Rivastigmine in Alzheimer’s disease: Cognitive function and quality of life

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Abstract: Alzheimer’s disease (AD) is a chronic neurodegenerative disorder characterized by a progressive loss of cognitive and functional abilities associated with various behavioral disturbances. Its impact on public health and society as a whole is devastating. Slowing of the cognitive impairment, and improvements in disease duration, self-sufficiency and behavioral disturbances represent the best outcomes of pharmacologic therapy. Cholinesterase inhibitors (ChE-I) have been shown to be effective in treating the cognitive, behavioral, and functional deficits of AD. Rivastigmine is a dual inhibitor of both acetylcholine esterase (AChE) and butyrylcholinesterase (BuChE), enzymes involved in the hydrolysis of acetylcholine. Although this drug has been shown to be beneficial in patients with AD, its benefits are limited and their long-term effectiveness has not been well demonstrated.

Keywords: Alzheimer’s disease, drugs, therapy

Introduction
Dementia of Alzheimer’s type (AD) (McKhann et al 1984) is a chronic neurodegenerative disorder. It is characterized by an insidious onset and a progressive loss of cognitive and functional abilities, associated with various degrees of behavioral disturbances, and progressively leads to total dependency.

AD is the most common form of dementia, accounting for 50%–60% of all cases. The prevalence of dementia is below 1% in individuals aged 60–64 years, but shows an almost exponential increase with age, so that in people aged 85 years or older the prevalence in the western world is between 24% and 33% (Ferri et al 2005). Representative data from developing countries are sparse, but about 60% of all patients with dementia are estimated to live in this part of the world. AD is very common and is thus a major public health problem. In 2001, more than 24 million people had dementia and, due to the probable increase in life expectancy (Ferri et al 2005), this number is expected to double every 20 years and reach 81 million in 2040.

Since AD has become a major health and economic burden to society, many efforts are being made to develop a therapeutic strategy to modify the natural history of this disease. Generally, AD has a mean duration of 6–10 years. The annual cognitive loss, measured with the Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-Cog) (Rosen et al 1984), is 8–10 points, and with the Mini Mental Status Examination (MMSE) (Folstein et al 1975), 2–4 points; the Clinical Rating and Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) (Schneider et al 1997) reports a 6-month decline of about 1.5%. Note that these scales are the ones most used in the assessment of cognitive disorders. Approximately 4–6 years elapse between AD patients’ total autonomy and total functional dependency. Behavioral disturbances are present in at least 90% of patients and, depending on environmental variables, with variable incidence at different stages, in different individuals and in the same patient at different times. Disease duration, leading to total dependency, can
stretch over many years and create unsatisfactory and poor quality of life, for patients, relatives and caregivers; therefore, the latter represents one of the most important outcomes for pharmacologic therapy.

Following the discovery of a substantial pre-synaptic cholinergic deficit in AD brains 25 years ago, a large body of experimental data has been gathered to examine the nature, extent, and clinical significance of this change. Several studies on AD have shown abnormalities of many neurotransmitter systems (particularly glutamatergic changes), the most prominent of which is severe damage of the cholinergic system with a selective loss of pre-synaptic cholinergic neurons projecting to cerebral cortex and hippocampus, leading to the so-called “cholinergic hypothesis”. Thus, some of the symptoms of AD are thought to be due to a cholinergic deficit, and this theory has led to several therapeutic attempts to restore cholinergic activity in the central nervous system (CNS). To date, the most successful approach involves the cholinesterase inhibitor (ChE-I), which increases the amount of acetycholine in the neuronal synaptic cleft by inhibiting the enzyme responsible for its degradation, thus improving neuronal transmission; the more recent molecules are selective, acting at the central level, minimizing side effects. It has also been shown that in the AD patient’s brain there is a loss of glutamatergic pyramidal neurons, while the number of glutamate receptors is maintained (in particular N-metil-D-aspartate [NMDA] receptor). Based on this evidence, the therapeutic use of glutamatergic-blocking molecules has been proposed.

Currently two classes of drugs, ChE-I and NMDA receptor antagonist, are recommended for the symptomatic treatment of AD, each targeting a different neurochemical component thought to underlie the condition. The cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are widely recommended for the treatment of mild to moderate AD (Davies and Maloney 1976; Doody et al 2001; Ballard 2002). In 2004, the first NMDA receptor antagonist (memantine) was approved for the treatment of moderate to severe AD. These drugs were initially used to improve memory and cognition; subsequently, they were also tested for use in improving global status and the capacity to remain independent in order to reduce the need for admission to residential/nursing care and to improve caregiver health-related quality of life (QoL).

The Health Technology Assessment (HTA) (Loveman et al 2006) Programme recently published a study to provide an updated review of the best quality evidence for the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine, and galantamine for mild to moderately severe AD. For mild to moderately severe AD, the results of the study suggested that all three treatments were beneficial when assessed using cognitive outcome measures. Global outcome measures were positive for donepezil and rivastigmine, but mixed for galantamine. Results for measures of functioning were mixed for donepezil and rivastigmine, but positive for galantamine. Behavior and mood measures were mixed for donepezil and galantamine, but showed no benefit for rivastigmine. For memantine, two published randomized controlled trials (RCTs) were included; in one of these trials the participants were already being treated with donepezil. The results suggest that memantine is beneficial when assessed using functional and global measurements. The effect of memantine on cognitive, behavioral, and mood outcomes is, however, less clear.

Moreover, the Cochrane Collaboration (Birks 2006) recently assessed the effects of donepezil, galantamine, and rivastigmine in people with mild, moderate, or severe dementia due to AD. The results of 10 randomized, double-blind, placebo-controlled trials demonstrate that treatment for 6 months with donepezil, galantamine, or rivastigmine at the recommended dose for people with AD produced improvements in cognitive function of, on average, 2.7 points (95% CI –3.0 to –2.3, p.0.00001), ie, in the mid range of the 70-point ADAS-Cog Scale. Study clinicians rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behavior. The effects were similar for patients with severe dementia, although there is very little evidence from only two trials.

These therapeutic indications and the guidelines for treatment (Davies and Maloney 1976; Ballard 2002) mainly derive from RCTs. Despite methodological doubts about the large clinical use of data derived from an experimental context, these indications are based on the only proven evidence of an effective use of pharmacologic therapy in dementia.

This review aims to explore the scientific evidence for the clinical use of rivastigmine for people suffering from mild to moderately severe AD. Potential benefits of rivastigmine will be demonstrated on measures of global functioning, cognition, function, behavior, and health-related QoL. To achieve this aim, a comprehensive assessment of cognitive and behavioral functions will be carried out using a set of standardized tests.

**Assessment tools used**

To determine the prognosis of an illness such as AD, in which there is a continuous neurodegenerative process, it is useful...
to assess how rapidly the disease is progressing clinically and how severely the patient is being affected. In the past, AD severity was most often defined by the degree of cognitive impairment and global functioning and by the presence of behavioral disturbances. Standardized rating scales are commonly used to obtain such information and to assess the disease progress. In this regard, instruments such as ADAS-Cog and MMSE are used to provide a measure of cognitive impairment. However, it has also been affirmed that the degree of functional impairment also reflects AD severity. The Global Deterioration Scale (GDS) (Reisberg et al 1997) was designed specifically to evaluate AD severity by measuring cognitive and functional performance. In addition, scores on an instrument such as the Progressive Deterioration Scale (PDS) (Dejong et al 1989) also provide an index of disease severity; they reflect the ability of the patient with AD to perform specific instrumental and basic activities of daily living, which become increasingly compromised as the disease progresses.

**Cognitive function**

ADAS-Cog is a primary instrument, specifically designed to assess cognitive functioning in AD, and proven to be valid and reliable. It assesses various cognitive abilities including attention, memory, orientation and language. The score range is 0–70, with higher scores indicating poorer functioning.

MMSE is in another scale for evaluating cognitive performance. It assesses many cognitive abilities: orientation, immediate recall, attention and calculation, delayed recall, and language. The score range is from 0 (severe impairment) to 30 (normal).

**Global assessment**

CIBIC-Plus provides a global rating of patients’ functioning in four areas: general, cognitive, behavioral and activities of daily living. The CIBIC-Plus is based on interviews with both patients and caregivers. The score range is on a scale of 1–7, with 1 showing marked improvement, 7 marked worsening and 4 no change.

GDS is a global rating of overall dementia severity. It was developed to assess primary degenerative dementia and to delineate disease stages. The stages are scored from 1 (no cognitive decline) to 7 (severe cognitive decline).

**Activities of daily living**

PDS is a disease-specific measure of changes in 29 items of the activities of daily living. It is a 100-point bipolar visual analog scale, based on caregiver input, that measures the ability of patients to perform various activities of differing complexity; a higher score represents better functional ability. The interview is conducted with the caregiver.

Instrumental Activities of Daily Living (IADL, also called Lawton’s scale) was developed by Lawton and Brody in 1969. It consists of a very useful questionnaire for evaluating the subject’s ability to perform daily tasks governed by cognitive functions (judgment, language, orientation, calculation, memory, planning). This scale focuses on complex activities important for independent living in the community. Activities include the ability to use the telephone, shop, prepare food, housekeep, and handle finances.

The Nurses’ Observation Scale for Geriatric Patients (NOSGER) (Spiegel et al 1991) is used to assess various cognitive functions and behavior related to activities of daily living (self-care, disturbing behavior, instrumental activities of daily living, memory, mood, and social behavior). The NOSGER questionnaire is completed by the next of kin or by the caregiver who has most contact with the patient.

**Cholinesterases and cholinergic hypothesis in Alzheimer’s disease**

Since Davies and Maloney (Bartus et al 1982) first proposed the “cholinergic hypothesis”, a large body of evidence has been gathered to support the view that impairment of cholinergic function is of central importance in the pathogenesis of AD (Whitehouse et al 1982; Katzman 1986; Gallagher et al 1995; Kasa et al 1997; O’Brian et al 2001). In patients with AD, cholinergic neuronal loss is particularly noticeable in the neocortex and hippocampus. These areas of the brain are associated with learning and memory, executive functioning, behavior and emotional responses (Cummings 2000). Building upon these studies, a number of therapeutic approaches have been developed with the aim of enhancing cholinergic function, the most successful of which has been the use of cholinesterase inhibitors (ChE-I).

Experimental data support an interaction between cholinergic deficits and the formation of amyloid plaques and neurofibrillary tangles. Further, in vitro modulation of the cholinergic system has a neuroprotective effect. Preliminary evidence supporting a neuroprotective effect of ChE-I derives from studies on human cells and rat brains and cells. In humans affected by AD, the muscarinic agonists modify the liquoral concentration of β-amyloid (Borroni et al 2001). In vitro studies demonstrate that acetylcholinesterase (ChE) has the capacity to stimulate β-amyloid aggregation and fibril formation.

