenced at 4mg twice a day and can be increased up to 12 mg twice a day. The extended release preparation is commenced at 8mg/d and can be increased to 24 mg/d.

Cholinesterase inhibitors for mild cognitive impairment

Cholinesterase inhibitors are not indicated for mild cognitive impairment. Randomised placebo controlled trials of cholinesterase inhibitors for mild cognitive impairment were not positive on their primary outcomes[9,10,11] and showed more adverse events[12,13]. Uncertainty on the definition of mild cognitive impairment limited the inferences obtained from the trials. Further there were broad variations in cognitive impairment and progression to Alzheimer disease.

Memantine

Memantine a moderate affinity, uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist is approved for moderate to severe Alzheimer disease based on two 6 month long placebo controlled clinical trials[14,15]. Cholinesterase inhibitors were not allowed in one trial and in the other trial the patients had been taking donepezil for at least 6 months and on an average for over 2 years before being randomised to memantine or placebo. Another trial did not show any significant effect of memantine in moderate to severe Alzheimer disease[16]. Memantine is not approved for mild Alzheimer disease[17].

Adverse effects include headache, dizziness, confusion, somnolence and sometimes hallucinations. There are no adverse drug interactions with cholinesterase inhibitors. Memantine is commenced at 5 mg/d for 1 week and increased in weekly increments of 5mg/d until a dose of 10mg twice daily. Its effectiveness is not known beyond 6 months.

Controversies of pharmacotherapy

The treatment of dementia with cholinesterase inhibitors and memantine result in statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia[18]. The United Kingdom's National Institute for Health and Clinical Excellence (NICE) suggests that cholinesterase inhibitors can delay cognitive impairment for 6 months[19] but they are not cost effective.

Efficacy versus effectiveness

Trends show a statistical significance, but there is overlap in outcomes between drug and placebo patients. There is only small or modest cognitive effects of cholinesterase inhibitors thus making an inference about their effects are difficult. It is difficult to identify individual patients who benefit from cholinesterase inhibitors or memantine because the outcome measures and mean changes on the scale scores do not identify responders.

Duration of treatment

Most trials have been for 6 months with a few lasting 12 months or more. Inferences were made that if the drug was effective over this period they will be effective for longer periods. Some observational studies and open label extension of clinical trials suggest that use of cholinesterase inhibitors over at least 1 year result in a delay in nursing home placement and that addition of

memantine could further delay the progression[20,21,22,23]. These observational studies were not controlled and were subject to bias. Thus optimal period of duration of treatment is uncertain.

Effectiveness for treatment of disruptive behaviour

In a post hoc analysis of 14 cholinesterase inhibitor trials only 3 showed significant effect in improving behaviour[24] and none of these effects were large. A meta-analysis showed significant but minimal effects on behaviour in the mildly cognitively impaired patients but no effect in the severely impaired[25]. Memantine and donepezil was not efficacious in improving behaviour[26,27].

Discontinuation of cholinesterase inhibitors has been associated with worsening of cognition and confusion in some patients[28]. However worsening of behaviour or confusion do not appear common in clinical practice, where only 19 to 23% of patients continue to take donepezil or rivastigmine for more than a year and about one third discontinue the drug within 2 months[29].

Overview of treatment of other forms of dementia

Frontotemporal dementia (FTD)

There is no approved treatment for FTD. Neuroleptics and antidepressants have some efficacy. Antidepressants are a safer initial choice due to better side effect profile. Selective serotonin reuptake inhibitors[30,31] and trazodone[32] and neuroleptics olanzapine[33], risperidone, and aripiprazole have shown to improve behaviour. Cholinesterase inhibitors should be avoided due to behavioural worsening in FTD and lack of cognitive improvement[34]. Early studies showed some improvement with memantine but subsequent large studies did not show any benefit[35].

Dementia with Lewy Bodies

There are currently no approved treatments for dementia with Lewy Bodies. Treatment and management are symptomatic. Cognitive features may benefit from acetylcholinesterase inhibitors and memantine[36,37].

Other dementias

There are no FDA approved drugs for the other common types of dementia. However rivastigmine has been approved for treatment of dementia associated with idiopathic Parkinson's disease[38].

Conclusion

The currently available FDA approved therapeutic agents for Alzheimer disease and other dementias are the cholinesterase inhibitors and memantine. Many other agents such as vitamins and food supplements are available in the market, however these have not proven to be efficacious. None of the pharmacological agents prevent or delay onset of minimal cognitive impairment or Alzheimer disease. The available FDA approved agents also produce statistically significant but clinically minimal effects. Thus the necessity to treat and the duration of treatment are mostly guided by the clinicians' decision.

Development of new drugs and molecules are in the process. But as there are no validated drug targets for Alzheimer disease the development of new drugs faces challenges.

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