Addressing Severe Alzheimer’s Disease: A Clinical Approach

The prevalence of Alzheimer’s disease (AD) is increasing incrementally within our aging Canadian population. As this change occurs there will be unprecedented numbers of affected individuals. Of particular concern will be the burgeoning population of AD patients in the severe stages of the disease. In this review, Drs. Feldman and Qadi address the scope of severe AD, its clinical features and its treatment options.

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Alzheimer’s disease (AD) is a progressive neurodegenerative disease that typically advances from its earliest stages of memory impairment to its most severe stages where there are multiple cognitive domains impaired, where functional autonomy is lost and where psychobehavioral symptoms crescendo. There are no biological or neuroimaging markers that can be used to reliably stage AD, leaving clinicians to rely on clinical symptoms and clinically derived staging instruments.

Figure 1 provides a view of how clinical symptoms progress in transition between AD stages. It should be appreciated that the more advanced stages of this disease account for an estimated 50% of the prevalence of the illness.1 This illness bears significant costs estimated at more than $3.9 billion in 1994. Figure 2 demonstrates the relationship of costs to disease severity where there are increasing costs through each severity stage of disease. Severe AD is estimated to cost $11,070 per annum more than moderate AD and $27,343 more than mild disease.2 The most significant component that drives the costs in severe AD is the cost of institutional care ($2.18 billion). Of lesser contribution are the costs of diagnostic procedures ($13.5 million) and pharmacotherapy ($60 million). It should be appreciated that this drug cost estimate was made before the introduction of symptomatic treatment for AD, including the cholinesterase inhibitors and memantine.3 Despite the magnitude of the problem of severe AD, until very recently, little attention has been paid to its detailed assessment and treatment.

Clinical Features of Severe AD

As noted from the cognitive standpoint, many if not all cognitive domains are typically affected by the severe stage of disease. The widely used Mini-Mental State Examination (MMSE)4 lacks sensitivity and reliability to meaningfully measure impairment in severe AD (MMSE score < 10). There are, however, a number of cognitive instruments that have been developed which can reliably be used in clinical practice. These include the Severe Impairment Battery (SIB),5 the Modified Ordinal Scales of Psychological Development (M-OSPD)6 and the Test for Severe Impairment (TSI)7. The SIB is most frequently used, particularly in clinical research studies.

In considering the memory impairment in severe AD, it is important to recognize that, while both episodic and explicit memory are markedly impaired, implicit memory may still be surprisingly retained. This is important, as the patients are still able to learn and recall their likes and dislikes of caregivers even when they cannot remember the month, year or events of an hour prior. Perceptual priming may also remain intact,

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with patients still being able to remarkably navigate their way to escape their care facilities.8

In language, there is typically a very significant loss of verbal fluency with impaired comprehension and often with evolution of frequent paraphasias. By the very severe AD stage, speech is often restricted to echolalia, verbal stereotypy, and crying out, yet mutism is rare even in the most advanced stages of AD.8

In executive functioning, only elemental problem-solving and reasoning remain, leading to a total loss of functional autonomy and the need for full-time care.

**Staging of AD**

It is valuable to be able to communicate to families about AD stages and expectations that may emerge from this. Table 1 provides a framework for the staging of AD from its prodromal stage to its most severe stages.

The Global Deterioration Scale (GDS)9 and the Clinical Dementia Rating (CDR)10 scale are assessment instruments that permit a multidimensional rating of cognition, function and behavioral symptoms which can allow an assignment of an overall disease stage. The GDS has 7 defined stages, with stages 6 and 7 describing severe AD. The stage 6 description includes patients being unaware of all the events which have occurred recently and where considerable assistance with activities of daily living (ADLs) are required. There are behavioral changes including agitation and anxiety. By stage 7, there is a near complete loss of language skills with patients being bed-bound and incontinent. The GDS is simple to use and readily applied in many settings of care, including institutions.

