Memantine (Ebixa®) in the later stages of dementia

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Memantine is the first agent licensed for the treatment of moderate to severe Alzheimer's disease. It is an N-methyl D-aspartate (NMDA) receptor antagonist which reduces glutamatergic excitotoxicity. Benefits are seen in cognitive, functional and global measures in both outpatients and nursing home residents. Prospective health economic benefits have been reported.

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Dementia is a strongly age-related illness. It creates a public health issue of considerable magnitude at present in developed countries (more than 4 000 000 sufferers in both Europe and the United States) and increasingly on a worldwide basis (more than 25 000 000 currently and set to rise to more than 35 000 000 by 2025) (Rocca, 2001). The costs of dementia care in the UK probably exceed those of cardiovascular disease and cancer combined (Bosanquet et al, 1998), with at least two-thirds of these resulting from institutionalization of people with severe dementia. The considerable methodological difficulties associated with the health economics of dementia are summarized by Wimo et al (2000).

Alzheimer's disease (AD) accounts for approximately 70% of all dementia, including combination with vascular dementia and dementia with Lewy bodies. Current treatment for AD is based on the cholinergic hypothesis. This relates the main clinical (i.e. cognitive) features of AD to degeneration of basal forebrain cholinergic neurones and related loss of cerebral cortical cholinergic transmission. The current first-line treatment is cholinesterase inhibitors, which increase levels of cerebral acetylcholine by inhibiting its breakdown in the brain. Donepezil (Aricept, Eisai, London/Pfizer, Sandwich), rivastigmine (Exelon, Novartis, Camberley) and galantamine (Reminyl, Shire, Andover) are the currently available drugs in this class and are licensed for use in mild to moderate AD. Despite approval by the National Institute for Clinical Excellence and the Health Technology Board for Scotland, use remains patchy at best and is well short of reaching all those who might benefit from it.

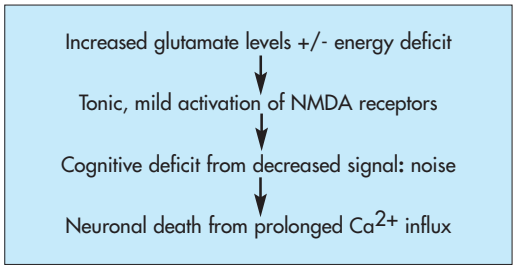

Figure 1. Glutamatergic excitotoxicity in Alzheimer's disease. Ca^{2+} = calcium ion; NMDA = N-methyl D-aspartate.

AN ALTERNATIVE HYPOTHESIS

Glutamate is the main excitatory amino acid neurotransmitter in the mammalian CNS. Of its four classes of receptors the ionotropic NMDA (N-methyl D-aspartate) form is believed to be overactivated in a tonic rather than a phasic manner in neurodegenerative disorders including AD. This excitotoxicity hypothesis links excessive activity of glutamate to increased neuronal influx of calcium ions (Ca^{2+}), and prolonged exposure to excessive Ca^{2+} leads to neuronal degeneration and cell death (*Figure 1*). The NMDA receptor requires the binding of co-agonist glycine as well as glutamate in order to depolarize. Physiologically extracellular magnesium ions (Mg^{2+}) bind in the ion channel pore, conferring voltage dependence upon the channel and restricting the influence of Ca^{2+}.

The glutamatergic and cholinergic hypotheses are compatible to the extent that they reflect potentially simultaneous abnormalities of separate neurotransmitter systems while differing as to which is of more central importance. Beta-amyloid peptide (Aβ), considered a prime candidate in the underlying pathogenesis of AD, is believed to increase glutamate release upon depolarization as well as inhibiting its uptake by glial cells. Energy deficit further contributes to tonic mild depolarization which produces an increase in 'background electrical noise' and difficulties in distinguishing the physiological signals necessary for new learn-

ing and synaptic plasticity (*Figure 1*). Animal models of this process are best developed in terms of hippocampal long-term potentiation. This area is well summarized by Cacabelos et al (1999).

