Treatment of Alzheimer’s disease with acetylcholinesterase inhibitors: bridging the gap between evidence and practice

Introduction

Modern medicine is facing a scenario of abundant but often inhomogeneous scientific evidence, increased demand for treatment but limited financial resources, and an increasing need for justifying medical interventions to the patient and to society at large. In this context, a line of research has developed that should provide the physician with instruments (guidelines, GLs) that translate scientific evidence coming from appropriately designed studies into daily clinical practice for the individual patient and should represent standards of reference for the medical community.

Alzheimer’s disease (AD) affects about 3 million people in the European Union, and its prevalence is expected to triple within the next 50 years [8]. Effective drug treatments are available, relatively expensive, and that can affect the response to acetylcholinesterase inhibitors. The effect on behavioral symptoms, severe Alzheimer’s dementia, and non-Alzheimer’s forms of degenerative dementia need to be clarified as well as the modulating effect of frequently associated conditions such as cognitive changes due to physical diseases and cerebrovascular disease. The gap between evidence and clinical practice might be closed with appropriately designed observational studies rather than randomized clinical trials.

Abstract Views on drug therapy with acetylcholinesterase inhibitors of the cognitive symptoms of Alzheimer’s disease are not uniform, varying from excitement at the possibility of significantly improving the personal and social burden of the disease to skeptical and nihilistic attitudes. Clinical practice from generous prescription to evidence-based guidelines and advising much stricter rules, mirror these attitudes. The epidemiological and clinical relevance of the issue requires understanding of the factors responsible for such discrepancies. Randomized clinical trials have only been able to address a few of the many variables their impact on the symptoms and progression of the disease seems, on the whole, modest. However, a sizable minority of patients obtain significant benefits on cognitive performance, function, and behaviour. GLs for the treatment of AD have been developed by a number of international agencies that are strictly based on evidence from randomized clinical trials (RCTs). However, such GLs are not followed in clinical practice.

The failure of evidence-based GLs to meet with daily clinical practice is not unique to the field of AD treatment [12]. After initial enthusiasm on the possibility of providing evidence for most – if not all – medical decisions, increasing skepticism has developed and awareness has arisen that a number of gray zones are not – and probably will never be – covered by evidence [41, 13]. For example, older patients, those with comorbid conditions, at the extreme ends of the severity spectrum of the disease of interest (very early and very severe), and with
Evidence and evidence-based guidelines

The most strongly supported evidence available today on the pharmacological treatment of the cognitive symptoms of AD concerns the acetylcholinesterase (AChE) inhibitors donepezil and rivastigmine. Galantamine, a drug with AChE-inhibiting activity is also effective on cognition [49, 59], but is not yet available for clinical use. However, its tolerability and efficacy profile seem to be similar to that of rivastigmine [49, 53, 59], and what will be discussed here will probably apply also to galantamine once it is on the market. Other drugs are either obsolete (tacrine) [20], or their use is less controversial for their good tolerability and lower cost (vitamin E) [54], or the experience of clinical use is not sufficiently wide to allow firm conclusions (memantine) [62].

In mild to moderate AD patients (Mini Mental State Examination – MMSE – between 10 and 26) with no evidence of cerebrovascular disease, RCTs of AChE inhibitors have shown a modest but detectable effect over about 6 months, amounting to 4.1 to 5.4% change of the cognitive test used to assess their efficacy [40]. This magnitude is such that it is barely detectable by the physician and by caregivers. The proportion of side effects and dropouts related to adverse events of donepezil is reasonably low [40]. On the basis of a systematic review of available evidence, authors from the Cochrane Collaboration conclude that “in selected patients with mild or moderate Alzheimer’s disease treated for periods of 12 or 24 weeks, donepezil produced modest improvements in cognitive function” and that “the practical importance of these changes to patients and carers is unclear” [5]. The efficacy of rivastigmine is similar, but it requires a longer titration phase, and the proportion of side effects is markedly higher [40, 53]. In the latest update of May 1999 on rivastigmine, the Cochrane reviewers concluded that “the available evidence shows a modest benefit for high dose rivastigmine on cognition and activities of daily living” and that “withdrawal rate due to side effects is significant” [6].

Evidence-based guidelines discourage the use of AChE inhibitors

The modest effectiveness suggested by systematic reviews is endorsed by the available guidelines. In 1997, Lovestone and colleagues [38] proposed simple guidelines that basically rephrased the inclusion criteria of RCTs, indicating that AChE inhibitors be prescribed to patients satisfying McKhann criteria of probable AD [43] and with MMSE between 10 and 24. Those patients with signs of cerebrovascular disease – who can be categorized as mixed dementia or possible AD with cerebrovascular disease [52] – were excluded from treatment. In the same year, the American Psychiatric Association issued “Practice Guidelines” that concluded that, in addition to tacrine, “donepezil has also been shown to lead to modest improvements in a substantial minority of patients” and “it may prove preferable [to tacrine] as a first-line treatment” [1]. In 1998, the North of England Evidence Based Guidelines for the Primary Care Management of Dementia concluded that “donepezil has shown a moderate effect on cognitive function in short term treatment trials of patients with mild to moderate AD” and that “whether donepezil is a worthwhile treatment for AD has not been established by current trials” [18]. At that time rivastigmine was not yet available, but, given its lower tolerability and similar efficacy, the conclusions on this drug should not be more positive.

- Guidelines are based on randomized clinical trials that include non-responders and exclude potential responders

Although it is true that on average the effect of AChE inhibitors is barely detectable by the physician and by caregivers, it is also true that RCTs of AChE inhibitors find a sizable minority of AD patients who have a marked clinical effect. In the original trial on donepezil [51], an improvement of 7 or more points on the Alzheimer’s Disease Assessment Scale (ADAS-cog, maximum score 70 points) after 6 months was seen in 25% of the patients on 10 mg, and 8% in the placebo group. The magnitude of this effect is equivalent to about twice the annual rate of progression of the disease [34, 58]. In a large trial of rivastigmine, the proportions of those showing an improvement of 4 or more points on the ADAS-cog was 27% in the treated and 18% in the placebo groups [53]. Thus, taking into account the “average” effect of AChE inhibitors obscures the wide variability of the treatment effect and the presence of a sizable group of patients with a marked positive response. Obviously, identifying these patients a priori, i.e. before administering the drug, would be of paramount clinical relevance. Unfortunately, despite a number of factors...