doi: 10.1111/j.1368-5031.2006.00970.x

Treatment effects of rivastigmine on cognition, performance of daily living activities and behaviour in Alzheimer's disease in an outpatient geriatric setting

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SUMMARY

We investigated rivastigmine effectiveness in 84 Alzheimer outpatients, with a special focus on behavioural problems. Cognition, activities in daily living (ADL) and behaviour were assessed during 30 months. Changes in test results between 6 months and baseline were compared with a historical control cohort of Alzheimer patients ($n = 69$) by performing *t*-tests and calculation of Cohen's d and standardised response mean (SRM).

During 6 months, rivastigmine showed effect on cognition ($p < 0.001$, Cohen's $d = 0.33$, SRM $= 0.78$), ADL ($p < 0.001$, Cohen's $d = -0.43$, SRM $= -0.54$) and memory-related behaviour ($p = 0.006$, Cohen's $d = -0.28$, SRM $= -0.28$). Depressive behaviour worsened ($p = 0.001$, Cohen's $d = 0.30$, SRM $= 0.37$) and disruptive behaviour ($p = 0.369$, Cohen's $d = -0.07$, SRM $= -0.09$) was not effected by rivastigmine. During 30 months, a gradual decline was shown in most domains. Most RMBPC items showed stabilization during 30 months. Improvement on disruptive behaviour items and depression items was shown after 6 months of treatment in a large proportion of patients in whom behavioural problems were present at baseline.

In conclusion, a huge discontinuation rate is experienced within the first half year of treatment. In the subpopulation of patients who continued rivastigmine for 6 months, it shows modest effectiveness on cognition, functionality and memory-associated behaviour compared with historical control patients. Unfortunately, disruptive behaviour is not altered by rivastigmine therapy, and depressive behaviour worsened slightly after initial treatment. During 30 months, rivastigmine showed stabilization on numerous behaviour items as measured by the RMBPC.

Keywords: Alzheimer's disease; rivastigmine; effectiveness; CAMCOG; IDDD; RMBPC; clinical care; neuropsychological assessment

INTRODUCTION

Rivastigmine (Exelon®), an acetylcholinesterase inhibitor, has shown efficacy in the symptomatic treatment of mild-to-moderately severe Alzheimer's dementia (AD) in randomised placebo-controlled trials These trials were rather liberal regarding inclusion criteria, for example comorbidity (1,2). Therefore, effectiveness in routine clinical practice would be expected to be in a similar range like the trial outcomes. However, patients in trials might respond differently to drugs than patients in routine care. Complementary research in a clinical setting may reveal additional data on the effectiveness of rivastigmine in different domains. To our knowledge, a number of clinically based studies have investigated the effects of rivastigmine on cognition and activities in daily living (ADL) in routine clinical practice (3,4). For example, Lopez-Pousa et al. (3) investigated cognition by MMSE and Mossello et al. (4) investigated cognition by MMSE and performance in daily living activities by ADL and IADL scores. In addition, an open label extension phase of the trials investigated cognition, using the MMSE, up to 5 years of treatment (5).

Most trials lasted for up to 26 or 52 weeks, some were extended as open-label studies (1,2,6). However, the long-term effects of cholinesterase inhibitor therapy remain largely unestablished.

Although it is becoming clearer that cholinergic deficits are involved in the behavioural symptoms present in AD (7) and

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that butyrylcholinesterase mediates behaviour (8), effect of rivastigmine regarding behaviour is less described as compared with cognition. In a German open-label extension study, B 305, behaviour was measured with the CIBICplus in 34 rivastigmine users (9). Meta analyses of three 6-month, double blind, placebo-controlled, regulatory trials investigated behavioural responses with the CIBICplus in rivastigmine users with mild-to-moderate severe AD (10). In the clinical setting, research has predominantly been performed in nursing home residents taking rivastigmine, where behaviour was assessed using the NPI-NH. Aupperle et al. (11) investigated long-term effects during a 52-week open-label study in moderate-to-severe rivastigmine users. Hatoum et al. (12) used the occupational disruptive scale of the NPI-NH to investigate the impact of rivastigmine on the disruptive behaviour of nursing home residents. Cummings et al. (13) described the effects of rivastigmine treatment on neuropsychiatric and behavioural disturbances also in nursing home residents with moderate to severe probable AD.

In the Netherlands, rivastigmine may only be prescribed if evaluation is regularly performed. Patients who are willing to start therapy are tested at baseline and at designated follow-up intervals during treatment. In our hospital, rivastigmine is prescribed via the Geriatric Outpatient Department since 1998, and every 6 months three domains are assessed: cognition, behaviour and performance in daily living activities. In this cohort of patients, we performed retrospective analyses regarding the effectiveness of rivastigmine during 30 months.

The study aims at investigating treatment effects of rivastigmine on different domains, with a special attention to behaviour, in a cohort of outpatients suffering from Alzheimer's disease.

PATIENTS AND METHODS

Patients

This retrospective study was carried out in patients with mild-to-moderate, probable or possible AD according to the NINCDS-ADRDA criteria (14) and using rivastigmine via the Geriatric Outpatient Department of a general hospital. Only patients who had relatives or friends who could monitor drug intake and patients in whom therapy was evaluated after 6 months were included. Patients were excluded if baseline cognitive test results were incomplete.

Dose titration

Patients started rivastigmine at 1.5 mg twice daily, and doses were titrated up after intervals of minimal 2 weeks at each dose level, until the individual maximum achieved dose (MAD) up to 6 mg twice daily. During titration, it was possible to omit a dose, to postpone dose increments or to return to a lower dose level if adverse events required this.

Assessment of domains

At baseline and at 6-month intervals, rivastigmine use was evaluated by assessment of three domains. Cognition was measured with MMSE (15) and Cambridge cognitive examination (CAMCOG) (16). CAMCOG consists of 60 items covering orientation, language, memory, praxis and calculation/attention, abstract reasoning and perception. Total sum scores range from 0 to 107. CAMCOG can be subdivided into a memory (maximum score 37) and a non-memory (maximum score 70) section (17). Functional disability was measured with the performance subscale of the interview for deterioration in daily living activities in dementia (IDDD), a caregiver-based paper-and-pencil questionnaire, which consists of 11 items with sum scores ranging from 0 to 44 (18). Behaviour was measured with the Revised Memory and Behavioural Problems Checklist (RMBPC). It is also a caregiver-based paper-and-pencil questionnaire and consists of three subsections. First, a 7-item memory subscale (score per item 0–4, maximum score 28) that includes forgetting recent events, repeated questions, losing things, forgetting the day, forgetting past events, reduced concentration and not finishing tasks. Second, an 8-item disruptive behaviour subscale (score per item 0–4, maximum score 32) including verbal aggression, threats to hurt others, destroying property, to behave dangerous to self or others, talking loudly and rapidly, embarrassing behaviour, arguing and waking caregiver up. Third, a 9-item depression subscale (score per item 0–4, maximum score 36) includes comments about hopelessness, comments about being a burden, appearing sad or depressed, comments about dead, comments about being a failure, crying, comments about loneliness, appearing anxious and suicidal threats (19). Lower scores on MMSE and CAMCOG and higher scores on the IDDD and subscales of the RMBPC reflect a worse functioning.

Data collection

All assessment results and demographic variables like gender, age and level of education (20) were prospectively incorporated in a database. Place of living, number of concomitant drugs at baseline and MAD, all according to the medical records, were retrospectively obtained.

Historical control cohort

A research project was carried out at the memory clinic of an academic hospital in Amsterdam. In this project, 69 Alzheimer patients, who did not take rivastigmine, were tested at baseline and after 6 months with MMSE, CAMCOG,

IDDD and RMBPC (21). These 69 patients represent the historical control group in this study.

Statistical analysis

Statistical calculations were performed with SPSS for Windows (version 11.0, SPSS Inc., Chicago, IL, USA). A p-value of 0.05 or less was considered statistically significant.

Mean, standard deviation (SD) and range of baseline test results and differences between test results at 6-monthly follow-up visits and baseline were tabulated. For each of the RMBPC subitems, the percentages of patients who improved, deteriorated or remained stable after 6 months were calculated in a subpopulation of patients in whom that particular subitem was present at baseline. Deterioration was defined as an increase of equal or higher than one point and an improvement was defined as a decrease of equal or higher than one point on the RMBPC in this additional analysis.

Differences in test results between the first follow-up at 6 months and baseline were compared with the historical control cohort by performing a one-sample *t*-test. Cohen's *d* and standardised response means (SRM) were calculated to assess whether the differences are large enough to be clinically detectable. This is accomplished by dividing the raw effect size by the SD of the measures in their respective populations, as shown in equation 1.

$$\text{Effect size (ES)} = \frac{(Xt_2 - Xt_1) - (Yt_2 - Yt_1)}{\sigma} \qquad (1)$$

To calculate a SRM, s is the root mean square of the SDs of the change scores, and to calculate Cohen's d, s is the root mean square of the baseline deviations (22,23). In our calculations, X is the mean of test results in the rivastigmine group, Y is the mean of test results in the historical control cohort, t_2 is after 6 months of treatment and t_1 is at baseline. Effect sizes greater than 0.20 are conventionally held to be clinically detectable. Effect sizes can be roughly subdivided into small (0.2), medium (0.5) and large (0.8) (22).

Linear regression analysis were performed to investigate relationships between effectiveness and different dosages.

RESULTS

Patient characteristics

From the original population of 154 rivastigmine users, 61 patients discontinued treatment within the first 6 months because of adverse events ($n = 36$), decline as noted by caregivers ($n = 10$), incompliance ($n = 7$) or for other reasons ($n = 8$). Eight patients were lost to follow-up because of death or losing contact within 6 months. After 6 months of treatment, patients mainly discontinued because of ongoing decline in cognition, performance or behaviour. Discontinuation of rivastigmine in this cohort of patients has been described in more detail in a separate publication (24). One, six and eight patient(s) were excluded from MMSE/CAMCOG, IDDD and RMBPC analyses, respectively, because baseline data were lacking. In total, 84, 79 and 77 Alzheimer patients were included in this study for analyses on cognition, performance and behaviour, respectively.

Baseline characteristics are summarised in Table 1. Included patients had a mean age of 78.2 years, a mean baseline MMSE score of 20.4, 69% was female and patients lived primarily at home. Mean MAD of rivastigmine was 8.8 mg (range: 1.5–12.0 mg).

Neuropsychological assessment during follow-up

Results of neuropsychological assessment at baseline and differences compared to baseline, during follow-up until 30 months, are summarised in Table 2. It is shown that group sizes diminish gradually at subsequent follow-up visits. Discontinuation of therapy was mostly due to ongoing decline measured by clinimetrics. Other reasons for discontinuation included occurrence of adverse events, transfer to a nursing home and refusing to take rivastigmine.

In Table 2, it is shown that therapy resulted in an initial stabilization (MMSE) or even improvement (total and non-memory section of CAMCOG) of cognition but thereafter a slow and gradual decline during follow-up. However, the memory section of the CAMCOG showed no initial

Table 1 Baseline characteristics

Baseline characteristics (n = 84)	*n (%)**
Age, mean ± SD (range)	78.2 ± 6.0 (56–89)
Baseline MMSE, mean ± SD (range)	20.4 ± 4.4 (8–28)
Education	
<6 years elementary school	2 (2.4)
6 years elementary school	19 (22.6)
>6 years elementary school	14 (16.7)
Domestic science school, junior technical school	20 (23.8)
Secondary school for lower educational level	19 (22.6)
Secondary school for higher educational level	10 (11.9)
University degree	0 (0.0)
Gender, female	58 (69.0)
Maximum achieved dose, mean ± SD (range)	8.8 ± 2.8 (1.5–12.0)
Number of concomitant drugs, mean ± SD (range)	2.4 ± 2.0 (0–9)
Patients place of living, at home	76 (90.5)

*Unless otherwise noted.

Table 2 Test results at baseline and differences in test results compared with baseline at subsequent 6-month follow-up visits

Test	*Statistics*	*Baseline**	*6 months†*	*12 months†*	*18 months†*	*24 months†*	*30 months†*
MMSE‡	*n*	84	83***	52	34	18	7
	Mean ± SD	20.4 ± 4.4	0.1 ± 3.1	−0.9 ± 3.3	−1.8 ± 3.8	−1.5 ± 3.3	−2.9 ± 2.3
	Range	8–28	−11 to +7	−8 to +9	−9 to +6	−7 to +3	−6 to 0
CAMCOG§	*n*	84	83***	52	34	15	7
	Mean ± SD	68.8 ± 13.1	0.5 ± 6.3	−1.2 ± 8.3	−1.8 ± 9.8	−3.4 ± 10.0	−7.9 ± 6.9
	Range	33–92	−15 to +13	−17 to +17	−20 to +20	−27 to +15	−17 to +4
CAMCOG	*n*	84	83***	52	34	15	7
Mem¶	Mean ± SD	17.4 ± 5.5	−0.5 ± 3.4	−2.0 ± 4.2	−1.6 ± 4.7	−2.4 ± 5.3	−4.9 ± 4.8
	Range	5–29	−10 to +8	−9 to +8	−12 to +10	−13 to +5	−11 to +2
CAMCOG	*n*	84	83***	52	34	15	7
Non-mem**	Mean ± SD	51.5 ± 9.3	0.9 ± 4.6	0.7 ± 5.8	−0.1 ± 6.7	−1.3 ± 6.8	−2.9 ± 2.5
	Range	25–67	−9 to +16	−13 to +15	−18 to +15	−21 to +10	−6 to +2
IDDD††	*n*	79	79	45	30	16	6
	Mean ± SD	14.0 ± 8.8	0.7 ± 5.9	2.7 ± 7.8	4.5 ± 10.1	5.7 ± 10.1	3.7 ± 11.6
	Range	0–36	−18 to +13	−16 to +21	−18 to +22	−9 to +28	−14 to +19
RMBPC	*n*	77	77	46	29	14	5
Mem‡‡	Mean ± SD	17.1 ± 3.9	−0.4 ± 4.3	−0.5 ± 5.6	0.4 ± 5.3	1.0 ± 4.3	−1.2 ± 1.6
	Range	8–26	−10 to +9	−13 to +12	−14 to +9	−7 to +9	−3 to +1
RMBPC	*n*	77	77	46	29	14	5
Dis§§	Mean ± SD	4.3 ± 3.6	−0.5 ± 2.6	−0.4 ± 3.5	−0.6 ± 2.7	−0.8 ± 2.9	−1.0 ± 2.1
	Range	0–18	−9 to +7	−9 to +8	−6 to +5	−4 to +7	−4 to +2
RMBPC	*n*	77	77	46	29	14	5
Dep¶¶	Mean ± SD	7.7 ± 5.7	0.2 ± 4.6	−0.8 ± 4.8	−0.5 ± 4.5	1.9 ± 4.2	−4.0 ± 4.8
	Range	0–21	−10 to +12	−12 to +9	−12 to +11	−3 to +10	−10 to +1

*Lower baseline MMSE/CAMCOG scores/higher baseline IDDD/RMBPC scores represent worse cognitive performance, functional performance or behaviour.
†Negative differences reflect improvement on IDDD/RMBPC and deterioration on MMSE/CAMCOG.
‡Range 0–30.
§Range 0–107.
¶Memory subsection: range 0–37.
**Non-memory subsection: range 0–70.
††Range 0–44.
‡‡Memory subscale: range 0–28.
§§Disruptive behaviour subscale: range 0–32.
¶¶Depression subscale: range 0–36.
***Result of one patient missing.

stabilization or improvement. Performance of daily living activities (IDDD) showed a gradual decline during follow-up. The memory subsection of the RMBPC showed an initial stabilization and thereafter a gradual decline. The disruptive subsection of the behaviour scale showed an initial improvement, which stabilises during follow-up. The depression subscale, however, showed an initial increase of depressive symptoms and thereafter an decrease of these symptoms. In Table 3 are shown the test results at baseline and differences in test results compared to baseline during 30 months for each RMBPC item. Memory-related behaviour disturbances are most apparent, followed by depression and disruptive behaviour. Remarkable are the items 'Appears sad or depressed', 'Appears anxious or worried' and 'Arguing, irritability'. From this table, it is clear that during 30 months, numerous items remain stable. However, improvement is shown during the 30 months on 'losing or misplacing things', 'waking you or your family members at night', 'arguing, irritability', 'crying and tearfullness', 'comments about feeling like a failure' and 'appears anxious or worried'. A separate analysis was carried out in subgroups of patients in whom behavioural problems were present at baseline. The results of this analysis after 6 months are summarised in Table 4. The percentage of patients who deteriorated is small for the disruptive behaviour items; a large proportion of patients improved actually. For the depression items also, a minor part of the patients deteriorated; exceptions here are 'expressing feelings of hopelessness or sadness about the future' and 'comments about feeling worthless or being a burden to others'. For the depression subsection, large number of patients remained stable. For the memory-related behaviour items, around a half of patients remained stable, whereas approximately a quarter deteriorated and a quarter improved at 6 months. Of the patients who initially did not show behavioural problems, the memory-associated behaviour items deteriorated in approximately 50% of patients, the

Table 3 Test results at baseline and differences in test results compared to baseline at subsequent 6-monthly follow-up visits, for each individual RMBPC item

RMBPC item	*Baseline (n = 77)**	*6 months (n = 77)†*	*12 months (n = 46)†*	*18 months (n = 29)†*	*24 months (n = 14)†*	*30 months (n = 5)†*
Memory-related behaviour						
Asking the same question over and over	2.90 ± 0.77	−0.01 ± 0.85	−0.07 ± 0.80	0.10 ± 0.82	0.07 ± 0.73	0.00 ± 0.00
Trouble remembering recent events	2.81 ± 0.81	−0.09 ± 1.03	−0.09 ± 1.15	0.10 ± 1.18	0.07 ± 0.92	−0.40 ± 1.67
Trouble remembering significant past events	1.62 ± 1.00	−0.08 ± 1.06	0.15 ± 1.30	0.07 ± 1.03	0.00 ± 1.18	−0.20 ± 0.84
Losing or misplacing things	2.91 ± 0.69	−0.22 ± 0.94	−0.28 ± 1.09	−0.10 ± 0.90	−0.07 ± 1.21	−1.40 ± 1.14
Forgetting what day it is	2.74 ± 0.84	−0.04 ± 0.94	0.00 ± 1.10	0.28 ± 0.92	−0.07 ± 0.73	0.20 ± 0.45
Starting but not finishing things	1.82 ± 1.06	0.14 ± 1.33	−0.02 ± 1.31	0.14 ± 1.30	0.29 ± 1.64	0.00 ± 0.71
Difficulty concentrating on a task	2.13 ± 1.0	0.13 ± 1.24	0.02 ± 1.13	0.10 ± 1.21	0.07 ± 0.92	0.60 ± 0.90
Disruptive behaviour						
Destroying properties	0.22 ± 0.53	−0.01 ± 0.60	−0.02 ± 0.58	0.00 ± 0.54	0.14 ± 0.36	0.20 ± 0.45
Doing things that embarrasses you	0.77 ± 0.92	−0.08 ± 1.00	−0.07 ± 1.00	−0.21 ± 0.94	0.14 ± 0.77	0.60 ± 0.55
Waking you or family members at night	0.39 ± 0.91	−0.10 ± 0.80	−0.11 ± 0.88	−0.21 ± 1.15	−0.14 ± 1.29	−0.40 ± 2.07
Talking loudly and rapidly	0.52 ± 0.94	−0.09 ± 0.83	0.02 ± 1.30	−0.10 ± 0.98	0.57 ± 1.16	0.00 ± 0.00
Arguing irritability	1.56 ± 1.09	−0.22 ± 1.11	−0.13 ± 1.05	0.00 ± 1.13	−0.21 ± 1.05	−0.80 ± 0.84
Engaging in behaviour that is potentially dangerous to self or others	0.42 ± 0.68	−0.01 ± 0.66	−0.02 ± 0.65	0.07 ± 0.59	−0.07 ± 0.62	0.20 ± 0.45
Aggressive to others verbally	0.39 ± 0.75	0.00 ± 0.80	0.07 ± 0.85	−0.10 ± 1.11	−0.07 ± 1.39	−0.40 ± 0.55
Threats to hurt others	0.06 ± 0.25	0.03 ± 0.40	0.00 ± 0.30	−0.03 ± 0.19	0.07 ± 0.62	0.00 ± 0.00
Depressive behaviour						
Threats to hurt oneself	0.09 ± 0.33	0.03 ± 0.43	0.11 ± 0.64	0.03 ± 0.19	0.07 ± 0.27	0.20 ± 0.45
Appears sad or depressed	1.49 ± 1.03	−0.08 ± 1.07	−0.09 ± 1.05	0.17 ± 0.89	0.21 ± 0.80	−0.20 ± 0.84
Expressing feelings of hopelessness or sadness about the future	1.06 ± 1.04	0.03 ± 1.08	−0.04 ± 0.97	0.10 ± 1.08	0.64 ± 1.15	−0.20 ± 1.10
Crying and tearfulness	0.95 ± 1.08	−0.10 ± 0.97	−0.20 ± 0.91	0.00 ± 0.96	0.07 ± 1.33	−0.80 ± 0.84
Commenting about dead of self or others	0.66 ± 1.08	0.09 ± 0.71	−0.07 ± 0.68	0.03 ± 0.94	0.29 ± 0.73	−0.80 ± 1.10
Talking about feeling lonely	0.84 ± 1.14	0.06 ± 0.95	0.07 ± 1.06	−0.29 ± 1.12	0.00 ± 0.56	−0.40 ± 0.89
Comments about feeling worthless or being a burden to others	0.65 ± 0.90	0.22 ± 1.05	0.11 ± 0.97	0.10 ± 1.15	0.29 ± 0.91	−0.60 ± 1.14
Comments about feeling like a failure	0.35 ± 0.72	−0.04 ± 0.75	−0.17 ± 0.68	−0.03 ± 0.50	−0.21 ± 0.58	−0.40 ± 0.89
Appears anxious or worried	1.56 ± 1.13	−0.14 ± 1.07	−0.33 ± 1.16	0.00 ± 0.96	−0.21 ± 1.48	−0.80 ± 0.84

*Higher baseline RMBPC scores represent worse behaviour, †negative differences reflect improvement on RMBPC.

disruptive items deteriorated in around 10% of patients with exception for 'doing things that embaresses you' (25%) and 'aggressive to others verbally' (20%) and 'arguing' (50%). The depression subitems deteriorated in approximately 25%, with exceptions for 'comments about feeling like a failure' (10%) and 'appears sad or depressed' (50%) and threats to hurt oneself (7%).

