EDITORIAL

Persistence with Cholinesterase Inhibitor Treatment in Alzheimer's Disease

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Three cholinesterase inhibitors (ChEI) are approved in Canada for the symptomatic treatment of Alzheimer's disease (AD): donepezil, rivastigmine, and galantamine. This class of drugs provides modest improvement of some symptoms of the disease but it does not alter its course[1]. The fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) concluded that the three ChEI demonstrated comparable efficacy for mild to severe AD, and that a trial of one of these medications should be proposed for most patients with AD[2]. As ChEI are relatively costly and their clinical benefits are mild, persistence with treatment has been an issue since their arrival on the Canadian market. In most provinces, these medications are reimbursed according to very specific criteria. For example, in Quebec, reimbursement of these medications is conditional on a clear diagnosis, a general rating of disease severity in five clinical domains, and specific cut-offs on the Mini-Mental Status Examination (MMSE). Upon renewing ChEI prescription, reimbursement is granted if the patient improves, stabilises, or does not deteriorate significantly in several clinical domains and on the MMSE. These criteria, which are based on the results of clinical trials with ChEI, are far from perfect, but they do serve as a general guide to their use in clinical practice. In clinical trials, patients are followed very closely and their symptoms are monitored on a regular basis. This will tend to reinforce persistence to treatment, but may be difficult to reproduce in real-life clinical practice. In that respect, the setting of clinical trials is "artificial". Nevertheless, the rate of withdrawal from ChEI after six months of treatment has varied between 20% and 30% in clinical trials, depending on the molecule used and the method of administration (immediate release vs extended release, oral vs transdermal, etc.)[3-5]. There are few clinical trials beyond six month duration, and they have usually demonstrated similar withdrawal rates.

In this issue of the Canadian Journal of Neurological Sciences, Saleh et al investigated persistence to ChEI in a small group of patients in a memory clinic in rural Saskatchewan[6]. Several factors were examined including socio-demographic, cognitive, functional and behavioural measures. The level of education was the only factor associated with discontinuation of ChEI. Out of the 63 patients initially started on ChEI, 19 discontinued treatment, and those with fewer years of formal education had higher rates of drug discontinuation at six months. Authors explain this finding by speculating that patients with more years of formal education were better able to understand the importance of treatment persistence and dealing with its side effects. The main limitation of this study is its modest sample size, meaning that type II error cannot be excluded. Also, it is unclear why such a small proportion of all patients evaluated (318) was included in the study. We assume that some individuals referred to this clinic were already on ChEI, and they were excluded, but this cannot be the case for most patients. Nevertheless, this study population represents a "real life" sample of individuals living in the community, who received an extensive evaluation by experts in a specialized clinic. Previous studies of ChEI persistence, including three from Canada[7-9], yielded persistence rates between 57% and 69% at 6 months, and between 34% and 57% at 12 months. Many of these studies consisted of analysing administrative healthcare databases including several thousand patients. One French study showed a surprisingly high persistence rate at one year (96.4% per 100 persons-years), but the study sample consisted of patients diagnosed and treated in AD expert centers[10]. In previous studies, factors associated with increased persistence have included extended-release and transdermal formulations, the chronic disease score (an indicator of comorbidity based on the number and type of medications prescribed), higher functional performance, multiple concomitant medications including memantine, the number of physician visits and the number of hospitalisations in the previous year (Table). Factors associated with decreased persistence include side effects, female gender, increasing age, lower MMSE score at initiation, concomitant anticholinergic medications, and having to pay for a significant proportion of the prescription cost. Hence, persistence seems to be facilitated by better tolerance (transdermal formulation), ease of use (extended-release formulation), "exposure" to the healthcare system (number of visits to the physician and of hospitalisations, higher chronic disease score), severity of the disease, use of concomitant medications, and reimbursement issues. A very important factor, which is not well captured in persistence studies, is setting realistic expectations with theses medications. In the study by Saleh et al, 10 out of 19 individuals discontinued ChEI because of "ineffectiveness of the drug". This can be difficult to assess after six months of treatment. As stated earlier, this class of medication does not alter progression of the disease, and provides modest symptomatic benefits. In many patients, these benefits are not clearly observable. Nevertheless, considering the neurodegenerative nature of the disease, stabilisation is an acceptable outcome of treatment. This element is essential, although sometimes difficult to convey to patients and their caregivers, as well as to prescribing physicians who are less familiar with these medications and their expected benefits. A simple guide to assess "satisfactory" response to ChEI during the first year of treatment is the following: stabilisation, improvement, or a deterioration of no more than 2 points on the MMSE, lack of significant functional deterioration, and absence of new behavioral symptoms[11].

The optimal duration of treatment with ChEI is still a matter of controversy. Unfortunately, there are no randomized clinical trials beyond 12 months to guide this decision. There is some compelling evidence from observational data as to the long-term benefits of treatment, such as delaying nursing home placement[12]. Arguments for discontinuation of ChEI are often vague and subjective. In a clear effort to avoid arbitrary criteria (such as a cutoff on the MMSE or nursing home placement), the

Table: Factors associated with persistence to cholinesteras inhibitor treatment

Factor	Increased Persistence	Decreased Persistence
Related to Medication		
Tolerability	Transdermal formulation	Side effects
Ease of use	Extended-release formulation (once daily)	
Related to the Patient		
Demographic factors		Female sexe Increased age Non-caucasian patients
Socioeconomic factors		Paying for a significant proportion of prescription cost
Comorbidity	Chronic disease score	
Disease severity	Higher functional performance	Lower MMSE score at initiation
Concomitant medication	Multiple anti-dementia medications Concomitant memantine	Anticholinergic medications
Medical follow-up	Number of physician visits Hospitalisations	Hospitalisations

MMSE: Mini-Mental Status Examination

most recent CCCDTD has updated its guidelines on discontinuation of treatment[2]. Proposed recommendations for discontinuation include intolerable side effects that are convincingly related to ChEI, more rapid clinical deterioration with treatment, and progression to the severe stages of AD (Reisberg stage 7). In the absence of clearer recommendations, many experts would contend that long-term treatment of AD should be pursued as long as benefits are observed. These benefits, especially in a deteriorating patient, should be determined by an open discussion between the physician, healthcare personnel involved in the patient's care, the patient himself if possible, and caregivers.

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