

Research article

## To what degree does cognitive impairment in Alzheimer's disease predict dependence of patients on caregivers?

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### Abstract

**Background:** Patients with Alzheimer's disease experience a progressive loss of cognitive function, and the ability to independently perform activities of daily life. Sometimes a dependent stage is reached quite early in the disease, when caregivers decide that the patients can no longer be left alone safely. This is an important aspect of Alzheimer's for patients, their families, and also health care providers. Understanding the relationship between a patient's current cognitive status and their need for care may assist clinicians when recommending an appropriate management plan. In this study, we investigated the relationship of cognitive function to dependence on caregivers before the patients reach a severe stage of the disease.

**Methods:** Data were obtained on 1,289 patients with mild-to-moderate Alzheimer's disease studied in two randomised clinical trials of galantamine (Reminyl®). Cognition was assessed using the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Mini-Mental State Examination (MMSE). Patients were considered dependent if they required >12 hours of supervision each day or had high care needs. The Disability Assessment for Dementia (DAD) scale was also used as a measure of dependence. Disability was predicted directly using MMSE and ADAS-cog and compared to predictions from converted scores.

**Results:** The odds ratio of dependence was significantly higher amongst the patients with worse cognitive impairment, adjusting for age, gender and antipsychotic medication use. For example, a 4-point difference in ADAS-cog score was associated with an increase of 17% (95% CI 11–23) in the adjusted odds for >12 hours of supervision, and of 35% (95% CI 28–43) for dependence. Disability predicted directly using actual ADAS-cog and scores converted from MMSE values had close agreement using the models developed.

**Conclusion:** In patients with mild-to-moderate Alzheimer's disease, even relatively small degrees of poorer cognitive function increased the risk of losing the ability to live independently.

### Background

Patients with Alzheimer's disease experience a progressive

cognitive loss leading to increasingly shorter periods during which they can safely be left alone and to dependence

on their caregivers for help with the activities of daily life [1–5]. The Mini-Mental State Examination (MMSE) [6] is commonly used in clinical practice to assess cognition, whereas in research, the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-cog) [7] predominates. There is, therefore, interest in how cognitive function observed for patients in clinical trials compares with the results from clinical practice and the likely effects on patients' wider functioning [8].

In this study, we investigated the relationship of patients' cognitive function to dependence on caregivers before the patients reach a severe stage of the disease. Cognitive function was assessed with both the ADAS-cog and the MMSE. Our analyses employed three different definitions of dependence. In one approach, caregivers assessed the number of hours of supervision patients required each day, in another patients were assigned a level of dependence based on their care needs [9], and in the third, caregivers were asked questions about the patients' ability to independently perform activities of daily living that had been attempted in the preceding two weeks [10].

In a clinical setting, MMSE scores are frequently available, and conversions of cognitive scale scores from one to the other have been proposed [11,12]. One aspect of this study evaluates whether it is reasonable to convert MMSE to ADAS-cog and predict dependence based on the converted score. The reasonableness of doing this is judged based on how similar the results are to what would be obtained if a subject's actual ADAS-cog score were known.

## Methods

### Data sources

Data were obtained on 1,289 patients diagnosed with mild-to-moderate Alzheimer's disease studied in two randomised clinical trials of galantamine (Reminyl®) [13,14]. This is a post-hoc analysis employing data obtained from patients' baseline visits, before they began treatment in the trials. All patients enrolled in these trials were diagnosed with Alzheimer's disease according to NINCDS-ADRDA classification [15]. The patients had a mild-to-moderate disease (MMSE scores 10–24) with a history of cognitive decline, gradual onset, and progressive disease over a period of at least six months. Cognitive function was assessed using both the ADAS-cog and MMSE scales. Caregivers of the patients included in these analyses agreed to participate in the trial.

### Dependence

Dependence was measured using three definitions derived from the hours of supervision needed from a caregiver, the amount of care needed and the patient's ability to carry out the activities of daily life.

The caregivers were asked to assess whether the patient required 24-hour supervision, and if this was not considered necessary, caregivers reported the number of hours the patient could be left alone each day. From these data, the amount of supervision time required by a patient during the course of a day was derived. Patients were considered to have become dependent on caregivers if the caregivers reported that they required more than twelve hours of supervision each day.

