Long-term cognitive and functional decline in late onset Alzheimer’s disease: therapeutic implications

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Abstract

Background: National Institute of Clinical Excellence guidelines advocate the use of the Mini-Mental Test Examination and a functional assessment as a means of measuring treatment response. However, there is little knowledge of the change expected in those with Alzheimer’s disease in clinical practice.

Objective: to describe the long-term variability of the Mini-Mental Test Examination and Blessed Dementia Rating Scale.

Method: 374 Alzheimer’s disease patients referred to psychiatric services in south-east London were followed annually over a 3-year period.

Results: the mean Mini-Mental Test Examination score for the total group at baseline was 9.9 points. Individual variability in the rate of cognitive and functional decline is large and around 40% of patients after 1 year, and up to one-quarter of patients after 3 years who survived, show no change or an improvement in scores compared with baseline measures.

Conclusions: in the evaluation of individual treatment response the rate of change, as measured by the Mini-Mental Test Examination and Blessed Dementia Rating Scale, is of limited value.

Keywords: Alzheimer’s Disease, cognitive decline, National Institute of Clinical Excellence, functional decline

Introduction

The determination of response to dementia treatments is an important and pressing clinical issue. In clinical trials of cholinesterase inhibitors the primary assessment measure most often used is the ADAS-cog [1]. However, this scale takes approximately 45 minutes to complete. As a consequence shorter scales such as the Mini-Mental State Examination (MMSE) [2] have been recommended as tools for assessing response to treatment [3]. In addition, recent National Institute of Clinical Excellence (NICE) guidelines [4] have also advocated the additional use of functional assessment as a means of measuring treatment response. However, concerns have been raised about the validity and reliability of such scales [5, 6]. In addition, long-term studies of cognitive and functional change in Alzheimer’s Disease (AD) are relatively few [7] and the rate of change in ordinary clinical practice is largely unknown. We have therefore examined change in both function and cognition over time in a cohort of patients referred to a clinical service.

Subjects and methods

Five hundred and twenty-eight subjects who fulfilled both the ICD10 [8] and DSMIV [9] criteria for dementia were selected from the community based Camberwell Dementia Case Register. This case register has been previously reported [10] and includes all those with dementia referred to the clinical Old Age Psychiatry service of the Maudsley Hospital in South London from April 1993 to April 1995. Of these subjects 374 fulfilled NINCDS/ADRDA criteria [11] for late onset AD. Validation of the clinical diagnosis of AD against post-mortem in this sample has been previously reported with high positive predictive values (0.89) against CERAD diagnostic criteria [12]. Cognitive and functional assessment was recorded by trained clinical research nurses using the MMSE and an abbreviated form of the Blessed Dementia Rating Scale (BDRS) [13], respectively. Assessment followed a standardised protocol to maximise inter-rater reliability. All subjects were followed up in their homes by the same rater at yearly intervals, for a period of 3 years with repeat
MMSE and BDRS assessments on each occasion. No patients were prescribed cholinesterase inhibitors or were part of any clinical drug trials during the course of the study.

**Statistical analysis**

The annual rate of change for the MMSE and BDRS was determined by simple subtraction of the baseline score from follow up score in the proceeding year. The average rate of cognitive and functional decline for the 3-year period was determined using information from all possible time points and was based upon the average slope of MMSE or BDRS points change per year. Improvements in cognitive ability result in an increase in MMSE score, whereas improvements in functional ability result in a decrease in the BDRS score. Following one-way Kolmogorov–Smirnov testing, baseline and average rates of cognitive decline were considered as non-parametric variables whereas baseline and average rates of functional decline were considered as parametric variables.

A separate analysis was made of cases with evidence of mild to moderate dementia at baseline (defined as MMSE >11 points and <27 points).

All of the above tests were performed using the statistical package SPSS for Windows version 8.

