

Realistic expectations for the management of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized clinically by cognitive and functional deficits and behavioural disturbances. Over the past two decades, the devastating nature of AD has captured the attention of the general and medical communities alike. This is due partly to the increased prevalence of AD and the expansion of the aged population. Furthermore, and perhaps inappropriately, the media have encouraged speculation concerning a 'cure' for AD. Such treatment strategies are in the early stages of pre-clinical investigation and well-designed clinical trials are awaited. Nevertheless, other strategies, aimed at reducing the progression or effects through pharmacological symptomatic therapies and psychosocial interventions have demonstrated some clinical benefit and are now available and practicable. This paper critically evaluates the merits of both currently available and potential future therapeutic strategies according to primary, secondary and tertiary levels of preventative treatment. © 1999 Elsevier Science B.V./ECNP. All rights reserved.

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1. Introduction

Awareness of Alzheimer's disease (AD) among physicians, caregivers, patients, the media and the community at large has increased dramatically over the past two decades. This is due, in part, to the accelerated expansion of the ageing population and to the exponential rise in the incidence of AD with age. Consequently, expectations for an effective treatment of AD have risen. How realistic are these expectations? What strategies are currently available, what might be anticipated soon and what, theoretically, might become available in the future?

The term 'realistic expectations' warrants closer examination as various levels of expectation exist. For example, will it be possible to cure or prevent AD? More realistic perhaps, is to anticipate a reduction in disease progression. Other expectations include ameliorating the decline in cognitive symptoms and global function of AD patients, the requirements currently necessary for the licensing approval of a drug for AD by government regulators, improving the treatment of depression and behavioural complications, and providing better methods of caring. During late stages of the disease, expectations of treatment

change as ethical issues arise. For instance, is a management strategy for advanced AD justifiable if it prolongs a life of little quality?

2. The natural history of Alzheimer's disease

The clinical hallmarks of AD are progressive loss of memory, intellect and autonomy. In common with most chronic diseases in later life, AD is an evolving disorder that develops over a period of time which, including the preclinical period, may extend over three decades or more (Masters and Beyreuther, 1994; Mayeux, 1996). Over such long periods, the timing of intervention is important as there may be critical periods or 'windows' that exist in which prevention and treatment strategies are more likely to be successful (Morrison, 1992).

The earliest critical period in the disease course of AD is before the development of pathological changes. Here, reducing risk factors in susceptible or genetically predisposed individuals by prophylactic treatment would be pertinent. During the second critical period, a reversal or reduction of pathological changes to subthreshold levels is still possible. The third critical period is characterized by early symptomatic disease. During this period, treatments may be capable of slowing or halting disease progression,

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reducing the symptoms of disease and maintaining quality of life (Larson and Kukull, 1996).

In the fourth critical period that follows diagnosis, effective treatment aims to ameliorate the effects of disease (Larson and Kukull, 1996). At this phase of AD, patients progress through several consecutive stages of deterioration (Fig. 1). Patients begin to lose higher intellectual abilities, frequently classified as instrumental activities of daily living (IADLs) and finally, basic activities of daily living (ADLs; Galasko et al., 1995). Behavioural disturbances and psychiatric comorbidities become apparent in the middle to late phases of the disease, at which time, nursing home placement is common (O'Donnell et al., 1992).

Clearly, AD is not a static disorder but it evolves over a period of approximately 8–10 years from onset to death. As the appropriateness of different treatment and management strategies for AD varies according to the sequential processes of this disease, it is convenient to divide them into three categories. These are briefly outlined below, illustrated in Fig. 2A, Fig. 2B and Fig. 2C, and discussed subsequently in more detail:

1. Primary prevention strategies (A): The prevention of the onset or occurrence of disease (line a) or in the case of AD, to delay onset beyond the normal life span (line b).
2. Secondary prevention strategies (B): Reverse or cure the disease (line c), or improve (line d) or stabilize (line e) the symptoms of disease. Stabilization, which includes symptomatic therapy, may be temporary after which clinical decline runs parallel to that of untreated patients (line f).
3. Tertiary prevention strategies (C): The reduction of the disability and complications of AD such as depression and behavioural disturbances, or improved methods of

coping, i.e. the stabilization or reduction in severity of the disease outcome (line g).