Similarly, the CDR is a global staging scale that uses a semi-structured interview to evaluate three cognitive domains (memory, orientation, and judgment/problem solving) and three non-cognitive domains (community affairs, home
and hobbies, and personal care). The global stage is derived from these individual domain ratings, where global CDR scores of 3 and 4 represent severe dementia. This scale requires an interview that may take as long as 45 minutes. While it may be useful at entry into a nursing home, it is not likely to be used repeatedly and is more involved than the GDS. It has less clinical applicability than the GDS.

**Other Issues**

There are a number of other issues that commonly arise in severe AD. Issues related to weight and nutrition in patients with severe AD are very important. There is a well-defined relationship between mortality risk and malnutrition in AD, where weight loss is correlated to declining cognition, function and worsening neuropsychiatric symptoms. The evaluation of nutrition in severe AD can be performed in nursing homes or other care settings through the use of an instrument such as the Mini Nutritional Assessment.11

Problems of gait and movement disorders in patients with severe AD significantly contribute to their functional decline. Within three years of diagnosis, it has been estimated that 50% of AD patients report problems with their gait.12 Approximately 30% to 60% of patients develop extrapyramidal symptoms (EPS), including bradykinesia, gait impairment and parkinsonism.13-15 There is also an increased frequency of gait apraxia in severe AD patients that is ascribed to the progressive impairment in frontal-lobe function.16 This apraxia includes a constellation of impaired trunk and leg movements as well as impaired postural reflexes, disequilibrium, dyskinetic movements, and problems with locomotion.

Falls are associated with the severity of dementia occurring in more than one third of patients.17 As mobility problems increase and bedridden status develops, contractures occur commonly.18 Myoclonus may become evident in severe AD or may develop in the presence of delirium.19 Patients with AD frequently develop both urinary and fecal incontinence as the dementia progresses, with incontinence being a major factor associated with the decision of caregivers to seek institutional care.20 Cholinergically active drug use may exacerbate incontinence, while the prescribing of anticholinergic drugs to treat urinary incontinence should be consciously avoided.

Severe AD can also be associated with a range of other health issues, including pressure ulceration, limb contractures, and pain which can be quite challenging to assess and treat.21

**Management of Severe AD**

There are currently two classes of medications that have demonstrated efficacy in managing moderate to severe AD: the NMDA non-competitive antagonist, memantine, and the cholinesterase inhibitors, donepezil, galantamine and rivastigmine.

Studies have identified glutamate as being critical in the formation of memory as well as synaptogenesis. Memantine’s utility in AD emerges from its ability to inhibit pathologic stimulation of NMDA receptors while allowing physiologic stimulation. This duality can potentially lessen the effects of excessive glutamatergic stimulation and calcium damage to neurons in the neurodegenerative pathway of AD, while preserving cognitive functioning.

Acetylcholine is also an excitatory neurotransmitter that is important in cognition and memory. There is well-documented cholinergic neuronal degeneration in AD, particularly in the more severe stages. The acetylcholinesterase
inhibitors (AchEIs) inhibit the degradative enzyme acetylcholinesterase, allowing more acetylcholine to remain active at central synapses for neurotransmission.

Within the current review, we will restrict our discussion of therapy to these AD medications, and will leave the treatment of target psychobehavioral symptoms outside its scope. The dosage, frequency and titration of AD treatments are presented in Table 2.

**Memantine.** At present, memantine is the only agent conditionally approved in Canada for the treatment of moderate-to-severe AD. The evidence that led to its approval came from two mono-therapy, placebo-controlled, randomized clinical trials (RCTs) and a study performed in combination with donepezil.