MEMANTINE

Memantine (Ebixa, Lundbeck, Milton Keynes) was released in 2002 for the symptomatic treatment of moderate to severe AD and is the only agent licensed for this purpose.

Memantine was originally introduced in Germany in 1982 for a range of relatively non-specific CNS indications. In 1991 its use for 'dementia syndrome' was approved. Memantine is an adamantane derivative which constitutes a new therapeutic class. It has some chemical similarity to the antiviral and antiParkinsonian agent amantadine. It is a moderate affinity, voltage-dependent, uncompetitive NMDA receptor antagonist with fast receptor kinetics. This means that the drug enters the ion channel only in its open state, thus only blocks overstimulated channels. It is perhaps most easily regarded as providing a replacement for Mg^{2+} and its similarly rapid unblocking more closely mimics the physiological state than previous NMDA antagonists (*Figure 2*).

Memantine does not appear to induce psychosis under normal circumstances (Parsons et al, 1999), although hallucinations have been reported (Jarvis and Figgitt, 2003). Tsapakis and Travis (2002) speculated about it meriting testing for antidepressant activity. A possible adjunctive role in human immunodeficiency virus (HIV) dementia has been suggested (Everall, 2000), but no trial date is yet available. A neuroprotective role of memantine in dementia has been suggested (Jain, 2002) but there is no agreed methodology for concluding this in clinical practice.

CLINICAL TRIALS OF MEMANTINE

The ^{9}M-BEST (Benefit and Efficacy in Severely demented patients Treated with Memantine) study (Winblad and Poritis, 1999) was conducted in one psychiatric hospital and six nursing homes in Latvia. Dementia was defined by *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1987) criteria and severity assessed by the Global Deterioration Scale. Primary end points comprised the physician-rated Clinical Global Impression of Change and the nursing staff-rated 'care dependence' subscore of the Behavioural rating scale for Geriatric Patients. A total of 49% of the subjects had dementia in AD, 51% had dementia of the vascular type, and the dose of memantine was 10 mg daily.

Memantine showed benefit on both measures over a treatment period of 12 weeks in this care-dependent population with severe dementia. It was reported to have been well tolerated. The authors concluded that improved functional capacities plus reduced care dependence were clinically meaningful as well as statistically significant.

A more recent trial of memantine in moderately severe to severe AD was conducted in American outpatients (Reisberg et al, 2003). A total of 252 patients were recruited in a double-blind, placebo controlled, multicentre design with equal numbers receiving either memantine 20 mg or placebo for 28 weeks. Active treatment was significantly better than placebo on global, cognitive and functional outcome measures. The primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input and the Alzheimer's Disease Cooperative Activities of Daily Living Inventory modified for severe dementia, with the Severe Impairment Battery of Saxton et al (1990) added to other secondary end points of cognition, function and behaviour. Adverse events were similar in both groups.

On completing the double-blind study, 175 patients participated in an open label extension, receiving memantine 10 mg twice daily for a further 24 weeks. The 80 patients who switched from placebo showed improvement on the same measures relative to their projected rate of decline on placebo. Safety and tolerance remained good.

A first prospective pharmacoeconomic assessment, using the Resource Utilisation in Dementia tool of Wimo et al (2003), was incorporated in the above study and quantified reports from caregivers needing to spend, on average, 51.5 fewer hours per month providing care in the memantine-treated relative to the placebo-treated group. While acknowledging considerable ongoing uncertainty

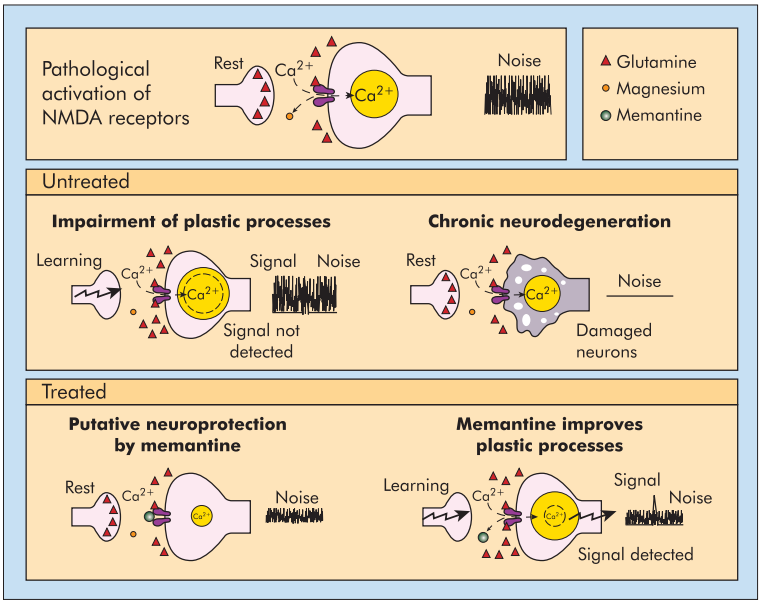

Figure 2. Proposed mode of action of memantine. Adapted from Danysz et al (2000). Ca^{2+} = calcium ion; NMDA = N-methyl D-aspartate.

as regards best methodology in this area, resource utilization and total health costs were less in the memantine group. The incidence of institutionalization at study endpoint was also lower in the memantine-treated than the placebo group.

USE IN VASCULAR DEMENTIA

As well as the [9]M-BEST study, in which 51% of the patients had diagnoses of vascular dementia, much of the early German experience with memantine was in mixed dementia populations although the studies were generally small (Areosa Sastre and Sherriff, 2003) and some were open label. Two trials have added to this information.

In a multicentre 28-week French study (Orgogozo et al, 2002) of memantine 20 mg daily in mild to moderate vascular dementia there was consistent improvement in cognition across different scales. The authors noted 'at least no deterioration in global functioning and behaviour' and felt the agent 'was devoid of concerning side-effects'. A 57-centre UK outpatient trial (Wilcock et al, 2002) also focused on mild to moderate probable vascular dementia and noted relative stabilization of the memantine arm relative to worsening cognition in the placebo arm. The largest therapeutic benefit was seen in patients with Mini Mental State Examination (MMSE; Folstein et al, 1975) scores less than 15, i.e. at least moderately severe illness.

There is an increasing body of opinion that most clinically diagnosed dementia is mixed in origin (e.g. data from the Nun Study; www.nunstudy.org) and precise subsyndromal diagnosis of dementia is particularly difficult in the later stages. It is important to emphasize, however, that memantine's product licence at this time is solely for moderately severe to severe AD.

TREATING MODERATE TO SEVERE DEMENTIA IN PRACTICE

Many patients treated with cholinesterase inhibitors improve. In some cases this improvement can last more than 2 years. Longer-term follow up suggests that the decline of patients on cholinesterase inhibitors is slower than in untreated patients (Rogers et al, 2000). There is little to suggest that cholinesterase inhibitors prolong lifespan (Lopez et al, 2002; Ott and Lapane, 2002). Delaying the onset of more severe illness may compress the period of terminal morbidity, but many people will still reach a stage of moderate to severe dementia despite treatment with cholinesterase inhibitors.

Clinical trials show that treating people at this stage of their illness can be effective. The ethical dilemma of whether patients with end-stage dementia 'deserve' intensive treatment is unresolved, in contrast to those with terminal cancer. The quality of life of patients and carers in dementia does not have a high profile. Whether further delay in progression of AD or in entry to institutional care can be achieved by use of memantine remains to be demonstrated in more 'naturalistic' settings than randomized controlled trials.

In severe dementia emphasis shifts to reducing the burden on the care giver and health-care systems. Institutional care is the most expensive item in the management of severe AD. Psychiatric long-stay beds are closing more gradually in Scotland than in the rest of the UK but the lost capacity has already been more than replaced by residential and nursing home places (Wood and Bain, 2001). Despite this, patients with dementia can become trapped in hospitals to their own detriment and sometimes that of others. Admissions are prolonged well beyond treatment of intercurrent illness while home support packages or care home placements are awaited. The risk of hospital-acquired infection and the impact on a busy medical or surgical ward of behavioural complications such as wandering are both very real.