With regard to cholinesterases, acetylcholinesterase (AChE) is located mainly in neurons and butyrylcholinesterase
(BuChE) in glial cells. BuChE action is more general and less understood than AChE activity, which is mainly devoted to hydrolyzing acetylcholine. BuChE activity is detected in all CNS areas receiving cholinergic innervation. Although it represents only 10% of AChE activity in the normal brain, with disease progression BuChE increases by 40%–90% in the AD brain and AChE simultaneously decreases its activity by up to 45%. AChE and BuChE are present in several molecular isoforms and in normal brain globular forms of four (G4) catalytic units they are the most common, followed by one (G1). In the AD brain, the globular form G1 becomes predominant as the disease progresses and the G4 level declines, and some data suggest that BuChE, rather than AChE, action may be particularly relevant in subjects with moderate-severe dementia (Tasker et al 2005).

ChE-I were initially used to improve memory and cognition. Subsequently, they were tested for their efficacy in other aspects of AD treatment: to improve functional level and patient’s and caregiver’s quality of life; and to modify behavioral and cognitive status in a clinically significant way (Davies and Maloney 1976; Doody et al 2001; Ballard 2002).

**Rivastigmine**

Rivastigmine tartrate is a carbamate pseudo irreversible inhibitor of AChE and BuChE, which selectively inhibits ChE-I in the CNS as demonstrated using cerebrospinal fluid ChE activity. The pharmacokinetic and pharmacodynamic characteristics of rivastigmine are presented in Table 1.

Rivastigmine is prepared in capsules and solutions for oral administration. In healthy adults it is adsorbed rapidly after oral administration; in AD patients no difference in absorption was found with age. Taking rivastigmine with food slows absorption and increases tolerability, because the adverse gastrointestinal effects are associated with high plasma levels. Rivastigmine binds to both the esterasic and ionic sites of AChE, preventing the enzyme from metabolizing ACh, but is dissociated much more slowly than AChE (“pseudoirreversible” action). Rivastigmine is metabolized by AChE and BuChE at the synapse. Its elimination, which is mostly renal, is complete approximately 24 hour after administration (Williams et al 2003). Relevant pharmacokinetic drug–drug interactions are unlikely because rivastigmine has low protein binding and is not metabolized via the hepatic CYP system, as are the ChE-I donepezil and galantamine. No clinically significant interactions with 22 classes of concomitant medications were found in pooled data from RCTs (Grossberg et al 2000). Adverse effects in trials are mainly cholinomimetic gastrointestinal symptoms, predominantly in the titration phase. These effects include nausea (17%–48%), vomiting (16%–27%) and diarrhea (11%–17%), minimized by increasing the dose slowly (every month) in clinical practice and taking with food. In clinical trials, the theoretical cholinomimetic risk of bradycardia, especially in elderly patients, was not demonstrated to have any significant effect on cardiac function. A large meta-analysis of 16 randomized controlled trials documented the tolerability of AChE inhibitors (Lancot et al 2003). While the withdrawal rate due to adverse events was greater in the AChE inhibitor group than in the placebo groups, the rate was 14% in rivastigmine recipients; the corresponding rate for overall frequency of adverse events was 12%. Direct comparative studies of donepezil and rivastigmine (Wilkinson et al 2002) reported tolerability findings similar to those of the above meta-analysis; the double blind, randomized, comparative trial Exceed has been conducted. More patients treated with rivastigmine than with donepezil reported “any adverse event” during the 4- to 14-week titration phase (82.0% and 64.7%, respectively). The higher rate of adverse events in the rivastigmine group, compared with the donepezil group, during the titration phase appeared to be driven by an increased rate of nausea (32.9% vs 15.2%) and vomiting (27.9% vs 5.8%). In the maintenance phase, weeks 17–104, adverse event rates in the two groups were similar (78.7% for the rivastigmine group and 76.9% for the donepezil group). Premature discontinuations due to adverse events were higher in the rivastigmine group during the titration phase (14.1% vs 7.0% for donepezil) but similar in the maintenance phase (17.9% vs 14.1% for donepezil). There were no differences between rivastigmine- and donepezil-treated patients with respect to number of serious adverse events (SAEs) and SAEs leading to discontinuation. Because the adverse events are associated with peak plasma levels, rivastigmine transdermal

| Table 1 Pharmacokinetic and pharmacodynamic characteristics of rivastigmine |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Half-life pharmacokinetic       | 15 h            | Half-life pharmacodynamic | 10 h            | T_max            | 0.5–2 h         |
| Bioavailability                 | 36%             | Protein binding     | 40%             | Metabolism by CYP system | no             |
| Elimination                     | renal           | Dose starting       | 1.5 mg bid      | Dose maximum     | 6 mg bid        |
| Drug interaction                | no              | AChE G1             | yes             | AChE G4          | yes             |

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patches with better tolerability and equal bioavailability and efficacy are in advanced development.

**Efficacy of rivastigmine**

The efficacy of rivastigmine in the symptomatic treatment of patients with mild to moderate AD has been demonstrated in several large, 6-month, double-blind, placebo-controlled trials. Furthermore, over the past few years data have emerged suggesting that this agent may have long-term benefits. Available data on the use of rivastigmine are summarized below.

**Short-term therapy**

Four controlled double blind vs placebo studies for treatment duration ranging from 13 to 26 weeks have been conducted (Table 2). Participants included in all trials were classified as having probable AD of mild to moderate severity. All studies had 3 treatment arms, comparing various dosage levels of rivastigmine with a placebo. Two trials (Corey-Bloom et al 1998; Rosler et al 1999) had treatment groups with doses of 1–4 and 6–12 mg/day (flexible-dose studies) and one trial had doses of 4 and 6 mg/day (Agid et al 1998). By the end of the follow-up, the mean doses were similar in the two flexible-dose studies: 3.7 and 10.4 mg/day for the two groups in one (Rosler et al 1999) and 3.5 and 9.7 mg/day in the two groups in another (Corey-Bloom et al 1998). The remaining trial (Forette et al 1999) compared the effects of a twice-daily regimen compared with a three-times daily regimen, giving average doses of 9.6 and 10.1 mg/day, respectively. The trials were all multicenter studies, with total sample sizes ranging from 114 to 725 participants. The studies demonstrated a statistically significant difference between drug and placebo on neuropsychological scales, clinician-rated global clinical state and activities of daily living.

In the study by Corey-Bloom et al (1998), participants in the high-dose group showed an average decline that was 3.78 points less than the decline shown by placebo participants in the ADAS-Cog. The study reported a statistically significant difference on the MMSE between the high-dose treatment group and the placebo group with an improvement in the high-dose group of 0.30 points and a decline in the placebo participants of –0.79 points. In the CIBIC-Plus, the authors reported an average difference of 0.29 points between high-dose and placebo participants. In the GDS, the high-dose group scores deteriorated by 0.19 points less than the placebo group scores. Finally, in the PDS the study showed a statistically significant difference of 3.38 points between the 6–12 mg/day rivastigmine participants and the placebo group.

The study by Agid et al (1998) compared two fixed-dose groups (4 and 6 mg/day) with a placebo, and did not report any statistically significant differences between treatment and placebo groups for cognitive and functional outcome measure. In particular, on the NOSGER scale this study compared two different dose treatment groups with placebo. No p-values were reported for this outcome measure, but the high-dose rivastigmine group (6–12 mg/day) seemed to show an average improvement in memory and IADL performance (mean differences of –0.2 and –0.5, respectively).

In the study conducted by Forette et al (1999), patients taking rivastigmine bid improved more significantly in the CIBIC-Plus assessment of global functioning than those taking the placebo. The treatment size was large: 57% responders in the rivastigmine bid group vs 16% in the placebo group. ADAS-Cog scores also improved in patients receiving rivastigmine bid compared with the placebo, but just failed to reach statistical significance (p = 0.054). In addition, rivastigmine produced a significant improvement in the memory dimension of the NOSGER. Although this study suggests an improvement in global functioning as rated by the physician (CIBIC-plus), functioning as assessed by psychometric tests (ADAS-Cog), and ADL as assessed by the carer (NOSGER), the sample sizes were very small (<30 participants in each group) and no information was presented on power calculations.

In the study by Rosler et al (1999), ADAS-Cog improved in patients in the higher dose group compared to patients taking the placebo (p < 0.05). Significantly more patients in the higher dose group improved by 4 points or more than those in the placebo group (24% [57/242] vs 16% [39/238]). Global functioning as rated by the CIBIC-plus scale significantly improved among those in the higher dose group compared to those taking the placebo (p < 0.001), and significantly more patients in the higher dose group showed improvement than in the placebo group (37% [80/219] vs 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.

On the MMSE, patients receiving the placebo deteriorated by 0.47 points from baseline on the MMSE and those receiving 6–12 mg/day rivastigmine improved by 0.21 points over baseline using the intention to treat analysis. On the GDS, significantly less deterioration occurred in patients taking 6–12 mg/day rivastigmine than in those taking the placebo.

In summary, statistically significant differences between the 6–12 mg/day treatment groups (mean dose ~10 mg/day)
### Table 2 Randomized controlled trials of rivastigmine

| Study                  | Number of patients | Time/doses | Results                      | p-value vs placebo |
|------------------------|--------------------|------------|------------------------------|--------------------|
| Corey-Bloom et al 1998| 699 (centers: 22)  | 1.26 weeks, 1–4 mg/day | ADAS-Cog 2.36 (3.13 to −1.59) | MMSE −0.34 |
|                        |                    | 2.26 weeks, 6–11 mg/day | MMSE 0.31 (1.08 to −0.46) | CIBIC-plus 0.23 (0.07 to 0.39) |
|                        |                    | 3.26 weeks, placebo     | ADAS-Cog 4.09 (4.86–3.32) | MMSE −0.79 |
| Agid et al 1998        | 402 (centers: 54)  | 13 weeks, 4 mg/day      | MMSE 0.0 ± 3.3 | CIBIC-plus 0.49 (0.33–0.65) |
|                        |                    | 13 weeks, 6 mg/day      | MMSE 0.3 ± 3.1 | NOSGER (memory) 0.2 ± 2.4 |
|                        |                    | 13 weeks, placebo       | MMSE −0.0 ± 2.6 | NOSGER (memory) −0.7 ± 3.5 |
| Forette et al 1999     | 114 (centers: 11)  | 18 weeks, twice/daily, mean dose 9.6 mg/day  | ADAS-Cog −2.6 | NOSGER (memory) −0.7 ± 2.9 |
|                        |                    | 18 weeks, 3 times/daily, mean dose 10.1 mg/day | ADAS-Cog 0.41 | NOSGER (memory) 0.014 |

(Continued)
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and the placebo participants were reported in two of three published trials on ADAS-Cog and MMSE. In these studies, no statistically significant effects were seen in the low-dose treatment groups. Both of the published studies (Corey-Bloom et al 1998; Rosler et al 1999) that included CIBIC-plus as a global outcome measure reported statistically significant improvement in high-dose participants (6–12 mg/day) compared with placebo participants. One study reported that a higher proportion of high-dose rivastigmine participants than placebo participants had a “successful” CIBIC assessment, ie, obtaining a score of 1 or 2 on the scale. The same trials (Corey-Bloom et al 1998; Rosler et al 1999) found a statistically significant improvement on the GDS measure in participants treated with 6–12 mg/day of rivastigmine compared with placebo participants. These studies reported the PDS as a functional outcome measure. One of these found a statistically significant improvement in participants treated with 6–12 mg/day rivastigmine compared with participants taking a placebo, and the other reported that a statistically significantly higher percentage of these high-dose participants, but not placebo participants, showed an improvement of at least 10%.

Long-term therapy

Additional evidence is available from studies that were not randomized and double blind, open label extension studies. These studies recruit patients who have been participating in a phase III, randomized, double-blind, placebo-controlled study to continue on open label treatment (Table 3).

Table 2 (Continued)

| Study | Number of patients | Time/doses | Results | p-value vs placebo |
|-------|--------------------|------------|---------|-------------------|
|       |                    | 18 weeks   | ADAS-Cog 2.0 |
|       |                    | placebo   | NOSGER (memory) 1.3 ± 3.7 |
| Rosler et al 1999 | 725 (centers: 22) | 26 weeks 1–4 mg/day | ADAS-Cog 1.37 (2.27–0.53) |
|       |                    | MMSE –0.62 (–1.05 to –0.15) |
|       |                    | CIBIC-plus 4.24 (4.02–4.38) |
|       |                    | GDS –0.22 (–0.3 to –0.1) |
|       |                    | PDS –3.37 (–4.99 to –1.61) |
|       | 26 weeks 6–11 mg/day | ADAS-Cog –0.26 (0.66 to –1.06) |
|       |                    | MMSE 0.21 (–0.24 to 0.64) |
|       |                    | CIBIC-plus 3.91 (3.71–4.09) |
|       |                    | GDS –0.06 (–0.2 to –0.0) |
|       |                    | PDS 0.05 (–1.57 to 1.77) |
|       | 26 weeks placebo   | ADAS-Cog 1.34 (2.19–0.41) |
|       |                    | MMSE –0.47 (–0.96 to –0.04) |
|       |                    | CIBIC-plus 4.38 (4.22–4.58) |
|       |                    | GDS –0.26 (–0.4 to –0.2) |
|       |                    | PDS –2.18 (–3.91 to –0.49) |

Derived from Loveman et al (2006).

Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale Cognitive Subscale; CIBIC-plus, Clinical Rating and Clinician’s Interview-Based Impression of Change Plus Caregiver Input; GDS, Global Deterioration Scale; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental Status Examination; NOSGER, Nurses’ Observation Scale for Geriatric Patients; PDS, Progressive Deterioration Scale.
Farlow et al (2000) reported the results of a 52-week “delayed start” rivastigmine study in mild to moderate AD. For the first 26 weeks, patients received a placebo or rivastigmine. All patients were then eligible to receive open-label rivastigmine for another 26 weeks. On ADAS-Cog, there was a significant, 5.7-point treatment difference for patients who remained on rivastigmine for 52 weeks (p < 0.001) compared with the projected decline if they were left “untreated”, calculated by using a statistical model. In addition, patients who received a placebo for the first 26 weeks and were then switched to rivastigmine for weeks 27–52 did not “catch up” with those who had been on rivastigmine from the beginning of the trial (1.4-point difference on ADAS-Cog).

The effects of rivastigmine on cognition were shown to persist for up to 2 years in a meta-analysis of 2010 patients with AD who took part in four, 26-week, placebo-controlled studies followed by open-label extensions (Grossberg et al 2004). Patients remaining on rivastigmine for up to 2 years showed 4–5 points less decline on ADAS-Cog compared with the projected decline if they were left “untreated”. These conclusions are based on a comparison of the actual clinical changes measured in patients treated with rivastigmine in open-label studies, with hypothetical clinical changes derived by predicting the scores of those same patients had they been left untreated, using a baseline-dependent model derived from data in an untreated AD population (Grossberg et al 2004).

More recently, this meta-analysis (Grossberg et al 2004) was “updated”, with patients remaining on treatment for up to 5 years (Small et al 2005). These data provide the longest-term efficacy data for any ChE-I to date. Even though only 83 patients remained under study conditions at 5 years, these data can be considered informative because most patients tend to discontinue ChE-I treatment over time (Bullock et al 2005). Mean baseline MMSE and ADAS-Cog scores at entry into the placebo-controlled studies were 19.3 and 24.6, respectively. Mean MMSE and ADAS-Cog scores of patients remaining on rivastigmine for 5 years were 12.7 and 36.8 (both showing “moderate” AD) (Small et al 2005). Patients remaining on rivastigmine for 5 years on average declined 1.7 points each year on the MMSE, or 3.9 points each year on ADAS-Cog. These cognitive declines were smaller than those predicted using baseline-dependent models of “untreated” patients and smaller than those reported for untreated patients in the literature (Bullock et al 2005).

### Head-to-head drug comparisons

Three randomized studies were designed to compare two ChE-Is, donepezil and rivastigmine (Fuschillo et al 2001; Wilkinson et al 2002; Bullock et al 2005).

#### Table 3 Long term studies of rivastigmine

| Study          | Time      | Study design                                                                 | Objectives                                                                                                                                 |
|----------------|-----------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Farlow et al 2000 | 1-year data | 26-week open-label extension of a 26-week, placebo-controlled study (n = 533) | ADAS-Cog: significant 5.7-point improvement compared with the projected placebo decline at 52 weeks (the end of the open-label extension) |
| Grossberg et al 2004 | 2-year data | Meta-analysis of two open-label continuations of four placebo controlled studies, total duration 104 weeks (n = 2010) | ADAS-Cog: declined by 4–5 points less than predicted, had patients been left “untreated”                                                   |
| Small et al 2005   | 5-year data | Meta-analysis of two open-label continuations of four placebo controlled studies, maximum total duration 260 weeks (n = 2010) | ADAS-Cog: mean annual decline of 3.9 points; patients remaining on rivastigmine for 5 years declined by about 20 points less than predicted for model-based “untreated” patients |
|                  |           |                                                                             | MMSE: mean annual decline of 1.7 points; patients remaining on rivastigmine for 5 years declined by 7 points less than predicted for model-based “untreated” patients |

Derived from Bullock et al (2005).

**Abbreviations:** ADAS-Cog, Alzheimer’s Disease Assessment Scale Cognitive Subscale; MMSE, Mini Mental Status Examination.
In the Fuschillo et al (2001) single-center study of only 27 participants, those in the donepezil group were given 5 mg/day and those in the rivastigmine group 1.5 mg/day for 1 week, increasing weekly in steps of 1.5 mg up to 6–9 mg/day; treatment duration was 30 weeks.

In the Wilkinson et al (2002) study, those in the donepezil arm were given 5 mg/day for 28 days followed by 10 mg/day; those in the rivastigmine arm were initially given 1.5 mg twice daily for 14 days, then 3 mg twice daily for 14 days, then 4.5 mg twice daily for 14 days and finally, if tolerated, 6 mg twice daily. The study was a multi-center, open label study (19 centers) with 112 participants who knew which drug they were taking; treatment duration was 12 weeks.

On measures of cognitive ability, both studies reported that treatment with rivastigmine (1.5–12 mg/day) led to greater improvement than treatment with 5 mg/day donepezil; however, these trends were small, were not tested for statistical significance, and could also reflect differences in the doses given. Rates of adverse events tended to be higher in the rivastigmine group than in the donepezil group, and more participants withdrew owing to adverse events in the rivastigmine groups. The effects of the doses reported may reflect these differences.

Recently, Bullock et al (2005) designed a double-blind, randomized, controlled, multi-center international trial to evaluate the efficacy and tolerability of ChE-I treatment in patients with moderate to moderately severe AD over a 2-year period. The randomized number was 994. The titration period was 16 weeks. The rivastigmine group started at 3 mg/day, and the dose was increased by 3 mg/day at 4-week intervals until a maximum of 12 mg/day was reached. The donepezil group received 5 mg/day in weeks 1–8 and 10 mg/day thereafter. Following the 16-week titration, patients were maintained at the highest tolerated dose level. The study showed that ChE-I treatment may offer continued therapeutic benefit for years in patients with moderate AD and, although both drugs had the same effect on cognition and behavior, rivastigmine may provide greater benefits in activities of daily living and global functioning.

**Conclusions**

Rivastigmine has been shown effective and safe in the treatment of the cognitive, behavioral, and functional deficits of AD (Birks et al 2002). RCT studies have demonstrated a statistically significant difference between drug and placebo on neuropsychological scales, clinician-rated global clinical state and activities of daily living. Although these ChE-I have been approved by the FDA for the treatment of mild to moderate AD, there are still doubts about their actual efficacy and many problems still exist regarding the transfer of information from an experimental setting to clinical practice (Schneider 2006).

The National Institute for Clinical Excellence (NICE 2001) (www.nice.org.uk) appraised these drugs in 2000 and endorsed their use provided a number of conditions were met. Treatment guidelines recommend that ChE-I treatment should be continued only if there is an increase, or no decrease, in the MMSE score 2–4 months after reaching the suitable dose.

The guidelines for clinical practice (Davies and Maloney 1976; Doody et al 2001; Caltagirone et al 2005) have derived treatment indications from RCTs. One limitation of RCTs on AD is the long disease duration (years) compared with the short duration of clinical trials (weeks), which could impede obtaining long-term information on treatment effects.

Moreover, RCTs’ end-point estimates are surrogate endpoints (eg, the ADAS-Cog cognitive improvement of 3–6 months) considered as valid substitutes of real end points (eg, to stabilize or totally improve functions of the affected subject in the long term). Still, in randomized clinical studies the effect of this variability, analogous to misclassification of exposition and/or disease in the case of control or cohort epidemiological studies, is that of underestimating the true efficacy of interventions.

