Treatment of Advanced Alzheimer's Disease (Part 1)

In the past five years, a number of instruments have been made available for the treatment of moderate to advanced Alzheimer's disease (AD). The first installment of this two-part article focuses on the use of cholinsterase inhibitors and memantine in the treatment of moderate to severe AD. Look for the second part of this article in the next issue of *The Canadian Alzheimer Disease Review*.

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Until 1999,[1] there had been relatively little interest in medical literature for the study of severe dementia, despite the high number of individuals affected and the emotional and financial burden on families and society. One of the difficulties inherent in studying the later stages of Alzheimer's disease (AD) was the lack of reliable instruments to measure cognition, activities of daily living (ADL) and behavior. Fortunately, a number of instruments and scales validated for this stage of AD are now available and are being used in randomized clinical studies providing evidence on which to build a rational approach to the symptomatic treatment of advanced AD.[2] The most widely used scales are the clinical global impression of change, the Severe Impairment Battery, a modification of the ADCS-ADL Inventory and the NeuroPsychiatric Inventory.

As in the mild to moderate stages of AD, this symptomatic treatment approach should be part of, and not a substitute for, a more comprehensive management of the condition in the advanced stages.[3] This review discusses the use of cholinesterase inhibitors (CI) and of the N-methyl-D-asparate (NMDA) receptor antagonist, memantine, in moderate to severe AD. It should be noted that the use of CIs in severe AD and the use of memantine in moderate to severe AD are not yet approved by Canada's Therapeutic Drug Directorate.

Evidence for Safety and Efficacy of Cholinesterase Inhibitors in Advanced AD

The best data available about CI is from the Moderate to Severe

AD (MSAD) study, which involved out-patients from Canada, France and Australia, randomized to donepezil or to placebo for six months. The overall results have been published[4] and sub-analysis by severity[5] and by symptomatic domains such as ADL[6] and behavior[7] have added to our understanding of the benefit of CIs in advanced dementia. These data will be taken into account in the next update of the Canadian Consensus Conference on Dementia (CCCD),[8] to be held in early 2005. Did the MSAD data have an impact on clinical practice? At the very least, patients in moderate functional stages, independently of scores on the Mini Mental State Examination (MMSE), are kept on therapeutic doses of CIs whether they are at home or in an institution. When reaching a severe functional stage, and after discussion with family, the CI is withdrawn and observations are made over the subsequent three weeks to monitor for the occurence of a discontinuation syndrome, rare at that stage, that would require restarting the CI. New data on the efficacy of CIs in advanced AD will be available at the end of 2004 from a two-year head-to-head study comparing donepezil to rivastigmine, and placebo-controlled studies are underway with the different CIs with "severe AD" defined as MMSE score of 10 or less.

Evidence for Safety and Efficacy of Memantine in Advanced AD

Placebo-controlled pivotal studies in Europe and the United States have demonstrated the safety and efficacy of memantine vs. placebo in moderate to severe AD.[9,10] Furthermore, clinical studies have confirmed the tolerability of combining memantine with CI,[11] and the latest randomized study has demonstrated additive benefit in combination with donepezil.[12] Thus, there is Class I evidence that memantine, acting through non-cholinergic mechanisms, offers benefits in patients with moderate to severe AD—both as monotherapy and in combination with a CI. A randomized study is underway in Canada with memantine or placebo added to standard treatment (which may include any of the three CIs), in order to better define the behavioral effects of memantine. Sub-analysis of behavioral effects from completed studies is also underway.

Need for Evidence-based Guidelines in Advanced AD

As data from randomized studies are fully analyzed and reported, and more randomized studies are completed in later stages of AD, evidence-based clinical guidelines will emerge for the best use of CI and memantine in clinical practice. Until then, clinicians will have to treat each person under their care with the best available evidence, in combination with their clinical experience. Practical issues about when to start symptomatic drugs in later stages of AD and when to stop should be discussed on a case-by-case basis with the patient and the patient's legal representatives. Pharmacoeconomic modeling and validation based on real data will be required to convince provincial formularies and other third-party payers about the societal benefit of CI and memantine in later stages of AD. At the very least, a delay in loss of functional autonomy and a delay of emergence of neuropsychiatric symptoms will be achieved in a substantial number of patients, delaying the need to move to institutional care.

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