3. Primary prevention strategies

The greatest opportunities for primary prevention and the maintenance of the patient's quality of life involve the first three of the critical periods mentioned above, that is, before the formation of early pathological changes, after the changes but before symptoms arise or, in early symptomatic disease. Primary prevention aims to prevent or slow the neuropathology of AD. As such, an understanding of the disease aetiology or, at least, its risk factors is required.

3.1. Risk factors for Alzheimer's disease

Apart from the minority of patients with early onset familial AD (less than 2–3%) who possess certain identified autosomal dominant abnormal genes (Mayeux, 1996), the cause(s) of AD remains unknown. Nevertheless, several risk factors exist including age, family history of AD, Down's syndrome, family history of Down's syndrome, a history of head injury and apolipoprotein (Apo) E4 genotype (Jorm, 1990; Saunders et al., 1993; Mortimer, 1994). Females have a slight but statistically significant increased risk of AD, which is particularly intriguing given that males are over-represented amongst hereditary cases. This implies that females are more likely to develop AD for non-genetic reasons (Lautenschlager et al., 1996).

Other controversial risk factors for AD include previous thyroid disease, depression, aluminium exposure, anosmia, or clinical vascular disease (Breteler et al., 1991, 1992; Jorm et al., 1991; Breteler et al., 1994; Graves and Kukull, 1994; Mortimer et al., 1996), and low education (Zhang et al., 1990; Evans et al., 1993; Snowdon et al., 1996). For example, one study assessed 593 non-demented subjects (from a register of individuals at risk of dementia) over 1–4 years (Stern et al., 1994). Low education, defined as less than 8 years, was associated with a significant increased relative risk of dementia of 2.02 (95% CI=1.33–3.06). However, such studies cannot distinguish between the effects of innate intelligence and education or whether further education and mental stimulation in adult life has a beneficial effect.

The pathological cascade of AD results from ill-defined primary events leading to the formation of β -amyloid protein (β AP) and neuritic tangles of abnormally phosphorylated *tau* protein. Concomitantly, an inflammatory response occurs with the release of neurotoxins and free radicals. ApoE, which assists in lipid transportation and appears to be necessary for nerve cell growth and synapse generation, is a risk factor for AD, as is evident from work with transgenic mice genetically engineered not to express

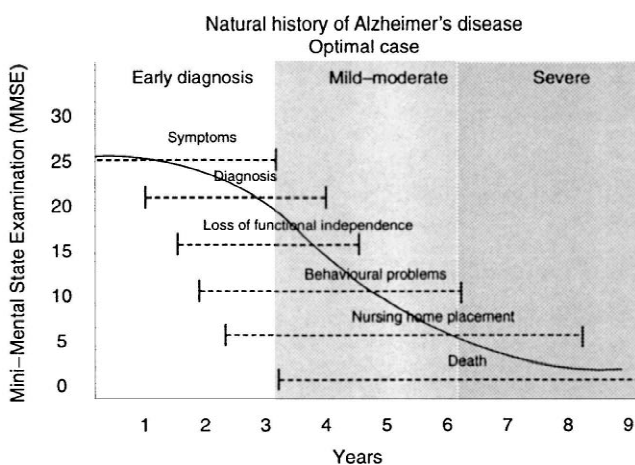


Fig. 1. Natural history of Alzheimer's disease. (Reproduced from Feldman and Gracon (1996), with the kind permission of Martin Dunitz Publishers.)

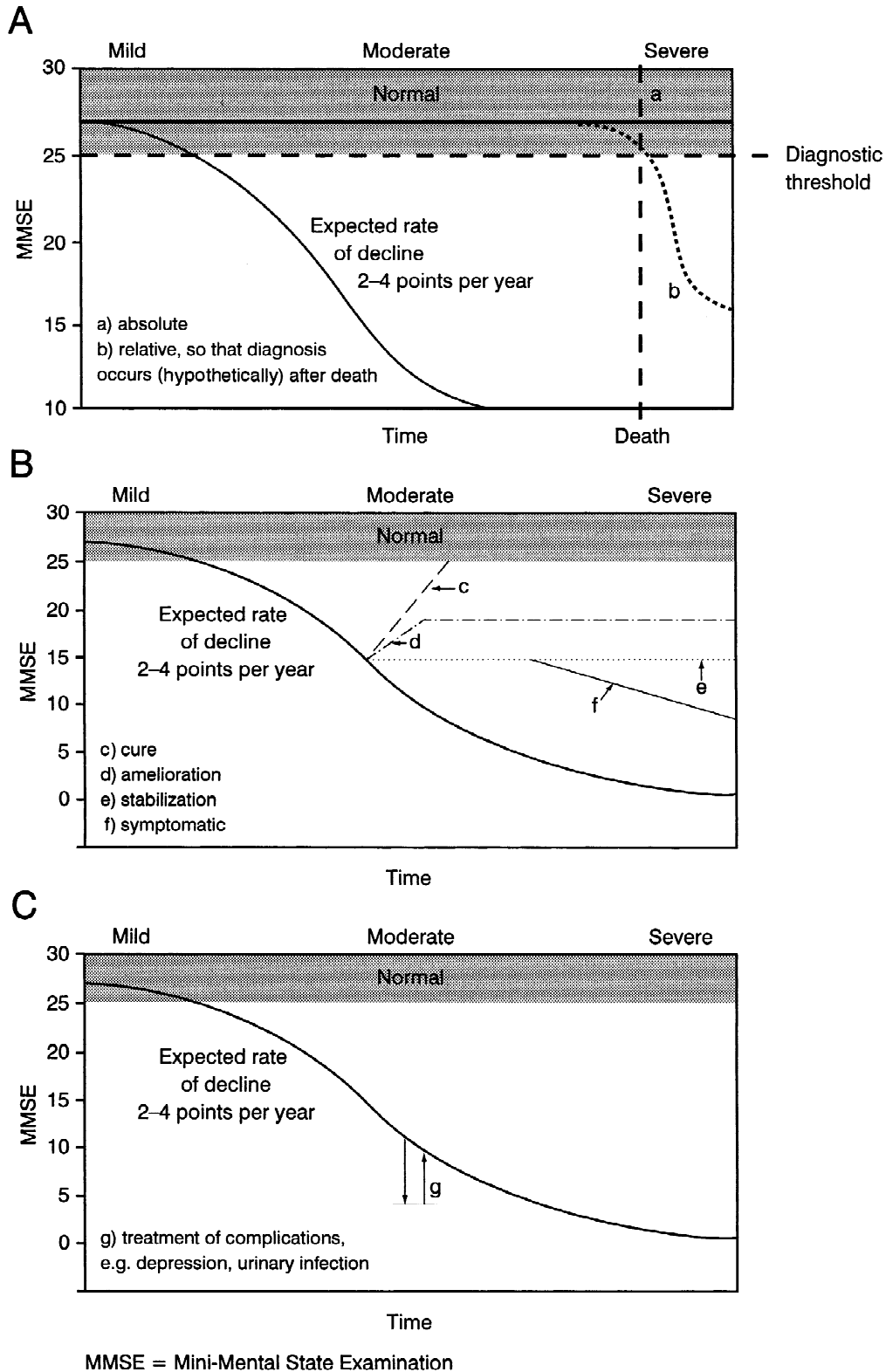


Fig. 2. Primary (A), secondary (B) and tertiary (C) prevention of Alzheimer's disease. (Adapted from Gray and Gauthier (1996), with the kind permission of Martin Dunitz Publishers.)

it. Such ApoE 'knock-out' mice begin to deposit β AP in the brain spontaneously (Andersen and Jurma, 1996). Thus, the absence or relative inefficiency of ApoE, as in individuals with the ApoE4 allele rather than the E3 allele, may lead to increased β AP deposition, facilitating the development of AD (Locke et al., 1995). Consequently, it may be possible to compensate for the relative inefficiencies of ApoE4 by developing drugs that slow, prevent or block β AP deposition, the hyperphosphorylation of *tau*, the inflammatory response or other components of the neurotoxic cascade.

