1. **The effects of rivastigmine on neuropsychiatric symptoms in the early stages of Parkinson’s Disease: A systematic review**

2. Siobhan Reilly1, Simran Dhaliwal2, Usman Arshad3,4, Antonella Macerollo5,6, Nusrat Husain4,7, Antonio Da Costa8

3. 1Greater Manchester Mental Health NHS Foundation Trust, UK, 2George Eliot Hospital NHS Trust, UK 3Pakistan Institute of Living and Learning, Karachi, Pakistan, 4The University of Manchester, UK, 5The Walton Centre NHS Foundation Trust for Neurology and Neurosurgery, Liverpool, UK, 6Institute of Systems, Molecular and Integrative Biology, University of Liverpool, UK, 7Mersey Care NHS Foundation Trust, 8 Peninsula Health, Frankston South, Melbourne VIC, Australia 3199.

4. Corresponding author: Siobhan Reilly, siobhancreilly@gmail.com

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**Abstract**

**Background**

Neuropsychiatric symptoms including depression, apathy and psychosis occur frequently in patients with Parkinson’s disease. A subgroup of patients develop cognitive impairment, which may increase the risk of falls due to reduced attention. The acetylcholinesterase inhibitor rivastigmine is beneficial in Parkinson’s disease dementia (PDD), but the consensus for the use of rivastigmine earlier in the disease course is unclear. This systematic review aims to assess the evidence for rivastigmine in the treatment of neuropsychiatric symptoms in Parkinson’s disease without dementia.

**Methods**

Embase, Medline, PsychINFO, Cochrane CENTRAL, NGLC, NICE Evidence and medRxiv.org were searched for studies with terms relating to population (Parkinson’s disease) and intervention (rivastigmine). Of 1922 references identified, 358 were duplications. Following title and abstract review, 1331 articles were excluded. After full text review, 9 articles remained.

**Results**

Outcomes were heterogenous, therefore, the results are presented in narrative form. The articles included 6 Randomised Controlled Trials (RCTs), 2 open-label trials and 1 case-series. Outcome measures included: time to develop psychosis, frequency of rapid eye movement behaviour disorder (RBD) episodes, apathy, gait variability, falls, cognitive ability, neuropsychiatric inventory (NPI) score and regional spontaneous brain activity.

**Conclusions**

There is evidence that rivastigmine is beneficial for RBD and apathy in Parkinson’s disease patients without dementia. There is high level evidence that rivastigmine reduces falls, which may be due to improved attention. The impact of rivastigmine on psychotic symptoms is less clear, but is supported by current theoretical models which involve acetylcholine dysfunction in the generation of visual hallucinations in Parkinson’s disease.

**Key words:** Rivastigmine, Acetylcholinesterase, Parkinson disease, Neuropsychiatry, Hallucinations

**Introduction**

Parkinson’s disease is a neurological disorder which is characterised by the progressive degeneration of dopaminergic neurones in the substantia nigra. Dopaminergic deficits contribute to the classical motor features of Parkinson’s disease: tremor, rigidity and bradykinesia. There are also deficits in the cholinergic system1, which, in combination with dopamine loss, may contribute to the neuropsychiatric symptoms experienced as the disease progresses. Neuropsychiatric symptoms associated with Parkinson’s disease include: sleep behaviour disorder, cognitive impairment, delusions, hallucinations, mood disorder and apathy2. In the late stages of Parkinson’s disease, dementia develops in up to 40% of patients3.

Rivastigmine is a cholinesterase inhibitor which inhibits both acetylcholinesterase and butyrylcholinesterase4. This mechanism is in contrast to the other approved cholinesterase inhibitors which only inhibit acetylcholinesterase. This review focuses on rivastigmine as it is the most widely studied anticholinesterase for the neuropsychiatric symptoms of Parkinson’s disease. Existing evidence indicates that donepezil has beneficial effects for psychosis5, gait6 and dysexecutive syndrome7 in Parkinson’s disease, however, it has not been studied to the same extent as rivastigmine. A double-blind placebo controlled RCT examining the effects of galantamine on cognition in non-demented Parkinson’s disease patients did not show any benefit8.

The use of rivastigmine is well established in the treatment of Parkinson’s disease dementia. When compared with placebo in a large multicentre double-blind Randomised controlled trial (RCT), rivastigmine was shown to have a beneficial effect on psychotic symptoms in Parkinson’s disease dementia9. There is also established evidence that rivastigmine is beneficial for cognition in mild-moderate Parkinson’s disease dementia10. However, the consensus on the use of rivastigmine earlier in the disease course is less clear. The aim of this systematic review is to examine the available evidence for the use of rivastigmine in patients with Parkinson’s disease without dementia.