Effectiveness of rivastigmine during 6 months as compared with historical control cohort

In Table 5, the baseline characteristics and baseline test results of both the experimental group and the historical control cohort are summarised. The experimental and control group did not significantly differ in age. The control cohort, however, consisted of more women. MMSE and CAMCOG baseline scores were significantly lower in the control cohort ($p < 0.001$). Baseline IDDD and RMBPC scores differed not significantly. For both the experimental and the control group, the differences between test results at 6 months and baseline and effect sizes are also presented in Table 3. All domains except disruptive behaviour showed significant and clinical detectable differences between rivastigmine users and controls. Rivastigmine users showed stabilization on MMSE and a slight improvement on the CAMCOG, whereas controls significantly deteriorated on both tests ($p < 0.001$). Performance (IDDD) showed significantly less deterioration in rivastigmine users compared with the control group ($p < 0.001$). Rivastigmine significantly improved memory-related behaviour ($p < 0.05$) and non-significantly disruptive behaviour. Depression, however, significantly worsened during rivastigmine use compared with controls where this diminished ($p < 0.001$).

If the follow-up results of the treated cohort are compared with those of the historical control cohort, it can be seen that decline as shown in 6 months in untreated controls is comparable with

Table 4 Number of patients with behavioural problems at baseline and number of patients (% of total patients experiencing problems at baseline) who showed stabilization, deterioration or improvement at 6 months

RMBPC-item	*Baseline*	*Stable*	*Deteriorated*	*Improved*
Memory-related behaviour				
Asking the same question over and over	76/77	44 (57.8)	16 (21.1)	16 (21.1)
Trouble remembering recent events	76/77	33 (43.4)	22 (29.0)	21 (27.6)
Trouble remembering significant past events	66/77	23 (34.8)	14 (21.2)	29 (44.0)
Losing or misplacing things	77/77	38 (49.4)	14 (18.2)	25 (32.4)
Forgetting what day it is	76/76	32 (42.1)	21 (27.6)	23 (30.3)
Starting but not finishing things	68/77	30 (44.1)	18 (26.5)	20 (29.4)
Difficulty concentrating on a task	73/77	29 (39.7)	25 (34.3)	19 (26.0)
Disruptive behaviour				
Destroying properties	13/77	2 (15.4)	3 (23.1)	8 (61.5)
Doing things that embarrasses you	38/77	16 (42.1)	4 (10.5)	18 (47.4)
Waking you or family members at night	16/77	4 (25.0)	2 (12.5)	10 (62.5)
Talking loudly and rapidly	23/77	10 (43.5)	3 (13.0)	10 (43.5)
Arguing, irritability	60/77	21 (35.0)	12 (20.0)	27 (45.0)
Engaging in behaviour that is potentially dangerous to self or others	25/77	10 (40.0)	3 (12.0)	12 (48.0)
Aggressive to others verbally	19/77	5 (26.3)	1 (5.3)	13 (68.4)
Threats to hurt others	5/77	2 (40.0)	0 (0.0)	3 (60.0)
Depressive behaviour				
Threats to hurt oneself	6/77	3 (50.0)	0 (0.0)	3 (50.0)
Appears sad or depressed	58/77	28 (48.3)	9 (15.5)	21 (36.2)
Expressing feelings of hopelessness or sadness about the future	45/77	12 (26.7)	14 (31.1)	19 (42.2)
Crying and tearfulness	39/77	18 (46.2)	3 (7.7)	18 (46.2)
Commenting about dead of self or others	25/77	13 (52.0)	4 (16.0)	8 (32.0)
Talking about feeling lonely	32/77	15 (46.9)	5 (15.6)	12 (37.5)
Comments about feeling worthless or being a burden to others	32/77	7 (21.8)	11 (34.4)	14 (43.8)
Comments about feeling like a failure	17/77	4 (23.5)	3 (17.6)	10 (58.9)
Appears anxious or worried	59/77	20 (34.0)	13 (22.0)	26 (44.0)

Table 5 Baseline characteristics and assessment results of rivastigmine users and historical controls, differences in assessment results between 6 months and baseline of rivastigmine users and historical controls and effect sizes of rivastigmine treatment after 6 months

	*Baseline characteristics/assessment scores [mean (SD)]**			*Differences in assessment scores between 6 months and baseline [mean (SD)]†*			*Effect size†*	
Characteristics/ assessment scales	*Rivastigmine cohort (n = 84)*	*Historical control cohort (n = 69)*	*p-value*	*Rivastigmine cohort (n = 84)*	*Historical control cohort (n = 69)*	*p-value*	*Cohen's d*	*SRM‡*
Age	78.2 (6.0)	78.3 (6.2)	0.773					
Gender, female	69%	81%						
MMSE§	20.4 (4.4)	17.5 (5.4)	<0.001	0.1 (3.1)	−1.6 (3.1)	<0.001	0.35	0.55
CAMCOG¶	68.8 (13.1)	61.0 (16.6)	<0.001	0.5 (6.3)	−4.5 (6.5)	<0.001	0.33	0.78
IDDD-performance**	14.0 (8.8)	12.5 (8.5)	0.146	0.7 (5.9)	4.4 (7.7)	<0.001	−0.43	−0.54
RMBPC mem††	17.1 (3.9)	17.4 (5.8)	0.468	−0.4 (4.3)	1.0 (5.4)	0.006	−0.28	−0.28
RMBPC dis‡‡	4.3 (3.9)	4.2 (4.3)	0.786	−0.5 (2.6)	−0.2 (3.9)	0.369	−0.07	−0.09
RMBPC dep§§	7.7 (5.7)	8.4 (6.1)	0.259	0.2 (4.6)	−1.6 (5.0)	0.001	0.30	0.37

*Lower baseline MMSE/CAMCOG scores/higher baseline IDDD/RMBPC scores represent worse cognitive performance, functional performance or behaviour.
†Negative differences/effect sizes reflect improvement on IDDD/RMBPC and deterioration on MMSE/CAMCOG.
‡Standardised response mean.
§Range 0–30.
¶Range 0–107.
**Range 0–44.
††Memory subscale: range 0–28.
‡‡Disruptive behaviour subscale: range 0–32.
§§Depression subscale: range 0–36.

decline in treated patients in 18 months as measured on scales for cognition (MMSE) and activities of daily living (ADL) or 24 months as measured on scales for cognition (CAMCOG) and memory-associated disturbances in behaviour.

DISCUSSION

In a cohort of Alzheimer patients, rivastigmine shows a significant but modest clinically detectable effect on cognition, performance in daily living and the memory part of the behaviour scale during 26 weeks compared with a historical control group of Alzheimer patients. Disruptive behaviour was not significantly altered and depressive behaviour worsened slightly. During 30 months, rivastigmine users showed stabilization compared with baseline test results on numerous RMBPC items. Improvement was shown on a number of depression and disruptive behaviour subitems in particular.

Baseline assessment results were not significantly different for the IDDD and all subsections of the RMBPC, and therefore, rivastigmine effectiveness after 6 months can be easily interpreted. On the contrary, baseline assessment results differed significantly for both MMSE and CAMCOG. Although rivastigmine showed a significant and clinical detectable effect after 6 months on cognition, this should be interpreted with caution. MMSE scores can be subdivided into no cognitive impairment (24–30), mild cognitive impairment (18–23) and severe cognitive impairment (0–17) (25). The control cohort may present a more advanced state of cognitive impairment, and this might result in a different rate of cognitive decline compared with the experimental group of rivastigmine users. Therefore, the shown effectiveness can possibly not be attributed solely to rivastigmine use.

A review by Grossberg described effects of rivastigmine on behaviour. A significant reduction in the frequency of aggressiveness as compared with placebo was shown after 6 months of treatment (26). In nursing home patients, significant improvement was shown after 52 weeks for hallucinations, anxiety, euphoria, apathy, disinhibition, irritability, abberant motor behaviour, nighttime behaviour and appetite/eating change among patients with these symptoms at baseline (11). In another study, in a population of nursing home patients, 26 weeks of rivastigmine showed improvement of anxiety in 56% of patients showing disturbances at baseline, improvement of irritability in 66% of patients and also nighttime disturbances improved in 82% of patients (13) Our cohort study showed that after 26 weeks of rivastigmine treatment, around 45% of patients with symptoms present at baseline improved for irritability and anxiety and in 62% of patients improvement of nighttime behaviour was shown.

It must be pointed out also that in the studied cohort, only six patients did not receive daily doses above 6 mg. A meta-analysis showed a relation between efficacy and rivastigmine dose (27). The shown effectiveness in our cohort may therefore be only representative for doses of rivastigmine above 6 mg daily. In addition, in the studied cohort, no relation was found between dose of rivastigmine and effectiveness in the three studied domains (results not shown).

Our experimental cohort shows initial improvement of cognition as well as initial worsening of depressive symptoms. A possible relation could be hypothesised. Lopez et al. (28) did not find a difference in presence of depression between patients who were aware of their cognitive deficits and those who were not. Harwood et al. (29), however, found a positive relation between greater insight and more depressive symptoms.