3.2. Protective factors for Alzheimer's disease

Several protective or negative risk factors for AD have been identified. For example, a lower rate of AD may occur among post-menopausal women who use oestrogen therapy compared with those who do not. A relative risk for developing AD or a related dementia of 0.69 (95% CI=0.46–1.03) was demonstrated in 2529 users of hormone replacement therapy (HRT) who died between 1981 and 1992 (Paganini-Hill and Hendersen, 1994). Cognition in post-menopausal women who use HRT has also been studied. Improved cognition, function and decreased depression has been noted in 15 women treated with HRT compared with 15 controls (Ohkura et al., 1994). In addition, the recall of proper names was enhanced in 72 women taking HRT compared with 72 age- and education-matched, community-dwelling women not taking HRT who volunteered for memory research (Robinson et al., 1994). However, there was no significant difference in word recall between the two groups. Other studies to investigate this postulate further are in progress (Shumaker and Rapp, 1996).

Likewise, the risk of developing AD, which may involve an inflammatory component, may be lessened by chronic ingestion of anti-inflammatory drugs. A low relative risk of 0.38 (95% CI=0.15–0.95) for AD has been demonstrated among recipients ($n=365$) compared with non-recipients ($n=5893$) of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (Andersen et al., 1995), but not paracetamol (Broe et al., 1990; Henderson et al., 1992; Dent, 1996). However, no support for this attractive hypothesis was found in a larger (2313 individuals, ≥ 65 years of age) prospective, community study (Beckett et al., 1996). More recently, however, it has been hypothesized that highly selective inhibitors of the inducible form of cyclo-oxygenase, COX-2 may be effective in AD.

3.3. Problems of primary prevention studies

The evaluation of primary prevention strategies is a logistical challenge. The investigation of a large number of subjects is required over long periods of time resulting in enormous costs. The incidence of AD is 1–1.5% per annum or 5–7.5% over 5 years in a population of

individuals of 75 years of age or older (Thal, 1996). Therefore, a sample of 2000 subjects would yield 100–150 new cases over 5 years. Thus, allowing for an equivalent control group, attrition and death, such a study would require approximately 5000 subjects. Over a reasonable duration of 5 years, such a study would cost over US\$20 million (Thal, 1996). There are also considerable ethical issues in trial subjects receiving placebo for such long periods of time.

Reducing these costs may be achieved by combining large epidemiological surveys with preventative studies ('piggy-backing') or by designing 'enrichment studies' – using populations with a high risk of AD. These may include the following subjects groups:

- those with a family history of AD,
- those possessing a known genetic marker, such as ApoE4,
- those over 85 years of age (but the high attrition from death would make this group unacceptable), or
- those who have an additional risk factor such as vascular disease or mild cognitive impairment.

4. Secondary prevention strategies

Secondary prevention is the early detection and treatment or control of the disease (Collier et al., 1995). This is generally attempted by pharmacotherapy (although it has been suggested that the transplantation of neural tissue may be advantageous in altering the pathology of AD, but this seems to be a dubious management prospect in the short term).

4.1. Cholinergic replacement therapies

The therapeutic approach that has accounted for much of the recent clinical research effort is the augmentation of certain neurotransmitters known to be deficient in AD, particularly those of the cholinergic pathway. Strategies to enhance cholinergic neurotransmission include (Table 1):

- administering or 'loading' with acetylcholine (ACh) precursors, e.g. lecithin or choline,
- facilitating the discharge of ACh with 'release enhancers', e.g. DuP-996,
- stimulating ACh receptors with muscarinic or nicotinic agonists, e.g. bethanacol, arecoline, milameline, and
- inhibiting one or more of the cholinesterases (ChEs) responsible for the hydrolysis of ACh, e.g. tacrine, velnacrine, physostigmine, donepezil, rivastigmine, galantamine and metrifonate.

The latter approach has provided the greatest clinical effectiveness to date. Until very recently, tacrine was the only ChE inhibitor to be registered and approved spe-

Table 1
Some possible drug treatments for Alzheimer's disease

<i>Cholinergic strategies</i>
Precursor loading
Lecithin
Choline
Muscarinic agonist
Bethanechol
Oxtremorine
Arecholine
RS 86
Besipiridine
Milameline
Xanomeline
Cholinesterase inhibitors
Tacrine
Velnacrine
Donepezil
Rivastigmine
Physostigmine
Metrifonate
Galantamine
<i>Biogenic amines</i>
Lazebemide
L-deprenyl (selegeline)
Moclobemide
<i>Phosphatidyl serine</i>
Acetyl-L-carnitine
<i>ACE inhibitors</i>
<i>NMDA antagonists</i>
Nimodipine
Remacemide
Dizolepine
SDZ EEA 49
Memantine
<i>Calcium channel blockers</i>
Nimodipine
<i>Nootropics</i>
Piracetam
<i>Neurotrophic factors (growth factors)</i>
NGF (intra-ventricular)
Alkaloids which potentiate NGF
<i>Anti-inflammatory drugs</i>
Prednisone
Aspirin
Non-steroidal anti-inflammatory drugs
Cyclo-oxygenase inhibitors
<i>Odansetron</i>
<i>Sabeluzole</i>
<i>Gangliosides</i>
<i>Opiate agonists</i>
<i>Hydergine</i>
<i>Anti-oxidants</i>
α -tocopherol (Vitamin E)
<i>Neuroprotective</i>
Propentofylline
<i>Vasodilators</i>
Papaverine
Cyclandelate
Isoxuprine
<i>Hormone replacement therapy</i>

cifically for the treatment of AD. Its clinical efficacy was demonstrated in an intention-to-treat analysis of a double-blind, placebo-controlled trial in which forced titration of

tacrine up to doses of 160 mg/day improved cognitive function compared with placebo. This was despite a high rate of side-effects and discontinuation of patients receiving tacrine (Knapp et al., 1994).

The proportion of patients that respond to such treatment is unclear. Data suggest that those individuals who have at least one ApoE4 allele may be poor responders whereas women receiving HRT and subjects with features of diffuse Lewy body disease may be good responders (Levy et al., 1994; Schneider and Farlow, 1995). Moreover, the course of disease is variable in all patients with AD including responders to treatment. Theoretically, patients administered treatment that cures or reverses the underlying pathology of AD should recover to their baseline level of normal ageing. If a drug produces improvement by inducing structural repair, the rate of decline after its discontinuation should be parallel to that of untreated patients. However, if a drug produces symptomatic effects only (line f, Fig. 2B), the cognitive function of AD patients should return to a level similar to that of untreated patients upon drug discontinuation (Leber, 1996).

As the effect of tacrine on the disease process is ill defined and the trajectory of subsequent decline remains undetermined, it is unknown whether such pharmacotherapy will be able to reverse the long-standing pathology of AD. In an open study of long-term tacrine therapy, the median time to clinical decline of responders was 91 weeks (Eagger et al., 1994). Thus, although tacrine appears to offer some symptomatic benefit to a small proportion of patients, its side-effects are known to be a limiting factor. However, the multicentre tacrine trial has provided a benchmark for the treatment of AD and newer cholinergic drugs are emerging. Donepezil, for example, has fewer side-effects, is at least as effective as tacrine and has a simple, convenient once-daily dosing regimen compared with four times-a-day for tacrine (Rogers and Friedhoff, 1996, 1998; Rogers et al., 1998). Rivastigmine and metrifonate also represent advances over tacrine in their lower rates of side-effects and comparable efficacy.

