

Effects of two-year treatment with the cholinesterase inhibitor rivastigmine on behavioural symptoms in Alzheimer's disease

Michael Rösler^a, Wolfgang Retz^{a,*},
P. Retz-Junginger^a and Hans Joachim Dennerl^b

^a*Study Group Gerontopsychiatry, Psychiatric
Department, University of Saarland, D-68421
Homburg/Saar, Germany*

^b*Novartis Pharma GmbH, Roonstrasse 25, Nürnberg,
D-90429, Germany*

Alzheimer's disease (AD) is accompanied by prominent behavioural disturbances. They cause significant distress for both caregivers and patients and can play a major role in the decision to institutionalise AD patients. Recent evidence suggests that cholinergic deficiencies not only contribute to the memory and cognitive abnormalities of AD but are also responsible for some behavioural abnormalities seen over the course of the disease. In this study we assessed the ability of rivastigmine, a pseudo-irreversible cholinesterase inhibitor, to improve behavioural and psychopathologic symptoms in AD. The analysis included 34 patients present in the German arm of the international study B303 who received and completed long-term treatment with rivastigmine in the open-label study B305. Assessments of behaviour and psychopathological symptoms were performed using the behavioural component of the Clinicians Interview Based Impression of Change Plus (CIBIC-Plus). Results show that long-term treatment with rivastigmine can slow the progression of behavioural and psychopathological symptoms of AD. Behavioural symptoms showing stabilisation included aggressiveness, activity disturbances, hallucinations and paranoid features. Results also suggest that patients treated earlier with rivastigmine may attain a greater benefit compared with patients whose treatment is delayed 6 months. Further studies examining the effects of rivastigmine on behavioural disturbances in AD are therefore warranted.

Keywords: CIBIC-Plus, cholinesterase inhibitors, behavioural symptoms, Alzheimer's disease, rivastigmine

*Corresponding author: Dr. Wolfgang Retz, Study Group Gerontopsychiatry, Department of Psychiatry, University of Saarland, D-66421 Homburg/Saar, Germany. Tel.: +49 6841 166351; Fax: +49 6841 166335; E-mail: wolfgang.retz@med-rz.uni-sb.de.

1. Introduction

Cognitive decline is the most prevalent symptom in Alzheimer's disease (AD). However, it represents only a part of the loss of functional ability associated with the disease. The full spectrum includes loss of ability to perform activities of daily living (ADL) and the appearance of non-cognitive symptoms, in particular behavioural abnormalities (delusions, hallucinations, agitation, aggression, mood disorders and sleep disturbances) [3, 10]. In addition, behavioural disturbances are a major source of caregiver stress resulting in psychological distress and clinical depression [13, 14]. However, few experimental studies and clinical trials investigating new therapeutic agents for AD have examined the effects of such interventions on behavioural abnormalities.

Changes underlying the psychopathological symptoms of AD can be divided into neuropathologic and neurochemical. The most prominent neurochemical change seen in AD is the marked deficit in cholinergic neurotransmission. In addition, there is a less pronounced functional decline in non-cholinergic neurotransmitters and modulators [7, 19]. Morphological and functional alterations may be responsible not only for loss of cognitive function, but also behavioural abnormalities associated with AD. Indeed, there is evidence that loss of cholinergic function may be responsible for some of the behavioural changes in AD [5, 11]. It has been reported that loss of temporal neocortical function and decreased cholinergic activity in the reticular and lateral geniculate nuclei of the thalamus are associated with hallucinations observed in AD and other neurodegenerative diseases such as dementia of the Lewy body type and Parkinson's Disease [11]. Cholinergic deficiency, which is most pronounced in the limbic region, results in a hypodopaminergic state, that may be crucial in the gen-

Table 1
Behavioural component of CIBIC-Plus patient and caregiver interview

Behavioural domains	Patient		Caregiver	
	No. of items	Maximum score ^a	No. of items	Maximum score ^a
Mood disorders				
Anxieties and phobias	2	6	4	12
Affective disturbances	2	6	2	6
Aggressiveness	3	9	3	9
Activity disturbances	3	9	3	9
Diurnal rhythm (sleep) disturbances	–	–	1	3
Hallucinations	1	3	5	15
Paranoid and delusional symptoms	1	3	7	21

^aSpecific items scored on a four point scale: 0 = not present, 1 = presence of behavioural symptoms, 2 = presence of symptoms generally with emotional content, 3 = presence of the symptom, generally with an emotional and a physical component.

esis of delusions. Limbic system dysfunction interferes with assessment of environmental threat, produces incorrect assessment of danger and may cause inappropriate fear, which often manifests as paranoia [6]. Moreover, a cholinergic-monoaminergic imbalance has been implicated in the pathogenesis of mood disorders [8].

Therefore, therapeutic interventions, which are able to reverse the cholinergic deficit, may be of benefit in the treatment of behavioural disturbances in AD.

Rivastigmine is a new-generation cholinesterase (ChE) inhibitor of the carbamate type, which has been described as a pseudo-irreversible inhibitor of ChE. Rivastigmine is centrally selective for acetylcholinesterase (AChE) and demonstrates brain-regional selectivity for the hippocampus and cortex [12].

As part of the global clinical study program, ADENA [1], an international multicentre, randomised, placebo-controlled trial (B303) was performed to evaluate the efficacy and safety of rivastigmine in the treatment of mild to moderately severe AD. In the study, patients treated with rivastigmine 6–12 mg/day for 26 weeks demonstrated significant benefits on all outcomes measured – cognition, global assessment of change, ADL and disease severity [18].

Following the 26-week study period all patients were given the opportunity to participate in the long-term (104 week) open-label study B305. In this trial, patients previously randomised to one of the three treatment arms (rivastigmine 1–4 mg/day, rivastigmine 6–12 mg/day or placebo) were assigned to open-label treatment with rivastigmine. Both treating physician and patient remained blinded to the randomised treatment received during the first 26 weeks.

This behavioural analysis is based on the B303 study population evaluated at seven German centres who

received and completed long-term treatment with rivastigmine in the open-label study B305. Details of patient recruitment and dose titration have been discussed in detail elsewhere [18].

2. Method

Assessments of behaviour and psychopathological symptoms were performed using the Clinicians Interview Based Impression of Change Plus (CIBIC-Plus). The CIBIC-Plus is principally an instrument designed to evaluate complete global change in AD by assessing three symptom domains: cognition, functioning and behaviour. Psychopathological and behavioural assessments are made using an interview with and direct observation of the patient and a semi-structured interview with the caregiver. The behavioural component of the CIBIC-Plus interview is adapted from the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [17]. In the caregiver interview, the carer is queried regarding the magnitude of behavioural symptoms in seven major areas and the magnitude of symptomatic disturbance in terms of 25 specific symptoms (or items) in these categories is assessed on the basis of caregiver reports (see Table 1). The CIBIC-Plus interview with the patient assesses the magnitude of observable behavioural symptomatology in six areas, with 12 specific symptoms in these six areas of disturbance assessed [17]. The behavioural component also contains a global assessment of the overall magnitude of behavioural disturbance.

The scores for the different behavioural components of the CIBIC-Plus caregiver and patient interview together with the change score for the CIBIC-Plus behaviour domain were assessed for each group. A baseline video-taped rating was performed by an experi-

Table 2
Demographics and characteristics of study patients (observed cases) and patients discontinuing treatment

	Observed cases	Patient dropouts
<i>Sex^a</i>		
Male	13	28
Female	21	36
<i>Age (years)^a</i>		
Mean (SD)	66.5 (8.5)	69.9 (9.1)
<i>Dementia, duration of illness (months)^a</i>		
Mean (SD)	38.2 (18.7)	40.4 (26.9)
<i>Patient characteristics (baseline), mean (SD)^a</i>		
MMSE ^b	19.4 (4.6)	18.5 (5.1)
ADAS-Cog ^c	27.9 (13.7)	28.9 (12.7)
GDS ^d	4.2 (0.9)	4.2 (1.1)

^aMann-Whitney-U-test/*t*-test 2 tailed: no significant difference.

^bMMSE = Mini-Mental State Examination.

^cADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subscale.

^dGDS = Global Deterioration Scale.

enced clinician at Week 0; follow-up evaluations were performed at Week 26, 52 and Week 104.

CIBIC-Plus data for analysis of non-cognitive behavioural symptoms were available for 98 patients from the German centres. Only patients maintained on treatment during the entire two year study period were included in the statistical evaluation.

Patient demographics are shown in Table 2. No psychotropic drugs were allowed during the study except for small doses of short-acting benzodiazepines and haloperidol for a maximum duration of 3 days. Patients medicated with the former drugs had a washout period of 72 hours before a testing session.

The effects of treatment on the behavioural component of the CIBIC-Plus were analysed using the Wilcoxon rank test. Analyses for patients with evaluations made while on study drug at designated assessment times are presented (observed cases). Demographic differences between study completers (observed cases) and non-completers were compared using the Mann-Whitney-U and *t* test.

3. Results

Of the 98 patients in the German arm of the international multicentre B303 study, 34 patients completed treatment at Week 104 of the open-label extension study. Reasons for discontinuation included withdrawal of consent ($n = 32$), death ($n = 4$), adverse events ($n = 10$), failure to return ($n = 4$), treatment failure and non-specified events ($n = 11$). No significant differences were reported with regard to age,

sex, duration and severity of illness and cognitive impairment as measured on the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) between patients completing the study (OC) and patients discontinuing treatment (see Table 2).

3.1. Parallel group evaluation

Assessment of the global ratings of the CIBIC-Plus behavioural domain revealed that at Week 26 symptoms of patients receiving rivastigmine 6–12 mg/day improved, while the symptoms of patients treated with placebo showed no improvement. The difference between the two groups at Week 26 was statistically significant ($p = 0.02$) (Fig. 1). At Week 52 additional improvements on behavioural symptoms were observed in patients in the former 6–12 mg/day group who continued open label treatment with rivastigmine. At Week 104 the improvements for this group were rated as mild to moderate. By contrast patients initially included in the placebo group who went on to receive rivastigmine after the 26 week period showed mild improvement at Week 52, and at the end of the study, behavioural symptoms remained stable and were similar to Week 26 placebo total scores. The difference in improvement in terms of the CIBIC-Plus behaviour change score between both groups was significant at Week 52 and 104 ($p \leq 0.05$).

3.2. Longitudinal changes

Following administration of open-label rivastigmine the CIBIC-Plus ratings for the study population