Dementia may put a burden on relatives and the health system (30), and therefore, it is of primary importance if symptomatic therapy could delay deterioration in cognition, performance and behaviour. In this study, rivastigmine therapy shows 12–18 months delay in deterioration of ADL, cognition and memory-associated behaviour compared with the historical control cohort. However, a positive bias is introduced. Responders to rivastigmine continue therapy after the first follow-up evaluation at 6 months, while others discontinue therapy, because of non-response. Therefore, only in initial responders therapy could postpone cognitive and functional deterioration with 1–1.5 years. In addition, because only 6-month data are available of the control cohort, a direct comparison cannot be made. However, a dropout study suggested an effect of rivastigmine on disease progression (31).

Moreover, a huge bias is introduced during the first period of 6 months of treatment. Rivastigmine shows more adverse events as compared with donepezil (32). A large dropout rate is the result, which is also apparent in our cohort. So only in initial survivors up to the first follow-up visit after 6 months, rivastigmine effectiveness is measured and in the subcohort of responders, therapy is continued.

Our results show a gradual decline up to 30 months after treatment initiation. However, the long-term results of our cohort are purely descriptive in nature. Long-term effects of rivastigmine and other cholinesterase inhibitors remain largely unknown. Studies following patients beyond 12 months are scarce and descriptive in nature, and placebo responses are sometimes modelled (6,33).

Lopez-Lousa et al. (3) reported great variability in treatment response between rivastigmine users. Our results confirm this. A wide range of differences in scores between follow-up assessments and baseline scores was shown during the complete follow-up period. Rockwood and MacKnight (34) proposed cholinesterase inhibitor users to be subdivided into a group of responders, a group of non-responders and a group remaining at equivocal results at retesting. In the future, more research should be performed to identify these subgroups and make it ideally possible to identify individual

patients in routine clinical care as a responder or not. If it is possible to identify patients as responders or non-responders, therapy should be initiated only in patients who fulfil the characteristics for a responder. The non-responders will be spared then from the frequently occurring adverse events. Moreover, even a part of the identified responders will experience adverse events and some patients will possibly discontinue therapy before the initial follow-up visit at 6 months. However, it is currently unclear which characteristics define the (long-term) rivastigmine responders, and therefore, all patients should be offered therapy, as it is unethical to withdraw a possible effective therapy from patients.

Strengths of our study are a relatively large population in a naturalistic setting, a total follow-up time of 30 months and full accessibility to all relevant clinical data. This study is an example of rivastigmine monitoring in clinical practice and could serve as a model for other memory clinics. The scales that are used are easy to apply and cover a wide range of domains; both memory and non-memory cognitive function, performance in daily living, memory, disruptive and depressive behaviour are assessed. Monitoring rivastigmine effectiveness in different domains is an advantage over only using the MMSE as instrument to monitor treatment effects. The use of CAMCOG, IDDD and RMBPC in clinical practice is not highly time-consuming, as CAMCOG screening takes about an average of 30 min only, and in the meantime, proxies are able to fill in the IDDD and RMBPC questionnaires. It is important that the same proxy accompanies the patient for every follow-up visit. An unacceptable low level of agreement was found between primary and secondary informants on the RMBPC. The RMBPC, however, is very useful for longitudinal follow-up as it showed an acceptable test-retest agreement and did not show a ceiling effect (35). The CAMCOG evaluates a broad range of cognitive functions that are often affected in dementia and thus an advantage over brief screening tests (16). Previous research showed this instruments' utilities for assessing and monitoring cognitive decline in moderate and moderately severe dementia patients (36). Ceiling effects are not supposed when using CAMCOG for cognitive evaluation in AD, as it showed little ceiling effect when used in the non-demented elderly (37) and appeared to be sensitive to the early stages of dementia (38). The IDDD, developed for community-dwelling dementia patients, has a high internal consistency, and all the activities that are mentioned in this instrument are relevant and applicable to both men and women (18).

Our results show that the non-memory section of the CAMCOG, consisting of items regarding for example attention, praxis, abstract reasoning and perception, initially improved, whereas the memory section initially deteriorated in the rivastigmine group. As we performed a cohort study without a placebo group, the results may be shaded in this descriptive open-label setting and future research should focus on investigating and confirming this further. Identification of responders is also of primary importance and should be involved in future research.

In conclusion, a huge discontinuation rate is experienced within the first half year of treatment. In the subpopulation of patients who continued rivastigmine for 6 months, it shows modest, significant effectiveness on cognition, functionality and memory-associated behaviour as compared with historical control patients. Unfortunately, disruptive behaviour is not significantly altered by rivastigmine therapy, and depressive behaviour increased slightly after initial treatment. During 30 months, rivastigmine showed stabilization on numerous behaviour items as measured by the RMBPC.

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Paper received December 2005, accepted February 2006