Moreover, the benefits from this drug are limited and its long-term effectiveness has not been well demonstrated. In fact, as AD generally progresses slowly and a clinical course of 5–10 years is not unusual, clinical trials involving 6 or 12 months of treatment are of limited use. Unfortunately, randomized trial evidence of longer-term effects is not currently available and, given the widely differing rates of progression of AD in different individuals and in groups selected in different ways, extrapolation could be misleading. There are reports of open-label extensions to some of the included studies. Data suggest that patients who remained on rivastigmine for up to 5 years showed a smaller decline on cognitive aspects compared with the projected decline had they been left untreated. The results of open-label extension trials should be interpreted with caution. In fact, there may be several reasons for bias: not all patients participate in the extensions of the trials, only a self-selected group; comparisons are made using historical controls or a hypothetical placebo decline obtained by extrapolation from the randomized phase. Although these preliminary data suggest a reduction in AD progression, there is a need for randomized, placebo-controlled trials of longer than one year to establish...
the benefits of these drugs in the long term; at the moment, in fact, only one study spanned a 5-year period.

The issue regarding duration of treatment and criteria of suspension is still unresolved, and further studies are needed to help establish the maximum duration of treatment and the indicators that could show when treatment is no longer beneficial. Nevertheless, new data suggest that cholinesterase inhibition may continue for up to 5 years.

Another unsolved and frequent problem is the decision about which ChE-I to use. Existing trials indicate no major differences in efficacy between rivastigmine and the other ChE-Is. Very recently, the Cochrane Collaboration (Birks 2006) confirmed the positive effect of donepezil, galantamine, and rivastigmine in people with mild, moderate, or severe dementia due to AD without indicating any significant differences among the ChE-Is for improving cognition and global status.

In fact, head-to-head, rivastigmine vs donepezil trials are limited; thus no guidelines for clinical treatment are provided (Bullock et al 2005). Both drugs performed the same way on cognition and behavior, but rivastigmine seemed to improve ADL and global functioning even though there were some differences in the doses given (Wilkinson et al 2002).

Nevertheless, previous findings (Gauthier et al 2006) support the hypothesis that many patients failing to respond to ChE-selective inhibitors may benefit from being switched to rivastigmine and that patients unable to respond adequately to any ChE-I may obtain cognitive benefits from concomitant therapy with memantine. A recently published, open-label study evaluated the efficacy of the ChE-I rivastigmine on cognition, functional autonomy, and behavior in patients with mild to moderate AD previously treated with other ChE-Is (switched patients). The authors concluded that patients switched from previous ChE-I therapy to rivastigmine can obtain measurable benefits, but the treatment effect may be less than in de novo patients (Dantoine et al 2006).

In conclusion, a number of large, placebo-controlled, double-blind trials have demonstrated that the use of rivastigmine results in significant improvements in cognitive, functional and global performances of AD patients (Birks et al 2002). Preliminary evidence also indicates the potential efficacy of this drug in the treatment of behavioral and psychiatric symptoms and disturbances (Weinstock 1999; Minger et al 2000; Giacobini 2000).

Despite evidence from clinical studies and intervening clinical experience, the debate continues about whether ChE-Is are effective; in particular, information regarding their impact on quality of life and cost-effectiveness is lacking, resulting in some uncertainty about the guidance provided.

It is important for patients and caregivers to understand that they should not expect increasing improvements long term; indeed, the aim should be to maintain patients’ status at a manageable level, and to make it possible for patients to continue to be themselves.

References

Agid Y, Dubois B, Anand R, et al. 1998. Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp, 59:837–45.

Ballard CG. 2002. Advances in the treatment of Alzheimer’s disease: benefits of dual cholinesterase inhibition. Eur Neurol, 47:64–70.

Bartus RT, Dean RL 3rd, Beer B, et al. 1982. The cholinergic hypothesis of geriatric memory dysfunction. Science, 217:408–14.

Birks J, Grimley Evans J, Jakovidou V, et al. 2002. Rivastigmine for Alzheimer’s disease (Cochrane Review). In The Cochrane Library, Issue 3. Oxford: Update Software.

Birks J. 2006. Cholinesterase inhibitors for Alzheimer’s disease. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD005593. DOI:10.1002/14651858.CD005593.

Borroni B, Colciaghi F, Pastorino L, et al. 2001. Amyloid precursor protein in platelets of patients with Alzheimer’s disease: effect of acetylcholinesterase inhibitor treatment. Arch Neurol, 58:442–8.

Bullock R, Dengiz A. 2005. Cognitive performance in patients with Alzheimer’s disease receiving cholinesterase inhibitor for up to 5 years. Int J Clin Pract, 59:817–22.

Bullock R, Touchon J, Bergman H, et al. 2005. Rivastigmine and donepezil treatment in moderate to moderately severe Alzheimer’s disease over a 2-year period. Curr Med Res Opin, 21:1317–27.

Caltagirone C, Bianchetti A, Di Luca M, et al. 2005. Italian Association of Psychogeriatrics. 2005. Guidelines for the treatment of Alzheimer’s disease from the Italian Association of Psychogeriatrics. Drugs Aging, 22(Suppl 1):1–26.

Corey-Bloom J, Anand R, each J. 1998. V. for the ENA 713 B352 Study Group. 1998 A randomized trial evaluating the efficacy and safety of ENA 713 rivastigmine tartrate, a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer’s disease. Int J Geriatr Psychopharmacol, 1:55–65.

Cummings JL. 2000. Cholinesterase inhibitors: A new class of psychotropic compounds. Am J Psychiatry, 157:4–15.

Dantoine T, Auriacombe S, Sarazin M, et al. 2006. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer’s disease who failed to benefit from previous cholinesterase inhibitor treatment. Int J Clin Pract, 60:110–8.

