RESEARCH PAPER

Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial

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Received 29 July 2013
Revised 14 October 2013
Accepted 18 October 2013
Published Online First 11 November 2013

ABSTRACT

Background Even with optimal dopaminergic treatments, many patients with Parkinson's disease (PD) are frequently incapacitated by apathy prior to the development of dementia. We sought to establish whether rivastigmine's ability to inhibit acetyl- and butyrylcholinesterases could relieve the symptoms of apathy in dementia-free, non-depressed patients with advanced PD.

Methods We performed a multicentre, parallel, double-blind, placebo-controlled, randomised clinical trial (Protocol ID: 2008-002578-36; clinicaltrials.gov reference: NCT00767091) in patients with PD with moderate to severe apathy (despite optimised dopaminergic treatment) and without dementia. Patients from five French university hospitals were randomly assigned 1:1 to rivastigmine (transdermal patch of 9.5 mg/day) or placebo for 6 months. The primary efficacy criterion was the change over time in the Lille Apathy Rating Scale (LARS) score.

Finding 101 consecutive patients were screened, 31 were eligible and 16 and 14 participants were randomised into the rivastigmine and placebo groups, respectively. Compared with placebo, rivastigmine improved the LARS score (from −11.5 (−15/−7) at baseline to −20 (−25/−12) after treatment; $F_{(1,\ 25)}$=5.2; p=0.031; adjusted size effect: −0.9). Rivastigmine also improved the caregiver burden and instrumental activities of daily living but failed to improve quality of life. No severe adverse events occurred in the rivastigmine group.

Interpretation Rivastigmine may represent a new therapeutic option for moderate to severe apathy in advanced PD patients with optimised dopaminergic treatment and without depression dementia. These findings require confirmation in a larger clinical trial. Our results also confirmed that the presence of apathy can herald a pre-dementia state in PD.

Registration Clinicaltrials.gov reference: NCT00767091.

To cite: Devos D, Moreau C, Maltête D, *et al*. *J Neurol Neurosurg Psychiatry* 2014;**85**: 668–674.

INTRODUCTION

Apathy is a frequent consequence of neurological and psychiatric disorders. It is characterised by lack of interest, loss of initiative, indifference and flattening of affect. As noted by Marin, apathy is not just a symptom of depression or dementia, but can exist as a syndrome on its own.[1] Apathy severely impacts the patient's activities of daily living and those of the caregivers and relatives. In studies of Parkinson's disease (PD), the prevalence of apathy ranges from 17% to 50%,[2] with a mean value of 29%.[3] This high value reflects the involvement of the frontal-subcortical circuits and suggests a dysfunction of the most ventral parts of the striatum (ie, those receiving inputs from the cortical limbic regions). Indeed, the fact that apathy is associated with cognitive impairment but not motor symptoms[3] suggests the involvement of non-motor circuits. The neurochemical substrates of apathy have yet to be unambiguously identified. Indeed, there are probably several substrates—even though the central dopaminergic system's role in reward and motivation is often mentioned.[4 5] In fact, 'dopaminergic apathy' has been described in patients receiving subthalamic nucleus deep brain stimulation (STN DBS). In this particular group, apathy is probably related to changes in dopaminergic regimens after surgery and is relieved by increasing the dosage of dopamine agonist.[6 7] Several studies have highlighted dopaminergic limbic cortex denervation[5] and cortical hypometabolism[8] in apathetic patients. However, apathy may also occur in patients with optimised dopaminergic treatments. Apathy is more frequent in patients with PD with cognitive decline and may even precede dementia.[9] Cholinergic depletion has been considered to be an important cause of cognitive worsening in PD.[10] Moreover, apathy is also frequent in Alzheimer's disease (AD), in which the dopaminergic system is relatively unaffected. Cummings and Back[11] proposed that medial frontal and limbic cholinergic deficits may underlie apathy in AD. This hypothesis is supported by the observed, beneficial effects of cholinesterase inhibitors (which were originally developed to treat the cognitive symptoms of AD) on one hand on neuropsychiatric symptoms including apathy,[12] and on the other hand on parkinsonian dementia.[13 14]

Hence, we reasoned that cholinesterase inhibitors (such as rivastigmine) might compensate for impaired cholinergic transmission within the limbic

and associative subcorticofrontal loops in PD and thus relieve the symptoms of apathy in advanced PD (for which there are currently no treatments). We also wondered whether rivastigmine treatment might reduce the burden placed on caregivers and relatives.