**Results**

**Baseline measures**

Two hundred and eighty-two (75%) of the AD patients were female and the mean age at the point of initial interview was 83.0 years (s.d. 6.4 years). The mean MMSE for all patients at first interview was 9.9 points (s.d. 7.1 points) (median 10 points) with a mean BDRS of 8.8 points (s.d. 4.0 points). At the end of the first year of the study 237 subjects were still alive. This fell to 158 after the first year 90 out of 231 subjects (39.0% of the reassessed survivors) had shown no change or an improvement in cognitive score compared to baseline. A lack of change or an improvement in cognitive scores compared to baseline scores was also found in 37 (24.0%) and 27 (24.7%) subjects after the second and third years, respectively (Table 1). Subjects who survived more than 3 years from baseline did not show significantly less cognitive decline during the first year than those subjects who died earlier. Thus, during the first year 47 (43%) of the 109 surviving subjects showed no change or an improvement in cognitive score compared to 43 (35%) of 122 non-survivors ($\chi^2 1.5 P=0.2$).

There was a low negative correlation between the rate of cognitive decline over the first year of follow up compared with the second year (Spearman rank –0.23 P=0.006). A very low correlation between cognitive decline between the second year of follow up compared with the third year was not significant (Spearman rank –0.14 P=0.2).

**Relationship between baseline measures and cognitive and functional decline**

No association was found between either cognitive or functional decline over the 3-year period with gender (MWU $P=0.21$; $t$-test $P=0.50$, respectively) or age (Spearman rank –0.08 $P=0.21$; Pearson 0.02 $P=0.78$, respectively). Modest negative correlations were found between baseline cognitive scores and rates of cognitive decline over the 3 year period (Spearman rank –0.41 $P<0.0001$) and low negative correlations were found between baseline functional scores and rates of functional decline (Pearson –0.29 $P<0.0001$, respectively).

**Cognitive decline**

Nearly all surviving subjects were successfully reassessed with the MMSE at 1 year ($n=231$, 97% of survivors), 2 years ($n=154$, 97% of survivors) and 3 years ($n=109$, 99% of survivors). The mean rate of cognitive decline was 2.4 (s.d. 4.5) points over the first year period, 1.9 (s.d. 3.9) points over the second year period and 1.4 (s.d. 3.3) points over the third year period. The average rate of decline over the 3-year period was 2.2 (s.d. 3.4) points per year (median 1.8 points).

After the first year 90 out of 231 subjects (39.0% of the reassessed survivors) had shown no change or an improvement in cognitive score compared to baseline score. A lack of change or an improvement in cognitive scores compared to baseline scores was also found in 37 (24.0%) and 27 (24.7%) subjects after the second and third years, respectively (Table 1). Subjects who survived more than 3 years from baseline did not show significantly less cognitive decline during the first year than those subjects who died earlier. Thus, during the first year 47 (43%) of the 109 surviving subjects showed no change or an improvement in cognitive score compared to 43 (35%) of 122 non-survivors ($\chi^2 1.5 P=0.2$).

There was a low negative correlation between the rate of cognitive decline over the first year of follow up compared with the second year (Spearman rank –0.23 P=0.006). A very low correlation between cognitive decline between the second year of follow up compared with the third year was not significant (Spearman rank –0.14 P=0.2).

**Functional decline**

The majority of surviving subjects were successfully reassessed with the BDRS at 1 year ($n=176$, 74% of survivors), 2 years ($n=156$, 99% of survivors) and 3 years ($n=110$, 100% of survivors). The relative lack of follow up data at 1 year was due to the unintentional omission of the BDRS in some of the first year follow up data protocols which was later rectified. The mean rate of functional decline over the first year period was 0.8

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**Table 1. Cognitive (MMSE) change in late onset Alzheimer’s disease over a 3-year period**

<table>
<thead>
<tr>
<th>Direction of change</th>
<th>First year MMSE scores $n=231$ (% of survivor cohort)</th>
<th>Second year MMSE scores $n=154$ (% of survivor cohort)</th>
<th>Third year MMSE scores $n=109$ (% of survivor cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>45 (19.5%)</td>
<td>13 (8.4%)</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>No change</td>
<td>45 (19.5%)</td>
<td>24 (15.6%)</td>
<td>20 (18.3%)</td>
</tr>
<tr>
<td>Decline</td>
<td>141 (61.0%)</td>
<td>117 (76.0%)</td>
<td>82 (75.3%)</td>
</tr>
</tbody>
</table>
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points (s.d. 3.2), 2.5 points (s.d. 2.9) over the second year period and 1.0 point (s.d. 2.2) over the third year period. The mean rate of functional decline over the 3-year period was 1.3 points (s.d. 2.2) per year.

