EXPERT REVIEWS

Rivastigmine in Parkinson's disease dementia

Expert Rev. Neurother. 8(8), 1181–1188 (2008)

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Dementia associated with Parkinson's disease (PD) ultimately develops in approximately 70% of patients with PD older than 80 years of age. The neuropathology of PD dementia (PDD) is likely multifactorial and affects several neuronal populations. There is evidence that PDD is associated with a cholinergic deficit, supporting the therapeutic role of cholinesterase inhibitors, which are already first-line agents in the treatment of Alzheimer's disease. Open-label and small controlled studies suggested a clinical efficacy of cholinesterase inhibitors in PDD. One large randomized placebo-controlled trial of 541 patients demonstrated that oral rivastigmine improved cognition, attention and executive functions, activities of daily living and behavioral symptoms after 6 months of treatment. Rivastigmine is a dual cholinesterase inhibitor, being effective on both acetylcholinesterase and butyrylcholinesterase. This paper reviews the pharmacokinetic and pharmacodynamic properties of rivastigmine (oral and transdermal administration). It also reviews evidence on clinical efficacy, safety and tolerability of the oral administration in PDD patients at doses of 3–12 mg/day.

Keywords: cholinesterase inhibitor • dementia • Lewy body disease • Parkinson's disease • rivastigmine

Idiopathic Parkinson's disease (PD) is a chronic and progressive disease of the nervous system. It is one of the most common neurodegenerative disorders. A recent paper reviewed the incidence of PD and estimated that the median incidence is 14 per 100,000 (range: 12–15) [1]. In all studies, the incidence of PD rises with age, and rapidly increases after 60 years of age. Cognitive impairment leading to dementia is also more common in the elderly. A population-based study has shown that the prevalence of dementia in PD is age-correlated, ranging from 12.4% in the group aged 50–59 years to 68.7% in the group older than 80 years [2]. The association of older age with the development of dementia in PD has been confirmed in prospective cohort studies [3–7]; other longitudinal investigations have also shown an association of older age with faster rate of cognitive decline in patients with PD [8,9]. In addition to cognitive impairment, psychiatric symptoms (e.g., depression, hallucinations, anxiety and apathy) are common [10].

Although the hallmark of PD is the occurrence of motor impairment and most therapeutic strategies are focused on motor disability, cognitive features are also frequent and have a major impact on quality of life, as they generate disability associated with motor and functional decline, increased institutionalization and increased mortality [7,11,12].

It has been shown that, as with Alzheimer's disease (AD), dementia observed in PD is associated with a cholinergic deficit, resulting particularly in decreased innervation of the cerebral cortex, and contributing to the observed cognitive and behavioral problems [13,14]. Cholinesterase inhibitors prevent the breakdown of acetylcholine by inhibiting the activity of acetylcholinesterase (AChE) or butyrylcholinesterase (BuChE), the two enzymes that metabolize acetylcholine [15]. These agents are effective in improving cognition and delaying the need for institutionalization of patients with AD [16] or with dementia with Lewy bodies (DLB) [17–19]. Open-label studies have reported clinical improvement in patients with PD dementia (PDD) after treatment with rivastigmine or other cholinesterase inhibitors [20–23]. Rivastigmine, in addition, has been the object of a large randomized clinical trial showing improvement of cognition and attention in PDD patients [24]. Another randomized double-blind, placebo-controlled crossover study of 22 PDD patients demonstrated good tolerability and the improvement of some aspects of cognition after treatment with a different class of cholinesterase inhibitor, donepezil [25].

 10.1586/14737175.8.8.1181 ISSN 1473-7175

Parkinson's disease dementia & dementia with Lewy bodies

PDD and DLB are two common causes of dementia and show an overlap of pathological and clinical features [26]. There is ongoing debate on whether DLB has to be considered a separate disease from PDD, the distinction between the two terms being arbitrary based on the so-called '1-year rule' [27]. A diagnosis of PDD is made when dementia develops within the context of established PD, whereas a diagnosis of DLB is feasible when dementia precedes or coincides within 1 year of the beginning of motor features. Most likely, these two disease categories indicate, in fact, a more severe or a milder phenotype of a same pathophysiological condition featuring brainstem and cortical impairment with Lewy body pathology.

The predominant presentation in PDD is a dysexecutive syndrome. Impairment of attention, or of executive and visuospatial functions, can be considered a characteristic feature, while memory impairment is not usually prominent [28]. Conversely, DLB is commonly associated with rapid eye movement behavior disorder, pronounced fluctuations in vigilance, peculiar psychiatric

Box 1. Features of Parkinson's disease dementia.

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuospatial functions: impaired. Impairment in tasks requiring visual–spatial orientation, perception or construction
   - Memory: impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: core functions largely preserved. Word-finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest and effortful behavior
   - Changes in personality and mood, including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features which do not exclude PDD, but make the diagnosis uncertain

1. Coexistence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia; e.g., presence of relevant vascular disease in imaging
2. Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD

1. Cognitive and behavioral symptoms appearing solely in the context of other conditions, such as:
   - Acute confusion due to:
     - Systemic diseases or abnormalities
     - Drug intoxication
   - Major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
   - Features compatible with 'probable vascular dementia' criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions and fluctuating, stepwise progression of cognitive deficits)

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; PDD: Parkinson's disease dementia. Data from [31].

symptoms, such as complicated scenic hallucinations, increased sensitivity to neuroleptic agents and a rapid progression of dementia [29]. Formal diagnostic criteria have been developed for DLB [30]. Recently, a task force organized by the Movement Disorder Society has developed an algorithm for the diagnosis of PDD, which comprised the key features reported in Box 1 [31].

Several risk factors have been associated with the development of dementia in PD: advanced age, advanced age at onset of motor symptoms, presence of speech or axial involvement, severe hypokinesia and prominent depression (Box 2) [27]. Moreover, the risk of dementia increases if the clinical features include visual hallucinations [3]. These symptoms impact the patient's quality of life, course of the disease and the caregiver's distress.

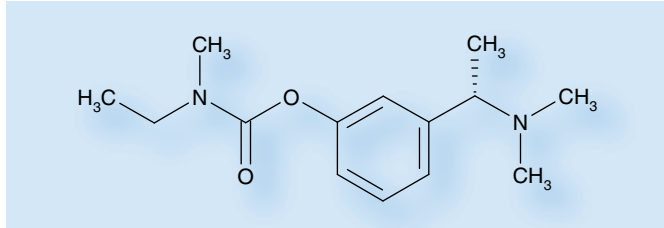

Figure 1. Rivastigmine.

Rivastigmine

Rivastigmine is available as a transdermal patch, oral capsules or oral solution (Figure 1). Oral rivastigmine has been approved for the treatment of AD since 1997 [32], and in 2005 it became the first pharmacological agent to be approved for the treatment of PDD [33]. Furthermore, in Europe its use in DLB is recognized, based on the encouraging results of some clinical trials [17–19], whereas registration is still pending. In 2007, rivastigmine transdermal patch was approved in the USA for the treatment of both AD and PDD, and in Europe for the treatment of AD. Rivastigmine oral continues to provide the only therapeutic option registered for PDD patients in Europe.

A large placebo-controlled study of 541 patients was the first prospective, large-scale trial to show benefit in patients with PD-associated dementia [24]. The patients enrolled in the study had mild-to-moderate dementia (Mini Mental State Examination [MMSE] 10–24) with onset delayed by at least 2 years after the onset of motor PD signs. Patients received a diagnosis of PD according to the Queen Square Brain Bank diagnostic criteria [34] and a diagnosis of dementia according to the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (code 294.1). Patients were randomly treated with rivastigmine capsules at a dose of 3–12 mg/day or placebo over 24 weeks. Rivastigmine-treated patients did better than those treated with placebo. There was a statistically significant improvement in overall functioning, cognitive performance, attentional and executive functions, and behavioral symptoms in rivastigmine-treated patients relative to the deterioration seen in placebo-treated patients. Patients receiving rivastigmine also had less deterioration in their ability to perform activities of daily living. In addition, data from an open-label extension study suggested that treatment with rivastigmine (3–12 mg) leads to sustained benefits over the long term (up to 48 weeks) and is well tolerated [35].

Pharmacology

Current knowledge on the pharmacokinetics of rivastigmine derives from the studies performed on healthy volunteers or on patients with AD. It is classified as an intermediate acting or 'pseudo-irreversible' cholinesterase inhibitor based on the duration of the inhibitory effect, which lasts for 10–12 h after a single dose [36,37]. Other cholinesterase inhibitors (e.g., donepezil and galantamine) have a much shorter duration of inhibition (for some minutes after binding) and are classified as short acting. On the contrary, the half-life of donepezil is much longer than that of rivastigmine (60–90 vs 1–2 h). This may be of relevance to clinicians, given clinical implications such as in emergency situations or when surgery is required.

Rivastigmine displays linear pharmacokinetics at doses up to 3 mg twice daily (b.i.d.), becoming nonlinear at higher dosages. After oral administration, absorption is rapid and nearly complete [38]. Food slows absorption and decreases the C_{max} by approximately 30% and also the area under the curve [101]. Nevertheless, it is recommended to take oral rivastigmine with meals to reduce gastrointestinal side effects. Peak plasma concentration (t_{max}) is reached on average after 0.8 h (range: 0.5–1.7 h) following oral administration (Table 1). Pharmacokinetic studies have shown that transdermal delivery of rivastigmine prolongs t_{max}, lowers C_{max} and reduces fluctuations in plasma concentration. The 9.5 mg/24 h rivastigmine patch provides an exposure to the drug similar to that of an oral dose of 6 mg b.i.d., with C_{max} decreased by 70% compared with the 6 mg b.i.d. capsule dose [39]. Clinical data suggest that this pharmacokinetic profile allows similar efficacy for the 9.5 mg/24 h patch and an oral dose of 6 mg b.i.d., with a threefold lower incidence of nausea or vomiting [40].

The absolute bioavailability of rivastigmine is approximately 35% after a single oral dose of 3 mg, and 60% after 6 mg [41]. Plasma protein binding of rivastigmine is quite low at 40% and its volume of distribution ranges from 1.8 to 2.7 l/kg [101]. The drug easily penetrates the BBB and, through the inhibition of acetylcholine hydrolysis, increases the level of acetylcholine in brain synapses. In cerebrospinal fluid, the t_{max} ranges from 1.4 to 3.8 h with a half-life of 0.31–2.95 h [42].

Box 2. Risk factors for Parkinson's disease dementia.

- Older age
- Older age at onset of motor symptoms
- Speech and axial involvement
- Severe motor symptoms
- Poor cognitive tests scores (especially verbal fluency)
- Depression
- Early episodes of levodopa related confusion or psychosis
- Smoking

Adapted from [27].

Table 1. Pharmacokinetic parameters of rivastigmine.

Bioavailability	t_{max} (h)	Protein binding	Elimination half-life (h)	Hepatic metabolism	Linear/nonlinear
36% (3 mg dose)	0.8–1.2 (plasma)	40%	1 (plasma)	Nonhepatic (cholinesterase-mediated decarbamylation)	Linear
60% (6 mg dose)	1.4–3.8 (CSF)		0.3–3 (CSF)		

CSF: Cerebrospinal fluid. Data from [57].

Rivastigmine is rapidly metabolized, primarily by cholinesterases (the same enzymes that it inhibits) into the active decarbamylated metabolite NAP 226–90; the clearance has a $t_{1/2}$ that ranges from 0.3 to 3.0 h. Rivastigmine is not metabolized by hepatic oxidative cytochrome P450 isoenzymes. After metabolism, the drug is excreted primarily through renal elimination (>90% in the urine in 24 h). Less than 1% of the intake dose is excreted in the feces.

The plasma half-life of rivastigmine is slightly prolonged in the elderly, but the resulting increase in $t_{1/2}$ is not clinically significant [42]. In patients with renal or mild hepatic impairment, the pharmacokinetics are altered compared with adult volunteers, but specific dosage adjustments may not be necessary [43].

The majority of data on rivastigmine pharmacodynamics come from the data obtained in AD patients where positive effects on cognitive impairment, behavioral symptoms and functional changes in daily activities have been consistently observed.

Rivastigmine is a carbamate-type dual cholinesterase inhibitor of both AChE and BuChE with equal potency [36]. The two cholinesterases hydrolyzing acetylcholine in the human brain are both targets for the cholinergic treatment of dementias. Tacrine and rivastigmine inhibit both enzymes, while donepezil and galantamine specifically inhibit AChE. The role of brain BuChE has been increasingly recognized in recent years. It has been proved that BuChE can potentially substitute for AChE, and that this enzyme is likely to play a constitutive role in the hydrolysis of acetylcholine in the normal brain [44]. In the healthy human brain, BuChE is present in lower concentrations than AChE and is usually thought to have a much more restricted neuronal distribution in the CNS [45]. However, in the AD brain, AChE activity is lost early by up to 85%, while the BuChE to AChE ratio increases from 0.2 to as much as 11 in cortical regions affected by AD. If so, this might indicate that BuChE has some specific role in AD pathogenesis beyond the mere supportive function in hydrolyzing excess acetylcholine that was classically affirmed [46]. Furthermore, in DLB, the rate of cognitive decline has been shown to correlate with BuChE levels in the temporal cortex [47]. Therefore, a dual inhibition of both AChE and BuChE (e.g., as provided by rivastigmine) may have an added value over selective AChE inhibition. In keeping with this, a brain perfusion single-photon emission computed tomography study with ^{99}TC-ethyl cysteinate performed in patients with PDD after 6 months of treatment with rivastigmine showed a bilateral increase of perfusion in the cingulate and frontal regions [48]. This result suggests a possible role of rivastigmine in frontal reafferentation.

Along this line, further evidence, mainly from *in vivo* imaging, indicates that not only AChE, but also BuChE, is decreased in AD, indicating that the overall contribution of BuChE in AD cerebral cortex has yet to be quantified [49]. The lack of good quality head-to-head studies still leaves it unclear if the dual inhibition of AChE and BuChE is superior to just AChE inhibition.

Clinical efficacy

The clinical efficacy of rivastigmine in PDD has been reported by a large controlled study [24]. Primary efficacy outcomes were the scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC) after 24 weeks of treatment. The ADAS-cog has been designed to monitor cognitive decline in AD by assessing orientation, memory, language, visuospatial and praxis functions. Secondary outcome variables were: the ADCS-Activities of Daily Living scale (ADCS-ADL), the 10-item Neuropsychiatry Inventory (NPI), the MMSE, the Cognitive Drug Research (CDR) Computerized Assessment System power of attention, the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test for the assessment of verbal fluency and the ten-point Clock-Drawing test. Patients treated with rivastigmine improved significantly in the ADCS-CGIC score compared with the placebo group. The mean scores for the ADCS-CGIC at week 24 were 3.8 in the rivastigmine group and 4.3 in the placebo group ($p = 0.007$). Cognitive performance improved more in the treated group compared with placebo, as measured by the ADAS-cog score: mean improvement of 2.1 points as compared with worsening of 0.7 point in the placebo group; in both groups the mean value did not deteriorate below baseline. Furthermore, compared with placebo, rivastigmine provided benefits in several cognitive fields as revealed by the MMSE (mental status), the D-KEFS verbal fluency test, the CDR power of attention tests and the ten-point Clock-Drawing test. Behavioral symptoms were also improved more in the rivastigmine group compared with placebo, as measured by the NPI. Functional decline, as assessed by the ADCS-ADL, was significantly less in the rivastigmine group compared with placebo.

In the same population of the previous studies, Burn and colleagues prospectively examined whether rivastigmine provides benefits in a subpopulation with visual hallucinations at baseline compared with the population without visual hallucinations [50]. Based on the NPI from the original 541 patients, 188 with visual hallucinators and 348 without hallucinations were prospectively studied. Primary measures were the ADAS-cog

and the ADCS-CGIC. Secondary outcomes were: ADCS-ADL, D-KEFS, power of attention from the CDR attention battery, the MMSE and the NPI. After 24 weeks from baseline, rivastigmine provided improvements on the ADAS-cog in both groups, with a larger benefit in the group with visual hallucinations (4.27 points; p = 0.002) than in the group without (2.09; p = 0.015). Moreover, it was observed that, in the group with visual hallucinations, decline of ADCS-CGIC scores was milder after 6 months of treatment compared with placebo (p = 0.03); these effects were less marked in patients without visual hallucinations (not significant). Secondary outcome measures demonstrated benefits from rivastigmine treatment compared with placebo, which was more pronounced in the group with visual hallucinations. PDD patients with visual hallucinations seemed to receive a greater benefit from rivastigmine treatment.

A *Cochrane* meta-analysis reviewed the available data and found that almost 15% of PDD patients treated with rivastigmine had a clinically meaningful benefit [51].

Safety & tolerability

In the PDD study, the most frequent side effects associated with rivastigmine capsules were gastrointestinal symptoms, such as nausea and vomiting, which were mild to moderate in nature [24]. An increase of tremor was the third most frequent side effect in the rivastigmine capsule group.

Table 2 summarizes the tolerability profile of rivastigmine capsules in PDD patients [24]. It has been observed that rivastigmine is associated with a similar rate of serious adverse events compared with placebo. No clinically relevant side effects on several hematologic and biochemical tests were reported, and no modification of cardiovascular vital signs were associated with rivastigmine in this population. Significantly fewer patients died in the rivastigmine group, compared with the placebo group ($p < 0.05$) [52]. Side effects related to the gastrointestinal system occurred more frequently as doses were increased. Hence, if oral rivastigmine treatment is interrupted for longer than several days, it should be reinitiated with the lowest daily dose and up-titrated in order to prevent the possibility of severe vomiting and its potentially serious consequences. Heart diseases or stomach ulcers should be treated before starting rivastigmine. In clinical studies with rivastigmine capsules, some patients also experienced fainting, weakness and an upset stomach.

A novel treatment approach is the rivastigmine transdermal patch, which provides a maintenance dose (4.6 or 9.5 mg/24 h), delivering comparable rivastigmine exposure and similar therapeutic effect up to the maximum recommended oral doses of 6 mg b.i.d [53,54]. The rivastigmine patch offers better tolerability and easy access to an optimal therapeutic dose [39]. This may, in turn, lead to improved efficacy and compliance [39]. In patients with cognitive impairment it is indeed difficult to make sure that the oral capsules are correctly swallowed once they are administered.

Dosage & administration

In patients with AD or PDD, the recommended starting dose of rivastigmine capsule is 1.5 mg b.i.d. with meals (breakfast and dinner). If this dose is well tolerated, it can be increased and up-titrated until optimal therapeutic responses are achieved, usually within the range of 3–12 mg/day with 4-week steps at each dosage.

Rivastigmine transdermal patch is available in two sizes and dosages strengths: 5 cm^2 (4.6 mg/day) and 10 cm^2 (9.5 mg/day) containing 9 and 18 mg of rivastigmine, respectively. The recommended starting dose of the rivastigmine patch is 4.6 mg/24 h in *de novo* patients. This can be increased to the target dose of 9.5 mg/24 h after 4 weeks. The body sites at which 9.5 mg/24 h patches should be applied to obtain the greatest

Table 2. Adverse events in a cohort of Parkinson's disease dementia patients treated with rivastigmine versus placebo.

Adverse event	Rivastigmine (%; n = 362)	Placebo (%; n = 179)
Nausea	29	11
Vomiting	17	2
Tremor	10	4
Diarrhea	7	5
Falls	6	6
Anorexia	6	3
Dizziness	6	1
Hypotension	5	8
Constipation	5	7
Hallucination	5	10
Fatigue	4	3
Confusion	4	6
Headache	4	3
Asthenia	2	1
Orthostatic hypotension	2	5
Abdominal pain	1	1
Flatulence	1	0
Malaise	1	2
Sweating	-	-

Data from [24].

Table 3. History of drug development for Parkinson's disease dementia.

Country	Registration date (oral)	Registration date (transdermal)
EU	28 February 2006	
USA	27 June 2006	06 July 2007
Switzerland	30 January 2006	
Latin America	30 January 2006	
Brazil	28 November 2005	

Data from [101,102].

bioavailability are the upper back, the chest or the upper arm, to provide continuous delivery of medication through the skin over 24 h [55].

Regulatory affairs

Rivastigmine oral capsules were initially approved in Switzerland for AD in 1997, and since then have been available for marketing in over 70 countries worldwide, including Europe, the USA and Canada. In addition, the transdermal patch formulation of rivastigmine has been developed as an alternative to the oral formulation and it was registered for AD in the USA and Europe in 2007.

In March 2006, rivastigmine capsules were granted European marketing authorization for the treatment of dementia associated with PD, making it the only medication available to treat this type of dementia in the EU (Table 3) [101]. In the USA, rivastigmine transdermal patch has also been approved for PDD [102].

Based on the guidelines on PD published by European Federation of Neurological Society (EFNS), dementia in PD is treated by adding cholinesterase inhibitors: rivastigmine (level A), donepezil (level C) or galantamine (level C) [56]. The guidelines published in 2006 by the American Academy of Neurology (AAN) suggest using rivastigmine as a symptomatic remedy for patients with PDD [33].

Expert commentary

The introduction of rivastigmine in the management of non-motor problems associated with PD has pioneered a new treatment approach in these patients. Rivastigmine is a potent cholinergic enhancer. When orally administered, it requires careful up-titration at the start of treatment, but then provides stable and long-lasting cognitive improvement. A novel alternative treatment approach in many countries (where it has been approved) is the rivastigmine transdermal patch, which is associated with improved tolerability, easier access to optimal therapeutic doses and potentially enhanced efficacy and compliance. The availability of these new powerful treatments requires updating of daily clinical practice by making available better organized care services (e.g., daily community visits) to ensure that patients are complying and any side effects can be promptly dealt with to avoid withdrawal from the drug.

Further data are necessary in order to ascertain the long-term outcome of PDD patients treated chronically with rivastigmine compared with untreated patients. Currently, there is no systematic information on the use of rivastigmine beyond 1 year. In addition, various imaging techniques can be used to evaluate the functional changes produced by cholinesterase inhibitors in the short and long term. Another limitation of the available data is that cognition in PDD patients was measured with tools originally designed for AD-type dementia. Further studies should be performed using appropriate tools to monitor cognitive functions specifically involved in PDD, such as frontal and executive functions.

Information on head-to-head comparisons between rivastigmine and other commercially available cholinesterase inhibitors is also lacking. Being an inhibitor of both AChE and BuChE, rivastigmine may be superior to selective AChE inhibitors (e.g., donepezil and galantamine), but this assumption requires confirmation by direct comparison of the two types of cholinesterase inhibitors. Furthermore, specific studies on the pharmacokinetics and pharmacodynamics of rivastigmine in PDD, and on its interactions with dopaminergic medications, are also warranted.

An important issue, inadequately addressed, is the evaluation of cost–benefit efficacy of the use of rivastigmine in PDD. Pharmacoeconomic trials are difficult to adapt to this kind of study, because of hardly definable variables, such as disease-related changes (being PDD chronic and progressive), costs of nursing and home care, value of unpaid caregiver's time and of the use of community support services.

Five-year view

Treatment of cognitive impairment associated with PDD is a new and expanding field. In the foreseeable future, PDD patents will be regularly and systematically treated for cognitive impairment, and specific scales will be developed aside motor scales. Clinical data will be correlated more reliably to the patients' genetic make-up, allowing better prediction of the role of known genes (e.g., α-synuclein and the tau gene) in cognitive decline associated with PD. This will generate new treatment hypotheses for cognitive decline.

Data on long-term treatment of PDD patients with rivastigmine will become available in the coming years. This will provide recommendations for long-term management, which are currently lacking. In the coming years, other cholinesterase inhibitors may receive licensing for dementia associated with PDD, and the results of an ongoing study on the efficacy of memantine for PDD will be published. North American and European practice parameters for dementia associated with PDD will be updated to encompass a number of different medications and different disease subtypes.

Key issues

- Rivastigmine is a dual inhibitor for both acetylcholinesterase and butyrylcholinesterase.
- Rivastigmine is indicated for the management of Parkinson's disease dementia (PDD) and Alzheimer's disease (AD).
- A *Cochrane* review of the efficacy, safety, tolerability and health economic data relating to the use cholinesterase inhibitors in PDD concluded that rivastigmine improves cognition and activities of daily living.
- Rivastigmine capsules are well tolerated at doses of 3–12 mg/day in patients with PDD; the most common adverse events are mild-to-moderate gastrointestinal symptoms (mainly nausea and vomiting) and tremor.
- The rivastigmine transdermal patch has recently been approved for the treatment of patients with AD worldwide, and for PDD in some countries including the USA.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this review manuscript.

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