**Methods**

The systematic review was registered in the PROSPERO database with ID CRD42021279367. Embase, Medline (see appendix 1 for search strategy), PsychINFO, Cochrane CENTRAL, NGLC, NICE Evidence and medRxiv.org were searched for studies with terms relating to population (Parkinson’s disease) and intervention (rivastigmine). Of the 1922 references initially identified, 358 were deleted due to duplication.

Criteria for inclusion were: diagnosis of Parkinson’s disease, reference to rivastigmine and the presence of neuropsychiatric symptoms or falls. Falls were included along with neuropsychiatric symptoms as they may be a manifestation of impaired cognition, in particular, deficits in attention and visuospatial domains. Articles were excluded if they solely related to patients with dementia as the evidence base for rivastigmine in PDD has been firmly established9,10.

Following initial title and abstract review, 1331 articles were excluded. The high level of attrition among some studies was mainly due to exclusion of articles solely focusing on PDD. Of the remaining 233, 140 were excluded because they were not original studies, but were reviews, recommendations, guidelines or comments. The references of these publications were reviewed for any other relevant studies, then excluded. After full text review, 9 papers remained. The review process is represented by the flow chart in Figure 1.

**Figure 1**

**Figure 1** represents the review process which identified 9 relevant articles. Embase, Medline, PsychINFO, Cochrane CENTRAL, NICE Evidence were searched for relevant articles. Unpublished manuscripts were searched for using medRxiv, and grey literature was searched for using NGLC, but did not identify any further studies.

The risk of bias was assessed by two authors independently (SR and SD) and any differences in assessments were resolved through discussion. For RCTs, the Cochrane Collaboration Tool for Risk of Bias11 was used. The open label trials were assessed with the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group12. The case series was assessed using the NIH Quality Assessment Tool for Case Series Studies12.

Due to the heterogenous outcomes, meta-analysis was not appropriate and the results are delivered in a narrative form.

**Results**

Ultimately 9 studies were included: 6 RCTs, 2 open trials and 1 case-series. The risk of bias analysis for the RCTs is displayed in Table 1.

**Table 1,** risk of bias analysis of RCTs using Cochrane risk of bias tool (key: + = low risk of bias, ? = unclear risk of bias).

**Table 1**

For the Reading et *al*. study13, risk of bias was overall rated fair. This rating was given due to small sample size and the lack of assessor blinding. It was also unclear if all eligible participants that met the prespecified entry criteria were enrolled. On the other hand, the study objectives were clearly stated and selection criteria prespecified. There was also minimal loss to follow up and outcome measures were taken multiple times before and after intervention.

An overall quality rating of fair was also given to the Possin et *al*. study14. Whilst the objectives, rationale and eligibility criteria are clearly stated, the lack of placebo controls to compare response to treatment introduced a risk of bias. Outcome measures were only taken once before and once after treatment and the sample size was relatively small (n=12).

The risk of bias analysis for the Sobow15 study found that the subjects were not comparable, in that one subject was treated with Donepezil. It was also unclear from the information provided whether the cases were consecutive. If not consecutive, there is a high risk of bias, as eligible patients who did not respond favourably to rivastigmine may have been excluded. Therefore, the overall quality rating is poor.

The study design, study characteristics, primary and secondary outcome measures in each of the studies are summarised in Table 2.

Table 2 summarises the 9 studies identified from the literature search.

**Table 2**

The outcome measures were heterogenous and will be discussed under the following broad headings:

*Psychosis*

Psychotic symptoms were the primary focus of three studies: one RCT16, one open trial13 and one case-series15.

The first of these studies in 2001, by Reading et *al.*13, was an open-label trial of 12 patients. Rivastigmine was titrated to a maximum of 6 mg twice a day and maintained on the highest tolerated dose for 6 weeks. The rivastigmine group showed a significant improvement in NPI scores compared to baseline (mean baseline score 40, mean experimental score 15, Z = 2.85, p < 0.004). The subsections scores of hallucinations (Z = 2.24, p < 0.025), sleep disturbance (Z = 2.43, p < 0.015) and carer distress (Z = 2.71, p < 0.007) showed significant improvements. Additionally, there was a deterioration of NPI score 3 weeks after withdrawal of rivastigmine to a mean score of 28.

The improvement in psychotic symptoms were corroborated by a case series15 of 5 patients. The patients included in the series had a diagnosis of Parkinson’s disease with visual hallucinations unresponsive to atypical antipsychotics. Four of the patients were given either 3 mg or 6mg rivastigmine a day for 12 weeks; one patient was given donepezil. In all cases, psychotic symptoms either completely resolved or reduced. However, it is worth noting the risk of bias in this study is high due to nature of case-series.

