In this issue of The Canadian Alzheimer Disease Review, a variety of important topics related to both the pharmacologic and nonpharmacologic treatment of Alzheimer’s disease (AD) are explored. When considering pharmacologic interventions, it is important to understand the broad approaches to treatment that are being developed in research and where both currently approved medications and those in development are likely to allow AD to become a more treatable disease.

There has been a general acceptance in the field that treatment approaches can be divided into those that are preventive, those that alter disease progression and those that are symptomatic. The cornerstone of a preventive approach would center on the concept that delaying the onset of the disease by five years would decrease the incidence of AD by 50% within a generation.1 The delaying interventions would involve modifying known risk factors with candidate medications that would have sufficient tolerability to allow for long-term exposure with a satisfactory risk-benefit profile. The leading candidates at the present time for such research studies include estrogens or estrogen analogues for postmenopausal women and anti-inflammatories for men and women. Such studies are in the planning stages and will likely require at least a further five years before there is available study data.

Therapeutic strategies to delay disease progression are a most attractive approach, yet the methodology for how such a claim might be demonstrated has been difficult to work out.2 A study in moderate to severe AD undertaken by the U.S. Alzheimer Disease Cooperative Study group defined disease milestones to show the delay of progression.3 Conducted over two years, the study evaluated vitamin E (2,000 IU daily), deprenyl (10 mg daily) or both in delaying a series of disease milestones, including death, institutionalization, loss of three important activities of daily living and progression to stage 3 on the Clinical Dementia Rating (CDR) scale. There were significant benefits to vitamin E in delaying these milestones, but there were no similar benefits in cognitive scores (Alzheimer’s Disease Assessment Scale [ADAS-cog], Mini-Mental State Examination [MMSE]) or behavior measures (Behavioral Rating Scale for Dementia), raising the question of whether vitamin E effectively altered disease progression or whether there might have been other explanations for the milestone effects. Currently, the only novel noncholinergic candidate that is well along in development is an adenosine agonist propentofylline, where some longer term efficacy data to support such a claim have been presented.4,5

There is only one symptomatic treatment presently approved for the treatment of AD in Canada. Symptomatic treatments are directed in practice at cognitive as well as noncognitive symptoms. It has been proposed that for a new symptomatic drug to reach regulatory approval in Canada, it should demonstrate symptomatic benefits on either cognitive or noncognitive symptoms with concurrent efficacy on a clinician’s global assessment.6 In clinical trials to date, it has been the cholinesterase (AChE) inhibitors (e.g., tacrine, donepezil, rivastigmine, metrifonate, galanthamine) that have been the only drugs to consistently meet these criteria. This led to the approval of donepezil in September 1997 and the anticipated approval of some of these other AChE inhibitors in the next year or two.

In his article, Dr. Serge Gauthier focuses on donepezil as the prototype cholinesterase inhibitor and the first approved drug to have been introduced for widespread clinical use in Canada. He provides an overview of donepezil’s preclinical and clinical trial development with consideration of the issues that must be addressed in clinical practice. He underlines the limitations of our knowledge in predicting clinical response with the need to pay particular attention in defining treatment responses, not only to evident cognitive changes, but also to functional activities where more meaningful responses may be evident to caregivers and families. His comments underline the importance for prescribing physicians to have realistic expectations of the AChE inhibitors. A
suggestion that treatment with donepezil should be stopped when the disease has reached a severe stage is an important consideration for prescribing physicians.

Dr. Gauthier also touches on the difficult issue of "non-responders". This designation can certainly be applied when a treatment period of three to six months with an AChE inhibitor is not associated with any symptomatic benefit and where the rate of decline on treatment does not differ from the period before treatment was initiated. The more difficult and currently unresolved issue is whether an individual who does not have symptomatic benefit during a three- to six-month treatment and who has no measurable decline should also be considered a non-responder and be discontinued from the AChE medication that has been prescribed. At present, it seems that most patients, families and physicians prefer to carry on with treatment in such an unchanging clinical state, even though discontinuation of the drug with close follow up for decline and with a plan to reintroduce medication is an alternative and potentially rational approach to this problem. As this may apply to as many as 40% of treated individuals, prescribing physicians will need to carefully consider their approach to this problem, particularly with the anticipated market presence of as many as four AChE inhibitors, which are likely to become available over the next 12 to 18 months. Further research on outcomes with AChE inhibitor discontinuation/rechallenge or response to alternative AChE inhibitors will be very helpful to clinicians.

In this issue as well, Dr. Nathan Herrmann provides a practical pharmacotherapeutic approach to some of the behavioral disturbances of AD. As clinicians involved in the care of patients with AD are well aware, it is the behavioral disturbances that are most difficult for caregivers to contend with and often for nurses, physicians and other health professionals to manage. Behavioral disturbances are a driving influence on decisions to engage institutional care. In his article, Dr. Herrmann touches on a number of key principles in treating the behavioral symptoms in AD. He emphasizes the need to try and identify specific psychotropic medications for particular target symptoms, taking into account the side-effect profile that can result. For neuroleptics, this will involve choosing the medication with the best profile for a given target symptom, while balancing the extrapyramidal, sedative and undesired anticholinergic side effects. The potential merits of the atypical neuroleptics (i.e., risperidone and olanzapine) are noted in this context. For sleep problems, the imperative to exhaust nonpharmacologic alternatives is worth emphasis, with the avoidance of daytime sleeping. Some considerations of antidepressant therapy are provided as well.

One of the most interesting emerging treatment concepts this past year has been the identification of the efficacy of the AChE inhibitors on some of the noncognitive aspects of AD. This relationship has emerged following the regulatory approval of tacrine (in the U.S.) and donepezil. Kaufer et al demonstrated symptomatic benefits for behavioral symptoms in AD in an open label, uncontrolled trial of tacrine. This has been followed by a number of additional reports by Cummings and colleagues from the University of California at Los Angeles of the benefits in attenuating behavioral symptoms in participants in AChE clinical trials. In particular, symptoms such as apathy, agitation, motor restlessness and depression have benefited from AChE treatment. Further study of these very important observations will undoubtedly be forthcoming. Whether AChE inhibitors will emerge as the drugs of choice for specific behavioral symptoms remains to be determined. These relationships in particular may be of key importance in building the case to formulations of the advantages of the AChE inhibitors.

It has been almost a year now since donepezil was released for widespread use in Canada. This medication has provided the first solid treatment option for cognitive enhancement and will be followed by the release of a series of AChE inhibitors and possibly by medications of novel classes for AD treatment. We are indeed beginning to find treatment options to explore for AD, at last.

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References: