Holistic considerations in the management of Alzheimer’s disease

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In the pharmacological management of Alzheimer’s disease (AD) it is important to consider the broader perspectives for patients, families and carers. For example:

• Most people with dementia (AD or other dementia subtypes) have co-morbid physical disorders. Where these disorders are characterised by pain a patient may have difficulty / be unable to communicate their discomfort and need in the usual way.

• Depression and anxiety are common, may precede the onset of dementia or occur during the course of disease.

• Many factors can contribute to behavioural symptoms including culture, dementia stage and subtype, environment, interpersonal relationships, physical illness, personality, sensory deficits.

• There are specific needs at ‘end of life’ to ensure patients are kept as comfortable as possible; care of contractures, hydration, nutrition, prevention of constipation, skin care.

• The negative impact of dementia on the physical and psychological health of family and carers.

Although AD is the commonest form of dementia there does need to be appreciation of the similarities and differences with other dementia subtypes – frontotemporal, Lewy body, Parkinson’s disease, mixed, vascular dementias.

Signature pathologies (amyloid plaques, neurofibrillary tangles, Lewy bodies) frequently overlap; behavioural symptoms are influenced by neurobiological changes seen across the dementias (lower perfusion in frontal and temporal lobes; polymorphisms of neurotransmitter transporters that affect availability of serotonin, noradrenaline and dopamine).

ACHEs: not just AD, not all the same

Although the majority of clinical trials have focussed on AD there are also placebo-controlled data that demonstrate efficacy of acetylcholinesterase inhibitors (ACHEs) in Parkinson’s disease and Lewy body dementias. Indeed, rivastigmine is licensed for the treatment of Parkinson’s disease dementia. Patients with Lewy body or Parkinson’s disease dementia have a much more pronounced and severe cholinergic deficit than in AD; this is reflected in the clinical trial data where the effect size for AChEs in these dementias was much larger. Endorsement of the wider use of cholinesterase inhibitors is supported by this evidence.

One subgroup of people at high risk of AD who must not be forgotten is those with Down’s syndrome. The trisomy of chromosome 21 results in an excessive production of amyloid from early life and an increased risk of early onset AD. Symptoms (usually a change in behaviour) can manifest as early as 35 years; by 60 years of age 50% of people will have AD. This patient population can benefit from AChEs.

In addition to differences in pharmacological profile, ACHEs show important differences in tolerability profile. As acknowledged in this CMHP review, poor tolerability of one AChEI does not necessarily predict poor tolerability to a different AChEI. Tolerability may also be improved by changing formulation. The AChEs are available in a range of non-tablet formulations that include orodispersible, prolonged release, solution and transdermal; memantine is also available as drops.

It has only been relatively recently that safety issues such as increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture have emerged as a concern in older adults with dementia prescribed AChEs. Rare instances have been reported of an association of AChEs with heart block and sinus bradycardia with potentially serious consequences. Vigilance is recommended regarding the potential for cardiovascular adverse effects with AChEs.

Guidelines suggested by the Royal College of Psychiatrists for monitoring pulse, blood pressure, syncope and seizures are a means of...
minimising cardiovascular risk in routine clinical practice.\(^3\)

Dizziness, a more common side-effect seen with AChEIs, is usually mild and transient and usually not associated with cardiovascular problems.

**Behavioural and psychological symptoms**

Understanding factors that can contribute to the appearance of Behavioural and psychological symptoms (BPSD) and preventing them from occurring wherever possible is the best form of management. Carers and health professionals need to remember that painful conditions appearing *de novo* (eg toothache) or occurring because of physical comorbidity (eg arthritis) are a common cause of BPSD when they go unrecognised. Just because a person now has dementia does not mean that treatment with paracetamol for their arthritis or proton pump inhibitor for heartburn or hiatus hernia should be discontinued.

For BPSD related to dementia this article refers briefly to the potential benefit of AChEIs and memantine. A review of evidence by McKeith *et al.* in *Lancet Neurology* in 2005 gives more detail:\(^4\)

- Cholinesterase inhibitors may improve apathy and mood symptoms
- Memantine may decrease agitation
- Antidepressants can benefit depression and emotional lability.

It is important to recognise and treat BPSD because of their strong association with impairment of activities of daily life, reduced quality of life, risk for nursing home placement, and adverse effects on carers.

**Non-pharmacological interventions**

There is increasing recognition of the benefit of non-pharmacological interventions for cognitive, functional and behavioural symptoms. The NICE guideline for dementia (CG42) published in March 2006 recommends group cognitive stimulation therapy for all people with mild / moderate AD. Equally, the NICE Commissioning Guideline (CMG 48) published in April 2013 recommends commissioning non-pharmacological (behavioural and social) interventions for people with dementia:

- Aromatherapy, multisensory stimulation, music and/or dancing, animal assisted therapy and massage for agitation
- Life history and biography work, to promote individual understanding and enabling insights into behaviour.

**Future approaches to treatment**

There is no doubt that disease modification strategies are urgently needed. As with many long-term conditions future management is likely be a stage-dependent treatment model targeted at both specific pathology (amyloid, tau, synuclein) and processes common to all dementias (inflammation, mitochondrial dysfunction, oxidative stress). A major factor that has contributed to many recent treatment failures is administration to patients too late in the disease course. Optimal outcomes will be achieved only if interventions are administered at the appropriate time(s) during the course of disease.

The field is also seeing a resurgence of interest in new approaches to symptomatic treatment for AD and other dementias. This is also very welcome and likely to have an easier path to general approval and availability than disease-modifying strategies.

Dr Rasmussen is a GP in Surrey, RCGP Clinical Champion for Dementia, Dementia Lead for the SE Strategic Clinical Network.

**References**


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