More recently, van Mierlo et *al*. conducted a RCT of 91 individuals investigated whether rivastigmine could delay the progression of minor visual hallucinations in Parkinson’s disease to psychosis16. Participants in the rivastigmine group were given either 3 mg or 6 mg twice a day for 24 months. The primary outcome of this study was the time taken to develop psychosis (defined by the use of antipsychotic medication) in a 24-month period. There was no significant difference between the rivastigmine and placebo group, with 4/46 developing psychosis in the rivastigmine group and 5/45 developing psychosis in the placebo group. Additionally, there was no significant difference in psychotic symptoms (Scale to Assess Positive Symptoms score) between rivastigmine and placebo groups at 6 months. The risk of bias from the study design was low, as it was a multicentre double-blinded randomised placebo-controlled trial analysed by intention-to-treat. However, the attrition rate was high and the study was ultimately underpowered.

*REM Behaviour Disorder (RBD)*

Di Giacopo et *al*. investigated the use of rivastigmine as an alternative treatment for RBD in Parkinson’s disease with a cross-over RCT17. The inclusion criteria for this study were a diagnosis of idiopathic Parkinson’s disease and RBD confirmed by polysomnography. The primary outcome was RBD episode frequency reduction, as measured by the bed partner. Twelve patients were enrolled in the study and treated with a 4.6 mg rivastigmine patch for 3 weeks. Two participants dropped out during the rivastigmine phase of the trial, due to orthostatic hypotension and asthenia. Rivastigmine significantly reduced RBD episodes compared to baseline (Z = -2.524; p = 0.012). There was no difference detected between placebo and baseline (Z= -1.289; p = 0.197).

*Apathy*

Devos et *al.* focused on the effects of rivastigmine on apathy experienced by Parkinson’s disease patients18. This study assessed the effects of rivastigmine in apathetic, non-depressed, dementia-free patients with Parkinson’s disease. The primary outcome was change over time in the Lille Apathy Rating Scale (LARS) at 6 months of treatment with 9.5 mg or 4.6 mg rivastigmine patch compared to placebo. At 6 months there was an improvement in LARS scores in the rivastigmine group from a median of -11.5 at baseline to -20 after treatment. The placebo group only improved from median scores of -13.3 to -13.5. Covariance analysis indicated that the improvement in the rivastigmine group was statistically significant, F(1, 25) = 5.2; p = 0.031. Specific improvements in the LARS subscale were seen in the rivastigmine group for intellectual curiosity and action initiation. A significant improvement was also observed for the secondary outcome of Zarit Burden Interview score, which is a measure of everyday consequences of Parkinsonian apathy, from 27.5 at baseline to 25.5 after 6 months of rivastigmine treatment, F(1, 25) = 5.5; p = 0.026 (−0.9).

Apathy was also measured as a secondary outcome by Mamikonyan19 in a cross-over RCT. After 10 weeks of treatment (4 weeks 4.6 mg patch, followed by 6 weeks 9.5 mg or 4.6 mg if the higher dose was not tolerated), no significant difference was observed between rivastigmine and placebo (regression coefficient -0.89, *df* 1, 19.96, *F* Value 0.42, p = 0.52).

*Cognition*

The main objective of the Possin et *al*. study14 was to investigate the effect of rivastigmine on brain function. By comparing functional Magnetic Resonance Imaging (fMRI) scans of patients with cognitive impairment and Parkinson’s disease with healthy controls, brain areas with reduced spontaneous activity were identified. The brain areas with reduced spontaneous activity in Parkinson’s patients included the lateral prefrontal cortex, which is a region involved in the cognitive domains of attention and executive function. Patients were given a 4.6 mg rivastigmine patch for 4 weeks, followed by a 9.5 mg patch for 8 weeks. Brain activity in the areas with reduced activity were compared to baseline scans. The study found that rivastigmine was able to restore spontaneous brain activity in the left premotor cortex, inferior frontal gyrus, and supplementary motor area to a level which was comparable to levels recorded in the healthy controls. Additionally, the Continuous Performance Test (CPT) was used to measure controlled attention at baseline and post treatment. The increase in brain activity observed in the left premotor cortex and the inferior frontal gyrus after treatment correlated with decreased reaction time on the CPT (r = −0.82, P < .01). However, there was no correlation between changes in brain activity and Montreal Cognitive Assessment (MoCA) score (r = 0.18, P = .58). There was also no significant difference between baseline and posttreatment scores for MoCA (baseline: 23.0 ± 4.8; posttreatment: 24.3 ± 4.7; p = 0.16) or CPT (baseline: 579 ± 108; posttreatment: 571 ± 108; p = 0.44).

