Introduction

Often it is not for the benefit of patients, when a clinical issue is debated in public domain. Currently, patients with dementia who are considered for treatment with one of the cholinesterase inhibitors are in danger of being crushed between clinical opinion leaders, national guidelines, pharmaceutical companies and politicians. After a review of the cost effectiveness of cholinesterase inhibitors for Alzheimer’s disease (AD), the UK National Institute of Clinical Excellence recently recommended that these drugs should be used only in patients with a score for cognitive impairment within a specific range [1]. Patients’ organisations orchestrated street protests, two companies started a judicial review of the process leading to this recommendation and an American politician contended that restrictive guidelines ultimately hinder development and innovation in biomedical research. Where does that leave patients with dementia? Is there an alternative for the power play of solicitors and politicians? We believe that conscientious analysis of all available data should offer a rational solution for this escalating conflict. More so because it concerns essentially a clinical issue that is to be solved by clinical reasoning rather than by a vigorous legal battle.

Do patients with dementia benefit from cholinesterase inhibitor therapy?

Some 10 years ago, the worldwide licensing of cholinesterase inhibitors (CEIs) has brought a little hope on the previously dim scene of treatment of dementia. Several meta-analyses of CEIs like rivastigmine, donepezil and galantamine have documented consistent treatment effects for patients with mild to moderate AD [2]. Treatment effects were measured with cognitive assessment scales and scales for behavioural problems and activities of daily living. Though statistically significant at the level of groups consisting of hundreds of patients, the clinical relevance of these treatment effects remains questionable, especially for each and every individual patient using a CEI. This is clearly illustrated by a long term study of donepezil, that indeed reproduced the short term and small improvements in cognition and activities in daily living in AD, but failed to show any reduction in the rate of institutionalisation or progress of disability after 2 years of treatment [3].

The randomised clinical trials that served the licensing of CEIs have been subject to various criticism such as the high drop out rates that were observed in almost all studies, the way data on dropouts were handled and the fact that masking of treatment allocation may have been hampered because of frequently occurring side-effects. Also the relatively small differences in average scores at the group level are the subject of the heated controversy surrounding the CEIs. Some argue that these drugs hardly offer any benefit at all, whereas others are convinced that withholding this small benefit from any patient is to be considered as unethical. Because of the rising temperature of this debate, the simple fact tends to be ignored that some patients may have substantial benefit from these drugs, whereas others may not benefit at all.

Depending on the exact criterion that is used for labelling individual ‘responders’, 10–20% of Alzheimer patients using a CEI satisfy this criterion, whereas the same holds 5–15% of patients using placebo [4]. The latter illustrates that the responder criteria proposed so far are not too restrictive at all. Thus, most probably about only 5–15% of patients with AD truly benefit from the consequences of cholinesterase inhibition, and the remainder of so-called responders may benefit from non-specific factors that are associated both with drug as well as placebo treatment. In dementia with Lewy bodies and Parkinsons’ disease, the percentage of true responders may be somewhat higher [5, 6]. These drugs are by no means miracle drugs, but they appear to be not completely worthless either. CEIs simply are effective in some patients and not in others, a fact that is common wisdom for many other drugs used in other fields of medicine. Acknowledging this self evident fact by all parties involved could be the beginning of a solution.
Defining patients who will benefit from cholinesterase inhibitor therapy

Clinical symptoms of confusion, disorientation or frank dementia can be elicited by different functional impairments. With a somewhat circular line of reasoning, patients with clinical symptoms that respond well to CEI therapy, can be considered to have suffered from a cholinergic deficiency before starting treatment (Figure 1). On the basis of data on the effects of anticholinergic drugs, case studies of patients receiving CEI therapy and on experimental work relevant to the functional ramifications of cholinergic neurotransmission, we have speculated on the clinical characteristics of such a 'cholinergic deficiency syndrome' (CDS) [7]. Treatment with anticholinergic drugs can cause restlessness, some excitement, confusion, and at higher doses impaired consciousness, perceptual distortions, memory deficits, anxiety, illusions and most frequently visual hallucinations may develop. Interestingly, administration of the CEI tetrahydroaminoacridine, currently better known as tacrine, has been reported in the past to reverse this neuropsychiatric syndrome within minutes [8].

