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MEMANTINE IN SEVERE DEMENTIA: RESULTS OF THE ^{9}M-BEST STUDY (BENEFIT AND EFFICACY IN SEVERLY DEMENTED PATIENTS DURING TREATMENT WITH MEMANTINE)

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SUMMARY

Objectives. To assess clinical efficacy and safety of memantine—an uncompetitive *N*-methyl-**D**-aspartate (NMDA) antagonist—in moderately severe to severe primary dementia.

Materials and methods. Dementia was defined by DSM-III-R criteria and severity was assessed by the Global Deterioration Scale (stages 5–7) and the Mini-Mental State Examination (<10 points). Primary endpoints were the Clinical Global Impression of Change (CGI-C) rated by the physician, and the Behavioural Rating Scale for Geriatric Patients (BGP), subscore 'care dependence', rated by the nursing staff. Secondary endpoints included the modified D-Scale (Arnold/Ferm).

Results. The ITT sample comprised 166 patients and 151 patients were treated per protocol. At 12-week ITT endpoint analysis, 82 received memantine 10 mg per day, 84 placebo. Dementia was in 49% of the Alzheimer type and in 51% of the vascular type (CT, Hachinski score). A positive response in the CGI-C was seen in 73% versus 45% in favour of memantine (stratified Wilcoxon $p < 0.001$), independent of the etiology of dementia. The results in the BGP subscore 'care dependence' were 3.1 points improvement under memantine and 1.1 points under placebo ($p = 0.016$). A coincident response of the two independent target variables was observed in 61.3% (memantine) versus 31.6% (placebo). Secondary endpoint analysis of the D-Scale assessing basic ADL functions support the primary results. Regarding the safety profile, no significant differences between treatment groups were observed.

Conclusions. The results of this trial support the hypothesis that memantine treatment leads to functional improvement and reduces care dependence in severely demented patients. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS—dementia; Alzheimer's disease; vascular dementia; memantine; glutamate modulator; NMDA antagonist; drug effects; D-Scale; BGP

The prevalence of dementia is ever growing in developed countries where elderly patients make up an increasing proportion of the population. Private and institutional care for patients with dementia cause considerable cost to public health care. Causal therapy of dementia is not yet available. Current treatment focuses on the mobilization of remaining cognitive and functional capacities and eventually the prevention of further disease progression. The aim is to optimize the patients' autonomy and independence, focusing on self care and activities of daily living.

The theory that Alzheimer's disease (AD) and the resulting typical cognitive and functional impairments are due primarily to a cholinergic brain deficit is increasingly challenged by the glutamatergic hypothesis of dementia. There is growing evidence that glutamate, the most prevalent excitatory neurotransmitter in the brain, is central to the pathology of dementia (Müller *et al*., 1995; Greenamyre *et al*., 1988). This theory, which is gaining in acceptance, suggests that the extent of glutamatergic neuronal loss correlates with the degree of dementia (Francis *et al*., 1993; Li *et al*., 1997). The basis for the glutamatergic hypothesis of dementia

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is based on the following facts (Greenamyre *et al*., 1988; Francis *et al*., 1993; Palmer and Gershon, 1990):

- glutamate is the main fast excitatory neurotransmitter in the regions associated with cognition and memory, the cerebral cortex and hippocampus;
- cortical and subcortical structures that contain glutamatergic receptors are structurally damaged during the course of AD;
- glutamate also acts as an excitotoxin, causing neuronal death when excessive levels are chronically released;
- the neurochemical changes and some of the clinical symptoms seen in dementia can be induced experimentally with excitotoxins, such as potent glutamate agonists (eg quinolinic acid or NMDA);
- clinical signs of dementia correlate with deficits of glutamatergic association fibres.

Memantine (Merz & Co., Frankfurt/Main, Germany) is a blocker of glutamate gated NMDA receptor channels (Kornhuber *et al*., 1989; Bormann, 1989; Parsons *et al*., 1993), which allows the physiological activation of NMDA receptors during memory formation whilst blocking their pathological activation. This property is due to the rapid, voltage-dependent nature of the interactions of memantine with the NMDA receptor channel (Parsons *et al*., 1993). Under physiological conditions memantine fulfils the same action as magnesium. Memantine blocks NMDA receptor channels in the resting state and, like magnesium, can leave the channel upon physiological activation during memory formation. However, in contrast to magnesium, memantine does not leave the channel under pathological activation. In fact, memantine has been shown in animal models to provide neuroprotection against the pathological, excitotoxic activation of glutamate receptors, whilst preserving or even restoring their physiological activation (Misztal *et al*., 1996; Wenk *et al*., 1996; Zajaczkowski *et al*., 1997, 1996).