Cholinergic enhancers clearly exert their effect by increasing ACh levels. Nevertheless, it is highly unlikely that they act on the cholinergic system alone. For instance, tacrine has been shown to have several additional properties (Table 2; Wagstaff and McTavish, 1994). Further, cholinergic drugs may confer some structural advantage by reducing the postulated compensatory catabolism of cell lipids by diseased neurones attempting to enhance ACh levels (Nitsch et al., 1992). There is also evidence of a beneficial effect of tacrine on selected behavioural symptoms in AD patients, particularly at higher doses and in patients with moderate cognitive deficits (Cummings and Kaufer, 1996; Kaufer et al., 1996).

4.2. Multi-therapeutic strategies

AD is a disease of multiple, inter-related neurotrans-

Table 2

Summary of the postulated pharmacological effects of tacrine. (Reproduced from Wagstaff and McTavish, 1994, with the kind permission of ADIS International Ltd.)

Inhibits acetylcholinesterase and butyrylcholinesterase activity.
 Inhibits muscarinic and nicotine receptor ligand binding.
 May restore density of nicotine receptors in patients with Alzheimer's disease (normally decreased in these patients) to control values.
 Increases synthesis and release of acetylcholine under certain conditions.
 Inhibits cyclic AMP phosphodiesterase.
 Inhibits potassium-evoked release of excitatory amino acids.
 Inhibits monoamine oxidase activity.
 Affects noradrenaline, dopamine and serotonin (5-hydroxytryptamine) uptake and release.
 Inhibits histamine-*N*-methyl-transferase, increasing histamine levels.
 Blocks potassium, sodium and calcium ion channels.
 Stimulates insulin secretion.
 Increases glucose metabolism.
 Alters the physical properties of membranes.

mitter and neuropeptide insufficiencies (Table 3; Davies and Terry, 1981; Peabody et al., 1986; Gottfries, 1994). As well as lower levels of ACh, lowered levels of noradrenaline, dopamine, serotonin, glutamate and many neuropeptides including somastatin and corticotrophin releasing factor occur. Although cholinergic enhancement is clearly one therapeutic strategy, it is conceivable that the development of drugs that augment several neurotransmitter pathways may prove more effective than enhancing a single neurotransmitter, thereby providing additive benefits.

Some of the other treatment approaches under consideration for AD are included in Table 1. It may be possible to combine some of these treatments. One such randomized, double-blind, placebo-controlled, factorial-design, clinical trial investigated two drugs with different putative actions, selegiline (10 mg/day) and α -tocopherol (vitamin E; 2000 IU/day), in patients with established AD and

moderate dementia, as defined by a Clinical Dementia Rating Scale (CDR; Burke et al., 1988) score of 2 monitored over 2 years (Sano et al., 1996, 1997). Compared with placebo, selegiline and vitamin E, but not their combination, each delayed the loss of ADLs by approximately 7 months and reduced the need for institutionalization. However, there was no improvement in cognition (memory, attention, language and comprehension).

5. Tertiary prevention

5.1. Compensation of cognitive impairment

The aim of tertiary prevention strategies is to prevent the complications of a disease when symptoms have become apparent (Collier et al., 1995) and to reverse the excess disability of patients (line g, Fig. 2C). One technique is to

Table 3

Neurotransmitters and neuropeptides in Alzheimer's disease. (Reproduced from Feldman and Gracon, 1996, with the kind permission of Martin Dunitz Publishers.)

		Cortex cerebri			Subcortical areas		CSF
		Frontal	Hippocampus	Temporal	Hypothalamus	Caudate	
ACh	CAT	↓	↓	↓	↓	↓	
	AChE	↓	↓				↓
5-HT	5-HT	↓	↓	↓	↓	↓	
	5-HIAA	↓	↓	↓	↓		↓
NA	NA	↓	↓	↓	↓	↓	
	HMPG		↓			↑	
DA	DA		↓		↓	↓	
	HVA	↓		↓		↓	↓
MAO	MAO-A					↑	
	MAO-B	↑	↑	↑		↑	
GABA	GABA			↓			
	GABA-T	↓		↓		↓	
Neuropeptides	Somatostatin		↓	↓	↑		↓
	Vasopressin		↓		↑	↓	↓
	CRF					↑	↓
	Substance P		↓			↑	
	Neuropeptide Y		↓		↑		↓
	Glantin	↑			↑	↑	
	VIP					↑	

compensate for the cognitive deficits of AD patients by implementing programmes such as memory training, use of memory aids, advice about the organization of routine daily activities, and reality orientation programmes. In one small study (Zanetti et al., 1995), a marginal improvement of Mini-Mental State Examination (MMSE) score ($n=16$; mean= 0.68 ± 2.44) was demonstrated in subjects receiving reality orientation therapy (ROT) over 8.5 months (20 classes per cycle over 1–4 cycles), whereas the controls declined ($n=12$; mean= 2.58 ± 5.68). This suggests that patients benefit from stimulation of cognitive abilities (Woods, 1996a).

Interestingly, the placebo response frequently observed in drug trials, may support the above hypothesis. Mean levels of cognitive function improve in approximately 20% of patients receiving placebo, albeit only for the first few weeks after initiation of treatment (Knapp et al., 1994; Rogers et al., 1998). As this response may be due, in part, to stimulation, attention, support, hope and interaction with others, these components should become standard management practices in all patients, regardless of participation in drug trials.

More speculative strategies rely on the development of artificial intelligence or computer-assisted memory programmes. It may be possible in the future to develop a form of memory boosted artificial intelligence or prosthetic memory. For instance, relevant past memories could be loaded onto a computer programme that could then be accessed as required.

5.2. *Treatment of psychiatric comorbidity*

A consistent finding from the literature is that behavioural disturbances and psychiatric comorbidities are strong predictors of caregiver distress and nursing home placement (Steele et al., 1990; Brodaty, 1996). In a review of 30 studies of affective symptoms in AD, prevalence rates of between 40–50% for depressive mood and 10–20% for depressive disorders were reported (Wragg and Jeste, 1989). Patients with AD and depression are more functionally impaired compared with matched AD patients without depression (Fitz and Teri, 1994). However, although antidepressant medication improves the symptoms of depression and decreases excess disability in the majority of depressive disorder cases, cognitive impairments will not be improved (Reifler et al., 1989; Carrier and Brodaty, 1996). Delusions, hallucinations and behavioural disturbances are also common. For example, significant behavioural symptomatology including delusions, agitation and diurnal rhythm disturbances have been reported in 58% of outpatients with AD (Reisberg et al., 1987; Carrier and Brodaty, 1996).

The correction of excess disabilities, psychiatric comorbidities and behavioural disturbances may be achieved by pharmacological and behavioural treatments. For example, one pilot study demonstrated that behavioural treatment

can decrease depression in AD. Treatment consisted of a 9-week, clinical research protocol of altering the aversive events and interactions that maintain patient depression, increasing pleasurable events and interactions, maximizing cognitive abilities and teaching caregiver strategies for behaviour change and effective problem solving (Teri, 1994).

5.3. *Caregiver-focused programmes*

A relationship has been demonstrated between caregiver stress and depression in patients with AD (Brodaty and Luscombe, 1998). If competent and psychologically healthy caregivers are able to provide better care than psychologically stressed caregivers, this can result in a more satisfactory quality of life for both the patient and caregiver. Caregiver-focused interventions include:

- comprehensive training programmes,
- access to a key worker,
- individual therapy,
- family therapy, and
- support groups including Alzheimer's Associations.

Studies of such programmes have demonstrated decreased caregiver burden and depression, increased morale and quality of life, and improved satisfaction with life for caregivers. Importantly, placement of patients in nursing homes is also delayed (Brodaty, 1992; Mittelman et al., 1996). Indeed, moderate effect sizes (0.15–0.63) in the improvement of caregivers have been calculated from a meta-analysis of caregiver interventions studies (Knight et al., 1993).

