

More aggressive pharmacotherapy in Alzheimer's disease

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The prevalence of dementia exceeds that of stroke and Parkinson's disease and the incidence of dementia increases dramatically with age. Is there a place for more aggressive pharmacological management of Alzheimer's disease – diagnosing earlier, commencing symptomatic therapy and persisting with or modifying such therapy? Unfortunately, there is no way to accurately predict who will respond to current treatments. New formulations are likely to improve compliance and tolerability. New symptomatic therapies that target other neurotransmitters or brain receptors may be available soon, as will disease-modifying drugs such as monoclonal antibodies.

Diagnosis

Alzheimer's disease (AD) patients show a greater rate of brain atrophy seen on CT scan, compared to those with mild cognitive impairment (MCI) alone. Changes in the brain are more noticeable with other scans, such as functional MRI, 11C-PIB PET scans that demonstrate amyloid, and FDG-PET scans that show early brain metabolism changes.

Biological markers may help distinguish those people likely to progress to Alzheimer's disease, following a diagnosis of MCI. For example, CSF total tau and A β levels in MCI predict progression to AD over a period of five years. However, because levels of either marker can increase in non-AD dementia, the positive predictive value (81%) of this testing for AD is less than the negative predictive value (96%).

Assessment of interventions

This presents a dilemma. Although measuring brain pathology (e.g. degree of atrophy or amount of amyloid deposited) may serve as a disease modification target in clinical trials, such targets must coincide with symptomatic change if they are to have clinical meaning.

Is it appropriate to ignore pathological markers while pursuing symptomatic targets alone? For example, as AD progresses, a worsening of cognition and functional autonomy are obvious targets but what if these fail to improve yet the marker/s of pathology do show a potential benefit of therapy? Similarly, mood disturbance and abnormal behaviours may respond to symptomatic therapy but not track the biomarker response.

Current symptomatic therapies

These include cholinesterase inhibitors (AChEIs) donepezil (AriceptTM) and rivastigmine (ExelonTM), and an agent which also has cholinomimetic activity, galantamine (ReminylTM). Memantine (EbixaTM) targets the NMDA receptor. [Atypical antipsychotics are not covered here.]

Pivotal studies demonstrate the symptomatic benefits of these agents including:

- Compared to placebo, donepezil showed a significant positive effect on cognitive decline trials over 24 and 52 weeks, respectively.
- Compared to placebo, galantamine showed a significant improvement in goal attainment scores, but this was only evident between 2 and 8 months on treatment.
- The Southampton Health Technological Assessment Centre's review of 26 RCTs

of the three AChEIs found that all three can delay cognitive impairment in mild to moderate AD by at least 6 months.

- A Canadian meta-analysis of 16 RCTs of AChEIs showed that global responders (in excess of placebo) were 9% but the rate of adverse events and dropouts was 8%. In 2005, a BMJ article concluded that RCTs had many flaws and thus it was not possible to determine efficacy of AChEIs but this report was itself criticized and only served to polarise views.



Long term use of AChEIs

For medications prescribed to limit symptomatic progression, compliance is surprisingly low. One study showed the cessation rate after the initial oral six-month supply was lower for galantamine (45%) than donepezil (52%) and rivastigmine (56%) ($p < 0.0001$). Most cessations occurred in the first two months (20%-27%).

By way of contrast, a more recent study showed continuation rates were around 92% at 12 months in patients attending Australian centres of excellence. Also in Australia, a study of DVA patients on newly prescribed AChEIs showed continuation rates of 53%-54% at 12 months, across the three available drugs. Of those who ceased, 32% recommenced treatment, with 28% using the same AChEI.

These figures suggest that continuation rates are high in centres of excellence but unsatisfactory for the population as a whole. There is room for more aggressive maintenance.

When AChEIs are maintained in moderate to severe AD, significant ongoing cognitive benefits may occur and longer-term trials have shown benefits for at least 12 months. Even initiation in the severe stages of AD has been shown to be beneficial. There is no good evidence that these drugs delay death or will lower the overall community burden of dementia care by modifying the disease.

The decision to continue AChEIs must be made after evaluation with the individual patient and carers. In general terms, there is no need to cease as dementia progresses. Treatment may delay admission to residential care, which may have individual benefits for families and carers.

New formulations of AChEIs

Predictable advantages from a patch administration (compared to oral) are:

- Smoother drug delivery reduces side effects from blood level peaking.
- Reduced side effects allows higher doses, to improve therapeutic effect.
- Improved compliance, depending on carer support.

Efficacy of rivastigmine patches has been shown to be equivalent to tablet form, with a lower side effect profile with respect to nausea/vomiting.

Slow release donepezil oral (23mg daily) is also likely to be released after trial conclusion in 2009.

Memantine usage

Memantine is a N-methyl-D-aspartate receptor antagonist that counteracts the brain glutamate deficits seen in later stage AD. PBS listing in Australia is therefore for MMSE 10-14 scores, and it is only subsidised as monotherapy. In the USA, memantine is the most frequently prescribed anti-dementia drug, usually as add-on therapy to an AChEI.

Clinical trials of memantine have demonstrated improved cognition in more severe AD. A once-daily formulation has just received TGA approval here in Australia.

Aggressive modification of symptomatic therapy can be useful

There are three options to more aggressively manage symptoms as AD progresses:

1. Switch AChEI. Studies have yielded conflicting results regarding efficacy of doing this. One study suggested donepezil was more efficacious than galantamine, while another placed rivastigmine ahead of donepezil.
2. Increase dose or change formulation of AChEI – increasing dose has improved response in most trials but side effects are an issue.
3. Add memantine (non-PBS, but allowed by DVA).

References available on request. ■