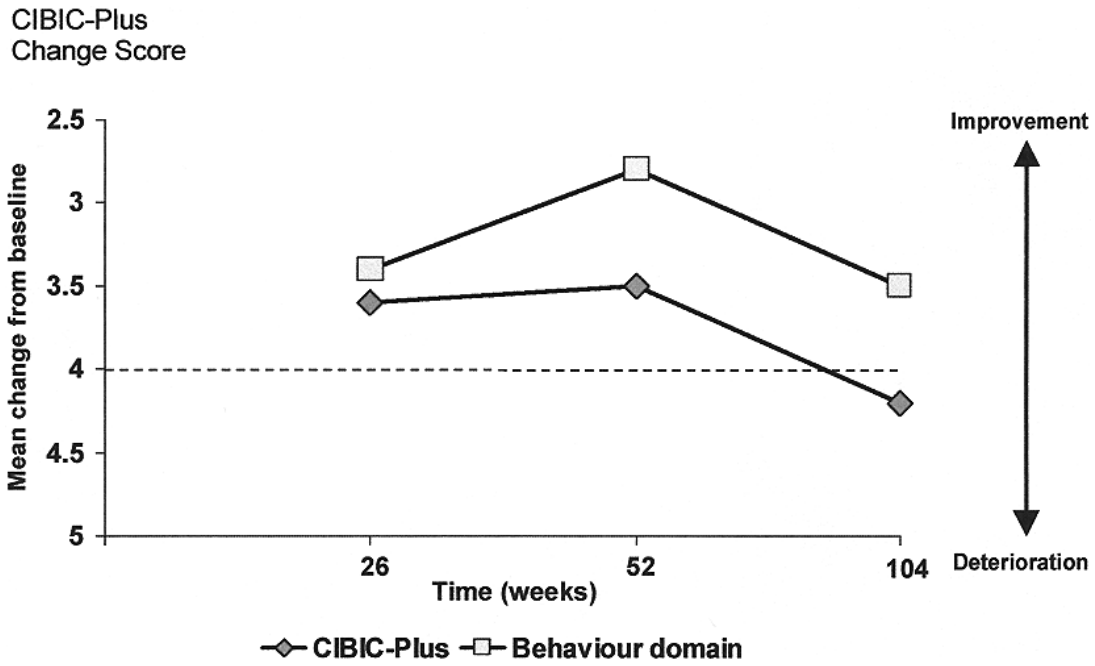


Fig. 1. Mean change from baseline in CIBIC-Plus and CIBIC-Plus behaviour domain rating during treatment with open-label rivastigmine (observed cases, $n = 34$). A score of 4 means unchanged symptoms, a score below 4 is indicating improvement and a score above 4 displays that the symptoms had worsened.

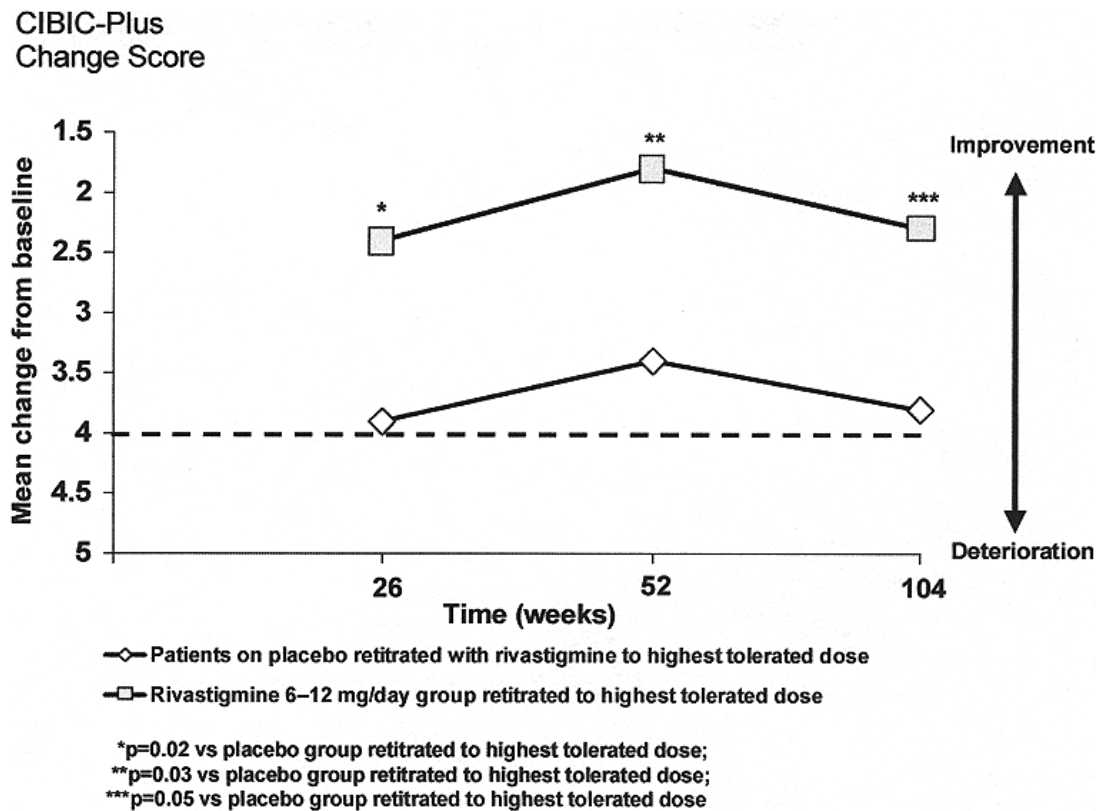


Fig. 2. Mean rating change from baseline in CIBIC-Plus behavioural domain.

Table 3

Mean scores of the different behavioural domains during treatment (observed cases, $n = 29$). P -values refer to differences between mean rating scores at week 52 and 104 compared with baseline.