The objective of the present proof-of-concept study (a multicentre, double-blind, placebo-controlled, randomised clinical trial) was to assess the effect of a 6-month course of rivastigmine on apathy (as measured on the sensitive Lille Apathy Rating Scale (LARS)[15 16] in non-demented, non-depressed, patients with advanced PD receiving optimal dopaminergic treatment.

METHODS

Participants

Patients were prospectively enrolled by the movement disorders departments at five university hospitals in France (Amiens, Caen, Lille, Marseille and Rouen). The inclusion criteria were as follows: confirmed PD, according to Gibb's criteria,[17] at an advanced stage with slight to severe motor and/or non-motor complications related with L-dopa and apathy (diagnosed according to the 2009 criteria[18] on the basis of a clinical interview and a score of −16 or higher (ie, −16 to +36) on the LARS[15]), despite optimised dopaminergic therapy (including L-dopa, in all cases). We carefully checked the optimised dopaminergic therapy for apathy (on LARS) through uptitration of their current dopaminergic medication: (1) when no dopamine D2/D3 receptor agonist (DA) was taken, a DA was added (pramipexole or ropinirole), (2) when a DA was taken, the dose was increased until the maximum recommended dose, (3) when DA was contraindicated or already taken at the maximum recommended dose, the L-dopa dose was increased by 33%. Apathy was reassessed, on LARS, 3 months after the last treatment modification. The treatment was considered optimised when the last modification brought no change of the LARS.

The exclusion criteria included (1) dementia, diagnosed according to the Movement Disorders Society criteria,[19] (2) concurrent axis I psychiatric disorders, as assessed in a semi-structured interview (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revised (DSM-IVr), Text Revision, 2000), (3) depression (a score greater than 18 on the Montgomery and Asberg Depression Rating Scale (MADRS) and semistructured interview according to DSM-IVr), (4) dopaminergic apathy (known to be frequent in patients with early stage PD receiving low doses of L-dopa, in patients with late-stage PD, or in patients not receiving dopamine agonists), (5) patients with changes in their dopaminergic regimen or STN stimulation parameters in the 3 months preceding the study or during the study, (6) deep brain stimulation for less than 2 years, (7) serious or unstable medical conditions (particularly myocardial infarction, angina pectoris, atrioventricular block, heart failure and liver failure, (8) on-going treatment with cholinomimetic drugs or carbamate derivatives, (9) age above 80 years.

The antiparkinsonian medication was held constant during the study.

The local independent ethics committee approved the study's objectives and procedures in 2008 (Protocol ID: 2008-002578-36; clinicaltrials.gov reference: NCT00767091). The full trial protocol (in French) can be requested from frc@chru-lille.fr. All patients provided their written, informed consent to participation. The study was performed in accordance with the precepts of the Declaration of Helsinki.

Randomisation and masking

Randomisation was balanced by centre. The 1:1 assignment sequence (based on a block size of four and the use of a computerised random-number generator) was produced by the Statistics Department at Lille University Hospital (Lille, France). The randomisation list was sent to an independent contract research organisation (LC2, Lentilly, France) for preparation and distribution of identical rivastigmine and placebo transdermal patches. Patients, carers, study staff and investigators were blinded to the assignment.

Procedures

Patients received either placebo or a rivastigmine maintenance dose of 9.5 mg/day. In the rivastigmine group, an initial month-long titration (with a dose of 4.6 mg/day) was performed. In the event of poor tolerance of the maintenance dose, the dosage was reduced to 4.6 mg/day for 2 weeks before returning to 9.5 mg/day, if possible. Tolerability (as assessed by interviews and examinations) and compliance (as assessed by interviews and patch counts) were checked every 3 months.

Efficacy criteria

The primary efficacy criterion was the mean change over time in the LARS score (ie, between inclusion and the 6-month visit). The LARS score ranges from −36 (no apathy) to +36 (extreme apathy). The everyday consequences of parkinsonian apathy were assessed with the Zarit Burden Interview,[20] the Instrumental Activities of Daily Living (IADL) scale[21] and the Parkinson's Disease Quality of Life scale (PDQ39).[22] The cognitive impact of rivastigmine in non-demented patients was measured on the Mattis Dementia Rating Scale (MDRS).

Tolerability and safety criteria

Tolerance was monitored with the MADRS for mood, the Epworth Sleepiness Scale[23] for sleepiness and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score for motor impairments. Each patient's general health status, weight, prone and standing systolic and diastolic blood pressures, heart rate and electrocardiogram were assessed every 3 months after randomisation. Standard laboratory blood tests were run monthly. The presence of cutaneous reaction to the transdermal patch was systematically evaluated. The study's data and safety monitoring board examined adverse event reports periodically.

Optional extension phase for long-term assessment

Compassionate administration of rivastigmine was offered to all patients at the end of the 6-month treatment period. We analysed the LARS score, the MDRS score and dementia (according to the Movement Disorders Society criteria) 12 months later (ie, 18 months after the initiation of treatment with rivastigmine or placebo).

Statistical analysis

The sample size in this pilot study was calculated on the basis of anticipated mean (SD) LARS score of −8.23 (7) in the placebo group in an earlier study.[3] We planned to adjust this score for the baseline value and, therefore, set the expected difference in LARS score to 5 (−3.23), which would corresponded to a size effect of 0.714. With a statistical power of 80%, a type I error of 5%, a SD of 7, a coefficient of 0.4 for the correlation between the baseline and the end-of-study measurement, and an expected drop-out rate of 10%, the required sample size was

estimated to be 30 participants per group (ie, 60 participants in total). There were no intermediate analyses.

Baseline characteristics were reported by applying descriptive statistics and were expressed as the median (range]. The respective mean LARS scores in the rivastigmine and placebo groups at 6 months were compared in a covariance analysis and adjusted for baseline differences. If a non-normal distribution was found, the data's robustness was checked after log transformation. The influence of each individual participant on the results was investigated by calculating the Cook distance. All individuals had a Cook distance <1, as recommended by Cook.[24] For statistically significant results, we computed the effect size (after adjustment for baseline differences). Numerical safety parameters were examined in an analysis of variance. All significance tests were two-tailed. The threshold for statistical significance was set to p=0.05 in all analyses (all of which were performed with SPSS software, V.15).

Role of the funding source

This academic, investigator-driven study was funded by a PHRC grant from the French Ministry of Health. Novartis Pharma provided the rivastigmine and the placebo but had no involvement in the study design, data collection, data analysis, data interpretation or report writing. The principal investigator (DD) had full access to all the study data and had final responsibility for submitting the study report for publication.

RESULTS

Termination of recruitment

Between 15 April 2009, and 7 July 2011, 101 patients with PD with their carers having complained of symptoms of apathy were consecutively screened for apathy, dementia and depression on the LARS, the MDRS and the MADRS, respectively. However, patient recruitment was slower than expected and, ultimately, was limited by the study medication's shelf life and the need to initiate the study before an extension had to be requested. We then calculated that if we refrained from performing an intermediate analysis, a LARS score difference of 5 with an observed SD of 5 (rather than the expected SD of 7) for the population as a whole would yield a size effect of 1 with 18 patients per group before adjustment for the baseline. Since sufficient statistical power had been achieved, we decided to initiate the study with the available participants.

Patient characteristics

Of the 101 screened patients, only 31 were eligible for inclusion. One patient was not included because of a severe cardiac disorder. Hence, 30 patients with moderate-to-severe apathy, with optimised dopaminergic treatment and without dementia were prospectively included and randomised (figure 1). The rivastigmine and placebo groups were well balanced in terms of baseline characteristics (table 1). All patients had a baseline score of MDRS above 130 except one patient in the rivastigmine group (MDRS: 128) and one in the placebo group (MDRS: 127). On the basis of patch counts and patient/caregiver interviews, treatment compliance was over 90% for the participants receiving 9.5 mg rivastigmine per day. The worsening of pre-existing orthostatic hypotension prompted a maintenance dose reduction to 4.6 mg/day in one case.

EFFICACY

A covariance analysis revealed a significant main effect of *group* for the primary efficacy criterion (ie, the change in the LARS score between baseline and the visit at 6 months) (table 2). The

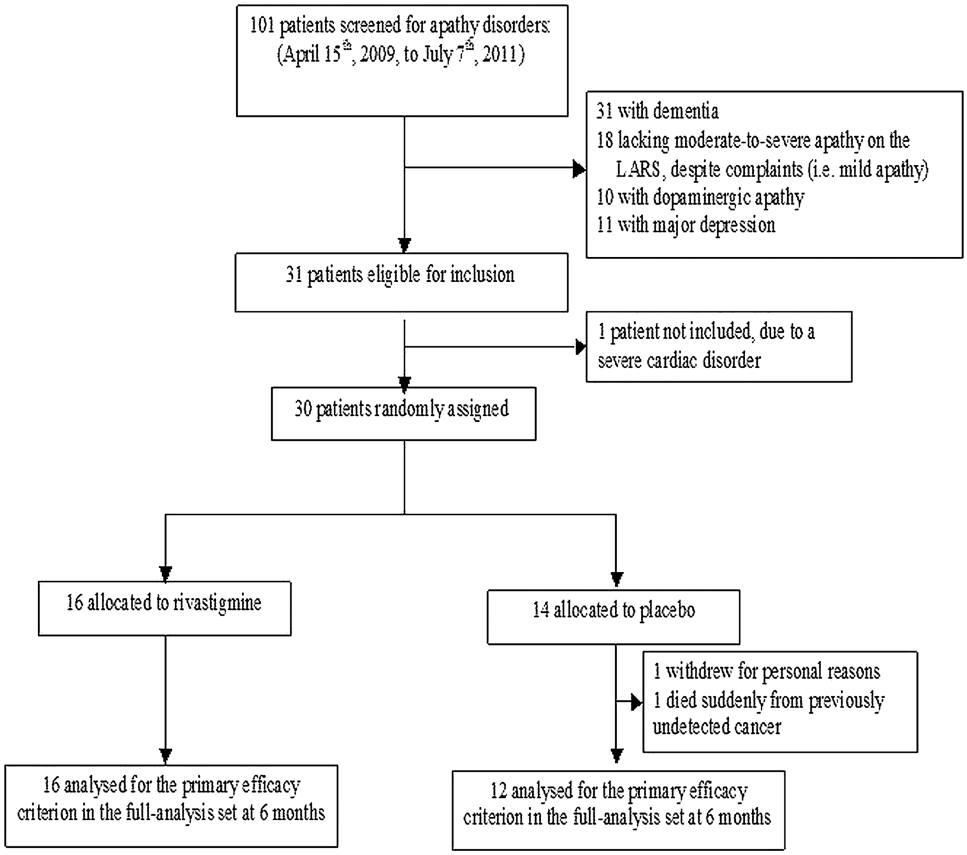

Figure 1 Flowchart.

Table 1 Baseline characteristics of the study participants in the rivastigmine and placebo groups

	Placebo	Rivastigmine	Mann–Whitney test p value
Number of participants	14	16	–
Age (years)	65 [58/73]	68 [63/71]	z=−1; p=0.3
Time since disease onset (years)	13 [6/19]	12 [8/15]	z=−1.2; p=0.2
Gender ratio (F/M)	6/8	5/11	Fisher's exact test: p=0.7
Body weight (kg)	69 [65/85.5]	75 [66/84]	z=−0.6; p=0.5
Heart rate (beats per minute)	72 [66/78]	66 [56/82]	z=−0.9; p=0.3
Systolic blood pressure (mm Hg)	134 [110/144]	139 [130/158]	z=−0.6; p=0.7
Diastolic blood pressure (mm Hg)	82 [69/92]	79 [73/89]	z=−0.4; p=0.6
L-dopa daily dose equivalent (mg)	700 [487/912]	700 [500/925]	z=−0.4; p=0.7
Percentage (n) of patients taking dopaminergic agonists	42% (6)	50% (8)	Fisher's exact test: p=0.7
Percentage (n) of patients on rasagiline	21% (3)	25% (4)	Fisher's exact test: p=1
Percentage (n) of patients on entacapone	57% (8)	68% (11)	Fisher's exact test: p=0.4
Percentage (n) of patients on amantadine	28% (4)	25% (4)	Fisher's exact test: p=1
Number of patients with STN DBS (mean duration±SD)	3 (6±3)	3 (5±3)	Fisher's exact test: p=1

The data are quoted as the median [1st quartile/3rd quartile] values, the number or the percentage of participants (%). Prone systolic and diastolic blood pressure values are quoted. There was no significant intergroup difference in the standing blood pressure values (data not shown).
F, female; M, male; STN DBS, subthalamic nucleus deep brain stimulation.

LARS score decreased in 81% of the patients in the rivastigmine group and in 25% of the patients in the placebo group. At 6 months, 37% of the patients in the rivastigmine group and 83% of the patients in the placebo group had a LARS score of −16 or higher, and were thus classified as apathetic. In terms of the LARS subscores, intellectual curiosity and action initiation improved more in the rivastigmine group than in the placebo, whereas, there were no significant intergroup differences in the changes in the self-awareness and emotion groups (table 2). When compared with placebo, rivastigmine was associated with significantly better Zarit Burden Interview and IADL scores, but was not associated with an improvement in the PDQ39 score. The MDRS scores in the two groups were within the normal range and did not differ significantly. However, we observed a trend towards worse outcomes in the placebo group (in which 58% of the patients worsened, 17% were stable and 25% improved), relative to the rivastigmine group (in which 31% of the patients worsened and 69% improved). No significant difference was observed between the subgroups of patients having or not dopamine agonists (data not shown).

Tolerability and safety criteria

A covariance analysis did not detect a significant main effect of *group* on the MADRS, Epworth Sleepiness Scale and UPDRS motor scores, the weight, the prone and standing blood pressures, the heart rate, the electrocardiogram or the blood biochemistry profile. Two patients from the placebo group withdrew from the study prematurely: one withdrew consent for personal reasons, and one patient suddenly died from previously undetected, generalised cancer (figure 1). The blinding code was not broken. Five patients in the placebo group and none of the patients in the rivastigmine group declared severe adverse events. Overall, adverse events were more frequent in the rivastigmine group than in the placebo group (table 3). We noticed no cutaneous reaction to the transdermal patch.

The 12-month extension phase for long-term assessment

Between the 6-month and 18-month visits, we observed a significant reduction in the symptoms of apathy in patients previously in the placebo group (median LARS score at 18 months: −16 [−21/−9], p<0.05). We found that 66% of the patients previously in the placebo group were apathetic at 18 months (compared with 86% prior to the start of their treatment with rivastigmine, p<0.05). In the group of patients having received rivastigmine from the outset, the frequency of apathy rose from 44% at 12 months to 54% at 18 months. The median LARS score at 18 months in this group was −16 (−21/−6), which did not differ significantly from the corresponding score in the placebo group. Eighteen months after the start of treatment, mild to moderate dementia was present in 44% of the patients previously in the rivastigmine group and 50% of the patients previously in the placebo group; there was no significant difference in the median MDRS score (131 (127–137) and 131 (125–135), respectively).

DISCUSSION

This double-blind, placebo-controlled trial showed that 6 months of rivastigmine treatment was associated with a reduction (vs placebo) in apathy (as rated on the LARS) in a highly selected population of non-demented, non-depressed, advanced PD patients with moderate to severe apathy that had not responded to dopaminergic treatments. Compared with placebo, treatment with rivastigmine was also associated with improvements in attention, the IADL score and a lower burden for caregivers and relatives (according to the Zarit Burden Interview) but failed to improve the quality of life (PDQ39). The observed benefit on the patients' and caregivers' daily life is noteworthy because there are currently no recommended treatments for apathy, which does not respond to optimised dopaminergic treatment. We suggest that apathy had a great impact of the patients' functional activity and thus the caregiver burden. However, the patients' quality of life (according to the PDQ39) did not change significantly; this may have been because (1) the reduction in the severity of apathy was only partial and/or (2) PD patients are not always aware of the symptoms of apathy. The trial's dropout rate was low and no serious adverse events were observed in the rivastigmine group.

The main limitation of the present study was its small sample size. This was partly due to the high number of screening failures. Indeed, moderate to severe apathy has to be confirmed in an extensive neuropsychiatric examination in order to rule out depression, other neuropsychiatric disorders and, most

Table 2 The main efficacy and tolerance criteria

(Number of patients)	Placebo		Rivastigmine		p Value (adjusted effect size) Covariance analysis
	Baseline (n=14)	6 months (n=12)	Baseline (n=16)	6 months (n=16)	
Efficacy on apathy					
LARS score (lower=better)	−13.3 [−16/−12]	−13.5 [−15/−12]	−11.5 [−15/−7]	−20 [−25/−12]	$F_{(1, 25)}$=5.2; p=0.034 (−0.9)
% (n) of apathetic patients	100 (14)	83 (10)	100 (16)	37 (6)	–
LARS: intellectual curiosity	−0.5 [−0.8/−0.2]	−0.5 [−0.8/0]	−0.5 [−1.3/0.6]	−1.8 [−2.8/0.2]	$F_{(1, 25)}$=4; p=0.05 (−0.8)
LARS: action initiation	−1.5 [−2/−0.9]	−1.3 [−2/−0.9]	−1.5 [−2/−0.4]	−2.8 [−3.5/−1.3]	$F_{(1, 25)}$=4.4; p=0.046 (−0.8)
LARS: emotion	−3 [−3.5/−2.4]	−3 [−3.6/−2]	−2 [−3.1/−1]	−3 [−4/−2]	$F_{(1, 25)}$=0.1; p=0.7 (−0.15)
LARS: self-awareness	−2 [−3/−2]	−2 [−3.3/−2]	−2 [−3.3/−1]	−4 [−4/−2]	$F_{(1, 25)}$=2; p=0.1(-0.4)
Zarit Burden Interview (lower=better)	27 [25/34]	28.5 [26/40]	27.5 [23/37]	25.5 [19/32]	$F_{(1, 25)}$=5.5; p=0.026 (−0.9)
Daily Living Activities scale (lower=better)	16.5 [14–23]	19.5 [15–24]	15 [13–19]	14 [13–16.5]	$F_{(1, 25)}$=7; p=0.01 (−1)
Quality of Life scale (PDQ39) (higher=better)	54 [42/64]	52 [45/70]	54 [44/62]	57 [48/64]	$F_{(1, 25)}$=0.8; p=0.3 (−0.4)
Efficacy on cognition					
MDRS (higher=better)	136 [134–138]	135.5 [132–137]	135 [132–138]	135 [132–139]	$F_{(1, 25)}$=2.9; p=0.09 (0.7)
Tolerance					
Depression on the MADRS (lower=better)	8 [4.5/10]	8.5 [6/10]	8 [7/9]	10.5 [6/12]	$F_{(1, 25)}$=0.1; p=0.6 (0.15)
Epworth Sleepiness scale score (lower=better)	10 [7/11]	8.5 [7/10]	9 [6/12]	7.5 [5/12]	$F_{(1, 25)}$=0.3; p=0.5 (0.1)
UPDRS motor score (lower=better)	23 [18/43]	25 [20/40]	22.5 [18/33]	24.5 [19/37]	$F_{(1, 25)}$=0.4; p=0.5 (0.1)

The data are quoted as the median [1st quartile/3rd quartile] values.
Apathy was defined as a score of −16 or higher (ie, −16 to +36) on the Lille Apathy Rating Scale (LARS).
The right column display the results of the statistical analyses.
The p values correspond to intergroup comparisons at 6 months (adjusted for baseline) in a covariance analysis. The adjusted effect size are provided between brackets (please see the statistical paragraph).
An effect size of 0.2 is considered to be small, an effect size of 0.5 is average and an effect size of 0.8 is high.[25]
MADRS, Montgomery and Asberg Depression Rating Scale; MDRS, Mattis Dementia Rating Scale; Ms, milliseconds; UPDRS, Unified Parkinson's Disease Rating Scale, motor part of the UPDRS (part III).

importantly, the onset of concomitant dementia, which has a high incidence in advanced PD (figure 1). We chose to exclude demented apathetic patients because the symptoms of dementia overlap with those of apathy; hence, rivastigmine's known impact on dementia could have biased our judgement of the drug's efficacy in apathy.[13 14] Finally, we systematically ruled out apathy responding to dopaminergic drugs (with dopaminergic agonist introduction or higher doses and/or L-dopa higher dose). Thus, the extensive neuropsychiatric examination, the preliminary treatment adaptations and the high number of screening failures means that recruitment was slower than expected and, ultimately, was limited by the study medication's shelf life and the need to initiate the planned study before an extension had to be requested. Before stopping the recruitment, we carefully checked that the study was still sufficiently powered to detect the expected effect of rivastigmine. In fact, the SD was lower than had been expected; this may have been due to careful selection of the target population, notably by excluding apathetic or pseudo apathetic symptoms of too slight expressions with the standardised and extensive neuropsychiatric exam. Hence, the lower-than-expected SD (thanks to the highly selected population) compensated for the smaller sample size, and so the study's statistical power was higher than initially anticipated.[3] In order to help the generalisation of the significant results of the main measures (ie, LARS, Zarit Burden Interview and IADL), we performed the adjusted effect size, which was high (table 2), leading us to conclude that rivastigmine's impact on symptoms was particularly prominent.

Table 3 Adverse events

	Placebo	Rivastigmine
Serious adverse events		
Worsening of the parkinsonian syndrome	1	0
Excessive drowsiness and headache	1	0
Sudden death due to previously undetected generalised cancer	1	0
Non-serious adverse events		
Asthenia/drowsiness (transient in one case and permanent in two cases)	0	3
Faintness (transient in two cases and permanent in one case)	0	3
Transient worsening of painful dyskinesia	0	1
Transient urinary retention	1	0
Severe nightmares	1	0
Total number of adverse events	5	7

The analyses were performed on the randomised population (16 patients in the rivastigmine group and 14 patients in the placebo group).

A systematic review of the literature failed to detect therapeutic studies in the field of apathy in advanced PD (despite optimised dopaminergic treatment); only the treatment of dopaminergic apathy has been considered. Dopaminergic apathy notably occurs in patients with PD on STN DBS after the tapering of dopaminergic medications, and can be improved by administration of methylphenidate[26] and dopamine agonists.[6 7] Methylphenidate also reduced the symptoms of apathy in a non-stimulated patient at an earlier stage of PD.[27] Cholinesterase inhibitors have been shown to reduce the symptoms of apathy associated with dementia in AD[12] and PD dementia (ie, improvement of the total score of the neuropsychiatric inventory (including apathy)).[13] The main pathophysiological mechanism of apathy improvement under cholinesterase inhibitors is probably related with the enhancement of the cholinergic neurotransmission within the cognitive and limbic striato-frontal loops (ie, improve the cholinergic depletion), as previously suggested for apathy in demented patients.[9–13] Cholinesterase inhibitors could, therefore, represent a new therapeutic option for moderate to severe apathy in non-demented, advanced, patients with PD.

As expected, the 'cognitive' and 'behavioural' dimensions of the apathy represented by the intellectual curiosity and action-initiation LARS subscores appeared more sensitive to cholinergic transmission enhancement. Emotion was not significantly modified and could be more related with other neurotransmission systems.[28]

Rivastigmine had a good safety profile in the present study. This was probably because (1) we warned the patients of the risk of benign, transient nausea and episodes of vomiting and (2) the prevalence of side effects with transdermal patches is lower than with oral administration.[29] No severe adverse events occurred in the rivastigmine group—possibly because we excluded patients with at-risk cardiac conditions. We did not observe a significant worsening of the rest tremor (as rated on the UPDRS or reported as an adverse event) in the rivastigmine group; in fact, the only case of worsening was reported by a patient in the placebo group. This general lack of worsening may have been due to (1) the absence of patients with severe, pre-existing rest tremor, (2) the small sample size and (3) the good motor symptom control observed prior to study inclusion.

We found that placebo-group patients who went on to receive rivastigmine during the open-label phase saw an improvement in the LARS score; this observation emphasises rivastigmine's ability to reduce the severity of symptoms in apathy. However, the apathy rarely disappeared completely. Moreover, some rivastigmine-treated patients displayed a worsening of apathy in the longer term (after 18 months). This may have been due to a worsening in overall cognitive status and the occurrence of dementia (in 44% of the patients having received rivastigmine for 18 months and in 50% of the patients having received rivastigmine for 12 months). This finding confirms previous reports in which apathy heralded the onset of dementia in PD.[9] The positive short-term risk/benefit balance for apathy observed here should now be investigated in a larger study population and over several years. Indeed, the present proof-of-concept study will enable calculation of the sample size required for a large Phase III clinical trial designed to assess rivastigmine's putative value in delaying the onset of dementia.

CONCLUSIONS

Rivastigmine may represent a new therapeutic option for moderate to severe apathy in patients with advanced PD with optimised dopaminergic treatment and without depression or dementia. Treatment with this medication was associated with positive changes in activities of daily living and the caregiver burden. These findings require confirmation in a larger clinical trial. Our results also confirmed that the presence of apathy can herald a predementia state in PD.

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Acknowledgements The authors wish to thank Valerie Vasseur, Francine Niset, Carine Piatek, Pascal Bechu and the Fédération de la Recherche Clinique du CHU de Lille for collecting the data and Dr David Fraser (Biotech Communication, Damery, France) for helpful comments on the manuscript's English. We thank Novartis Pharma for providing the rivastigmine and placebo for this investigator-driven study.

Contributors DD; The research project: conception, organisation, execution and the manuscript, writing of the first draft, review and critical comment; CM; The research project: conception, organisation, execution and the manuscript: writing of the first draft; AE; The research project: execution and the manuscript: review and critical comment; DM; The research project: execution and the manuscript: review and critical comment; JPA; The research project: execution and the manuscript: review and critical comment; AD; The research project: execution and the manuscript: review and critical comment; AD; carried out the biostatistical analysis; RB; The research project: conception, organisation; The manuscript: review and critical comment; LD; The research project: conception, organisation, execution and the manuscript: review and critical comment; KD; The research project: conception, organisation, execution and the manuscript: review and critical comment; MD; The manuscript: review and critical comment; AK; The research project: execution and the manuscript: review and critical comment; RL; The research project: execution and the manuscript: B. review and critical comment; Thavarak Ouk; The research project: execution and the manuscript: review and critical comment; CS; The research project: execution and the manuscript: review and critical comment; TW; The research project: execution and the manuscript: review and critical comment; DG; The research project: execution and the manuscript: review and critical comment.

Funding This academic study was funded by a PHRC grant (Protocol ID: 2008-002578-36) from the French Ministry of Health. Novartis Pharma provided rivastigmine and placebo.

Competing interests DD has served on the Scientific Advisory Board for Novartis and Aguettant and has received PHRC grants from the French Ministry of Health and research funding from the ARSLA charity. He has received various honoraria from pharmaceutical companies for consultancy and lectures on PD at symposia. CM has served on the Scientific Advisory Board for Aguettant. DM has no disclosures to report. RL has no disclosures to report. AE has served on the Scientific Advisory Board for Aguettant and has received research funding from the FRM charity and ANR grants from the French Ministry of Research. He has received various honoraria from pharmaceutical companies for consultancy and lectures on PD at symposia. J-PA has received PHRC research grants from the French Ministry of Health. He has received various honoraria from pharmaceutical companies for consultancy and lectures on PD at symposia. TW has received PHRC research grants from the French Ministry of Research. She has received various honoraria for consultancy and lectures on PD at symposia from pharmaceutical companies. Alexandre Kreisler has received honoraria from Allergan. Clémence Simonin has no disclosures to report. MD has no disclosures to report. TO has no disclosures to report. AD has potential conflicts of interest: Laboratories Novartis, Boehringer-Ingelheim, Schering-Plough, Merck-Serono, GSK, Merck-Scherring, Teva, Sanofi-Aventis, Lundbeck, Janssen-Cilag, GE Health care, Schawrtz, Bioprojet, Neurosearch, Synosia, Holmes, Impax. AD has no disclosures to report. RB receives funding from the French Ministry of Research. He has received various honoraria from pharmaceutical companies for consultancy and lectures at symposia. LD has served on the Scientific Advisory Board for Novartis and Aguettant. He has received various honoraria from pharmaceutical companies for consultancy and lectures on PD at symposia (Abbott and Boheringer). KD has served on the Scientific Advisory Board for Novartis. She has received a grant from the MJ Fox Foundation for Parkinson's research.

Patient consent Obtained.

Ethics approval Independent ethics committee of the CHRU of Lille (Protocol ID: 2008-002578-36).

Provenance and peer review Not commissioned; externally peer reviewed.

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