One randomized, cross-over and wait-list study investigated psychologically stressed caregivers (General Health Questionnaire [GHQ 28] score ≥ 5) of patients with dementia and behavioural disturbances (Hinchcliffe et al., 1995). Individual care packages were devised for each caregiver and patient that provided 12 hours of therapy. This included time with a senior psychiatric registrar, patient medication, day-centre respite, instruction in behavioural techniques to the caregiver, caregiver psychological support, linkage with the Alzheimer's Disease Society and, where necessary, medication for the caregiver. In the first phase of the study, disturbed behaviours decreased by 75% in the intervention group compared with 15% in the wait-list group ($p < 0.001$). Concomitantly, caregivers became significantly less stressed with GHQ scores declining by 6.8 points in the intervention group compared with 0.9 in the wait-list group ($p < 0.05$).

Three other studies are of particular interest. The first assessed a comprehensive training and support programme designed to improve the quality of life of dementia patients and their caregivers. Significantly lower psychological morbidity for caregivers, delayed institutionalization rates, lower death rates of patients, as well as net savings of

approximately US\$6000 per couple were demonstrated where caregivers had undertaken the course, compared with untrained caregivers (Brodaty and Gresham, 1989; Brodaty and Peters, 1991; Brodaty et al., 1993, 1997). The second study investigated the effect of two individual counselling sessions, four family counselling sessions, weekly support group participation and consultation with a counsellor as required (Mittelman et al., 1993, 1996). Compared with the control group, there was a decrease in caregiver depression and importantly, the relative risk of nursing home placement, after adjusting for caregiver sex, patient age, and patient income, was 0.65 (95% CI=0.45–0.94; $p=0.02$), indicating that caregivers were approximately two-thirds as likely to place their spouses in nursing homes if they were in the treatment group than if they were in the control group. The third study evaluated caregiver-administered behavioural interventions for patients with AD complicated by depression (Teri et al., 1997). Both patient and caregiver depression scores decreased significantly in the treatment groups but not in the control groups.

The final area of tertiary intervention is residential care. Excess disability can also be reduced by implementing factors such as good architectural design, best professional practice, proper training of staff, attention to staff attitudes and involvement of families (Woods, 1996b).

6. Conclusions

While considering the realistic expectations for the management of AD, it is important to realize that different groups will have varying expectations for disease management outcomes. For instance, patients with AD, their families and general physicians may hope for a cure or at least a slowing of the progression of the disease. However, a temporary stabilization of function is perhaps more realistically achievable today. Other groups such as physicians, researchers, the pharmaceutical industry, regulatory authorities, and society at large, while sharing similar expectations, may view potential benefits differently. Although all the previously stated goals may be considered appropriate, a different emphasis may be placed on their importance; for example, prolonging the life of patients as opposed to increasing their quality of life. Alternatively, reducing the costs of AD management may be a primary objective.

Several management strategies for AD currently exist. Neurotransmitter enhancing therapies that treat the symptoms of disease are perhaps the most widely available and their effectiveness is likely to improve resulting in better outcomes with fewer side-effects. However, their impact on the overall course of AD is not certain. Psychosocial interventions are also available and if properly conducted can delay institutionalization of patients as well as providing significant benefits for caregivers. In addition, better

identification and management of psychiatric and behavioural comorbidity should improve the quality of life for both patients and caregivers.

Combinations of drug and psychosocial treatments are a realistic option. Use of factorial-designed trials will be beneficial in determining additive effects. Large-scale trials of preventative treatment and of drugs that block the pathogenic cascade, combined neurotransmitter enhancement therapy and more accurate identification of treatment responders should all be possible in the future. Furthermore, drug trials for AD have been restricted to patients with pure AD who are essentially physically healthy and not taking contra-indicated drugs. It should be possible to extend drug trials to include patients with more severe AD, vascular dementia, mixed dementias, Pick's disease and diffuse Lewy body disease.

Of paramount importance is that patient, caregivers and allied healthcare professionals have realistic expectations of what can presently be achieved through AD management. Expectations of drug treatment must be realistic. Although pharmacotherapy exists, its efficacy is still limited. The future holds more promise (Selkoe, 1997).

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