After the first year 77 subjects (44.0% of the reassessed survivors) had shown no change or an improvement in their functional score compared to baseline. A lack of change or an improvement in functional scores compared to baseline scores was also found in 29 (18.6%) and 17 (15.5%) of subjects after the second and third years, respectively (Table 2). Subjects who survived more than 3 years from baseline did not show significantly less functional decline during the first year than those subjects who died earlier. Thus, during the first year, of those patients reassessed, 46 (43%) of the 110 surviving subjects showed no change or an improvement in functional score compared to 31 (48%) of the 65 non-survivors ($\chi^2 = 0.6, P=0.5$).

There was a low negative correlation between the rate of functional decline over the first year of follow up compared with the second year (Pearson – 0.36 $P<0.0001$). A very low correlation between functional decline in the second year of follow up compared with the third year was not significant (Pearson 0.08 $P=0.6$).

Of the 77 subjects who had shown no change or an improvement in their functional score compared to baseline after the first year, 29 (38%) had also shown no change or an improvement in their cognitive score compared to baseline. Of the 29 subjects who had shown no change or an improvement in their functional score compared to baseline after the second year, 10 (34%) had also shown no change or an improvement in their cognitive score compared to baseline. Finally, of the 17 subjects who had shown no change or an improvement in their functional score compared to baseline after the third year, 8 (47%) had also shown no change or an improvement in their cognitive score compared to baseline.

### Mild to moderate cases alone

We separately examined cases with mild to moderate AD. One hundred and fifty-one cases scored > 11 points and < 27 points on the MMSE at baseline (mean score 17.0, s.d 3.5). The mean rate of cognitive decline over the 3-year period was 3.4 (s.d. 3.5) MMSE points per year (median=3.0). Baseline MMSE score did not show a significant correlation with the mean rate of cognitive decline (Spearmann rank –0.004 $P=0.97$). After the first year 34 subjects (34.0% of the reassessed survivors) had shown no change or an improvement in cognitive score compared to baseline score. A lack of change or an improvement in cognitive scores compared to baseline scores was also found in 9 (13.4%) and 7 (14.5%) of subjects after the second and third years, respectively. A modest negative correlation was found between the rate of cognitive decline over the first year of follow up compared with the second year (Spearman rank –0.50 $P<0.001$) which was not significant when comparing the second year of follow up with the third year (Spearman rank –0.14 $P=0.4$).

The mean rate of functional decline over the 3-year period was 1.2 (s.d. 2.6) BDRS points per year. Baseline BDRS score showed a significant low negative correlation with the mean rate of functional decline (Pearson –0.31 $P=0.002$). After the first year 47 subjects (58.7% of the reassessed survivors) had shown no change or an improvement in functional score compared to baseline score. A lack of change or an improvement in functional scores compared to baseline scores was also found in 14 (20.8%) and 8 (16.6%) of subjects after the second and third years, respectively. No correlation was found between the rate of functional decline over the first year of follow up compared with the second year (Pearson – 0.16 $P=0.2$) or when comparing the second year of follow up with the third year (Pearson –0.02 $P=0.91$).

### Discussion

The mean rate of cognitive decline of 2.2 MMSE points per year for all cases and 3.4 points for mild to moderate cases falls within the range found in earlier studies of between 1.8 and 4.2 points per year [7, 14]. However, these figures hide a wide variation with some subjects showing a substantial deterioration and others showing little or no deterioration.