	Baseline	Week 52	Week 104	
Mood disorders	3.41 ± 2.61	1.56 ± 2.04**	1.45 ± 1.86**	** $p = 0.001$
Aggressiveness	0.72 ± 0.88	0.36 ± 0.70	0.69 ± 0.89	
Activity disturbances	1.20 ± 1.30	1.04 ± 1.37	1.14 ± 1.58	
Hallucinations	0.59 ± 1.90	0.12 ± 0.60*	0.35 ± 1.01	* $p = 0.02$
Paranoid and delusional symptoms	0.79 ± 1.10	0.52 ± 1.30	0.58 ± 1.15	

($n = 34$) showed no change compared with baseline suggesting no clinically meaningful change in the three domains assessed (cognition, functioning and behaviour). In contrast the rating for only the behavioural component of the CIBIC-Plus at Week 52 and 104 showed improvement which was most pronounced at Week 52 (Fig. 2).

Scores for the major behavioural symptom domains of the behaviour component of the CIBIC-Plus at baseline, at Week 52 and 104 are shown in Table 3. Mood disturbances improved significantly at Week 52 and 104 compared with baseline during the entire observation period. The greatest improvement was observed at the end of the study at Week 104. The mean score for hallucinations was significantly reduced at Week 52 compared with baseline. Although the improvement failed to reach statistical significance at Week 104, the mean score remained below baseline. No significant changes were reported for paranoid symptoms, aggressiveness and activity disturbances over the observation period. However, scores indicated that symptoms remained stable over the 2-year period.

4. Discussion

Few studies have addressed the effects of cholinergic treatment on non-cognitive symptoms. Of those reported, behavioural improvements have been demonstrated with the cholinesterase inhibitors physostigmine and tacrine [4, 9, 15] and the selective muscarinic (M1) receptor agonist xanomeline [2]. These early trials suggested that the cholinergic deficiency in AD contributed to both cognitive and behavioural dysfunction and that enhancement of cholinergic function may improve such symptoms.

The results of our study also point in the same direction. Comparison of treatment groups revealed that rivastigmine 6–12 mg/day reduced behavioural abnormalities significantly at Week 26 when compared with the placebo group. During the extension period the behavioural symptoms of patients initially randomised to

rivastigmine 6–12 mg/day continued to improve, and after two years of treatment significant benefits were still observed. Patients initially receiving placebo who went on to receive rivastigmine were seen to stabilise. Therefore, as patients receiving delayed rivastigmine treatment do not reach the same level of improvement as those receiving rivastigmine from day one, we may conclude that earlier intervention may offer a better chance to maintain the patients' functional ability for a longer period of time.

A more detailed observational evaluation of individual behavioural areas showed stabilisation of aggressiveness, activity disturbances, hallucinations and paranoid features in patients receiving open-label rivastigmine. Moreover, mood disorders improved.

There are several limitations to the study, which should lead to caution in generalising results. It should be noted that the drop-out rate for the study was high, with only one-third of patients completing two years of therapy. This may have resulted in sample bias, although we were unable to detect significant differences between completers and non-completers with regard to basic sociodemographic features and disease characteristics. Moreover, the small sample size reduced the statistical power of the study.

Another limitation was the lack of a control group post Week 26. This was unavoidable as long-term placebo-controlled study designs in patients with dementia are unethical. However, in our study, comparisons of patients treated with rivastigmine or placebo were possible up to Week 26.

The study design, a *post hoc* study of behavioural symptoms, also limits interpretation of the results. The original efficacy parameters focussed on cognition, ADL and a global clinical analysis.

Finally, the prevalence of behavioural symptoms (determined by the study inclusion and exclusion criteria) in the study population was low. The most prominent behavioural symptoms were mood disturbances, while all the other sections of the behaviour domain had clearly a very low expression of symptoms. This finding raises the question of whether the

sample was biased in the sense of failing to represent common behavioural problems in AD. However, it should be noted that the prevalence of the different behaviour symptoms increases as the disease progresses [3, 10, 16]. In terms of treatment expectations we can conclude that following long-term rivastigmine therapy the incidence of behavioural symptoms remains low.

Although the methodological limitations of the study lead to caution in generalising the results, they indicate that long-term treatment with the ChE inhibitor rivastigmine, stabilises and in some cases improves non-cognitive behavioural symptoms in AD. In order to further our knowledge of the long-term effects of cholinergic treatment strategies in AD, further studies investigating the effects of ChE inhibitors on non-cognitive symptoms are warranted.

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