One goal of therapies that may delay institutionalization is to add to clinical options for at least some patients. It is to be hoped that improvements in cognition and basic self care, even in relatively late stages of the illness, can be translated into more effective implementation of community care and the necessary psychological support for carers which is so crucial in influencing the timing of institutionalization.

CONCLUSION

Although the National Institute for Clinical Excellence (www.nice.org.uk) and Health Technology Board for Scotland (www.htbs.org.uk) guidelines on the use of acetylcholinesterase inhibitors for mild to moderate AD were ultimately supportive of these agents, there are significant gaps in the spectrum of treatment for AD and other forms of dementia. Of the scenarios shown in *Table 1*, cholinesterase inhibitors are indicated for only the first patient. There is unlikely to be a review of national guidance in the near future, and clinicians will have to make treatment decisions based on their own knowledge and experience.

The Royal College of Psychiatrists' Faculty for the Psychiatry of Old Age has issued interim advice on the use of memantine (Aquilina et al, 2003). Clinicians using this drug, and those who await that option, have expressed considerable interest in peer review of efficacy data on joint use with anticholinesterases (Tariot et al, 2003) and in the safety data for this (Hartmann and Möbius,

2003). Few guidelines exist, either in Europe or the USA, for the overall management of severe dementia, but it will be surprising if increasing interest is not shown in the overall cost effectiveness of current approaches, recognizing that drug costs are only a small part of total costs and that costs increase as dementia becomes severe. HM

Conflict of interest: Drs Connelly and Findlay have advised manufacturers of antidementia drugs and received honoraria or travel grants in connection with educational meetings.

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TABLE 1.
Treating Alzheimer's disease and dementia: some scenarios

Patient characteristics	Decision about ChI treatment
1. Alzheimer's disease, MMSE 12–26, healthy	ChI indicated
2. Alzheimer's disease, MMSE 12–26, chronic obstructive pulmonary disease, prostatism	Treatment excluded by comorbid pathology
3. Alzheimer's disease, MMSE 22, was 26 when ChI started 6 months ago	Non-responder, therapy should be changed or stopped
4. Alzheimer's disease, MMSE 22, was 21 when ChI started 12 months ago meet current criteria for initiation of memantine	Patient respopnded but has begun to decline – would not yet
5. Alzheimer's disease, MMSE 14, was 21 when ChI started 36 months ago wisdom of 2-year delay in initiation	Patient 4 2 years later, now fits memantine criteria but query the
6. Alzheimer's disease, MMSE 11, at home indicated under guidelines	Borderline of ChI treatment, not
7. Alzheimer's disease, MMSE 11, in care, no behavioural and psychological symptoms of dementia	Needs are probably being met in care, memantine might be a possibility
8. Alzheimer's disease, MMSE 11, in care, behavioural and psychological symptoms of dementia	Very limited licensed alternatives since atypical antipsychotics are off label in this population and doesn't meet guideline criteria for initiating ChI
9. 'Dementia', MMSE 4, in care, no behavioural and psychological symptoms of dementia	Would not qulify for ChIs and debatable whether or not memantine would be prescribed

ChI = cholinesterase inhibitor; MMSE = Mini Mental State Examination

KEY POINTS

- The increasing prevalence of dementia associated with steadily rising numbers of older people constitutes a public health issue of great and increasing magnitude across the entire world.
- Severe dementia accounts for approximately three quarters of costs which exceed those of cardiovascular disease or cancer.
- Alzheimer's disease (AD) is the commonest form of dementia.
- A glutamatergically-mediated excitotoxicity hypothesis has been proposed to explain impaired neurotransmission and eventual neuronal cell death in AD.
- Memantine is a selective, voltage-dependent, moderate-affinity, uncompetitive, N-methyl D-aspartate (NMDA) receptor antagonist with positive effects on rates of cognitive, functional and global decline relative to placebo in severe AD.
- Health economic analysis of dementia is at an early stage of development and faces appreciable methodological difficulties.
- Drug costs constitute a tiny fraction of total care costs in severe dementia.