

DRUG TREATMENT OF ALZHEIMER'S DISEASE

SUMMARY

- + Alzheimer's disease (AD) is the most common dementing disorder in the elderly with age being one of the greatest risk factors.**
- + Early and accurate diagnosis is important for the management of AD. Specialist assessment is recommended before drug treatment is initiated. Ongoing evaluation of response to treatment is essential.**
- + Donepezil and rivastigmine have been shown to have modest improvements on cognitive function and activities of daily living. However, little evidence of improvement on the quality of life of patients or their carers has been shown.**

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with characteristic clinical and pathological features.¹ It is now recognised as the most common dementing disorder in the elderly.² Age is one of the greatest risk factors for developing AD with nearly 50% of those over 85 years affected.^{1,2,3} AD affects approximately 33,000 Irish people.⁴ Epidemiological studies have shown a higher incidence of AD in women, the risk being 1.2-3.5 times greater than in men.⁵ Other risk factors include family history, presence of apolipoprotein E4 allele and mutations of chromosomes 1, 14 and 21.^{1,2,5} Management of these patients presents a multidisciplinary challenge. Possible, but not proven, protective factors against AD include the use of oestrogen replacement therapy, use of NSAIDs, education and challenging occupations.⁶ Recently two agents have been licensed in Ireland for the treatment of this condition namely donepezil and rivastigmine.

Aetiology

The aetiology of AD remains elusive although considerable progress has been made in understanding its biochemical and genetic mechanisms.⁷ The histopathologic hallmarks of AD are the presence of senile plaques and neurofibrillary tangles.⁸ These plaques and tangles interrupt normal neuronal transmission and are associated with cell death. Multiple neuronal pathways are destroyed leading to neurotransmitter deficits e.g. cholinergic, serotonergic, adrenergic.⁹ Although other neurochemical abnormalities have been described, the most striking and consistent changes of AD are in the cholinergic system, the so-called "cholinergic hypothesis".^{2,10} Genetic factors also thought to be involved include the discovery that the gene for apolipoprotein E4 allele is found three times more frequently in people with AD than in age-matched control subjects.⁷

Clinical Presentation

AD results in cortical atrophy which particularly affects the temporal lobes and hippocampus. The clinical presentation of the disease reflects the distribution of

pathology in these brain areas and consequently problems with higher cortical function are prominent. The clinical hallmark of dementia associated with AD is the gradual onset and progression of short-term memory loss and other cognitive functions.⁸ These deficits develop so insidiously that it is often years before patients or their families seek medical attention. Almost invariably the first symptom is short-term memory loss e.g forgetting appointments. As the AD progresses, the patient typically has difficulty performing routine tasks at home or work. Ultimately the patient becomes less able to perform basic activities of daily living and self care functions e.g. dressing.^{11,12} Agitation, anxiety, restlessness, depression, day-night disorientation, delusions, hallucinations and other behavioural disturbances frequently complicate the middle stages of AD.^{11,12} In the final stages the patient may be unable to recognise family members and unable to communicate.^{5,12}

Diagnosis

The clinical diagnosis of AD relies heavily on obtaining a good history from a reliable informant. Definitive diagnosis of AD requires histological demonstration of the characteristic plaques and tangles, this is rarely done as it requires autopsy or brain biopsy material.² The characteristic onset and course of memory and other cognitive deficits make AD a diagnosis of inclusion.⁸ Tests routinely performed include a cognitive assessment using qualitative tests e.g. Mini-Mental State Examination (MMSE - Table 1), general physical and neurological examinations, lab procedures, thyroid function, serum biochemistries.¹² These tests, combined with CT scan of the brain, MRI, and a cerebral single photon emission computed tomography (SPECT) scan can be 90-95% accurate.¹³ It is preferable that the decision to commence patients on therapy should be supported by a specialist review.

Table 1: Mini-Mental State Examination (MMSE)

Severity Of AD	Scale Values (0-30 points)
Mild AD	21-30
Moderate AD	11-20
Severe AD	0-10

Treatment

Treatment of AD is aimed at improving cognition, preventing further cognitive decline and reducing disruptive behaviour associated with the condition.⁵ An accurate diagnosis is required. A period of observation of 3-6 months may be required to confirm the progression of cognitive loss and assess its functional impact.¹ The “cholinergic hypothesis” suggests that potentiation of central cholinergic function should improve the cognitive, and perhaps even the behavioural manifestations, of AD.¹⁰ Most of the research and development into the treatment of AD has been based on this hypothesis. For AD treatments currently approved, evidence of efficacy is limited to studies in mild to moderate AD. The Alzheimer’s Disease Assessment Scale (ADAS- cog), the Clinician’s Interview Based Assessment of Change Plus (CIBIC-Plus) and Clinical Global Impression of Change (CGIC) are the parameters

used to assess efficacy of drug treatment. A thorough and repeated evaluation of response to treatment is essential and monitoring of compliance and response to treatment should include input from a carer. Criteria for early stopping of therapy would include poor tolerance and compliance, deterioration at the pre-treatment rate after 3-6 months of therapy and an accelerating deterioration.¹⁴ Symptomatic and palliative treatment of the disease is important. This should include management of depression, agitation and hallucinations.