The clinical safety and efficacy of memantine has been investigated in placebo-controlled clinical trials involving more than 500 demented patients of the mild-to-moderate stages (Tempel, 1989; Ditzler, 1991; Görtelmeyer and Erbler, 1992; Pantev *et al*., 1993). Using validated rating scales on the psychopathological, performance and behavioural level, significant improvements of cognitive disturbances, drive and motor function were observed. The usual daily dose ranged between 20 and 30 mg. These phase II trials had durations of 4–6 weeks. In general, there was no major difference in ADR frequencies between placebo and active. The most frequent ADRs related to memantine treatment were vertigo, restlessness, hyperexcitation and fatigue.

The aim of this study was to evaluate for the first time ever the clinical efficacy and tolerability of memantine in care dependent in-patients with moderately severe to severe primary dementia. No prospective stratification in Alzheimer disease and vascular dementia (resp. mixed type dementia) was planned, since in advanced stages of dementia the symptom areas of behaviour and functioning do not differ according to etiology in a clinically relevant manner. In addition, earlier clinical trials (Ditzler, 1991; Görtelmeyer and Erbler, 1992) led to the hypothesis that memantine might be equally beneficial in both etiological subgroups. As cognitive performance testing causes considerable methodologic problems in severe cognitive impairment, drug effects were evaluated with two independent primary efficacy variables on the clinical global and the functional level. On the functional level, the target efficacy criterion focused on the functional disability status as a decisive aspect of care-giving. Emphasis was put on the clinical relevance of observed effects by implementing a responder analysis.

MATERIAL AND METHODS

Ethics

Trial design and conduction were fully compliant with GCP and the declaration of Helsinki including amendments. The study protocol was approved by the independent Ethics Committee in Freiburg, Germany and also by the independent Ethics Committee of Latvia. Written informed consent was obtained from the patient or their nearest relative or the person authorized as legally responsible for the duration of the study. Every individual consent form had to be submitted to the committee of Pharmacology and Pharmacopeia of the Latvian Ministry of Welfare for review. All consent forms of the patients randomized in this trial were approved by this committee. Patients and relatives were informed by the physician about the nature, scope and risks of the trial. The patient, the patient's relative or the investigator were free to terminate trial participation at any time.

Patient population

Care-dependent in-patients of both gender were considered for enrolment if aged between 60 and 80 years, and were demented as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R: American Psychiatric Association, 1987). Further inclusion criteria were stages 5–7 of the Global Deterioration Scale (GDS) (Reisberg *et al*., 1982), Mini-Mental State Examination (MMSE) score <10 points (Folstein *et al*., 1975), duration of dementia >12 months, and no CNS-active drugs within 14 days prior to trial start.

Patients were not eligible if they had severe chronic or terminal diseases, progressive heart failure, severe hypertension, myocardial infarction during the last three months, severe cardiac arrhythmia, unstable diabetes mellitus, chronic liver diseases, severe renal impairment (serum creatinine >2.0 mg %), impaired thyroid function, lowered B_{12} blood level, abnormal blood chemistry, alcoholism or drug addiction, severe psychiatric diseases like schizophrenia, major depression (Hamilton Score >18; Hamilton, 1960) learning disability, epilepsy or Parkinson's disease. The following drugs were not permitted as concomitant medication: MAO inhibitors, neuroleptics, tricyclic antidepressants, hypnotics, nootropics or agents stimulating cerebral circulation. Basic medication of the mostly multimorbid patients which did not interfere with the assessments had to be kept constant 2 weeks before and throughout the trial.

Randomization and treatment

The study was performed at seven trial centres (one psychiatric hospital and six nursing homes) in Latvia. The trial was designed as a two-arm double-blind, parallel-group comparison and eligible patients were randomized to receive either memantine (5 mg/day during the first week and 10 mg/day during the next 11 weeks) or matching placebo tablets. Monitoring was performed according to GCP guidelines and took place in intervals of 1–6 weeks. In addition, for randomization and compliance control, blood samples were drawn for analysis of memantine plasma levels at the termination visit.

Patient selection variables

DSM-III-R defines the clinical diagnosis of dementia in a standardized operating procedure (DSM-III-R: American Psychiatric Association, 1987).

The GDS (Reisberg *et al*., 1982) is a seven stage rating scale in which each stage represents a stage of severity, ranging from normal (stage 1) to severe dementia (stage 7), and for each stage a detailed description of clinical characteristics is given. Patients in stages 5–7 were eligible for this trial.

The MMSE (Folstein *et al*., 1975) consists of two parts: verbal and performance. The total score has a maximum of 30 points. A score below 24 points is indicative of cognitive impairment. The MMSE was used for severity staging of dementia. A score of <10 points was required for inclusion.

The HAM-D (Hamilton Depression Rating Scale; Hamilton, 1960) is an observer-rated scale for the quantitative assessment of depressive symptomatology. The rater evaluates the severity for 21 symptoms on the basis of information gained on interview and on information obtained from caregivers. Depressive pseudodementia was excluded by clinical criteria and a HAM-D score of >18 points.

HIS (Hachinski Ischemic Scale) modified by Rosen *et al*. (1980) was used to separate clinically patient subgroups with Alzheimer's Disease (AD) or vascular dementia (VaD).

CT brain imaging was optionally performed for further classification of AD and VaD patients.

Primary efficacy criteria

Two independent ratings by the physician and the nursing staff, respectively, served to assess outcome and were used as primary endpoints for statistical analysis. Both, the CGI-C and the BGP are standardized assessments.

The GCI-C, Clinical Global Impression of Change (National Institute of Mental Health, 1986) is a 7-point global rating, performed by an experienced clinician. At baseline, the clinician had access to all information to assess the clinical global impression of severity of illness (CGI-S). The subsequent global assessments of change (CGI-C) had to be assessed by the same rater, independently of the caregiver rater. The three categories of improvement were defined as treatment response, 'no change' and the three categories of worsening as non-response.

The BGP, Behavioural Rating Scale for Geriatric Patients (van de Kam *et al*., 1971) is an observer-rated scale for the assessment of functional and behavioural disturbances of geriatric patients,

performed by the nursing staff. The BGP was proven to be a valid and reliable instrument to define patients' functional capacities and behavioural symptoms and can be utilized to assess treatment effects (van de Kam and Hoeksma, 1989). The BGP contains four subscales and consists of 35 items. The largest subscale, 'care dependence' was defined as one of the two primary efficacy variables. An improvement of $>15\%$ was regarded as clinically significant and defined as treatment response.

Secondary efficacy variables—D-scale

Ferm's D-test was designed and validated to evaluate descriptively behavioural activities and functioning in demented geriatric patients (Ferm, 1974). The D-scale applied in this trial is an extended and validated version of the D-test (Arnold *et al*., 1998). Sixteen functional variables comprise the most important criteria for characterizing independence, ranging from normal functioning to total care dependence. The extent of the patient's impairment is determined by the nurse on a 6-point rating scale.

In addition, GCI-S and the BGP total score were used as secondary efficacy variables.

Safety variables

Adverse events (AE) were reported describing spontaneous reports or symptoms observed. Comprehensive laboratory parameters (serum tests and haematological tests, urine analysis) were analysed before, during and after treatment. All adverse events were processed according to GLP.

Statistical methods

For sample size estimation purposes, success of treatment (responder) according to the GCI-C after 12 weeks was assumed to occur in 30% of the placebo patients and in 60% of the memantine patients. On the $\alpha = 0.05/2 = 0.025$ level of significance for two-sided testing, a sample size of $N = 68$ patients per treatment group was required to detect a difference of 30% on the GCI-C with 90% power (Program N, idv Gauting, version 2.2). On the BGP subscore 'care dependence' $N = 23$ patients per treatment group were necessary to demonstrate a treatment difference of 7.8 score points with the standard deviation of the same size ($\alpha = 0.025$ and $1 - \beta = 0.90$).

Assuming a rate of 20% non-compliant or drop-out patients, led to the total sample size estimation for randomized patients, namely $N = 168$ patients.

The null hypothesis of identical distribution on the BGP subscore as well as GCI-C responder in memantine and placebo-treated patients after 12 weeks of treatment was tested by means of non-parametric tests (Fisher's Exact test and Wilcoxon rank sum test). Priority was set on the analysis of the primary efficacy variables in the intent-to-treat sample (ITT). Missing endpoint data was replaced by worst ranks. These results were to be confirmed in the treated-per-protocol sample (TPP). The analysis of the secondary variables was performed in the TPP sample as well as in defined subgroups.

RESULTS

Patient characteristics

A total of 167 patients were enrolled, performed baseline visit, and were randomized to the double blind treatment period. One patient was excluded from the following description because he died suddenly the night after baseline visit without having received trial medication. Eighty-two patients were randomized to memantine treatment, 84 patients were on placebo. The baseline characteristics of the two groups were well balanced. As displayed in Table 1 there were no significant differences among the two groups for age, sex, weight and severity of dementia.

All 166 patients were evaluable for efficacy and tolerability analysis according to the definition of intent-to-treat (ITT) sample. Seven patients of the memantine and eight patients of the placebo group were excluded from the treated per protocol (TPP) sample because of discontinuation of therapy or protocol violations. There were no relevant differences at baseline between the 166 patients of the ITT and the 151 patients of the TPP sample. The same was true for the evaluation of efficacy results. The following tables depict the ITT efficacy results, only the secondary efficacy variables are analysed on the TPP basis.

Confirmative analysis of primary efficacy variables

Results of the CGI-C are shown in Table 2. In summary, there is a clear treatment difference in favour of memantine. Since the CGI-C results of six trial centres were indicating a group difference in favour of memantine and only the results of one trial centre showed a possible group difference

Table 1. patient characteristics at baseline (ITT sample, $N = 166$)

	Memantine	Placebo	Total
Sex (male/female (%)	33/49 (40.2/59.8)	37/47 (44.0/56.0)	70/96 (42.2/57.8)
Age (years) (mean ± SD)			
male	67.7 ± 5.1	69.1 ± 5.8	68.4 ± 5.5
female	73.6 ± 5.8	74.2 ± 5.3	73.9 ± 5.6
BMI (kg/qm) (mean ± SD)			
male	25.1 ± 3.9	25.8 ± 3.0	25.5 ± 3.5
female	25.9 ± 4.7	25.2 ± 3.7	25.6 ± 4.3
Smokers (%)	22.0	15.5	18.7
Patients with anti-dementia premedication (%)	39.0	39.3	39.2
Patients with concomitant diseases (%)	87.8	90.5	89.2
Patients with concomitant medication (%)	41.5	42.9	42.2
GDS (cognitive decline) (%)			
moderately severe	3.7	3.6	3.6
severe	91.5	89.3	90.4
very severe	4.9	7.1	6.0
MMSE total score (mean ± SD)	6.6 ± 2.7	6.1 ± 2.8	6.3 ± 2.7
HIS sum score (mean ± SD)	5.2 ± 2.9	5.7 ± 3.2	5.5 ± 3.1
HAM-D total score (mean ± SD)	8.5 ± 2.0	8.9 ± 2.1	8.7 ± 2.1
CGI-S (%)			
markedly ill	63	47	55
severely ill	32	39	36
extremely ill	5	13	9
BGP subscore 'care dependence' (mean ± SD)	21.3 ± 7.6	21.8 ± 7.7	21.5 ± 7.6
BGP:			
Aggressiveness (mean ± SD)	2.01 ± 2.2	2.13 ± 2.1	2.07 ± 2.1
Physical disability (mean ± SD)	2.78 ± 1.8	3.27 ± 2.0	3.03 ± 1.9
Depressive behaviour (mean ± SD)	2.49 ± 1.4	2.81 ± 1.3	2.65 ± 1.4
Neuropsych. disability (mean ± SD)	3.63 ± 1.9	3.51 ± 2.0	3.57 ± 1.9
Inactivity (mean ± SD)	10.93 ± 2.3	11.42 ± 2.0	11.17 ± 2.1

ITT = intention to treat.
SD = standard deviation.

Table 2. Primary endpoint CGI-C: results after 4 and 12 weeks (ITT analysis, $N = 166$)

	Outcome	Memantine		Placebo	
		N	%	*N*	%
Visit 3	Response	48	59	34	40
(week 4)	Non-response	34	41	50	60
Visit 5	Response	60	73	38	45
(week 12)	Non-response	22	27	46	55

ITT = intention to treat.
Response = improvement categories.
Non-response = no change and deterioration categories.
$p < 0.001$ stratified Wilcoxon test.

in favour of placebo, the stratified Wilcoxon test stratified by trial centre was used, resulting in a statistically significant treatment difference in favour of memantine ($p < 0.001$). Results at visit 3 (after 4 weeks) are nearly as clear-cut as at visit 5 ($p = 0.006$) suggesting early improvement after memantine medication.

Descriptive results on CGI-C on the original 7-point scale are shown in Table 3.

BGP-subscore 'care dependence'

Results per visit and pre–post changes (visit 5 versus visit 1) are given in Table 4. Mean score

Table 3. Descriptive results on CGI-C (7-point scale): results at visit 5 (week 12); (ITT analysis; $N = 166$)

Sample	Outcome	Memantine		Placebo	
		N	%	*N*	%
ITT	Very much improved	0	0	0	0
visit 5	Much improved	17	21	9	11
(week 12)	Minimally improved	43	52	29	35
	Unchanged	18	22	38	45
	Minimally worsened	0	0	3	4
	Much worsened	0	0	1	1
	Very much worsened*	4	5	4	5

*Discontinuations were replaced by worst cases.
$p \leqslant 0.003$ Likelihood ratio Chi-square; alternatively $p \leqslant 0.001$, stratified Wilcoxon test.

values continuously decreased in both groups during the trial. The changes are statistically remarkable in both treatment groups. Treatment differences between the two groups are statistically significant in favour of memantine as determined by the stratified Wilcoxon test ($p = 0.016$).

Subgroup analysis of CGI-C and BGP subscore 'care dependence'

To evaluate treatment effects in different subpopulations, a subgroup analysis was performed. Stratification by HIS intended to separate the diagnostic groups of possible Alzheimer's disease patients (HIS < 5) and patients suffering from mixed type or vascular dementia (HIS $\geqslant 5$). Tables 5 and 6 show the descriptive results of the two primary endpoints stratified by HIS categories (<5 points in the sum score versus $\geqslant 5$ points) and 'care dependence' categories (<20 points versus $\geqslant 20$ points at baseline) for patients at visit 5. For the CGI-C, response rates of patients with lower or higher HIS scores are nearly identical in the memantine group, in placebo patients response rates for patients with HIS sum scores $\geqslant$ 5 points

Table 4. Primary endpoint BGP subscore 'care dependence': results per visit and pre-post changes (ITT analysis, $N = 166$)

Visit	Memantine		Placebo	
	Mean $\pm$ SD	Min/Median/Max	Mean $\pm$ SD	Min/Median/Max
1	21.3 ± 7.6	6/20.5/38	21.8 ± 7.7	8/21/38
2	20.8 ± 7.5	6/19.5/38	21.2 ± 7.6	8/20/38
3	19.3 ± 7.5	3/18/38	20.5 ± 7.9	7/19.5/42
4	17.4 ± 8.5	1/16/37	18.9 ± 8.3	2/18/37
5	15.6 ± 8.8	1/13.5/37	18.1 ± 9.4	3/17/38
Change visit 5 versus 1	-3.1 ± 12.2	$-24/-5/46$*	-1.1 ± 11.8	$-17/-2/46$*

*Worst case replacement, $p = 0.016$, stratified Wilcoxon test.

Table 5. CGI-C results stratified by HIS category and 'care dependence' category (ITT analysis, $N = 166$). CGI-C response (dichotomized)

Category	Score	Outcome (visit 5)	Memantine		Placebo	
			N	%	*N*	%
HIS	<5 ($N = 79$)	Response	30	73	16	42
		Non-response	11	27	22	58
HIS	$\geqslant 5$ ($N = 87$)	Response	30	73	22	48
		Non-response	11	27	24	52
Care dependence	<20 ($N = 75$)	Response	30	77	16	44
		Non-response	9	23	20	56
Care dependence	$\geqslant 20$ ($N = 91$)	Response	30	70	22	46
		Non-response	13	30	26	54

Common Odds Ratios
Stratum = HIS. 0.3012; 95% CI (0.157, 0.5781); $p = 0.0005$.
Stratum = Care dependence. 0.3986; 95% CI (0.1594, 0.5855); $p = 0.0006$.

Table 6. BGP results stratified by HIS category and 'care dependence' category (ITT analyses, $N = 166$). BGP subscore 'care dependence' (pre-post changes)

Category	Score	Memantine		Placebo	
		Mean ± SD	Min/Median/Max	Mean ± SD	Min/Median/Max
HIS	<5	-3.5 ± 12.5	$-24/-5/+46$*	-1.6 ± 9.2	$-17/-1.5/+46$*
HIS	$\geqslant 5$	-2.6 ± 12.1	$-14/-4/+46$*	-0.8 ± 13.6	$-16/-2/+46$*
Care dependence	<20	-2.5 ± 12.3	$-15/-5/+46$*	-0.3 ± 12.0	$-13/-1.5/+46$*
Care dependence	$\geqslant 20$	-3.6 ± 12.3	$-24/-6/+46$*	-1.8 ± 11.7	$-17/-2/+46$*

*Worst case replacement.

Table 7. Frequencies of individual response in BGP subscore 'care dependence', CGI-C score, and coincidence of both criteria (ITT analysis, $N = 166$)

Criterion	Memantine ($N = 75$)		Placebo ($N = 76$)	
	N	%	*N*	%
BGP % response				
Responder ($\geqslant 15\%$ improvement)	49	65.3	30	39.5
Non-responder	26	34.7	46	60.5
CGI-C				
Responder (= any improvement)	57	76.0	34	44.7
Non-responder (no change and deterioration)	18	24.0	42	55.3
*Coincidence of both criteria**				
Coincident responder (BGP and CGI-C response)	46	61.3	24	31.6
Divergent response	14	18.7	16	21.0
BGP (+)/CGI-C(−)	3	4.0	6	7.9
CGI-C(+)/BGP(−)	11	14.7	10	13.1
Coincident non-responder	15	20.0	36	47.4

*Freeman-Halton Exact Test (2-sided) $p = 0.0008$.

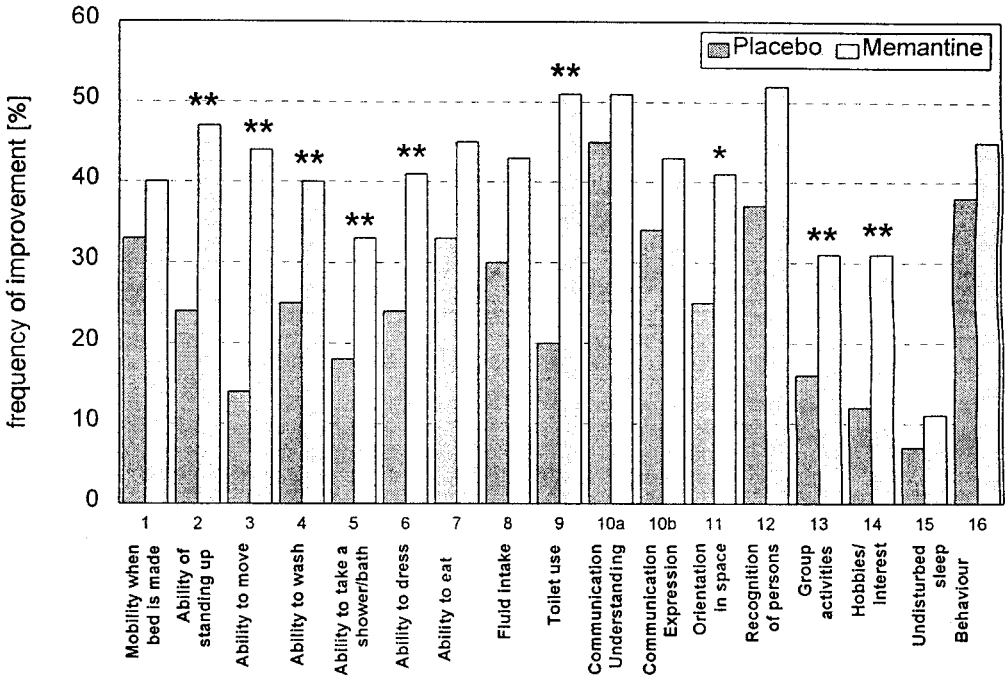
are slightly higher (48% versus 42%). With regard to the subscore 'care dependence', patients in the memantine group with <20 points at baseline show slightly higher response rates than those with >20 points. In the placebo-treated patients, the response rates differ only minimally among subgroups.

For the BGP, response subgroup analysis shows that changes are slightly more pronounced in the HIS category <5 and in the 'care dependence' category of 20 points or more for memantine treatment. For placebo, these subgroup differences appear to be less pronounced.

COINCIDENCE OF RESPONSE IN THE TWO PRIMARY EFFICACY VARIABLES (TPP ANALYSIS)

A descriptive response analysis was performed as described above. In Table 7, absolute and relative frequencies of responders and non-responders at visit 5 are given for BGP subscore 'care dependence' and CGI-C separately, together with coincidence of response in both primary variables. This descriptive analysis was performed in the TPP population. Of memantine patients, 65.3% showed a BGP response, as defined as individual improvement of $\geqslant 15\%$ of the subscore at baseline, whereas among placebo patients the percentage of responders was 39.5%. The response difference between the memantine and the placebo group was 25.8% on the BGP. For the CGI-C score the difference between memantine and placebo group was 31.3%.

Coincidental response of both primary efficacy criteria is observed in 61.3% of the memantine and in 31.6% of the placebo patients. Only three of the 49 memantine responders and six of the 30 placebo responders in the BGP were not assessed as improved by the physicians on the CGI-C score;



** = statistically significant treatment difference ($p < 0.05$)
* = trend to treatment difference, assessed by Wilcoxon rank-sum test on the detailed scale of change $p < 0.10$)

Figure 1. Frequencies in patient response per item of D-Scale (TPP analysis, $N = 151$)

11 of the 57 memantine responders and 10 of the 34 placebo responders on the CGI-C were not assessed as improved by the nursing staff in the BGP.

Analysis of secondary efficacy variables

In CGI-S (subscore severity of illness) results were better in memantine that in placebo patients (clear or slight improvement in 78% of memantine and in 53% of placebo patients).

The BGP total score changed by -7.2 ± 7.1 points (mean $\pm$ SD) with memantine and -4.6 ± 7 points with placebo. The stratified Wilcoxon test resulted in a p-value of 0.015, indicating a statistically significant treatment difference in favour of memantine. Results on the 16 items of the D-Scale at visit 1 and 5 are shown in Fig. 1. For every item, response rates are greater for memantine patients than placebo patients, reaching a statistically significant difference in 8 out of 16 items.

Safety and tolerability assessment

Eighteen memantine patients (22%) and 18 placebo patients (21%) had adverse events. Four memantine patients (5%) and five placebo patients (6%) had serious adverse events. One patient died before randomization (Pat. no. 0). Descriptions of all SAEs are listed in Table 8. In all SAE cases causal relationship to the trial medication was rated 'unlikely' by the investigators.

Laboratory parameters

Frequency of abnormal values were equally distributed in both treatment groups; intra-individual within-treatment group pre–post comparisons of standard laboratory safety parameters that changed significantly over the course of the trial, are given in Table 9. Overall, the changes observed are not clinically relevant. Tolerability was globally rated for each patient by the physician at the end of the treatment period. For 71% of the memantine patients and 69% of the placebo patients treatment was tolerated very well, 28% of the memantine patients and 31% of the placebo patients showed good tolerability. For one memantine patient, moderate tolerability was reported.

Table 8. Serious adverse event descriptions

Medication	Pat. no.	Description of event/symptoms	Outcome
None*	0	Acute heart failure	lethal
Memantine	15	Worsening of heart failure and hypostatic pneumonia; cardiac arrest, apnoea	lethal
	60	Unconsciousness, cardiac arrest, apnoea	lethal
	101	Acute heart failure, cardiac arrest, apnoea	lethal
	118	Cardiac arrest, apnoea	lethal
Placebo	29	Cerebral circulatory disturbance, tetraplegia, cardiac arrest, apnoea	lethal
	42	Unconsciousness, cardiac arrest, apnoea	lethal
	59	Hospitalization due to abdominal pain, fever, vomiting, cholecystectomy	improved
	91	Cardiac arrest, apnoea	lethal
	117	Myocardial infarction, weakness, unconsciousness, coma, cardiac arrest, apnoea	lethal

*Occurrence before randomization.

Table 9. Standard safety laboratory parameters with significant pre–post differences

Parameter	Treatment	Baseline value mean (±SD)	Mean change	*p*-value
BSR (mm/h)	Memantine	21.28 (9.41)	2.06	0.081
	Placebo	19.75 (9.47)	3.31	0.005
Hematokrit (%)	Memantine	41.35 (4.95)	1.85	0.001
	Placebo	42.14 (4.64)	1.70	0.008
Sodium (mmol/l)	Memantine	140.55 (3.99)	2.70	<0.001
	Placebo	141.17 (4.07)	2.46	0.003
ASAT (U/l)	Memantine	19.67 (7.73)	1.77	0.057
	Placebo	19.70 (10.76)	3.87	<0.001
Gamma-GT (U/l)	Memantine	25.79 (32.81)	−4.95	<0.001
	Placebo	21.44 (12.54)	−1.59	0.087
Glucose (mmol/l)	Memantine	5.51 (1.65)	−0.60	0.002
	Placebo	5.80 (2.24)	−0.47	0.103
Protein (g/l)	Memantine	73.97 (6.63)	1.35	0.021
	Placebo	72.76 (5.93)	1.51	0.033
Creatinine (μmol/l)	Memantine	77.0 (13.61)	1.91	0.045
	Placebo	76.67 (14.87)	4.92	0.003
Uric acid (μmol/l)	Memantine	285.41 (87.14)	7.72	0.359
	Placebo	279.70 (76.14)	17.41	0.037

DISCUSSION

In contrast to most reported dementia trials, this study was conducted in a target population of patients with severe dementia. In this group of patients, changes in cognitive test scores are clinically less relevant as compared to functional aspects (Franssen *et al*., 1991; Souren *et al*., 1995). Functional and clinical global endpoints were therefore selected as primary efficacy parameters.

The CGI-C is a global assessment of change, performed by an experienced clinician (physician) and the BGP subscore 'care dependence' is a scale that has been successfully used for years to assess behavioural and functional symptoms of psychogeriatric in-patients by the nursing staff (Diesfeldt, 1980; van der Kam and Hoeksma 1989; Loo *et al*., 1990). The rating of nurses, being in close and continuous contact with the patient, is of importance in the judgement of functional improvement. There are only few data available, especially with regard to the congruence between nurses and clinicians rating of therapeutic effects in anti-dementia drug trials (Herrmann and Kern, 1987; Spiegel *et al*., 1991; Weyer, 1992; Hermann and Stephen, 1992). A comparison of our data shows that the major baseline characteristics of the patients included in this trial, especially in this stage of dementia and the respective extent of care dependence, are representative for a severely demented population (Franssen *et al*., 1991; Souren *et al*., 1995). MMSE was not used as a secondary

endpoint, as its sensitivity to change in the population of this 3-month trial was considered to be questionable.