Patients' care needs were recorded using an instrument that was developed and validated specifically to assess dependency of patients with Alzheimer's disease [9]. This dependence scale was designed to assess levels of need and therefore the care expected to be required, as a result of the loss of cognitive and functional skills typically observed in patients with Alzheimer's disease. Each caregiver was asked thirteen questions about the type of care the patient required. Depending on the responses, patients were assigned to one of six levels of dependency, with level zero representing independence and level five the highest level of dependence. Items in level three and above indicate that patients need supervision and assistance with common tasks, for example they need to be watched when awake, or escorted when outside, or accompanied when bathing and eating. Patients assigned to dependency levels of three or higher were considered to be dependent.

The Disability Assessment for Dementia (DAD) scale was also completed by the caregivers [10]. This instrument was developed and validated to measure the functional disability of patients with Alzheimer's disease. Caregivers answered questions about the patients' ability to independently perform both instrumental and basic activities of daily living that had been attempted in the preceding two weeks. The proportion of DAD activities successfully completed out of those attempted is then determined and reported as a percentage.

### Analyses

Analyses were conducted separately for each measure of dependence. In addition to the two measures of cognitive functioning, age, gender, time since onset of cognitive problems, use of antipsychotic medication, presence of extrapyramidal symptoms, and living situation were considered as potential predictors. Since the MMSE and ADAS-cog are correlated, separate models were constructed for each of the outcomes using each cognitive scale alone.

The relation of the two dichotomous dependence outcomes (>12 hours supervision and dependence level≥3) to potential predictors, including cognitive function, was investigated initially in bivariate analyses. For continuous predictors such as MMSE and ADAS-cog scores, linearity

**Table 1: Characteristics of patients at the time of enrollment in the trials**

Characteristic		All Patients	Supervision per day		Dependence Level	
			≤ 12 hrs	> 12 hrs	< 3	≥ 3
Number		1287	407	880	692	595
<i>Socio-demographic details</i>						
Age. (years)	Mean (SD)	73.8 (8.3)	72.9 (8.5)	74.2 (8.2)*	72.1 (8.6)	75.8 (7.5)*
Female	N (%)	801 (62)	261 (64.1)	540 (61.4)	388 (56.1)	413 (69.4)*
Education beyond elementary school	N (%)	876 (68.8)	271 (67.6)	605 (69.3)	508 (74.1)	368 (62.6)*
Lives with caregiver	N (%)	934 (74.2)	203 (51.5)	731 (84.5)*	496 (73.0)	438 (75.5)
Spouse or partner caregiver	N (%)	781 (62.1)	175 (43.0)	606 (68.9)*	431 (62.3)	350 (58.8)
<i>Clinical characteristics</i>						
Time since onset of cognitive problems, (years)	Mean (SD)	3.8 (2.6)	3.6 (2.6)	3.9 (2.6)*	3.7 (2.6)	4.0 (2.6)*
Time since AD diagnosis (years)	Mean (SD)	1.0 (1.4)	0.9 (1.2)	1.1 (1.4)	0.9 (1.3)	1.1 (1.4)*
Extra-pyramidal symptoms	N (%)	68 (5.2)	15 (3.7)	53 (6.0)	29 (4.2)	39 (6.6)
Anti-psychotic medication	N (%)	328 (25.5)	81 (19.9)	247 (28.1)*	134 (19.3)	194 (32.6)*
MMSE	Mean (SD)	19.3 (3.7)	20.4 (3.4)	18.8 (3.8)*	20.5 (3.3)	18.0 (3.8)*
ADAS-cog	Mean (SD)	25.4 (10.4)	22.7 (9.7)	26.7 (10.5)*	22.0 (8.7)	29.5 (10.8)*
<i>Dependence</i>						
Dependence level ≥ 3	N (%)	583 (46.0)	134 (32.9)	461 (52.4)		
DAD	Mean (SD)	70.1 (22.5)	77.7 (20.0)	66.7 (22.7)*	81.9 (14.9)	56.3 (22.0)*

\* Statistically significant difference between groups ( $p = 0.05$ ).

in the log of the odds of the outcomes was verified over subintervals of the predictors. For categorical predictors such as gender, the odds ratio was computed and tested for significance. The significant predictors were retained and included in a logistic regression model to estimate the odds ratio for being defined as dependent, and to measure the effect of cognitive function, adjusting for other factors. A stepwise forward procedure was used to identify the most important predictors.