The first monotherapy study, with a duration of 12 weeks, evaluated memantine vs. placebo in 151 nursing-home patients with either AD or vascular dementia (VAD) whose initial MMSE score was < 10. A positive response in a clinician’s global assessment (CGI-C) was seen in 73% of patients treated with memantine vs. 45% in the placebo group ($p < 0.001$). Memantine-treated patients also fared significantly better on the Behavioural Rating Scale for Geriatric Patients ($p = 0.016$). These findings were consistent whether the dementia was AD or VAD.$^{22}$

These results were later confirmed by a second monotherapy study. In this study by Reisberg et al, a total of 250 patients with moderate-to-severe AD (MMSE score 3 to 14) were randomized for 28 weeks of treatment. The memantine group had a better outcome on the Clinician’s Global Assessment, the ADL and the SIB in this study (Figure 3).$^{23}$ The most frequently reported adverse events with memantine were agitation (18%), urinary incontinence (11%), insomnia (10%), diarrhea (10%) and urinary tract infection (UTI; 6%). However, in the placebo group, the rate of agi-
tation was 32% and the rate of UTI was 13%.

In 2004, a combination study evaluated the efficacy of memantine and donepezil. This study included 404 patients with moderate-to-severe AD (MMSE score 5 to 14) who had received donepezil for a mean of 126-129 weeks.\(^2\) The study group was then randomized to either memantine or placebo while continuing their donepezil. As seen in Figure 4, the placebo group declined in terms of SIB while the memantine group improved (\(p < 0.001\)). On the ADL measure, placebo-group patients declined significantly more than memantine-treated patients. Additionally, there were significant benefits of memantine therapy on measures of global functioning (Clinician’s Interview-based Impression of Change Plus, or CIBIC+),\(^2\) on neuropsychiatric symptoms (NPI)\(^\) and on the BGP. The most frequent side effects of memantine in this study were agitation, confusion, falls, flu-like symptoms, dizziness and headache. However, agitation occurred more frequently in the placebo group than in the memantine group (11.9% vs. 9.4%), while confusion and headache occurred less often with placebo than with memantine therapy (2.0% vs. 7.9%) and (2.5% vs. 6.4%) respectively.

Cholinesterase inhibitors. Each of the three cholinesterase inhibitors available in Canada (donepezil, galantamine and rivastigmine) have also received recent research attention in more advanced AD, with donepezil having been studied most extensively.

In a randomized, placebo-controlled trial of donepezil in AD patients with MMSE scores ranging from 5 to 17, there were positive results observed on all outcome measures including the CIBIC+, the SIB (Figure 5), the MMSE, the Disability Assessment for Dementia (DAD), and the NPI. The medication was generally well tolerated, with the most frequent side effects being diarrhea and headache.\(^2\)

Recently, a study conducted in Sweden in nursing-home patients reported cognitive and ADL benefits in patients treated with...
donepezil with MMSE scores ranging from 1 to 10.28

There have been limited clinical head-to-head studies in moderate-to-severe AD. However, a recently reported double-blind, randomized, controlled, multicentre trial compared rivastigmine to donepezil in a sample of 994 patients. There were no significant differences on the SIB, which was the primary outcome measure of the study. The major side effects within both treatment groups were nausea, vomiting and agitation,29 without significant differences at two years. A single study has reported a head-to-head comparison of donepezil and galantamine. The primary assessment measure of this study was an ADL scale that again did not reveal any significant difference between the agents.30

There is no current data to demonstrate that any of the AchEIs are superior in advanced AD, with some evidence that they all are efficacious.

Conclusion
Severe AD is associated not only with significant impairment of cognition, neuropsychiatric symptoms and ADLs, but also in a range of other problems including incontinence, movement disorders and nutritional difficulties. This constellation of problems represents a significant management challenge for the care teams that are called on in severe AD.

Recently, clinical-trial evidence has demonstrated there are treatment options for this stage of disease. Memantine and the cholinesterase inhibitors have demonstrated benefits across a range of cognitive symptoms and ADLs. They represent the first available treatment for this very challenging stage of disease and are welcome within the therapeutic armamentarium.

References: