Update on Rivastigmine

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Background: Rivastigmine is a carbamate drug designed to inhibit both acetylcholinesterase and butyrylcholinesterase by reversibly covalently bonding to these enzymes. Butyrylcholinesterase increases as Alzheimer disease progresses, so its inhibition may become more important as the disease worsens. Metabolism of rivastigmine occurs at the synapse rather than at the liver and previous studies have demonstrated no drug-drug interactions. Rivastigmine has a half-life at the synapse of 9 hours allowing for bid dosing.

Review Summary: Effective therapy requires up-titration from initial dosage of 3 mg/d to 6 mg/d with additional increases to 9 mg or 12 mg/d giving additional benefits in some patients. Beneficial effects with rivastigmine therapy in the functioning of activities of daily living, behavior, cognition, and global functioning have been demonstrated in patients with mild to moderate Alzheimer disease in 4 large double-blind, placebo-controlled multicenter clinical trials. Potential adverse effects of nausea, vomiting, or diarrhea in these original Alzheimer trials with rapid (every week) dosage increases occurred in up to 34% of patients and can be minimized by slower monthly up-titrations.

Rivastigmine also was proven effective in decreasing psychiatric symptoms and cognitive deficits in a large double-blind, placebo-controlled trial in patients with diffuse Lewy body disease. Other studies have suggested that rivastigmine improves symptoms in nursing home patients with more severe stage Alzheimer disease, Parkinson dementia, and subcortical dementia. Follow-up studies have suggested that rivastigmine may delay disease progression and, in patients discontinuing the drug, no withdrawal effects were seen.

Conclusion: Rivastigmine is an effective therapeutic agent for treating cognitive and behavioral symptoms in Alzheimer disease and diffuse Lewy body disease and may also have beneficial effects in vascular and Parkinson dementias.

Key Words: rivastigmine, butyrylcholinesterase, Alzheimer disease, diffuse Lewy body disease, disease progression

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DESCRIPTION AND PRECLINICAL DATA

Rivastigmine is a carbamate drug designed to inhibit cholinesterase.[1] The majority of cholinesterase, called acetylcholinesterase (AChE), is of neuronal origin and functions to metabolize acetylcholine at synapses throughout the nervous system. The remainder, called butyrylcholinesterase (BChE), is of glial origin and has more general actions in the brain that are less well understood.[2] As Alzheimer disease (AD) progresses and cortical neurons are lost, levels of acetylcholinesterase progressively decline, while levels of butyrylcholinesterase increase.[3] Butyrylcholinesterase can and does take over function to metabolize acetylcholine at the synapse when acetylcholinesterase is lost, a phenomenon that has been demonstrated in an acetylcholinesterase knockout mouse model and that probably occurs in AD.[4] Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase by covalently bonding to active sites on these enzymes, blocking their function. Breaking of these covalent bonds is the first and most important step in the degradation of this drug, which is not metabolized in the liver.[5]

Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase.

Rivastigmine is weakly bonded to plasma proteins (~20%), explaining its short half-life in plasma (~60 minutes) as compared with a 9-hour half-life for cholinesterase inhibition. The longer half-life for cholinesterase inhibition allows bid dosing of rivastigmine.

In the brain there are multiple forms of both acetylcholinesterase and butyrylcholinesterase named for the number of similar protein units with active sites that are linked together. In normal brain, a complex with 4 subunits (G4) is

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the most common form for both AChE and BChE, followed by the single protein unit (G1).[6] Levels of G4 decline as AD progresses until the G1 forms of both enzymes become the more common.[7] Rivastigmine selectively and predominantly inhibits the G1 forms; thus, its activity cannot be measured in red blood cells (rbcs), which only possess the G4 forms of cholinesterase, and its inhibitory effects may become selectively greater as AD progresses.[8]

Side effects are considerably reduced if up-titration is slowed to monthly and rivastigmine is taken only after full meals.

TOLERABILITY

Rivastigmine was originally investigated as a potential AD therapeutic drug in studies that employed a maximum-tolerated dosage design.[9,10] On a weekly basis, dosages of the drug in patients were rapidly up-titrated until either side effects occurred or until a dosage of 12 mg/d was achieved. Adverse effects in the 6-month pivotal trials that were significantly higher for the 6–12 mg/d group versus placebo included nausea (48%), vomiting (27%), and anorexia (20%).[9,10] Most drug-related adverse effects occurred chiefly during the titration phase of the protocols (34%) versus a much lower rate of occurrence during the maintenance phases (13%). Adverse gastrointestinal effects, if they occurred, generally were within the first 1 or 2 doses after up-titration and were usually transient and self-limited. In the pivotal trials, 13% of rivastigmine patients discontinued due to adverse effects as compared with 4% of placebo patients. Later studies and experience in clinical practice have suggested that side effects are considerably reduced if up-titration is slowed to monthly and rivastigmine is taken only after full meals.[11] Therapeutic effects have been demonstrated once the dosage reaches 6 mg/d. For patients who have discontinued the drug for longer than 1 week, it is recommended that they retitrate up to their therapeutic dose as a precaution since no data is available concerning possible adverse effects with immediate resumption of high-dose therapy.

Studies with 21 commonly prescribed medications given concomitantly with rivastigmine found no evidence for significant drug-drug interactions, a finding which may be at least partially due to the drug's lack of metabolism in liver and its weak binding to plasma proteins.[12]

Follow-up assessments of patients at 26 weeks who had discontinued rivastigmine for various reasons at earlier times during 3 large double-blind, placebo-controlled trials, which included Alzheimer Disease Assessment Scale-Cognitive Component (ADAS-Cog), Progressive Deterioration Scale (PDS), and the Clinician's Interview Based Impression of Change with Caregiver Input (CIBIC–Plus), revealed no evidence for accelerated deterioration or support for a withdrawal syndrome.[13]

CLINICAL EFFICACY

Four large multicenter, double-blind, placebo-controlled trials, each of 26 weeks' duration (over 3,000 patients), have been completed to assess clinical efficacy of rivastigmine in patients with mild- to moderate-stage AD. One of these studies was conducted in the United States and the other 3 were international.[10,14] Beneficial effects were consistently seen in measures of cognition, global functioning, and activities of daily living.

In these trials, cognition was assessed using the ADAS-Cog, an instrument that assesses memory, praxis, and language and that has previously been demonstrated to reliably measure change in patients with mild- to moderate-stage AD.[15] The magnitude of cognitive benefit determined by change in ADAS-Cog in patients treated with 6–12 mg/d of rivastigmine versus placebo in the U.S. study was relatively large as compared with reported trials with other cholinesterase inhibitors.[9] Interestingly, the natural rate of disease progression in this group of patients as indicated by deterioration in the placebo group was somewhat greater than seen in other trials. The greater decline of the placebo group may contribute to the apparent large cognitive benefit, which is measured as the difference in ADAS-Cog scores between the active and the placebo treatment groups. Administering the ADAS-Cog to patients before the study's baseline, a difference in design from some of the other cholinesterase inhibitor trials and the flexible titration to maximize dose permitted in this study also would tend to magnify efficacy (dose maximization could also increase adverse effects). Flexible titration was done in an attempt to reach the highest tolerated dose in each individual patient. Increased side effects were seen in this trial, particularly during the titration phase. Improvements in ADAS-Cog versus placebo in the 3 international trials also were significant but of lesser magnitudes.[10,14]

Global functioning was assessed by the CIBIC–Plus, an instrument where an experienced clinician assessed cognitive function in activities of daily living (ADLs) and behavior based on interviews with the patient and with the caregiver. Using this information, the clinician can globally assess change from baseline in the patient using a 7-point scale.[16] Statistically and clinically significant treatment effects with rivastigmine were seen in these trials for patients in the higher dosage (6–12 mg/d) groups.[10,14] In general, these beneficial effects versus placebo were present by the end of the titration phase at 12 weeks and persisted thereafter.

Function in activities of daily living in these trials was assessed by the PDS, an instrument given to the caregiver that surveys function in a variety of instructional and basic ADLs that have been previously determined to deteriorate during mild- to moderate-stage AD.[17] This instrument, as are all ADL scales, is relatively insensitive in measuring overall change, as different ADLs tend to be lost primarily during specific disease stages (i.e., loss of ability to balance a checkbook or do mathematical calculations is lost during mild-stage disease as compared with increased problems dressing with clothes during moderate-stage disease). Nevertheless, function in ADLs for the 6–12 mg/d rivastigmine treated groups was, on average, relatively preserved during each of the pivotal trials with minimal deterioration versus baseline, while there was significant falling off in function on average for patients in the placebo groups.

It is interesting that with regard to the 3 different domains of cognition, global functioning, and function in ADLs, individual patients showed great variability in how they responded to treatment with rivastigmine. Significant benefits in cognitive function do not necessarily correlate with improvements in global functioning or with functioning in ADLs. It is probably best not to judge response on the basis of change in a single domain such as cognition as assessed by ADAS-Cog or Mini Mental State Examination (MMSE). In pooled data from these rivastigmine trials, 30–55% of patients had stabilization or improvement in these individual domains, but overall 86% had a beneficial response in 1 or more domains.[18]

Behavioral change was not one of the principal outcome measures in the original phase III rivastigmine trials in patients with mild- to moderate-stage AD. However, other later studies have strongly suggested that the drug may help control or prevent onset of abnormal behaviors, with beneficial effects being demonstrated versus baseline in both a large open nursing home trial of rivastigmine in AD patients and in a double-blind, placebo-controlled trial of diffuse Lewy body disease.[19,20]

PREDICTORS OF RESPONSE

In the phase III clinical trials, rivastigmine exhibited dose-response characteristics. Groups treated with 6–12 mg/d of drug had significantly better clinical benefits than groups treated with lower dosages.[10] Patients with moderate-stage disease were more likely to show significant improvements as measured by ADAS-Cog and functions in ADLs (PDS) but not global functioning (CIBIC–Plus) or disease-stage [Global Deterioration Scale (GDS)].[21]

1. A more rapid rate of decline in placebo patients during the double-blind phase as measured by ADAS-Cog and PDS in these trials predicted greater magnitude of response to rivastigmine during the open-label phase that followed.[22] This finding suggests that naturally more rapidly progressing patients may be more responsive to rivastigmine. Patients with vascular risk factors, as measured by a positive Hachinski score, (1–4, predominantly history of hypertension) also had significantly better response on average to rivastigmine therapy than patients without such risk factors.[23] Demographic variables (age, gender, ethnicity) and APOE genotype did not predict response to drug (Mullan M. APOE and rivastigmine subgroup, personal communication; 2001).[10]

The longer-term effects of rivastigmine appear to remain clinically relevant for at least 2 years.

DURABILITY OF BENEFITS AND EFFECTS ON LONGER-TERM DISEASE PROGRESSION

Double-blind placebo-controlled trials longer than 26 weeks' duration have not been undertaken with rivastigmine in patients with AD.[24] Ethical concerns about denying effective therapy probably precludes such trials in the future. However, the longer-term effects of rivastigmine appear to remain clinically relevant for at least 2 years as demonstrated in extended follow-up studies of over 2,000 patients who participated in the original phase III trials of the drug.[25] Patients from these studies treated with 6–12 mg/d of rivastigmine showed significantly less deterioration on the ADAS-Cog at 52 weeks as compared with the projected decline for placebo patients, with the difference widening at 104 weeks. Furthermore, data from the U.S. 26-week, double-blind, placebo-controlled phase III trial with its 6-month extension were analyzed to approximate a delayed-start trial design.[26] The delayed-start trial design had previously been proposed as a means for demonstrating whether a drug has any effects in delaying disease progression.[27] If rivastigmine were to have an effect on disease progression, then treated patients should deteriorate less during the initial 6 months of therapy as compared with the patients on placebo. Differences in the placebo versus active treatment groups would not be expected to resolve in the next 6 months when both groups of patients were taking equivalent dosages of rivastigmine. In the U.S. study, patients originally on placebo responded very well to rivastigmine but were never able to "catch up" in either cognitive or ADL functions as compared with patients who had been on the drug from the very beginning (Fig. 1). These results suggest, but do not definitively establish, that rivastigmine may indeed have an effect on disease progression.

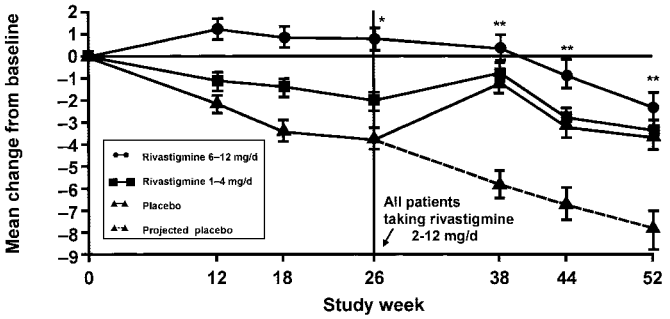

FIGURE 1. During the first 26-week, double-blind portion of this study, patients on placebo progressively declined as measured by ADAS-Cog while patients on high dose rivastigmine improved. During the second 26 weeks, patients originally on placebo switched to high dose rivastigmine improved, but not to the level of patients on high-dose rivastigmine from the beginning of the study.

The original pivotal trials of rivastigmine that demonstrated effectiveness and that led to approval by the FDA were limited to patients with mild- to moderate-stage AD. Examining the effects of rivastigmine in more severe-stage AD, such as nursing home patients, assesses whether beneficial effects might be expected to continue during later stages in the course of the disease.[19] Controlling behavioral abnormalities at this stage may be clinically more important than improving cognitive function. The Neuropsychiatric Inventory (NPI) is an instrument where the caregiver judges the frequency and severity of behavioral and psychiatric symptoms in several domains during the preceding 2 weeks.[28] In a large open study of nursing home patients receiving rivastigmine using this instrument, there was significant stabilization and or improvement in behavioral symptoms at both 26 and 52 weeks.[19] Over 50% of patients achieved a 30% or greater improvement in their NPI ratings. These findings are notable as the natural history of Alzheimer disease is for behavioral symptoms to increase as the illness progresses. Significant reductions in the use of psychotropic medications were also documented with these improvements in behavior.[29]

Another subanalysis retrospectively examined the rate of disease progression for up to 3 years (change in ADAS-Cog scores over time) in over 2,000 patients who participated in the open-label trials that followed the original 3 pivotal double-blind trials of rivastigmine in Alzheimer disease. Evidence for a disease-modifying effect of the drug was sought by examining whether there was a differential rate of clinical deterioration by dose. Patients were grouped into those taking less than 6 mg/d of rivastigmine and those taking 6 mg/d or more of the drug. Patients taking the higher dosage had 50% less deterioration as compared with patients maintained on lower dose of the drug. As in any retrospective analysis, an unknown factor might create bias between the groups. Nonetheless, these data further support a disease progression-delaying effect for rivastigmine.[30]

THERAPY FOR OTHER DEMENTIAS

A large multicenter, double-blind, placebo-controlled, 20-week trial of rivastigmine in patients with diffuse Lewy body disease has recently been completed.[20] There were significant beneficial effects on cognition as measured by MMSE and highly significant effects on abnormal behavioral and psychiatric symptoms as demonstrated by improvements for the rivastigmine-treated group with 63.4% of these patients achieving a greater than 30% reduction in NPI scores. Later analyses have suggested that the drug improved cognitive test scores that involved attention.[31] Improvements in attention were most prominent in patients who had hallucinations and delusions at baseline, and these same patients had the greatest improvements in cognitive test scores. Longer-term follow-up in an open study of patients with diffuse Lewy body disease demonstrated that cognition as assessed by MMSE and behavior as assessed by NPI did not deteriorate over a 96-week period.[32]

A 12-week open study in 28 patients with Parkinson dementia demonstrated significant improvements in cognition versus baseline and no changes in motor symptoms.[33] A 17-week open study of 12 patients with Parkinsonian psychosis and cognitive impairment demonstrated significant improvements in cognitive function, hallucinations, and sleep disturbances.[34]

A small open study of rivastigmine in patients with subcortical vascular dementia showed behavior and executive functions were significantly improved as compared with baseline.[35] A large multicenter placebo-controlled trial in patients with vascular dementia is currently underway.

Finally, anecdotal data have suggested that rivastigmine may have beneficial effects in patients with mild cognitive impairment (Prodromal AD). A large multicenter, double-blind, placebo-controlled trial investigating both symptomatic effects as well as potential effects on disease progression is currently underway.

CONCLUSION

Rivastigmine is an effective drug for delaying progression of clinical symptoms in patients with Alzheimer disease. Several trials have demonstrated beneficial effects on cognition, function in ADLs, global functioning, and behavior. Adverse cholinergic symptoms are minimized by titrating dosages upwards monthly rather than every 2 weeks as was originally recommended at the drug's approval by the FDA. No drug-drug interactions have been demonstrated. Analyses of previous trials have suggested that the magnitude of clinical benefit may be greater in patients with moderate stage or rapidly progressive disease. Benefit also is suggested for

patients with cerebrovascular risk factors and Lewy body disease.

The durability of beneficial clinical effects with this drug is unknown; however, open label data in over 2,000 patients following the original pivotal double-blind trials suggests that patients on the drug progress less rapidly than would be suggested by the natural rate of disease deterioration in previous epidemiological studies. During these open label trials, it appears that patients treated from the start did better than those who were originally on placebo in the preceding double-blind phase, suggesting a possible effect of this cholinesterase inhibitor on disease progression. Some data suggest there are continuing benefits to nursing home patients, particularly in reducing the new onset of abnormal behaviors and in reducing the need for psychotropic medications over time. Follow-up studies on patients who have discontinued the drug suggest there are no withdrawal effects.

REFERENCES

1. Weinstock M, Razin M, Chorev M, et al. Pharmacological activity of novel anticholinesterase agents of potential use in the treatment of Alzheimer disease. In: Fisher A, Hanin I, Lachman P, eds. *Advances in Behavioral Biology*, Volume 29, New York: Plenum Press; 1986:539–549.
2. Guillozet AL, Smiley JF, Mash DC, et al. Butyrylcholinesterase in the life cycle of amyloid plaques. *Ann Neurol*. 1997;42:909–918.
3. Perry EK, Perry RH, Blessed G, et al. Changes in brain cholinesterases in senile dementia of Alzheimer type. *Neuropath Appl Neurobiol*. 1978;4:273–277.
4. Mesulam M-M, Guillozet A, Shaw P, et al. Acetylcholinesterase knockouts establish central cholinergic pathways and can use butyrylcholinesterase to hydrolyze acetylcholine. *Neurosci*. 2002;111:627–639.
5. Farlow MR, Hake AM. Mechanism of action and metabolism of acetylcholinesterase inhibitors: implications for treatment. *Intl J Geriat Psychopharm*. 1998;1(Suppl 1):S2–S6.
6. Siek GC, Katz LS, Fishman EB, et al. Molecular forms of acetylcholinesterase in subcortical areas of normal and Alzheimer disease brain. *Biol Psych*. 1990;27:573–580.
7. Enz A, Chappuis A, Probst A. Different influence of inhibitors on acetylcholinesterase molecular forms G1 and G4 isolated from Alzheimer's disease and control brains. In: Shafferman A, Velan B, eds. *Multidisciplinary Approaches to Cholinesterase Functions*, New York: Plenum Press; 1992:243–249.
8. Enz A, Amstutz R, Boddeke H, et al. Brain selective inhibition of acetylcholinesterase: a novel approach to therapy for Alzheimer's disease. *Prog Brain Res*. 1993; 98:431–438.
9. Corey-Bloom J, Anand R, Veach J, et al. 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. *Intl J Geriatric Psychopharm*. 1998;1:55–65.
10. Schneider LS, Anand R, Farlow MR. Systematic review of the efficacy of rivastigmine for patients with Alzheimer's disease. *Intl J Geriatric Psychopharm*. 1998;1, Suppl 1, S2–S6.
11. Farlow MR. Do cholinesterase inhibitors slow progression of Alzheimer's disease? *Intl J Clin Practice* 2002;127:37–44.
12. Grossberg GT, Stahelin HB, Messina JC, et al. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. *Intl J Geriatric Psych*. 2000;15(3):242–247.
13. Anand R, Farlow, MR, Hartman R et al. Analysis of outcome in patient dropouts originally treated with rivastigmine versus placebo in a 26-week, Alzheimer's disease trial. *Neurol*. 2001;56:(Suppl 3) A339.
14. Rosler M, Anand R, Cicin-Sain A et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomized controlled trial. *Brit Med J*. 2000;318:633–638. [erratum appears in BMJ 2001, June 16;322 (7300): 1456].
15. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psych*. 1984;141:1356–1364.
16. Reisberg B, Schneider L, Doody R, et al. Clinical global measures of dementia. *Alzheimer Dis Assoc Disord*. 1997;11:8–18.
17. Dejong R, Osterlund OW, Roy GW. Measurement of quality-of-life changes in patients with Alzheimer disease. *Clin Therapeut*. 1989;11: 545–554.
18. Farlow MR, Anand R, Hartman R. Response to rivastigmine treatment in the key domains of Alzheimer's disease. *Proc Am Psych Assoc*. 2001:208 (NR770).
19. Edwards K, Goodman, W, Sethi J, et al. Flexible titration reduces side effects of rivastigmine. *Proc Am Assoc Geriat Psych*. 2001.
20. McKeith I, Del Ser, Spano P-F, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double blind, placebo-controlled international study. *Lancet*. 2000;356:2031–2036.
21. Farlow MR, Hake A, Anand R, et al. Moderate Alzheimer's disease is responsive to therapy with rivastigmine. *Neurol*. 2003; Accepted for publication.
22. Farlow MR, Hake A, Messina J, et al. Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. *Arch Neurol*. 2001;58:417–422.
23. Kumar V, Anand R, Messina J, et al. An efficacy and safety analysis of Exelon in Alzheimer's disease with concurrent vascular risk factors. *Eur J Neurol*. 2000;7:159–169.
24. Kawas CH, Clark CM, Farlow MR, et al. Clinical trials in Alzheimer's disease: the debate on the use of placebo controls. *Alzheimer Dis Assoc Disord*. 1999;13:124–129.
25. Farlow MR, Messina J, Anand R. Long-term cognitive benefits associated with the use of rivastigmine in the treatment of Alzheimer's disease: results following two years of treatment. *Proc Am Geriat Soc*. 2000;172 (P396).
26. Farlow MR, Anand RV, Messina J, et al. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. *Eur Neurol*. 2000;44:236–241.
27. Leber P. Slowing the progression of Alzheimer disease: methodologic issues. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 5):10–21.
28. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurol*. 1997;48(Suppl 6):S10–S16.
29. Messina J, Koumaras B, Sohn H, et al. Evaluation of the changes in concomitant psychotropic medications for patients with Alzheimer's disease treated with rivastigmine in a long-term care setting. *Proceedings of the Third International Meeting for College of Psychiatric and Neurologic Pharmacists*, 2002;April 16–19, Washington DC2.
30. Farlow MR, Hake AM, Messina J, et al. The response of patients with Alzheimer's disease to rivastigmine treatment is predicted by the rate of disease progression. *Proc Am Acad Neurol*. 2000;54:A469.
31. Wesnes K, McKeith IG, Ferrara R, et al. Predicting response to rivastigmine in dementia with Lewy bodies: the role of hallucinations and attention fluctuation. *Proceedings from the 7th International Geneva/ Springfield Symposium on Advances in Alzheimer Therapy.* April 3–6, 2002, Geneva.
32. Grace J, Daniel S, Stevens T, et al. Long-term use of rivastigmine in patients with DLB: an open-label trial. *Intl Psychogeriatr*. 2001;13:199–205.
33. Korczyn AD, Shabtai H, Benbunan B, et al. The effect of treatment with rivastigmine (Exelon) on cognitive functions of patients with dementia and Parkinson's disease. *Intl Cong Parkinson's Dis Movement Disorders*, July 31, 2001, Helsinki, Finland.
34. Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of Parkinsonian psychosis and cognitive impairment: peliminary findings from an open trial. *Movement Disord*. 2001;16:1171–1195.
35. Moretti R, Torre P, Antonello RM, et al. Rivastigmine in subcortical vascular dementia: a comparison trial on efficacy and tolerability for 12 months follow-up. *Eur J Neurol*. 2001;8:361–362.