Update on Drugs for Dementia

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The development of new anti-dementia drugs has opened new horizons in the treatment of Alzheimer’s disease, bringing hope to patients, caregivers and doctors. While this is still a relatively new field of research, we will try to review the new anti-dementia drugs currently in use in Hong Kong.

Cholinesterase Inhibitors

Cholinesterase inhibitors have shown consistent efficacy in the treatment of mild to moderate Alzheimer’s disease, and are FDA approved for this purpose. Three types of cholinesterase inhibitors are currently available in Hong Kong.

1. Donepezil (Aricept)

The drug with the greatest impact so far on the treatment of Alzheimer’s disease has been donepezil. Donepezil is an acetylcholinesterase inhibitor licensed for the symptomatic treatment of mild or moderate Alzheimer’s disease, approved by the FDA in 1996. The dosage is 5mg nocte, increased to 10mg nocte after a month if necessary. Peripheral side-effects, which include diarrhoea, nausea, vomiting, insomnia, muscle cramps and anorexia, are generally of mild intensity and transient, resolving during continued donepezil treatment. Caution should be used in patients with asthma, renal disease, cardiac disease, epilepsy, and prior upper gastrointestinal bleeding.

The 3 main placebo-controlled studies all showed an improvement in cognition as measured by ADAS-Cog scores. This has been estimated to be equivalent to a 6 to 12 month gain in cognitive function compared with baseline. The 2000 Cochrane review on donepezil concludes that in mild to moderate Alzheimer’s disease, it improves cognitive function and global clinical states but not quality of life; the 2003 Cochrane review extended the evidence for treatment effectiveness to those with severe dementia. There is also now clear evidence emerging from clinical practice that the behavioural or non-cognitive symptoms of dementia are also improved. Long term follow-up studies suggest that the cognitive advantage over placebo is maintained for up to two years.

However, symptomatic benefit of donepezil does not equate with a modulation of the underlying disease process, as once donepezil is withdrawn the treatment and placebo groups became indistinguishable in cognitive function.

Although vascular dementia is not an FDA approved indication, donepezil was also shown to be beneficial in improving cognitive function, clinical global impression and activities of daily living in patients with vascular cognitive impairment.

2. Rivastigmine (Exelon)

Rivastigmine is a centrally selective carbamate inhibitor of butyrylcholinesterase and acetylcholinesterase, and is licensed in the UK in 1998. Although it is metabolised predominantly by the liver, it is largely unaffected by cytochrome P450 enzyme, minimising the risk of significant drug interactions. Available data suggest that patients receiving 6 to 12 mg daily achieve clinical improvements in global functioning and cognition, and particularly in activities of daily living. Cockrane Review concludes from 8 trials involving 3450 subjects that rivastigmine was beneficial for people with mild to moderate Alzheimer’s disease. In comparison with placebo, improvements were seen in cognitive function, activities of daily living, and severity of dementia. Open studies of rivastigmine showed maintained effects on cognition up to a duration of 5 years.

Besides its beneficial effects in Alzheimer’s disease, rivastigmine was also shown to be useful in Lewy body dementia. Patients with Lewy body dementia taking rivastigmine were significantly less apathetic and anxious, and had fewer delusions and hallucinations than controls. Preliminary data from an open trial also showed some improvement in behavioural measures in patients with subcortical vascular dementia.

Because of its short half-life, rivastigmine has to be given twice daily. Slow titration at weekly to monthly intervals is necessary to minimise the cholinergic side-effects. Trial data suggest these are not severe, and may include nausea, vomiting and anorexia. Titration should start at 1.5mg BD, increased to 3mg BD after a minimum of 2 weeks, aiming at an effective maintenance dose of 3mg BD to 6mg BD.

3. Galantamine (Reminyl)

The third cholinesterase inhibitor, galantamine, was launched in Hong Kong in 2002. It has a dual mode of action, by specifically and reversibly inhibiting acetylcholinesterase and by allosterically modulating nicotinic cholinergic receptors. It has an elimination
half-life of about 6 hours, so BD dosing is necessary. Starting at 4mg BD, it can be increased to 8mg BD after 4 weeks and then to 12mg BD after another 4 weeks if tolerable and having clinical benefit. Adverse events are infrequent and mild, and may include nausea, vomiting, anorexia and diarrhoea. Gastrointestinal side effects can be minimised using the recommended slow dose-escalation regimen.

