

Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial

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Abstract

Objectives To assess the effects of rivastigmine on the core domains of Alzheimer's disease.

Design Prospective, randomised, multicentre, double blind, placebo controlled, parallel group trial. Patients received either placebo, 1-4 mg/day (lower dose) rivastigmine, or 6-12 mg/day (higher dose) rivastigmine. Doses were increased in one of two fixed dose ranges (1-4 mg/day or 6-12 mg/day) over the first 12 weeks with a subsequent assessment period of 14 weeks.

Setting 45 centres in Europe and North America.

Participants 725 patients with mild to moderately severe probable Alzheimer's disease diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

Outcome measures Cognitive subscale of the Alzheimer's disease assessment scale, rating on the clinician interview based impression of change incorporating caregiver information scale, and the progressive deterioration scale.

Results At the end of the study cognitive function had deteriorated among those in the placebo group. Scores on the Alzheimer's disease assessment scale improved in patients in the higher dose group when compared with patients taking placebo ($P < 0.05$). Significantly more patients in the higher dose group had improved by 4 points or more than had improved in the placebo group (24% (57/242) *v* 16% (39/238)). Global function as rated by the clinician interview scale had significantly improved among those in the higher dose group compared with those taking placebo ($P < 0.001$), and significantly more patients in the higher dose group showed improvement than did in the placebo group (37% (80/219) *v* 20% (46/230)). Mean scores on the progressive deterioration scale improved from baseline in patients in the higher dose group but fell in the placebo group. Adverse events were predominantly gastrointestinal, of mild to moderate severity, transient, and occurred mainly during escalation of the dose. 23% (55/242) of those in the higher dose group, 7% (18/242) of those in the lower dose group, and 7% (16/239) of those in the placebo group discontinued treatment because of adverse events.

Conclusions Rivastigmine is well tolerated and effective. It improves cognition, participation in activities of daily living, and global evaluation ratings in patients with mild to moderately severe Alzheimer's

disease. This is the first treatment to show compelling evidence of efficacy in a predominantly European population.

Introduction

One of the most successful treatments for Alzheimer's disease has been the use of acetylcholinesterase inhibitors to enhance surviving cholinergic neurotransmission by inhibiting the breakdown of released acetylcholine. The first of these drugs approved for treating Alzheimer's disease, tacrine, is effective but can cause an increase in liver enzyme concentrations; in some countries, such as in the United Kingdom, this has prevented it from being licensed.¹⁻³ More recently, a second acetylcholinesterase inhibitor, donepezil (a piperidine derivative) has become available.^{4,5} Clinical trials have reported benefits on cognition and global evaluations.^{4,5} Rivastigmine is a novel, "pseudo-irreversible," brain selective inhibitor of acetylcholinesterases, the metabolism of which is almost totally independent of the hepatic cytochrome P450 system.⁶⁻⁸

The aim of this study was to evaluate the safety and efficacy of two doses of rivastigmine (1-4 mg/day and 6-12 mg/day) compared with a placebo over 26 weeks in patients with probable Alzheimer's disease. The study was carried out predominantly in European centres using a design similar to that employed in a parallel study in North America⁹ as part of a global evaluation programme (Alzheimer's disease treatment with ENA-713)¹⁰ This programme is the largest programme of clinical trials conducted to date for treatment for dementia; it consists of four trials with over 3300 patients at 111 centres in 10 countries.

Participants and methods

Patients

To be enrolled in the study patients had to be 50-85 years of age and not able to bear children (older or younger patients could enter the study with the approval of the medical expert (MG or AC-S)). All patients met criteria for Alzheimer's type dementia as described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition¹¹ and criteria for probable Alzheimer's disease according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.¹² Participants also had to have scores of 10-26 on the mini-mental state examination.¹³ Most patients were recruited from the community either through their general practitioners or directly, and each patient had a responsible caregiver and, along with their caregiver, provided

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A list of the Exelon investigators and members of the international safety monitoring board can be found on the BMJ's website

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written informed consent. Patients with concomitant diseases such as hypertension, non-insulin dependent diabetes, and arthritis were included. Only those with severe and unstable cardiac disease, severe obstructive pulmonary disease, or other life threatening conditions (such as rapidly progressing malignancies) were excluded. Patients taking drugs for coexistent diseases were included except for those taking anticholinergic drugs, health food supplements containing acetylcholine precursors, putative memory enhancers, insulin, and psychotropic drugs (the use of small doses of short acting benzodiazepines, chloral hydrate, or haloperidol was allowed). The trial procedures were in accord with the ethical standards of the institutional committees on human experimentation and with the Helsinki Declaration. The study was overseen by an independent international safety monitoring board. (A list of members of the board appears on the *BMJ's* website.)

Design

The 26 week study, conducted at 45 centres in Europe (in Austria, France, Germany, and Switzerland) and in North America, utilised a randomised, double blind, placebo controlled, parallel group design. Patients were randomly allocated either to placebo or 1-4 mg/day rivastigmine (lower dose) or 6-12 mg/day (higher dose) according to a computer generated randomisation code at Novartis Pharma (Basle, Switzerland). To maintain blinding capsules containing rivastigmine and placebo were identical and the number taken was the same at each dose in all groups. Dosages were increased weekly in steps of up to 1.5 mg/day during weeks 1-12 (dose escalation phase) and had to be within the target range by week 7. Decreases in doses were not permitted during this phase. However, if adverse events occurred a dose could be omitted, maintained without increase for two consecutive weeks, or antiemetic drugs could be given. During weeks 13-26 (maintenance) doses could be increased or decreased within the assigned range with the aim of administering the highest dose that was well tolerated.

Efficacy measures fulfilled the US Food and Drug Administration's dual efficacy requirements for clinical trials for Alzheimer's disease—that is, improvement on a performance based cognitive instrument and demonstration that the improvement was clinically meaningful.¹⁴ Efficacy was assessed on the cognitive subscale of the Alzheimer's disease assessment scale,¹⁵ the clinician interview based impression of change

incorporating caregiver information,¹⁶ and the progressive deterioration scale.¹⁷ Efficacy evaluations were performed at baseline and weeks 12, 18, and 26 or at early withdrawal from the trial. Table 1 summarises the instruments used, symptoms and domains measured, the source of information, the range of scores, and their interpretation.

The mini-mental state examination¹³ and the global deterioration scale¹⁸ were used as staging measures at baseline and week 26.

Safety evaluations included physical examinations, electrocardiography, monitoring vital signs, and laboratory testing. Adverse events were coded using the Sandoz medical technology thesaurus, which is based on a WHO document. Three central laboratories (in Europe, the United States, and Canada) performed all clinical laboratory evaluations, and one cardiologist at a central analysis centre read all electrocardiograms.

Statistical methods

The study sample population of about 200 in each group was planned to enable achievement of 90% power with $\alpha=0.05$ for detecting at least a 3.0 point improvement on the Alzheimer's disease assessment scale and an increase from 15-30% among patients scoring <4 on the clinician impression of change scale.

Patients were classed for efficacy analyses as: classical intention to treat, traditional last observation carried forward (randomised patients with at least one evaluation while being treated), and observed cases (randomised patients with an evaluation made while on study drug at designated assessment times). Comparisons with placebo were two tailed with the critical level set at $P<0.05$. Analyses of efficacy utilised the clinician impression of change scale with analysis of variance and two tailed pairwise Student's *t* tests using the pooled error term from the analysis of variance (sas type III analysis); the Alzheimer's assessment scale and the progressive deterioration scale with analysis of covariance and variance and two tailed pairwise Student's *t* tests using the pooled error term from the analysis of covariance and variance (sas type III analysis); the Alzheimer's assessment scale, the clinician impression of change scale and the progressive deterioration scale (categorical analyses) with Mantel-Haenszel blocking for centre. Safety analyses used an analysis of variance for vital signs, laboratory data, and electrocardiograms, and Fisher's exact test for the occurrence of abnormalities on physical examina-

Table 1 Instruments used to evaluate the efficacy of rivastigmine in treating Alzheimer's disease

| Instrument | Symptoms or domains assessed | Source of information | Range of scale and interpretation |
|--|--|--|---|
| Alzheimer's disease assessment scale (cognitive subscale) | Cognition (memory, language, orientation, praxis) | Patient | 0-70 points 0=no errors (rarely achieved, even in general population) 70=severe impairment |
| Clinician interview based impression of change scale (incorporating caregiver information) | Global assessment of behaviour, general psychopathology, cognition, and activities of daily living | Patient and caregiver during interview with clinician* | 1-7 points 1, 2, 3=marked, moderate, or minimal improvement 4=no change 5, 6, 7=minimal, moderate, or marked deterioration |
| Progressive deterioration scale | Activities of daily living (dressing and eating independently, social interaction, participation in housework and hobbies, awareness of time, handling of financial matters) | Caregiver | 29 items Scores range from 0 to 100 |

*Clinicians had no access to data on efficacy or safety.

tions, electrocardiograms, vital signs, laboratory tests, and adverse events.

Results

The randomisation of patients and their progress through the study is summarised in figure 1. A total of 831 patients were recruited; 106 of these were excluded. Altogether 243 patients were randomly allocated to higher dose treatment, 243 to lower dose, and 239 to placebo. Demographic variables and disease characteristics at baseline were comparable across groups but there were more females (59% (428/725)) than males (41% (297/725)). Mean age was 72 years (range 45-95 years), and most patients (97% (703/725)) were white. The mean duration of dementia was 39 months; 41% (298/725) of patients had mild disease, 57% (411/725) moderate, and 2% (16/725) had severe disease.¹⁸ The mean scores at baseline on the Alzheimer's disease assessment scale and the progressive deterioration scale for the three groups are shown in table 2. The mean score on the mini-mental state examination was 19.9 (range 10-29).

About 80% of patients (579/725) reported prior or current medical conditions, or both. These were most commonly cardiovascular. About 81% (590/725) were taking concomitant drug treatment at baseline. The mean number of medical conditions per patient was 2.5 and the mean number of concomitant drugs being taken per patient was 4.0. The most common drugs—that is, taken by >10% in each group—included anti-infectives and drugs for cardiovascular, gastrointestinal, respiratory, musculoskeletal, blood, and nervous system disorders.

By the end of the study the mean dose of rivastigmine was 10.4 (SD 2.13) mg/day in the higher dose group and 3.7 (SD 0.59) mg/day in the lower dose group. Of the patients who were taking rivastigmine until the end of the study, 64% (107/166) in the higher dose group and 90% (190/210) in the lower dose group reached the maximum prescribed dose.

Table 3 summarises the effects of rivastigmine on all measures of efficacy.

Cognitive subscale of the Alzheimer's disease assessment scale

Cognitive function worsened progressively in patients taking placebo. The mean deterioration in the cognitive subscale was 1.41 points over 26 weeks among observed cases (fig 2). The mean score on the subscale improved among patients in the higher dose group (mean improvement 1.17 points). Differences between the two groups in the mean change from baseline scores were statistically significant at weeks 12, 18, and 26 for all three analyses. Of the patients completing the study 55% (86/157) of those in the higher dose group improved from baseline measurements compared with 45% (93/205) of those treated with placebo (analysis of observed cases). The proportion of patients with a clinically meaningful improvement in their scores (defined as a change of four points or more from baseline) at the end of the study was significantly greater among patients receiving higher dose rivastigmine than among those taking placebo (24% (57/242) higher dose group *v* 16% (39/238) placebo in intention to treat analysis; 27% (53/199) higher dose group *v* 18% (40/225) last observation

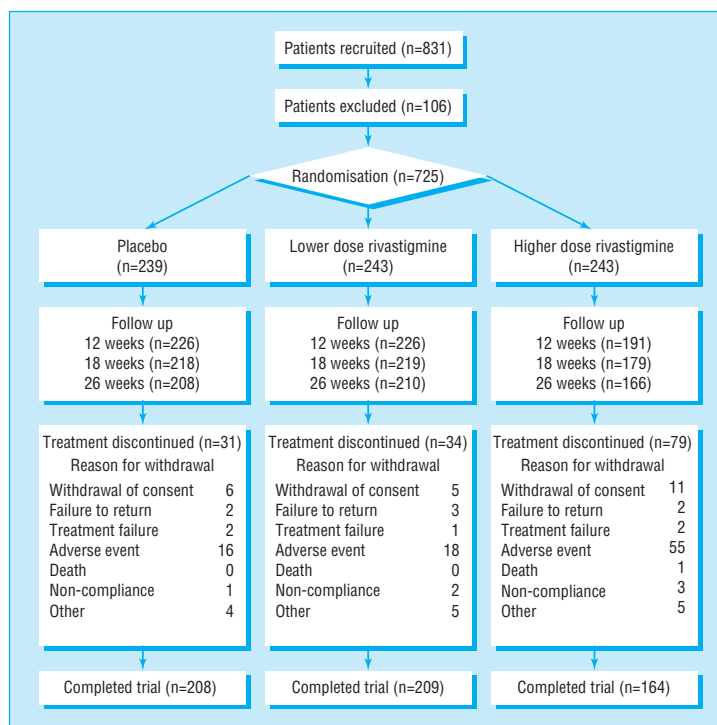


Fig 1 Outcome of allocation to treatment and reasons for withdrawal from the study

Table 2 Mean (range) baseline scores analysed on an intention to treat basis

| Instrument | Rivastigmine groups | | |
|---|---------------------|--------------------|------------------|
| | Higher dose (n=243) | Lower dose (n=243) | Placebo (n=243) |
| Alzheimer's disease assessment scale (cognitive subscale) | 23.57 (5.7-58.0) | 23.87 (4-60.7) | 23.29 (3.3-57.8) |
| Progressive deterioration scale | 55.22 (9.5-94.6) | 53.8 (9.9-94) | 54.1 (7.1-93.5) |

carried forward; and 29% (45/157) higher dose group *v* 19% (38/205) observed cases analysis ($P < 0.05$)).

Clinician interview based impression of change

At week 26 patients treated with placebo had deteriorated (mean rating 4.34) (table 4). Patients in the higher dose rivastigmine group had improved (mean rating 3.93). The difference between the two groups at week 26 was statistically significant for all three efficacy analyses. At week 26 significantly more patients in both rivastigmine groups had ratings of marked, moderate, or minimal improvement on this scale when compared with those taking placebo (20% (46/230) placebo group *v* 30% (69/233) lower dose group ($P < 0.05$) and 37% (80/219) higher dose group ($P < 0.001$) in the intention to treat analysis; 22% (49/226) placebo group *v* 32% (71/224) lower dose group ($P < 0.01$) and 40% (78/193) higher dose group ($P < 0.001$) in the last observation carried forward; 22% (44/197) placebo group *v* 31% (62/198) lower dose group ($P < 0.05$) and 41% (63/155) higher dose group ($P < 0.001$) in the observed cases analysis).

Progressive deterioration scale

At week 26 the difference in mean change from baseline in scores on the progressive deterioration scale between patients receiving placebo and those receiving higher dose rivastigmine was statistically significant in the analysis of the last observation carried forward ($P < 0.05$) (fig 3). Of the 581 patients completing the

Table 3 Mean (95% confidence interval) change from baseline on measures of efficacy of rivastigmine at week 26

| Instrument | Treatment group and analysis | | | | | | | | |
|--|------------------------------|---|-------------------------|-----------------------------|---|---------------------------|-----------------------------|---|---------------------------|
| | Higher dose rivastigmine | | | Lower dose rivastigmine | | | Placebo | | |
| | Intention to treat analysis | Last observation carried forward analysis | Observed cases analysis | Intention to treat analysis | Last observation carried forward analysis | Observed cases analysis | Intention to treat analysis | Last observation carried forward analysis | Observed cases analysis |
| Alzheimer's disease assessment scale (cognitive subscale) | 0.26 (-0.66 to 1.06) | 0.83 (-0.19 to 1.79) | 1.17 (-0.07 to 2.27) | -1.37 (-2.27 to -0.53) | -1.24 (-2.23 to -0.37) | -1.24 (-2.31 to -0.29) | -1.34 (-2.19 to -0.41) | -1.45 (-2.33 to -0.47) | -1.41 (-2.43 to -0.37) |
| P value v placebo | <0.1 | <0.001 | <0.001 | >0.05 | >0.05 | >0.05 | | | |
| No (%) patients with ≥4 point improvement | 57/242 (24) | 53/199 (27) | 45/157 (29) | 36/242 (15) | 36/226 (16) | 34/202 (17) | 39/238 (16) | 40/225 (18) | 38/205 (19) |
| P value v placebo | <0.1 | <0.05 | <0.05 | >0.05 | >0.05 | >0.05 | | | |
| Clinician interview based impression of change scale | 3.91 (3.71 to 4.09) | 3.88 (3.69 to 4.11) | 3.93 (3.67 to 4.13) | 4.24 (4.02 to 4.38) | 4.17 (4.0 to 4.4) | 4.20 (3.99 to 4.41) | 4.38 (4.22 to 4.58) | 4.32 (4.1 to 4.5) | 4.34 (4.09 to 4.51) |
| P value v placebo | <0.001 | <0.001 | <0.05 | >0.05 | >0.05 | >0.05 | | | |
| No (%) patients with improvement (scores 1, 2 or 3) | 80/219 (37) | 78/193 (40) | 63/155 (41) | 69/233 (30) | 71/224 (32) | 62/198 (31) | 46/230 (20) | 44/220 (22) | 44/197 (22) |
| P value v placebo | <0.001 | <0.001 | <0.001 | <0.05 | <0.01 | <0.05 | | | |
| Progressive deterioration scale | 0.05 (-1.57 to 1.77) | 0.5 (-1.32 to 2.52) | 1.3 (-0.95 to 3.55) | -3.37 (-4.99 to -1.61) | -3.31 (-5.1 to -1.5) | -2.9 (-4.83 to -0.97) | -2.18 (-3.91 to -0.49) | -2.23 (-4.02 to -0.38) | -1.9 (-3.84 to 0.04) |
| P value v placebo | <0.1 | <0.05 | <0.04 | >0.05 | >0.05 | | | | |
| No (%) patients with ≥10% improvement | 70/241 (29) | 66/198 (33) | NP | 45/241 (19) | 45/225 (20) | NP | 45/237 (19) | 45/223 (20) | NP |
| P value v placebo | <0.01 | <0.01 | | >0.05 | >0.05 | | | | |
| Global deterioration scale | -0.06 (-0.2 to 0.0) | -0.03 (-0.13 to 0.13) | NP | -0.22 (-0.3 to -0.1) | -0.2 (-0.31 to -0.09) | NP | -0.26 (-0.4 to -0.2) | -0.24 (-0.31 to -0.09) | NP |
| P value v placebo | <0.05 | <0.05 | | | | | | | |
| Mini-mental state examination | 0.21 (-0.24 to 0.64) | 0.34 (-0.25 to 0.85) | NP | -0.62 (-1.05 to -0.15) | -0.60 (-1.08 to -0.12) | NP | -0.47 (-0.96 to -0.04) | -0.54 (-0.99 to -0.01) | NP |
| P value v placebo | <0.05 | <0.05 | | | | | | | |

NP=analysis not planned.

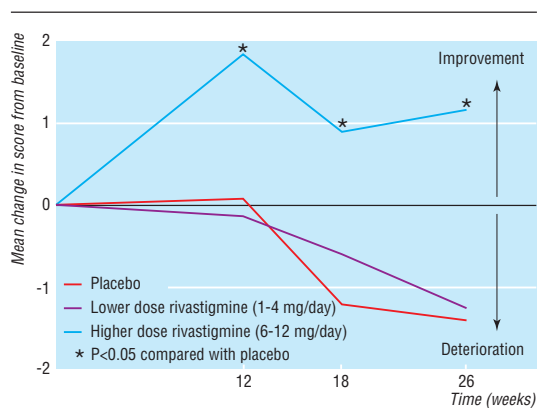


Fig 2 Mean change in baseline scores on cognitive subscale of Alzheimer's disease assessment scale, observed cases analysis. P<0.05 compared with placebo (two tailed pairwise Student's *t* tests using pooled error term from analysis of covariance and analysis of variance)

Table 4 Mean scores (95% confidence intervals) on the clinician interview based impression of change scale (incorporating caregiver information) at weeks 12, 18, and 26 among the observed cases population

| Week | Rivastigmine groups | | |
|------|---------------------|---------------------|----------------------|
| | Placebo | Lower dose | Higher dose |
| 12 | 3.96 (3.83 to 4.17) | 4.01 (3.83 to 4.17) | 3.88 (3.72 to 4.08) |
| 18 | 4.09 (3.92 to 4.28) | 4.06 (3.92 to 4.28) | 3.85 (3.7 to 4.1) |
| 26 | 4.34 (4.09 to 4.51) | 4.20 (3.99 to 4.41) | 3.93* (3.67 to 4.13) |

*P<0.05 compared with placebo (pairwise Student's *t* tests using pooled error terms from analysis of variance).

study, a significant difference in those showing any improvement in these scores was observed for those taking higher dose rivastigmine compared with those taking placebo (49% (98/198) v 39% (88/223) respectively; P=0.04 in analysis of the last observation carried forward). Significantly more patients in the higher dose group improved by at least 10% than did in the placebo group both in the intention to treat analysis (29% (70/241) v 19% (45/237), P<0.01) and the analysis of the last observation carried forward (33% (66/198) v 20% (45/223), P<0.01).

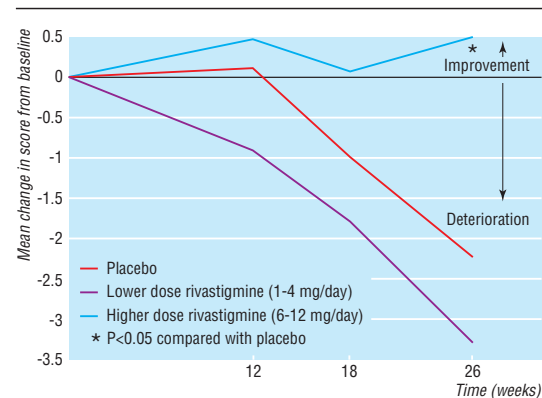


Fig 3 Mean change in baseline scores on the progressive deterioration scale, analysis of last observation carried forward. P<0.05 compared with placebo (two tailed pairwise Student's *t* tests using pooled error term from analysis of covariance and analysis of variance)

Global deterioration scale and mini-mental state examination

At week 26 patients who had received rivastigmine 6-12 mg/day had a significantly better response than those in the placebo group in the mean change from baseline scores on the mini-mental state examination and the global deterioration scale. Patients receiving placebo deteriorated by 0.47 points from baseline on the mini-mental state and those receiving rivastigmine 6-12 mg/day improved by 0.21 points over baseline using the intention to treat analysis. Significantly less deterioration occurred on the global deterioration scale among patients taking 6-12 mg/day rivastigmine compared with those taking placebo.

Safety

Of the 725 patients initially randomly allocated 581 (80%) completed treatment. The proportion who discontinued treatment for any reason was significantly higher in the higher dose group than in the lower dose or placebo groups (33% (79/243) *v* 14% (34/243) and 13% (31/239), respectively) as was the proportion who discontinued because of adverse events (23% (55/242) *v* 7% (18/242) and 7% (16/239), respectively). Most of the discontinuations related to adverse events occurred during dose escalation (69% (38/55) in the higher dose group).

The safety of the drug could be evaluated in 242 patients in each of the rivastigmine treatment groups and in 239 patients in the placebo group. A summary of the adverse events that occurred at least 5% more often with rivastigmine than with placebo or that occurred with an incidence significantly different from placebo is given in table 5. Overall, significantly more patients reported at least one treatment related adverse event in the higher dose group (91% (220/242)) than in the lower dose (71% (172/242)) or placebo (72% (172/239)) groups.

Adverse events related to treatment were generally not severe and occurred most frequently during the dose escalation phase. The adverse events most commonly reported with rivastigmine were cholinergic: nausea, vomiting, diarrhoea, abdominal pain, and anorexia. Dizziness, headache, fatigue, and malaise also occurred more frequently with higher doses of rivastigmine than with placebo. Apart from the incidence of nausea, there was no significant difference in the incidence of adverse events between the lower dose group and the group treated with placebo. The frequency of serious adverse events was similar in all groups (about 18%).

There were no obvious overall trends or clinically relevant differences between treatment groups in vital signs (mean systolic and diastolic blood pressure, abnormalities of blood pressure, heart rate, and body temperature), physical examination, haematological or biochemical analyses (including hepatic enzyme levels), electrocardiographic measurement, or urine analysis. Mean body weight increased in the placebo group (mean change +0.72 kg at week 26) but decreased in the rivastigmine groups (mean change -1.39 kg in the higher dose group and -0.13 kg in the lower dose). The difference in the mean change in body weight between the placebo group and the higher dose rivastigmine group was statistically significant (Fisher's exact test $P < 0.05$). In the higher dose group 24% of patients (55/

Table 5 Number (percentage) of adverse effects occurring at least 5% more often in patients taking rivastigmine than in patients taking placebo or occurring with an incidence significantly different from placebo

| Adverse effect | Rivastigmine groups | | Placebo (n=239) |
|----------------|----------------------|--------------------|-----------------|
| | Higher dose* (n=242) | Lower dose (n=242) | |
| Nausea | 121 (50) | 41 (17)* | 23 (10) |
| Vomiting | 82 (34) | 19 (8) | 14 (6) |
| Dizziness | 48 (20) | 25 (10) | 17 (7) |
| Headache | 45 (19) | 16 (7) | 18 (8) |
| Diarrhoea | 40 (17) | 23 (10) | 21 (9) |
| Anorexia | 34 (14) | 8 (3) | 4 (2) |
| Abdominal pain | 29 (12) | 11 (5) | 7 (3) |
| Fatigue | 23 (10) | 5 (2) | 6 (3) |
| Malaise | 23 (10) | 3 (1) | 5 (2) |

* $P < 0.05$ compared with placebo (pairwise comparison based on Fisher's exact test).

234) lost >7% of body weight compared with 9% of patients (21/236) in the lower dose group and 7% (16/236) in the placebo group.

Discussion

This study provides evidence of the efficacy of rivastigmine in alleviating the core cognitive and functional symptoms of patients with mild to moderately severe Alzheimer's disease over 6 months. Rivastigmine was effective on each of the measures of efficacy applied, reflecting improvements in cognition as rated by psychometricians, global functioning as rated by an independent clinician, and activities of daily living as rated by a caregiver. The effects of rivastigmine were dose dependent.

Cognitive and global assessments

Compared with the 55% of patients taking placebo who experienced a decline in cognitive function during the study, patients treated with 6-12 mg/day of rivastigmine improved. Cognitive function in patients with Alzheimer's disease who are not treated can be expected to deteriorate. Estimates of the rate of decline vary from as little as 1.28 points on the cognitive subscale of the Alzheimer's disease assessment scale over 24 weeks¹⁹ to as much as 9 points over 1 year.²⁰ Other estimates of the average rate of decline are 5.2 points on the cognitive subscale over 1 year,¹⁵ 7 points over 1 year,²¹ and about 5 points over 5 to 9 months.²² The stabilisation of cognitive decline seen over 6 months in this study in 55% of patients taking 6-12 mg/day of rivastigmine is therefore relevant to clinical practice.

Mean ratings on the clinician interview based impression of change were consistently and significantly superior for the group taking 6-12 mg/day of rivastigmine when compared with placebo, and significantly more patients treated with rivastigmine (in both dosage groups) experienced global improvement than did those taking the placebo.

Effects on activities of daily living

Perhaps the most relevant effects of rivastigmine observed in this study are those on activities of daily living. Poor performance of these activities is correlated with admission to long term care facilities.²³⁻²⁴ Poor performance is also recognised as an important determining factor of the use of support services by caregivers.²⁵ The improvements in these activities shown here are the first to be reported in a prospective analysis of a global clinical trial. More than

Key messages

- In a 6 month trial rivastigmine was effective in treating the core cognitive and functional symptoms of patients with mild to moderate Alzheimer's disease
- Rivastigmine at doses of 6-12 mg/day produces clinically relevant and statistically significant improvements in cognitive and global assessments, and in activities of daily living
- The effects of rivastigmine are dose dependent
- Rivastigmine was well tolerated in this population of elderly patients

one third of patients treated with 6-12 mg/day of rivastigmine showed more than a 10% improvement.

Tolerability and safety

Adverse events leading to the discontinuation of treatment were seen in 27% of patients taking 6-12 mg/day of rivastigmine. The majority of these occurred during the dose titration phase, which used a forced dose escalation procedure and introduced an artificial element into the trial design. Outside a clinical trial it is likely that the dose escalation phase would be more individualised and tolerance would improve.

The most common adverse events were related to effects on acetylcholinesterase and were gastrointestinal. Most were mild and short lived and were observed after increases in doses. There was no evidence that rivastigmine compromised cardiovascular function in these elderly patients, many of whom had concomitant cardiovascular disease. The overall incidence of serious adverse events was similar in all three groups. Despite the age of the patients, the high incidence of coexisting illnesses, and the use of concomitant drug treatment, rivastigmine produced no clinically relevant changes in laboratory tests, electrocardiograms, on physical examination, or in vital signs except for a small, statistically significant decrease in mean body weight at higher doses.

This study provides clear evidence that rivastigmine is effective in the treatment of patients with probable Alzheimer's disease and produces clinical benefits in a significant percentage of patients on the three domains measured. Improvements were still evident at the end of the 6 month study, although further data are required to determine the persistence of the results. Adverse events were generally mild or moderate and occurred early in treatment. The positive outcome of this study occurred despite the variability in clinical practice between countries and the difficulties presented by differences in language and culture. The results are qualitatively similar to those of a study of similar design carried out in the United States⁹ and add further evidence that rivastigmine offers clinically meaningful benefits to patients with Alzheimer's disease.

Professor Agid wishes to acknowledge the special contribution made to the study by his colleague Professor Bruno Dubois.

Contributors: Data collection and comments on study design were made by the International Exelon Investigators. (A list of members appears on the *BMJ's* website.) MR was the principal writer and participated in designing and executing the study, and helped with data collection and analysis. SG participated in designing and executing the study, collecting and analysing data, and contributed to writing the paper. YA was the principal investigator and contributed to designing the protocol, collecting and analysing data, and writing the paper. PD-B par-

ticipated in designing and executing the study, collecting and analysing data, and writing the paper. HBS participated in designing and executing the study, collecting and analysing data, and writing the paper. AC-S and MG were responsible for managing data collection, monitoring data, and analysing and interpreting data for Europe. RH was responsible for managing the monitoring of data and analysing and interpreting data in North America. RA acted as overall adviser on the content of the paper and is the guarantor. Quintiles Transnational was responsible for data collection in the United States. John Carpenter and Stephen Jones of Gardiner-Caldwell Communications, Macclesfield, UK, were contributing editors.

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Commentary: Another piece of the Alzheimer's jigsaw

Tony Bayer

Rösler et al have published the results of the first large trial of an acetylcholinesterase inhibitor used in a mainly European population of patients with Alzheimer's disease. It provides further evidence of modest cognitive and global benefits of acetylcholinesterase inhibitor treatment and also shows statistically significant functional benefits, with a greater proportion of patients on higher dose rivastigmine (6-12 mg/day) compared with placebo improving their total score on the progressive deterioration scale. This scale is completed by carers and was specifically developed for use with patients with Alzheimer's disease. It has been shown to be a valid and reliable measure of drug effects in clinical trials. However, the presentation—a visual analogue scale—can be problematic, and it is not suitable for use in everyday clinical practice. The absence of measures of neuropsychiatric outcome and the burden on carers is unfortunate, but in the past the choice of outcomes in clinical drug trials in dementia was governed by requirements of regulatory authorities rather than aims of measuring the real impact of the illness on the lives of patients and their families. The need for clinically relevant outcome measures should now be better appreciated.

The authors emphasise that their patient population was not highly selected. Nevertheless, all had been carefully diagnosed at specialist centres using standardised clinical criteria, had symptoms of mild to moderate severity, and only those with an available caregiver and who were not taking other central nerv-

ous system drug treatment were included. Such patients are not typical of those presenting to old age psychiatrists and geriatricians.

One third of the patients on the higher dose of rivastigmine discontinued treatment, presumably despite close monitoring; the authors attribute this in part to inappropriate forced dose escalation. How the trial results might translate to everyday clinical practice is therefore uncertain.

Response to treatment seemed to be variable, with substantial improvement in a few patients and no obvious benefit in many. Averaging the change in test scores, especially with selective presentation of observed cases or an intention to treat analysis, can easily mislead. Interpretation of the data would have been helped by presenting the "number needed to treat" to obtain clinically meaningful improvements in outcomes. Rösler et al's paper also tells us nothing about the long term impact of acetylcholinesterase inhibitor treatment on the considerable human and economic costs of Alzheimer's disease.

There are many pieces of the Alzheimer's jigsaw that are still missing. Future research efforts need to focus on identifying predictors and better measures of response, timing of treatment and optimum dose regimens, longer term follow up, and establishing how and when the use of acetylcholinesterase inhibitor drugs should be stopped.

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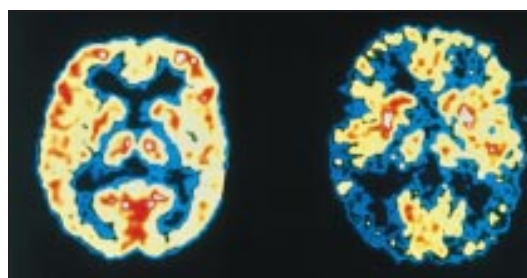
Science commentary: Rational drug design for Alzheimer's disease

The loss of cholinergic neurotransmitter activity was first identified in the 1970s at necropsy in brains removed from people with Alzheimer's disease, and it has since been confirmed in living patients by positron emission tomography (figure). These observations have led to the development of a number of acetylcholinesterase inhibitor drugs, which have been rationally designed to boost the apparent chemical deficiency in Alzheimer's disease (MR Farlow et al, *Neurology* 1998;51(suppl 1):36-44S).

Acetylcholinesterase inhibitors have been designed to stop the breakdown of acetylcholine in the brain. Unfortunately, these drugs are non-selective and thus the action of the enzyme is blocked in other parts of the body, causing an undesirable build up of the neurotransmitter at other sites. The gut is one of the more common sites where this happens, and this can lead to side effects such as increased motility and nausea. Most of the drugs in this family are reversible—that is, the action of the enzyme is only blocked while the drug is being taken.

The chief pathways of acetylcholine that are affected in Alzheimer's disease seem to be in the series

of nuclei that project from the forebrain nucleus up to the cerebral cortex and, more specifically, into the hippocampus, which is known to be involved with the function of memory. The aim is, therefore, to boost acetylcholine concentrations in the hippocampus.



Coloured positron emission tomography scans (horizontal sections) of the brain of a normal patient (left) and a patient with Alzheimer's disease (right). Red and yellow areas show high brain activity; blue and black areas show low activity. The scan from the patient with Alzheimer's disease shows that both function and blood flow in both sides of the brain are reduced. Acetylcholinesterase inhibitor drugs may boost the apparent chemical deficiency in Alzheimer's disease. The aim is to increase concentrations in the hippocampus, which is involved in memory

Science
commentary

To date, most trials of the effectiveness of acetylcholinesterase inhibitors in dementia have followed patients for a minimum of six months. But no one yet knows how quickly an alteration in acetylcholine concentrations might result in a measurable restoration of memory. And, to achieve optimal benefits, it may also prove necessary to offer a period of "retraining" to reorient the brain, in addition to improving the neurotransmitter concentrations.

It remains to be seen how well these drugs actually work in Alzheimer's disease. In future it may be shown that other types of dementia with less complex pathological processes may be more responsive. One example is the dementia associated with Lewy bodies in which the pathological process does not also include the presence of amyloid or tangles to the same extent as in Alzheimer's disease.

Abi Berger *Science editor, BMJ*

Patients' and doctors' attitudes to amount of information given after unintended injury during treatment: cross sectional, questionnaire survey

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Unintended injuries (adverse events) caused during treatment are much more common than previously believed.¹ Recent legal and disciplinary cases have shown that, although patients are increasingly dissatisfied with a perceived lack of openness in the medical profession, doctors are not legally obliged to provide an explanation after an adverse event.² Because of this, the General Medical Council has revised its guidance on good medical practice, stating that after an adverse event a full and honest explanation and an apology should be provided routinely.³ We surveyed patients' and doctors' attitudes to the provision of information to patients after a hypothetical adverse event in cataract surgery.

Information has occurred ($\chi^2 = 34.5$, 1 df, $P < 0.001$; odds ratio 7.4 (95% confidence interval 3.7 to 14.3)). The ophthalmologists who did not believe that patients should always be told replied that either the patient should never be told or that it depended on the circumstances. Two hundred (81%) patients, but only 16 (33%) ophthalmologists, believed that a patient should not only be informed of a complication but also be given detailed information on possible adverse outcomes ($\chi^2 = 47.1$, 1 df, $P < 0.001$; 8.7 (4.7 to 15.9)).

Comment

Our survey shows that after an adverse event patients expect more detailed information than doctors believe should be given. Doctors' reluctance to provide detailed information to patients after adverse events is often an attempt to protect the patient from potentially detrimental anxiety. However, doctors may also avoid telling patients because it is a time consuming, difficult, and unpleasant task and because they fear losing a patient's trust, being blamed, and perhaps sued. In addition, it has been suggested that the current medical culture, in which error is often automatically equated with professional incompetence or inadequacy, makes admission to either patients or colleagues difficult.⁴ Many studies show, however, that failure to provide information, an explanation, and an apology increases the risk of litigation and erodes the patient-doctor relationship.⁵ After an adverse event, patients want disclosure of the event, admission of responsibility, an explanation, an apology, and prevention of future similar errors; in some cases, they also want the offender to be punished and to obtain financial compensation.⁵

The practice of medicine can never be free of errors,⁴ and changes are required in the attitudes of both patients and the medical profession, with realistic expectations of the limitations of doctors and medicine and greater, blame free openness. In the light of the new regulations from the General Medical Council, failure to acknowledge an adverse event arising during treatment may now have serious professional consequences for a practitioner.

We thank Mr Jeremy Joseph for his advice.

Subjects, methods, and results

A specifically designed questionnaire (box) was used to survey all patients attending a consultant ophthalmologist's clinic during five weeks in 1998; 246 of 302 (81%) patients agreed to participate. All 48 ophthalmologists attending a regional meeting also participated. The questionnaire asked about the post-operative information that should be given routinely in a hypothetical situation in which a common intra-operative complication (posterior capsular rupture) occurred in cataract surgery, with an estimated 10% risk of an adverse effect on vision.

The attitudes of the patients differed substantially from those of the ophthalmologists: 226 (92%) patients, compared with only 29 (60%) ophthalmologists, believed that a patient should always be told if a compli-

Questionnaire

Please read the following story (which is typical but fictional):

Mrs Brown has an operation for cataract. During surgery, there is a complication. The lens capsule breaks and the surgeon has to make a bigger cut than planned, use stitches and put in a different style of lens implant. There is approximately a 1 in 10 chance of her vision being affected by these changes.

The next day, she sees well and is pleased.

Should Mrs Brown be told about the surgical problem? Yes / No

If yes, do we discuss the possible consequences? Yes / Only if she asks / No

Please comment on your decision overleaf.

What is your age? 25 and under / 26-60 years / over 60 years