By separate confirmatory analysis of the primary efficacy criteria at each independent assessment level (CGI-C and BGP subscore 'care dependence'), memantine showed statistically significant improvement in comparison to placebo. ITT and TPP analysis yielded very similar results. The congruence of treatment effects on independent assessment levels can be considered as an indicator of therapeutical relevance of the changes measured (Bundesgesundheitsamt, 1991). An important question arising in trials with anti-dementia drugs is whether improvements in cognitive and social behaviour, although statistically significant, are 'clinically meaningful'. Conclusions with regard to functional dimensions should be based on more differentiated evaluations and require further steps of therapy response definitions (Weyer, 1992). Herrmann and Schärer (1988) postulate an amount of individual improvement of more than 15%, a frequency of responders in the active treatment group of more than 50% and a difference in responder rates of at least 15% between the two treatment groups for the statement that a clinically meaningful therapeutic effect has been reached. As shown in Table 7, these criteria are fulfilled by memantine in this trial. According to the proposals of the Clinical Research Working Group (1990) and the Committee for Proprietary Medicinal Products (CPMP) (1997), the cumulative estimation of coincidence of response is a stricter approach of responder definition than the separate counting of therapy responders in single variables. As shown in Table 7, a high coincidence rate was found in both groups (61.3% coincidence of response in the memantine group and 47.4% coincidence of non-response in the placebo group on the two independent levels). In addition, there are statistically significant differences between the treatment groups on the single response levels for both variables. The results confirm the hypothesis that memantine treatment significantly improves functional capacities in severely demented patients and that this improvement may be considered clinically relevant according to the various criteria mentioned above. This equally holds true for Alzheimer's disease patients and patients with dementia of vascular or mixed type etiology.

The divergent response in both groups consists of a remarkable amount of positive response rated by the physician (CGI-C) which was not confirmed by the nursing staff (BGP). This divergence of approx. 20% in response rating cannot be explained by the step size of the two scales, since the nurse-rated BGP subscore care-dependence ranges from 0 to 46. It is more likely that the nursing staff, due to the close daily contact with the patient, takes more and also other observations into account. Conversely, nursing culture may have developed, where, for example, attitudes develop in particular wards resulting in an inability to see changes. On the other hand 'best behaviour effects' in the presence of a physician are possible. These considerations underline some of the fundamental methodological problems of trials in severe dementia.

In the placebo group, the general response rate observed in each of the efficacy variables is higher than described in trials performed at milder stages of dementia (Herrmann and Schärer, 1988). In advanced stages of dementia with a severe decline of cognitive functions, only a small bias of subjective anticipation of drug effects (the usual placebo effect) may be expected. The relatively high response rate observed in the placebo group of this trial shows that enhanced care-giving may result in a symptomatic improvement even in severely demented patients. The difference in response rates of the memantine group and the placebo group ($\Delta = 22\%$ coincident responders) reflects the additional therapeutic effect size of memantine.

Results of van de Kam and Hoeksma (1989) have shown that a global estimation of nursing staff's workload by BGP subscores is possible. Pearson correlation coefficients between time for basic care (mainly ADL care, representing 58% of total nursing time) and the BGP subscales are high: 'care dependence' ($R = 0.81$), physical disability ($R = 0.80$) and inactivity ($R = 0.81$). Therefore it can be expected that the statistically relevant reduction in 'care dependence' in 65.3% of memantine patients will also result in an evident time reduction in basic care. The results of the secondary efficacy variable, the D-scale items, corroborate the efficacy of memantine treatment observed in the primary efficacy variables.

The response profile reflected in Fig. 1 is pertinent for day-to-day care of severely demented patients. These promising results remain to be confirmed in larger clinical trials with longer duration and detailed assessment of the health-economic impact.

CONCLUSION

In this double-blind, placebo-controlled trial in care-dependent patients with severe dementia the benefit of memantine treatment (10 mg per day) could be shown on two independent assessment levels: the clinical global level (CGI-C) and the functional level (BGP subscore 'care-dependency'). The memantine effects observed are significant and are considered to be of clinical relevance using therapy responder definitions. Memantine treatment improved functioning, care dependence and behavioural symptoms of severely demented patients over a treatment period of 12 weeks. Memantine was well tolerated.

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