Due to a skewed spread of DAD scores over its range, a transformation was required to normalize the distribution. Since the DAD is scored as a proportion, the recommended transformation is arcsin (square root (DAD)). The relation of the transformed DAD scores to the predictors was determined using correlation coefficients, t-tests and ANOVAs. Predictors were retained in two multivariate regression models to investigate the relation of the transformed DAD score to either MMSE or ADAS-cog score and other determinants. A stepwise forward procedure was used to identify statistically significant predictors.

We then used these models to investigate how well MMSE values converted to ADAS-cog predict dependence compared to predictions based on the actual ADAS-cog values,

after adjusting for other factors. The MMSE scores were converted linearly to ADAS-cog values (a decrease of 1 MMSE = an increase of 2.33 ADAS-cog points, or  $ADAS-cog = 70 - 2.33 * MMSE$ ). For each patient, the DAD score was then predicted based on the actual and converted ADAS-cog scores. The difference between the two predictions was used as the measure of agreement. The predicted DAD scores were then compared to each other.

## Results

The socio-demographic and clinical characteristics of the 1,287 patients included in these analyses are summarized in Table 1. Two patients were excluded from the analyses because their MMSE score was reported as zero. On average, caregivers reported that their patients required about 14 hours of supervision each day (SD 9.3). There was considerable variation in the responses, as 25% ( $N = 326$ ) were reported to require no supervision while 15% ( $N = 188$ ) were felt to require 24-hour supervision. Approximately two-thirds required more than 12 hours of supervision, and their mean ADAS-cog, MMSE, and DAD scores, were significantly worse than those of patients who were deemed less dependent.

**Table 2: Odds ratios (95% CI) for dependence**

Characteristic	MMSE Model		ADAS-cog Model	
	Supervision Time	Dependence Level	Supervision Time	Dependence Level
-2log(L)	1538.9	1524.5	1509.8	1491.1
Age (years)	1.02 (1.00–1.03)	1.06 (1.04–1.08)	1.02 (1.00–1.03)	1.05 (1.04–1.07)
Male vs. female	1.29 (1.00–1.66)	0.66 (0.52–0.86)	1.34 (1.04–1.74)	0.70 (0.54–0.90)
Anti-psychotic medication use	1.55 (1.16–2.07)	1.95 (1.47–2.58)	1.51 (1.13–2.03)	1.89 (1.42–2.51)
MMSE	0.89 (0.86–0.92)	0.82 (0.79–0.85)	-	-
ADAS-cog	-	-	1.04 (1.03–1.05)	1.08 (1.06–1.09)

Overall, 46% of patients were assigned to the dependent care levels  $\geq 3$ , and their mean DAD score was significantly lower than that of those who were less dependent (56% vs. 82%, t-test  $p < 0.0001$ ). Antipsychotic medication was prescribed to 26% of the patients and they too had DAD scores lower than patients not prescribed antipsychotic medication (64% vs. 72%, t-test,  $p$ -value  $< 0.001$ ). Far fewer patients overall had extrapyramidal symptoms, however, among those that did, the mean DAD score was lower than for those without symptoms (62% vs 70%, t-test,  $p$ -value 0.0037).

The odds ratio for both categorical measures of dependence was significantly higher with worse cognitive impairment, increasing with each detrimental point change in ADAS-cog or MMSE score, adjusting for age, gender and use of antipsychotic medication (Table 2). For the MMSE model, a one-point difference was associated with an increase in the adjusted odds for requiring  $>12$  hours supervision per day of 13% (95% CI 9–17) and for dependence level  $\geq 3$  of 22% (95% CI 18–27). A one-point difference of the ADAS-cog score was associated with an increase in the adjusted odds for requiring  $>12$  hours supervision per day of 4% (95% CI 3–5) and for dependence level  $\geq 3$  of 8% (95% CI 6–9), after adjusting for age, gender and use of antipsychotic medication.

For predictions of dependence based on transformed scores from the DAD two separate models were developed. One model was based on the ADAS-cog and the second on the MMSE (Table 3). In each case, the cognitive score was found to be a strong predictor of dependence. No significant interaction was present.

Disability predicted directly using the actual ADAS-cog scores and other patient characteristics was compared to prediction based on ADAS-cog scores converted from MMSE scores, adjusting for other patient characteristics.