Donepezil (Aricept®)

Donepezil is a piperidine-based acetylcholinesterase (AChE) inhibitor with dose dependent activity. It displays selectivity for AChE, the predominant cholinesterase in the brain. Donepezil has a long duration of cholinesterase inhibition allowing once daily administration.¹⁵ It is licensed for the symptomatic treatment of dementia in mild to moderately severe AD.¹⁶ The initial recommended dose of donepezil is 5mg once a day which should be taken in the evening or prior to retiring. In order to allow the earliest clinical response to the therapy to be assessed this dose should be maintained for at least one month. After this time the dose may be increased to 10mg once a day.¹⁶

Donepezil is generally well tolerated with most side-effects being mild, transient and occurring early in the course of treatment. Dose dependent side-effects include nausea, diarrhoea, muscle cramps, fatigue, insomnia.^{9,17,18,19} No clinically significant effects have been reported on clinical laboratory tests or hepatic function.²⁰ More recently there have been reports of psychiatric disturbances including hallucinations, agitation and aggressive behaviour. These effects tend to resolve on reducing the dose or discontinuing the drug.²¹ Displacement studies have shown that donepezil has no effect on the binding of frusemide, digoxin or warfarin. Pharmacokinetic studies have shown that donepezil does not alter the clearance of theophylline, warfarin or digoxin.^{16,18,20} Drugs that are known to be inhibitors or inducers of CYP3A4 or 2D6 may inhibit or increase the rate of metabolism of donepezil e.g. erythromycin, fluoxetine, phenytoin.¹⁸

When donepezil was launched, only one published study was available, namely a 12 week double blind trial that assessed 5mg once a day versus placebo. A significant improvement was shown in ADAS-cog. However, twelve weeks is too short a period of time to highlight cognitive decline and no change was observed in the CGIC.^{17,22} More recent studies in 473 and 468 patients assessed over 24 weeks and 12 weeks respectively, randomised to receive 5mg or 10mg once a day found that donepezil produced improvement in global performance, as indicated by the CIBIC-Plus. However, most of these improvements were modest. When donepezil was discontinued, a greater deterioration was noted in all measures for the treated groups than would be expected in untreated, but otherwise similar patients with AD. Donepezil does improve rating scales of cognitive function in mild to moderate AD. These improvements though are small and must be balanced against the unproven effects on quality of life and day to day functioning. It is also not possible to predict in whom the possible benefits may occur.^{17,23,24}

Rivastigmine (Exelon®)

Rivastigmine is a novel “pseudoirreversible” selective inhibitor of acetylcholinesterase in the brain.²⁵ The pseudoirreversible mechanism of action results in prolonged inhibition of AChE after the drug has been cleared from the plasma.^{26,27} Treatment with rivastigmine therapy should be initiated and supervised by a physician experienced in the diagnosis and treatment of AD. Therapy should only be started if a carer is available who will regularly monitor drug intake by the patient. An initial dose of 1.5mg twice a day is recommended. If this is well tolerated, the dose may be increased to a maintenance dose of 3-6mg twice a day. Patients should be maintained on the highest tolerated dose; the maximum recommended dose is 6mg twice a day.²⁸

Studies have shown adverse effects to be generally mild and to occur most frequently during the dose escalation phase. The effects most commonly reported are cholinergic effects, nausea, vomiting, diarrhoea, abdominal pain and anorexia. Apart from nausea, no significant difference in the incidence of adverse effects between a dose of 1-4mg daily and placebo have been noted.²⁵ Gastrointestinal effects have been reported to occur more commonly in women. Cholinesterase inhibitors may cause weight loss and patients with AD tend to lose weight. Close monitoring of the patient's weight should be undertaken.²⁸ In comparison to donepezil, CYP450 is not involved in the metabolism of rivastigmine therefore reducing its propensity to interact with drugs metabolised by specific CYP450 isoenzymes.^{27,29} No pharmacokinetic interactions have been observed between rivastigmine and digoxin, warfarin, diazepam or fluoxetine, in studies in healthy volunteers. Rivastigmine may exaggerate the effects of succinylcholine type muscle relaxants during anaesthesia.²⁸

Most information available on the safety and efficacy of rivastigmine is known from a large trial involving over 3000 patients known as the ADENA trial. This multicentre study compared the effects of low-dose rivastigmine (1-4mg/d), high-dose rivastigmine (6-12mg/d) and placebo over a 26 week period. Stabilisation of cognitive decline and improvements in activities of daily living (by 10%) were found to occur at the high dose compared to placebo.²⁵

Other Treatments

Relieving the behavioural complications associated with AD is an important goal.¹⁰ Depression, agitation, hallucinations and insomnia can often complicate the management of this condition. Depression can be treated successfully with antidepressant agents. Agitation is often difficult to treat. Several agents have been tried such as benzodiazepines and neuroleptics. Hallucinations / delusions may be managed using an antipsychotic agent with a low potential for inducing extrapyramidal side-effects. Insomnia may be managed by the use of hypnotic agents.²

Future Developments

The management of AD has been an area of great therapeutic development in recent years. In addition to drugs acting on the cholinergic system e.g. metrifonate, other future developments include the use of neuroprotective agents e.g. alpha-tocopherol.⁶

In summary, the emergence of treatments for this condition is a welcome development. However, modest improvements have been shown and these must be

weighed against the cost of such treatments, the inability to decide which patients are likely to benefit and little proven effect on the quality of life of patients and carers. Early and accurate assessment and diagnosis are the key to management, along with ongoing evaluation of response to therapy.¹³

Cost of 28 Days Therapy (GMS May 99)

Preparation	Cost
Donepezil (Aricept®) 5mg OD	£74.88
Rivastigmine (Exelon®) 3mg BD	£69.18

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