These findings have immediate and concerning implications for clinical practice in relation to the use of cholinesterase inhibitors. Good clinical practice and cost-benefit considerations demand that the compounds are only used in those receiving benefit. But how do we detect such responders? When the first compound received a licence we reported a consensus meeting which recommended MMSE be used as the primary outcome measure in clinical practice [3]. These recommendations appear to be reflected in the recent

### Table 2. Functional (BDRS) change in late onset Alzheimer’s disease over a 3-year period

<table>
<thead>
<tr>
<th>Direction of change</th>
<th>First year BDRS scores n=176</th>
<th>Second year BDRS scores n=156</th>
<th>Third year BDRS scores n=110</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.f. baseline scores</td>
<td>(% of survivor cohort)</td>
<td>(% of survivor cohort)</td>
<td>(% of survivor cohort)</td>
</tr>
<tr>
<td>Improvement</td>
<td>65 (37.1%)</td>
<td>19 (12.2%)</td>
<td>11 (10.0%)</td>
</tr>
<tr>
<td>No change</td>
<td>12 (6.9%)</td>
<td>10 (6.4%)</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>Decline</td>
<td>98 (56.0%)</td>
<td>127 (81.4%)</td>
<td>93 (84.5%)</td>
</tr>
</tbody>
</table>
judgement from NICE who recommended that the drugs be used in those scoring between 12 and 26 points and, in most instances, stopped in those scoring below 12 points [4].

However, our current findings suggest that the MMSE is not a useful measure of response to treatment. A large proportion of subjects did not deteriorate, 40% over 1 year and a quarter over a 3-year period, despite receiving no drug treatment for impaired cognition. This was true even for those with mild to moderate AD – exactly that group considered suitable for treatment. Likewise, a lack of improvement compared with baseline cognitive scores cannot be equated with a lack of treatment response. It is quite possible, given the modest cognitive improvement found with cholinesterase inhibitors [15–17] compared to the wide variation in annual cognitive decline, that patients may be declining but that the decline is less rapid with treatment. In addition, it is clear that the rate of cognitive decline over one year is not predictive of the future rate of cognitive decline over the following year. Thus subjects who decline one year may show improvements the following year.

Nor would the addition of a simple assessment of function enable detection of responders. We find a large proportion also show no deterioration in function annually (around 44%). Even over 3 years around 16% of subjects showed no deterioration and these findings held even in those with mild to moderate AD.

The individual variation in cognitive and functional decline found in this study occurs for a number of reasons. These include direct factors such as treatment response but also a number of indirect factors including subject variables, such as concurrent psychiatric and physical illness, rater variables including inter and intra scoring inconsistencies and the non-linearity of rating scales [7]. In order to assess individual treatment response it is clear that, wherever possible, the wide variability caused by indirect factors should be minimised. However, whilst attention to inter and intra scoring inconsistencies in a controlled setting may reduce variability in the MMSE decline, subject variables cannot be controlled for and need to be assessed on an individual basis. The marked non-linearity of the MMSE is an added problem but it seems likely, from other smaller studies, that the use of other scales such as the cognitive section of the Alzheimer's Disease Assessment Scale [1] and the Cambridge Mental Disorders of the Elderly Examination [18] will have similar problems of wide variability [19, 20].

It is, perhaps, time to admit these difficulties and recognise that the rate of cognitive and functional change, even over extended periods, cannot be used as a simple indicator of individual treatment response in clinical practice. As suggested elsewhere [21], it is imperative that the natural variation in the rate of decline is taken into account when assessing individual treatment response. The probability that patients are not (or are) responding to treatment increases the further the subject falls outside the natural standard deviation of cognitive or functional decline. It is only beyond two standard deviations of the mean change (e.g. in this study 2\times4.5=9 MMSE points per year) that probability becomes compelling ($P=0.05$). Change that falls within this range may be the result of treatment, natural variation or both and its aetiology will always be uncertain.

### Key points

- Improvement, or deterioration, in patients with Alzheimer’s Disease, as assessed by the MMSE, cannot be equated with individual treatment response, or non-response, to cholinesterase inhibitors, even after a 3-year follow up period.
- The addition of a functional assessment scale, the Blessed Dementia Rating Scale, will not enable the detection of individual response or non-response to treatment.
- It is not possible to predict future rates of cognitive or functional decline based on previous rates of decline.

### Acknowledgements

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### Conflict of interest

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### References


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