Figure 1 shows a summary of these predictions. For MMSE scores ranging from 10 to 24, we calculated the average predicted DAD using the actual ADAS-cog scores (with standard deviation); the corresponding values for the predictions with converted values are also shown. There was a close agreement between the average predictions. For example, our sample contained 91 subjects with baseline MMSE score of 20; the average ADAS-cog score for these patients was 24.2, which is reasonably close to the converted value of 23.4. The average DAD score predicted from the actual ADAS-cog scores was 74% with a standard deviation of 10%. The average of predictions made with converted scores and other patient's characteristics was 76% (SD = 4.9%), for a difference of 1.4%. Similarly, the average difference in predictions for other MMSE scores were also reasonably small, ranging from -1.5% to 3.1%, equivalent to less than a single activity on the DAD.

## Discussion

The loss of a patient's ability to independently perform daily activities is an important aspect of Alzheimer's for patients and their families, and for health care decision-makers. Our study has demonstrated that relatively small degrees of loss of cognitive skills in patients at the mild-to-moderate stages of the disease leads to an increased risk of losing the ability to live independently. In our study of patients recruited for clinical trials at the mild-to-moderate stage, 69% already required more than 12 hours of supervision per day. This is consistent with other studies, which have shown that sometimes a dependent stage is reached quite early in the disease, when caregivers decide that the patients can no longer be left alone safely [3,16,17].

A three-point difference in MMSE score was associated with an increase in the adjusted odds of requiring more than 12 hours of supervision of 43% at the time of the assessment; and if dependence is measured as level three or

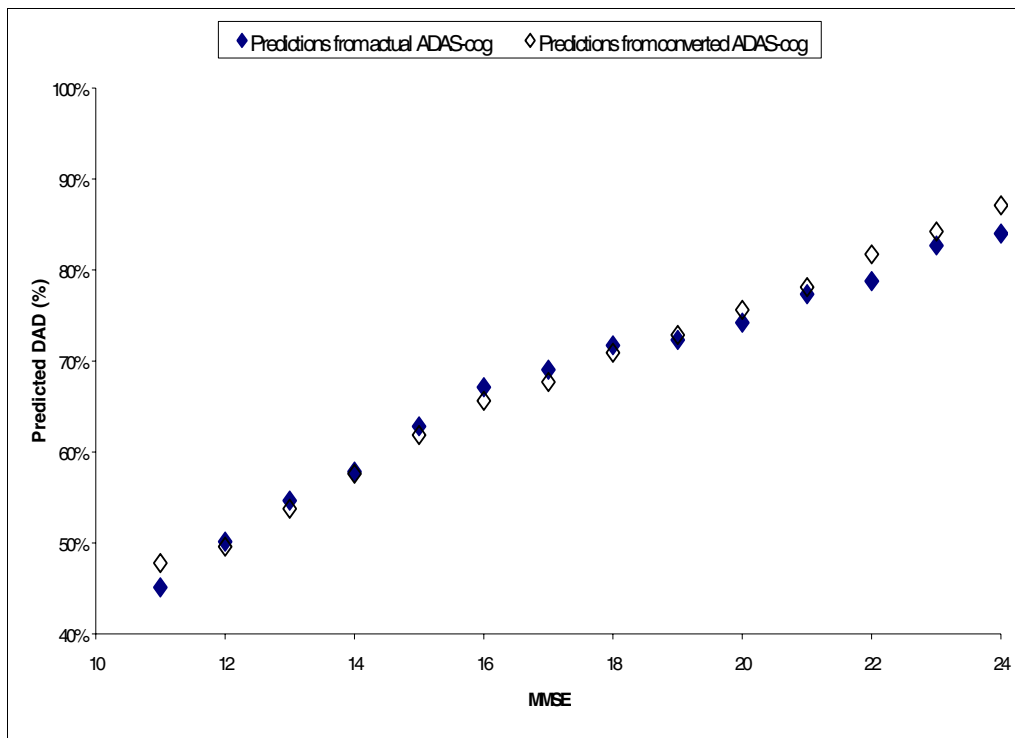


Figure 1

**Figure 1**  
Mean predictions of DAD scores based on actual and converted ADAS-cog scores.

higher, the odds increase by 82%, even after adjusting for age, gender and use of antipsychotic medication. Similarly, a 4-point difference in ADAS-cog score is associated with an increase in the adjusted odds for requiring more than 12 hours of supervision of 17%, and 35% for having a dependence level greater than two. The very comprehensive measures of dependence collected at the start of these trials allowed us to evaluate the association of dependence with a patient's cognitive functioning at that point in time. It is important to note that since this is a cross-sectional study we could not investigate the extent to which decreases or improvements in cognitive function would be associated with changes in dependence over time.