Davies KL, Maloney AJ. 1976. Selective loss of central cholinergic neurons in Alzheimer’s disease. Lancet, 2:1403.

Dejong R, Osterlund OW, Roy GW. 1989. Measurement of quality of life changes in patients with Alzheimer’s disease. Clin Ther, 11:545–54.

Doody RS, Stevens JC, Beck C, et al. 2001. Practice parameter: management of dementia (an evidence based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology, 56:1154–66.

Farlow M, Anand R, Messina J, et al. 2000. A 52-week study of the efficacy of rivastigmine in patients with mild-to-moderate severe Alzheimer’s disease. Eur Neurol, 44:236–41.

Ferri CP, Prince M, Brayne C, et al. 2005. Global prevalence of dementia: a Delphi consensus study. Lancet, 366:2112–7.

Folstein MF, Folstein SE, et al. 1975. Mini Mental State: a practical method for grading the cognitive state of patients for the clinicians. J Psychiatr Res, 12:189–98.

Forette F, Anand R, Gharabawi G. 1999. A phase II study in patients with Alzheimer’s disease to assess the preliminary efficacy and maximum tolerated dose of Rivastigmine (Exelonfinity). Eur J Neurol, 6:423–9.
Fuschillo C, La Pia S, Campana F, et al. 2001. Cognitive deficits in Alzheimer’s disease: treatment with acetylcholinesterase inhibitor agents. *Arch Gerontol Geriatr*, 7:151–8.

Gallagher M, Colombo PJ. 1995. Ageing: The cholinergic hypothesis of cognitive decline. *Curr Opin Neurobiol*, 5:161–8.

Gauthier S, Juby A, Morelli L, et al. 2006. A large, naturalistic, community-based study of rivastigmine in mild-to-moderate AD: the EXTEND Study. *Curr Med Res Opin*, 22:2251–65.

Giacobini E. 2000. Cholinesterase inhibitors: from the calabar bean to Alzheimer therapy In: Cholinesterases and cholinesterase inhibitors: from molecular biology to therapy. London M. Dunitz ed. p 181–226.

Grossberg GT, Stahelin HB, Messina JC, et al. 2000. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. *Int J Geriatr Psychiatry*, 15:242–7.

Grossberg G, Irwin P, Satlin A, et al. 2004. Rivastigmine in Alzheimer’s disease: efficacy over two years. *Am J Geriatr Psychiatry*, 12:420–31.

Kasa P, Rakonczay Z, Gulya K. 1997. The cholinergic system in Alzheimer’s disease. *Prog Neurobiol*, 52:511–35.

Katzman R. 1986. Alzheimer’s disease. *N Engl J Med*, 314:964–73.

Lancot K, Herrmann N, Yau KK, et al. 2003. Efficacy and safety of cholinesterase inhibitors in Alzheimer’s disease: a meta-analysis. *CMAJ*, 169:557–64.

Lawton MP, Brody EM. 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*, 9:179–86.

Loverman E, Green C, Kirby J, et al. 2006. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease. *Health Technol Assess*, 10:000–000.

McKhan G, Drachman D, et al. 1984. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS ADRDA Work group, Department of Health and Human Services Task Force on Alzheimer’s Disease. *Neurology*, 34:939–44.

Rosen WG, Mohs R, Davis K. 1984. A new rating scale for Alzheimer’s disease. *Am J Psychiatry*, 141:1356–64.

Rosler M, Anand R, Cicin-Sain A, et al. 1999. Efficacy and safety of rivastigmine in patients with Alzheimer disease: international randomised controlled trial. *BMJ*, 318:633–40.

Schneider LS, Olin JT, Doody RS, et al. 1997. Valiability and reliability of the Alzheimer’s disease Cooperative Study – Clinical Global Change. *Alzheimer Dis Assoc Disord*, 1(Suppl 2):S22–32.

Schneider LS. 2006. The post-modern world of Alzheimer’s disease trials: how much is an ADAS-cog point worth in central London? *Int J Geriatr Psychiatry*, 21:9–13.

Small G, Kaufer K, Mendiondo MS, et al. 2005. Cognitive performance in Alzheimer’s disease patients receiving rivastigmine for up to 5 years. *Int J Clin Pract*, 59:473–7.

Spiegel R, Brunner C, Ermini-Funfschilling D, et al. 1991. A new behavioural assessment scale for geriatric out-and in-patients: the NOSGER (Nurses’ Observation Scale for Geriatric Patients). *J Am Geriatr Soc*, 39:339–47.

Tasker A, Perry EK, Ballard GC. 2005. Butyrylcholinesterase: impact on symptoms and progression of cognitive impairment. *Expert Rev Neurother*, 5:101–6.

[NICE] The National Institute of Clinical Excellence. 2001. The National Institute of Clinical Excellence (NICE) approves drugs for Alzheimer’s disease. *BMJ*, 190:322.

Weinstock M. 1999. Selectivity of cholinesterase inhibition. *CNS Drugs*, 12:307–23.

Whitehouse PJ, Price DL, Struble RG, et al. 1982. Alzheimer’s disease and senile dementia: Loss of neurons in the basal forebrain. *Science*, 215:1237–9.

Wilkinson DG, Passmore AP, Bullock R, et al. 2002. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer’s disease. *Int J Clin Pract*, 56:441–6.

Williams BR, Nazarians A, Gill MA. 2003. A review of rivastigmine: a reversible cholinesterase inhibitor. *Clin Ther*, 25:1634.