Several exploratory studies have been undertaken in attempts to define characteristics of responders to CEIs and some study results are consistent with the clinical syndrome delineated above. In an early retrospective study, Mega et al. already pointed out that a pre-treatment behavioural profile can help to predict response to donepezil [9]. Others coined disease severity, fluctuating cognition, a diagnosis of Lewy body dementia (LBD) or PDD, and older age as possible predictors of beneficial therapeutic response in retrospective studies [10–14]. Post hoc analyses of trial data of AD and LBD patients proposed that patients with visual hallucinations and specific behavioural symptoms such as apathy and anxiety are more likely to respond to CEI treatment [15–17].

Unfortunately, large-scale post hoc analyses of baseline characteristics that define responders to CEIs have never been performed on the thousands of patients who provided the data that are on file with pharmaceutical industries (Table 1). Such analyses, even if they were exploratory in nature could very well provide a first in delineation of the clinical profile of patients who benefit most from cholinomimetic therapy. The validity of the resulting predictor profile could be investigated in subsequent cohort studies and even might apply to open label treatment. Such studies could document whether or not the benefits of CEI treatment in patients defined according to that profile outweigh the side-effects with a greater margin of profit than in unselected patients or in patients who do not have the characteristics of the CDS.

Access to Trial Data in the Interest of Future Patients

Such a strategy may eventually lead to a more satisfactory approach to CEI treatment than the present NICE proposal that advocates use of a rather arbitrarily defined range of scores on the Mini Mental Status Examination for selecting patients for CEI therapy. It may also reconcile those who fear a nihilistic therapeutic approach towards patients with dementia and those who contend that the indiscriminate use of CEIs subjects many patients to disturbing side-effects without offering any benefit. Till date there is hardly any data that provides a solid basis for selective use of CEIs. Instead of endless debates, protest manifestations or legal procedures this issue should be high on the agenda of dementia research, starting with a sound analysis of data that already have been collected in the past. Therefore, it is very unfortunate that despite many requests by independent researchers, none of the manufacturers of the various CEI preparations has consented to post hoc analyses on trial data as a first step. In some cases companies refused with reference to protection of patents. However, patients who in the past agreed to participate in clinical trials of cholinesterase inhibitors, as well as caregivers supporting this decision and facilitating the actual participation of patients did so in the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number trials</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>21</td>
<td>6138</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>9</td>
<td>3381</td>
</tr>
<tr>
<td>Galantamine</td>
<td>11</td>
<td>7502</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>17021</td>
</tr>
</tbody>
</table>

Table 1. Participants in trials by pharmaceutical companies

* Based on published reviews from the Cochrane Database.
belief that it would contribute to the advancement of science and the improvement of therapeutic care for patients with dementia. Most likely the informed consent form that they signed did not specify that access to the trial data would be strictly limited to employees of the pharmaceutical company involved. Protection of any patent or other interests of the pharmaceutical companies had most probably not a high priority for these trial participants. Failure to provide access to data that were generated with the generous help of patients with dementia and their caregivers not only violates their trust, but also hinders more rational use of CEIs by future patients.

**Key points**

- Cholinesterase inhibitors showed limited but consistent therapeutic effects in randomised clinical trials
- Defining clinical characteristics of true responders could help to select patients who will really benefit from these drugs
- On the basis of the cholinergic hypothesis such a predictive clinical profile will probably include attentional deficits and neuropsychiatric features
- Selective use of cholinesterase inhibitors could prevent unnecessary exposure to disturbing side effects
- Drug companies should release their data for independent post hoc analyses to find valid predictors for response to treatment with CEIs in patients with dementia

**Conflict of interest**

AWL & ER none declared; WAvG has been invited by NICE to act as an expert witness in the judicial procedure (no fee involved).

**References**

1. [http://www.nice.org.uk/CG035 2006; Ref Type: Electronic Citation.](http://www.nice.org.uk/CG035 2006; Ref Type: Electronic Citation.)
4. Committee for Proprietary Medicinal products. European public assessments report of rivastigmine. [http://www.eudra.org/emea.html 2002; Ref Type: Electronic Citation.](http://www.eudra.org/emea.html 2002; Ref Type: Electronic Citation.)


Received 30 May 2007; accepted in revised form 20 July 2007