Behavioral disturbances are common amongst patients with Alzheimer's disease [18] and antipsychotic medications were prescribed for about one-quarter of the patients in our study. Antipsychotic medication use was also consistently found to be a predictor of having an increased risk of disability, regardless of how dependence was meas-

ured. This is consistent with other studies, which found that patients using antipsychotic agents [19] or displaying psychotic symptoms [1,19–21] are more likely to experience a faster functional decline. Very few patients in our study had extra-pyramidal symptoms; it is therefore difficult to interpret their meaning with certainty. Other published studies however, have linked these symptoms with greater functional decline [1,20,21].

One limitation of this study is that these data were collected from patients enrolled in clinical trials, and therefore our sample may not be representative of patients routinely treated in clinical practice. Nevertheless, these data provide a unique opportunity for analyses as information was collected using both the MMSE and ADAS-cog scales, and three measures of dependence.

Both the instruments used to measure dependence in this study had been developed and validated specifically for use in patients with Alzheimer's disease [9,10]. The de-

**Table 3: Parameter estimates for models for the relationship between transformed DAD score and cognitive function**

	MMSE Model		ADAS Model	
	Parameter Estimate (SE)	P-Value	Parameter Estimate (SE)	P-Value
<b>Model R<sup>2</sup></b>	<b>0.29</b>		<b>0.32</b>	
Intercept	0.902 (0.080)	< 0.0001	1.870 (0.067)	< 0.0001
Age	-0.006 (0.001)	< 0.0001	-0.005 (0.001)	< 0.0001
Male vs. Female	-0.025 (0.015)	0.099	-0.034 (0.015)	0.023
Time since onset (years)	-0.009 (0.003)	0.001	-0.007 (0.003)	0.013
Anti-psychotic medication use	-0.078 (0.016)	< 0.0001	-0.074 (0.016)	< 0.0001
Lives with caregiver	-0.071 (0.017)	< 0.0001	-0.069 (0.016)	< 0.0001
MMSE	0.036 (0.002)	< 0.0001	-	-
ADAS-cog	-	-	0.014 (0.001)	< 0.0001

Legend: SE = Standard Error

pendence scale was designed to assess the care needs of patients and the DAD scale to measure functional disability. Both instruments were developed to avoid some of the common problems observed with other measures of functional decline, such as whether certain instrumental activities of daily living had ever been performed by the patient [23]. Our results were consistent between the models as the same predictors of dependence were found to be important regardless of how dependence was measured.

The MMSE is convenient to administer and practical to use during a routine clinic visit, but clinical trials conducted to study treatments for Alzheimer's disease have primarily used ADAS-cog as the measure of cognition. This study indicates that it is reasonable to convert MMSE to ADAS-cog and predict dependence based on the converted score. Our study suggests, that in clinical practice a conversion that assumes one MMSE point is equivalent to 2.33 ADAS-cog points (or  $ADAS-cog = 70 - 2.33 * MMSE$ ) will yield a reasonably accurate estimate of disability for patients at the mild-to-moderate stages. This is also consistent with the findings in another study ( $ADAS-cog = 72.2 - 2.41 * MMSE$ ) [11]. If its relation to dependence is the main reason to measure cognition, then clinicians can be reassured about these conversions.

### Conclusions

In our study, patients who had relatively small degrees of greater loss of cognitive function, whether measured using either the ADAS-cog or MMSE, did appear to be at increased risk of being dependent on caregivers. Understanding the relationship between a patient's current

cognitive status, current therapies and their need for care may assist clinicians in the management of patients diagnosed with Alzheimer's disease. Moreover, this information can facilitate discussions and planning with caregivers. Future studies conducted to evaluate these relationships longitudinally can further inform our understanding of the relationship between cognitive function and dependence.

### Competing interests

Caro Research of which Jaime Caro is a shareholder, received a grant from Janssen Research Foundation, Beerse, Belgium, which provided funding for portions of the study. No editorial control was allowed.

At the time of the study, George Papadopoulos and Koen Torfs were employed by Janssen, which provided funding for portions of the study.

### Authors' contributions

JJC conceived of and designed the study, and participated in drafting the manuscript. AW designed the study and the analysis plan, and drafted the manuscript. KI participated in the design of the analysis plan, conducted and reported the analyses. KMW participated in the design of the study and the drafting of the manuscript. DG participated in the conception, design and analyses of the study. GP participated in the study design and development of the analysis plan for the study. KT participated in the conception and design of the study.

All authors read and approved the final manuscript.

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