During randomised, double-blind, placebo-controlled trials of up to 6 months’ duration, galantamine consistently produced a broad spectrum of beneficial effects on cognitive and non-cognitive symptoms. Patients’ cognition, global function and abilities to perform activities of daily living were maintained, the emergence of recreational symptoms was postponed and apparent reductions in caregiver burden were seen. In long-term studies, galantamine maintained cognitive and functional abilities at or near baseline levels for at least 12 months, and was associated with decreases in caregiver burden.

In a recent randomised, double-blind, placebo-controlled trial, the effects of galantamine were investigated in patients with probable vascular dementia or Alzheimer’s disease combined with cerebrovascular disease. Galantamine showed greater efficacy than placebo in cognitive function, activities of daily living and behavioral symptoms in this group of patients.

**NMDA Receptor Antagonist**

Nine years after the initial approval of a cholinergic drug for the treatment of Alzheimer’s disease in USA, a compound with a completely different pharmacological approach, namely the NMDA receptor antagonist, was approved for the first time in Europe in 2002.

**Memantine (Ebixa)**

Memantine was launched in Hong Kong in April 2004, and is the only NMDA receptor antagonist currently available. It is approved for the treatment of moderate to severe Alzheimer’s disease, being the first anti-dementia drug to be available for this group of patients with advanced disease.

Glutamate is a major transmitter of the brain and is involved in long-term potentiation, a process believed to underlie learning and memory. Both glutamatergic and cholinergic dysfunction are strong correlates of cognitive decline in Alzheimer’s disease. Calcium-dependent neurotoxicity related to excess glutamate release in the central nervous system likely contributes to neuronal death in both Alzheimer’s disease and vascular dementia. Memantine, by achieving uncompetitive antagonism at glutamate (NMDA) receptors, may prevent cell death and retard the progression of dementia symptoms.

The recommended dosage of memantine is 10mg BD. Dosage reduction is needed in those with moderate renal impairment, and it is not recommended in patients with severe renal impairment. Caution should be exercised in patients with recent myocardial infarction, uncompensated congestive heart failure, uncontrolled hypertension or seizures. Adverse events were usually mild, including diarrhoea, insomnia, dizziness, headache, hallucinations, agitation and urinary incontinence.

In a 28-week randomised, double-blind, placebo-controlled study, memantine significantly slowed the rate of deterioration in cognition and activities of daily living in outpatients with moderate to severe Alzheimer’s disease, with a significantly lower requirement for caregiver time. Memantine has no in-vitro inhibitory effect on cholinesterase inhibitors, and has been shown to be superior in combination therapy with donepezil, in terms of improved cognitive function and less decline in activities of daily living in patients with moderate to severe Alzheimer’s disease, when compared to using donepezil alone. Its safety and tolerability has been shown in open label extension studies, up to a duration of 104 weeks.

**Guidelines for anti-dementia drugs**

Lovestone and colleagues in London have proposed guidelines for the drug treatment of Alzheimer’s disease. These restricted use of cholinesterase inhibitors to the indication of mild to moderate Alzheimer’s disease (as supported by a Mini Mental State Examination score of between 10 and 24) of at least 6 months’ duration. Response should be evaluated early at 2 weeks for side effects, at 3 months for cognitive function, and then every 6 months. The drug would be stopped if deterioration continues at the pretreatment rate after 3 to 6 months, or if a drug-free period suggests that it is no longer helping.

In March 2005, the National Institute Clinical Excellence (NICE), part of UK’s National Health Service (NHS), issued controversial guidelines on dementia drugs. The recommendations state that donepezil, galantamine, rivastigmine and memantine should not be used as a treatment of Alzheimer’s disease. The report states that there is evidence that all four drugs show some beneficial effects in patients, but recommends they are not prescribed for cost benefit reasons. General opinion in the UK is that this is a drastic recommendation and does not reflect the fact that some people have a good response to these medications or are slowed in their overall progression. Alzheimer’s organisations in the UK have also reacted strongly and have condemned this decision.

**Conclusion**

To date, the treatment options for Alzheimer’s disease are largely symptomatic, giving rise to temporary remissions in cognitive decline or the amelioration of troublesome behavioral and psychological symptoms. However, future research is showing a clear movement to treatments directed towards disease modification.

Hong Kong has maintained an open mind for the newest pharmacological treatments for Alzheimer’s disease. However, the non-pharmacological management of Alzheimer’s disease should not be forgotten and the use of both types of treatment should continue to benefit both patients and caregivers.
References


