EDITORIAL

Cholinesterase Inhibitors in Vascular Cognitive Impairment

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Vascular Cognitive Impairment (VCI) includes vascular dementia, mixed dementia (Alzheimer's disease [AD] with cerebrovascular disease), and vascular mild cognitive impairment, and it is a common cause of cognitive dysfunction[1]. Some may even contend that it is the most common cause of cognitive impairment. This is based principally on clinico-pathological data showing that most aged individuals with significant cognitive impairment have mixed vascular and neurodegenerative neuropathology[2]. Vascular risk factor prevention and treatment are a mainstay of VCI management. Based on data showing disruption of cholinergic pathways in vascular dementia, cholinesterase inhibitors (ChEI) have also been widely used for symptomatic treatment[3]. Following a comprehensive review and analysis of the literature, the third *Canadian Consensus Conference on the Diagnosis and Treatment of Dementia* (CCCDTD) published in 2007 concluded that there was fair evidence for a modest benefit of donepezil on clinical outcomes in vascular dementia[4]. The third CCCDTD also concluded that there was fair evidence of modest benefit of galantamine in mixed AD with cerebrovascular disease. Similarly, the *American Stroke Association* and *American Heart Association* in their statement on *Vascular Contribution to Cognitive Impairment and Dementia* recommended donepezil for "cognitive enhancement" in patients with vascular dementia, and galantamine for patients with mixed AD with vascular dementia[1]. Clinical trials in VCI published since then have shown positive results for other cholinesterase inhibitors in mixed dementia, but inconsistent results in vascular dementia. This led the fourth and most recent CCCDTD, published in 2012, to recommend all ChEIs as symptomatic treatment options in mixed dementia[5]. However, it concluded that there was insufficient evidence to recommend for or against symptomatic treatment with ChEIs in vascular dementia.

Vascular Cognitive Impairment, particularly vascular dementia, usually presents with a fronto-sub-cortical pattern of impairment with prominent executive dysfunction and relative sparing of memory, which is distinct from the typical clinical picture seen in cortical dementias such as AD. This poses a diagnostic challenge in clinical practice as commonly used cognitive screening tools such as Folstein's Mini-Mental Status Examination (MMSE) are limited by their capacity to capture executive dysfunction. More recently developed screening tests, the Montreal Cognitive Assessment (MOCA) being a salient example[6], have refined executive function evaluation and are better suited for screening of VCI[7]. The clinical pattern of VCI also constitutes a challenge in the selection of appropriate and responsive outcome measures in clinical trials of pharmacological interventions. The study published by Rockwood et al, in this issue of the Canadian Journal of Neurological Sciences deals specifically with this topic of using appropriate outcome measures in clinical trials of VCI and translating the results of these trials into practice[8]. The main objective of this six-month open-label study was to measure responsiveness of outcome measures in vascular and mixed dementia to donepezil treatment. The measures used were the standardized MMSE, the Disability Assessment for Dementia (DAD), CLOX-1 and 2 (executive clock drawing tasks), phonetic verbal fluency, a short neuropsychiatric inventory (NPI-Q), the Clinical Global Impression (CGI), and the SymptomGuide (SG). The SG is an assessment tool, developed by one of the authors of this study, which evaluates frequency and distress associated with common symptoms in dementia. Target symptoms are chosen by the patient and caregiver which are then used to assess response to the intervention. This guide allows individualisation of outcome assessment with explicit inclusion of patient and caregiver input. Such measures are seldom used in clinical trials in dementia[9]. In this study, there was insignificant improvement on the MMSE, no significant difference on the DAD, and statistically significant improvement in the NPI-Q, CLOX-1, CLOX-2, verbal phonetic fluency, and the SG. The CGI showed minimal improvement in most completers. The main limitations of the study are its open-label design, the relative short duration of the intervention, and the difficulty with recruitment which led to a smaller number of individuals being included. Nevertheless, the study shows that individualized assessment tools and those evaluating executive dysfunction are more responsive to intervention in VCI. It is of concern that commonly used measures in clinical practice and even in clinical trials lack these two important characteristics. In a previous study, the same group of researchers identified symptoms of AD that are clinically responsive to symptomatic treatment but are otherwise unmeasured by usual tools[10]. A list of symptoms potentially improving with treatment was developed based on a survey of Canadian physicians. Items related to frontal system function, also related to executive function, top this list (attentional capacity and initiative). Apathy, mood, agitation, social interactions and involvement in domestic activities constituted other important symptoms on the list. Disappointingly, of the top ten symptoms considered to improve with treatment in clinical practice, only four appeared to be captured by commonly used measures. This list, the TOPS checklist, was later used in a 24-week Canadian open-label study of donepezil in AD. The trial showed that the TOPS checklist was more suited to capturing response to donepezil than standard measures, such as the Alzheimer's Disease Assessment Scale – cognition (ADAS-cog) or the DAD[11].

Using appropriate tools to identify response to interventions is of utmost importance. There is no such unique measure in dementia. Unfortunately, many sub-optimal measures are used in clinical trials in dementia, and by provincial formularies for reimbursement purposes. Response to treatment, or lack of it thereof, is usually evaluated based on clinical judgment, which

may be subjective. In this era of high-technology biomarkers being proposed as diagnostic aids and in assessing response to treatment, simple individualized clinical tools able to capture response to treatment should continue to be sought.

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