Editorial Comment

How to Treat Vascular Dementia?

In clinical practice, we deal with a great proportion of elderly people. Many times, we are able to identify cognitive deficits (although not too scarce, we overlook dementia in our patients). However, the further division into the several subtypes of dementing disorders may be complicated and laborious for patients, caregivers, and physicians due to noncompliance, incomplete clinical history, or missing medical equipment. Moreover, considerable clinical overlap makes treatment decisions difficult. So the good news, presented by Black et al in this issue, is that the 3 most common forms of dementia—Alzheimer’s disease (AD), vascular dementia (VaD), and dementia with Lewy bodies—do have a common effective treatment schedule: acetylcholinesterase inhibitors (ACEI). Although their efficacy is, indeed, not overwhelming and a considerable proportion of patients will not profit by this medication, they still represent a ray of hope in the sad story of dementia treatment.

In the 1960s, it was widely recognized that AD was responsible for most cases of dementia in the elderly and that cerebral arteriosclerosis was a rare cause of dementia. A decade later, research found out that some people develop dementia not due to arteriosclerosis of brain vasculature but rather as a consequence of a series of strokes, affecting different brain regions, and the term multi-infarct dementia was introduced. In the 1990s, it also became clear that several other mechanisms (ischemic white matter lesions, lacunes) may underlie vascular damage to the brain, which culminates in cognitive decline; therefore, the broader term vascular dementia was accepted and recognized as the second most common cause of dementia. However, as things are going on, separate paths merge sometimes later on. The association between AD and VaD has recently turned out to be more complex. Both AD and VaD increase in prevalence with age; they frequently occur concomitantly; and considerable overlaps are seen in their symptomatology, pathophysiology, and comorbidity. Many patients show a combination of degenerative brain changes of the AD type along with evidence of strokes. One or two lacunes in elderly subjects with AD changes in the brain

<table>
<thead>
<tr>
<th>CIBIC-plus category, n (%)</th>
<th>Placebo 5 mg/day</th>
<th>Placebo 10 mg/day</th>
<th>Placebo</th>
<th>Placebo 5 mg/day</th>
<th>Placebo 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked improvement</td>
<td>2 (1.0)</td>
<td>4 (2.0)</td>
<td>3 (1.5)</td>
<td>2 (1.2)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>19 (9.8)</td>
<td>13 (6.6)</td>
<td>15 (7.7)</td>
<td>17 (10.5)</td>
<td>11 (6.9)</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td>37 (19.1)</td>
<td>53 (27.0)</td>
<td>37 (19.0)</td>
<td>33 (20.4)</td>
<td>46 (28.8)</td>
</tr>
<tr>
<td>No change</td>
<td>76 (39.2)</td>
<td>82 (41.8)</td>
<td>85 (43.6)</td>
<td>60 (37.0)</td>
<td>65 (40.6)</td>
</tr>
<tr>
<td>Minimal worsening</td>
<td>43 (22.2)</td>
<td>32 (16.3)</td>
<td>47 (24.1)</td>
<td>35 (21.6)</td>
<td>27 (16.9)</td>
</tr>
<tr>
<td>Moderate worsening</td>
<td>14 (7.2)</td>
<td>9 (4.6)</td>
<td>8 (4.1)</td>
<td>13 (8.0)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Marked worsening</td>
<td>3 (1.6)</td>
<td>3 (1.5)</td>
<td>0</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Change from baseline score, LS mean±SE

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo 5 mg/day</th>
<th>Placebo 10 mg/day</th>
<th>Placebo</th>
<th>Placebo 5 mg/day</th>
<th>Placebo 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog</td>
<td>0.72±0.40</td>
<td>-0.96±0.39†</td>
<td>-1.52±0.40‡</td>
<td>0.34±0.40</td>
<td>-1.56±0.43†</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.39±0.23</td>
<td>1.04±0.21*</td>
<td>1.49±0.20‡</td>
<td>0.57±0.24</td>
<td>1.10±0.24</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>0.11±0.12</td>
<td>-0.01±0.12</td>
<td>-0.25±0.11*</td>
<td>0.12±0.13</td>
<td>-0.07±0.13</td>
</tr>
<tr>
<td>ADFACS</td>
<td>1.44±0.42</td>
<td>0.64±0.36</td>
<td>0.53±0.38</td>
<td>1.68±0.46</td>
<td>0.37±0.38*</td>
</tr>
<tr>
<td>IADL</td>
<td>0.87±0.32</td>
<td>-0.02±0.25*</td>
<td>0.13±0.27</td>
<td>0.99±0.37</td>
<td>-0.11±0.28*</td>
</tr>
</tbody>
</table>

CIBIC-plus (comparison across all categories): P<0.05 for overall donepezil treatment (5 and 10 mg/day) vs placebo, and donepezil 5 mg/day vs placebo, at week 24 observed cases.

*P<0.05, †P<0.01, ‡P<0.001 vs placebo.
increase 20 times the risk of clinical expression of dementia. Moreover, MRI scans show the high frequency of vascular changes in older people with all forms of dementia. These similarities can on the one hand give reason to some (rather courageous) authors to propose that AD should be classified as a vascular disorder, and on the other hand explain somehow that AD and VaD both respond to ACEI.

Interestingly, there is growing evidence for the involvement of the cholinergic system in VaD, as is the case in AD. Spontaneously hypertensive stroke-prone rats display a number of symptoms characteristic of patients with VaD, such as cognitive impairment and marked behavioral changes. Studies in this animal model for VaD demonstrated significant reductions in the levels of acetylcholine and choline in the cortex, hippocampus, and striatum. This suggests that there is a general degeneration of cholinergic neurotransmission in VaD and would explain the therapeutic effect of ACEI. Compared with controls, patients with VaD have significantly lower postmortem CSF acetylcholine concentrations.

Black and colleagues present a well-designed study of 603 patients with VaD (70% probable, 30% possible VaD) treated with 5 or 10 mg donepezil or placebo for 6 months, most of them (>80%) in combination with antithrombotics for stroke prevention. A total of 478 patients completed the study, thus representing the largest clinical trial on VaD so far. Five cognitive tests were performed on 5 different study points, analyzed in 2 different modes. The results are no reason to get euphoric. The authors found improvement in some items of cognition and global function after half a year of treatment, whereas other items did not improve (interestingly, some items improved with 5 mg but failed to do so with the double dose). Anyway, no item deteriorated under donepezil, but this may be explained by the antithrombotic medication, as deterioration is lacking in the placebo group as well. It has to be counted as shortcoming of the study that the study was not powered for a subgroup analysis. It would be essential to know which subtype of VaD responds to inhibition of the acetylcholinesterase (not solely, but also from an economic point of view), and this question should be clarified by the next trials to reduce the immense number needed to treat.

Donepezil, rivastigmine, and galantamine are the first-line choices in the treatment of mild to moderate AD and dementia with Lewy bodies, although the treatment is only effective in about half of the patients for whom it is prescribed. This might be due to their lack of hepatotoxicity, ease of administration, few significant drug-drug interactions, and mild to moderate side effects. Moreover, there are few contraindications to the use of ACEI. For this reason, they have the potential to evolve to the first-line treatment in VaD as well (in combination with antithrombotics), as comparable results to Black’s data were published for galantamine in a similarly designed trial, and there are positive open-label data available on rivastigmine. After analyzing the available randomized, double-blind, placebo-controlled trials, most other treatment options available today show a clearly lower level of evidence: a potential therapeutic role for pentoxyfylline, posatrilin, vincamine, naftidrofuryl, and propentofylline in VaD cannot be ruled out; the evidence for a beneficial effect of vinpocetine, denbufylline, sulodexide, nicergoline, and nimodipine is inconclusive and does not support clinical use; and there seems to be no therapeutic effect of Gingko biloba on VaD.

So how to treat our patients with VaD? There definitely seems to be benefit with the N-methyl-D-aspartate receptor antagonist memantine—a drug that acts on the glutamatergic system rather than the cholinergic system. Its benefit seems to be at least comparable to the effect of ACEI. No study ever has combined those 2 substances in VaD, although the mechanism of action is very different, but—wouldn’t some of us treat our relatives with this combination, if they turned out to suffer from VaD?

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References


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