A number of studies assessed cognition as a secondary outcome. MoCA scores were measured by Henderson20, van Mierlo16, Mamikonyan19, Li21 and Possin14. Mini Mental State Examination (MMSE) scores were measured by van Mierlo16, Reading13 and Sobow15.

There was no significant difference in MoCA scores in the Henderson study20. Similarly, there was no significant difference in the van Mierlo16 study nor the Mamikonyan study19. However, in the Li study21, there was a significant difference in MoCA scores, measured 12 months after treatment with 3 mg rivastigmine twice a day. The patients who had cognitive impairment (both PD-MCI and PDD) in the Li study21 were randomised to receive 12 months of rivastigmine (n=41) or placebo (n=40). Following 12 months of treatment, there was a significant increase in MoCA score in the rivastigmine group compared to placebo (22.97 ± 1.03 and 19.66 ± 2.45 respectively, p = 0.002). There was no significant difference in MoCA score in the rivastigmine group before and after treatment, but there was a significant decline in the placebo group before and after treatment (23.43 ± 3.22 and 19.66 ± 2.45, p < 0.01).

Reading et *al*.13 measured MMSE scores before and after treatment with rivastigmine. The results showed an improvement after rivastigmine treatment of 5 points compared to baseline (Z = 2.81, p < 0.005). There was subsequently a deterioration in MMSE score 3 weeks after treatment withdrawal (Z = 2.12, p < 0.034). The mean (+/- SD) MMSE scores at baseline, after 14 weeks of treatment and 3 weeks after withdrawal were 20.4 (+/- 5.7), 25.4 (+/- 3.5), and 21.2 (+/- 5.1) respectively.

Sobow15 also measured MMSE at the beginning and after 12 weeks of treatment with rivastigmine. These results showed an increase from 21 to 23 in Case 1, from 26 to 27 in Case 2, remaining at 28 for Case 3 and an increase from 20 to 25 in case 4.

In the van Mierlo study16, MMSE scores were recorded and used as a measure of time to develop Parkinson’s Disease Dementia. Dementia was indicated by disability in more than one cognitive domain and an MMSE score less than 26. There was no significant difference in Kaplan Maier curve when the rivastigmine and control groups were compared, with 4/46 developing dementia in the rivastigmine group and 1/45 developing dementia in the placebo group.

*Gait and Falls*

Henderson et *al.*20 investigated the effects of rivastigmine on gait variability with a randomised, double-blind, placebo controlled trial. Patients who had fallen at least once in the previous year were included in the trial and were required not to have dementia. One hundred and thirty patients were recruited to the trial. Rivastigmine was titrated to a maximum of 12 mg and the highest tolerated dose was maintained for a total treatment period of 32 weeks. An identical titration regime was used for placebo. Following the 32 week treatment period, outcomes were measured and compared between Rivastigmine and placebo groups. The primary outcome of this study was difference in step time variability, which is an indicator of gait stability and an indicator of falls risk. Step time variability was measured in three conditions: normal walking, while performing a simple cognitive task and thirdly while performing a complex cognitive task. In the rivastigmine group, there was a significant improvement in step time variability during normal walking (geometric mean ratio = 0.72, 95% CI 0.58-0.89, p = 0.002) and during the simple dual task (geometric mean ratio = 0.79, 95% CI 0.62-0.99, p = 0.045) when compared to placebo. There was also an improvement in step time variability during the complex dual task, but this was not significant (geometric mean ratio = 0.81, 95% CI 0.60-1.09, p = 0.17). There was a significant reduction (p = 0.002) in falls in the rivastigmine group (mean = 1.4, SD = 2.47) compared to placebo (mean = 2.4, SD = 4.40). Additionally, there was a significant increase (p = 0.003) in gait speed during normal walking in the rivastigmine group (mean = 1.08 m/s, SD = 0.29) compared to placebo (mean = 0.99 m/s, SD = 0.33) as well as during the simple dual task (rivastigmine group mean = 0.79 m/s, SD = 0.33; placebo group mean = 0.74 m/s, SD = 0.30; p = 0.37). A small increase in gait speed was also observed during the complex dual task in the rivastigmine group (0.71 m/s, SD = 0.32) compared to placebo (0.66 m/s, SD = 0.29), p = 0.048.

Li et *al*.21 examined the effect of rivastigmine on falls and cognitive ability. Cognitive ability was assessed with the MoCA test and patients were classified according to level of cognitive impairment: no impairment, mild cognitive impairment (MCI) or Parkinson’s disease dementia (PDD). Patients who had cognitive impairment (both PD-MCI and PDD) were randomised to receive 12 months of rivastigmine (n = 41) or placebo (n = 40). The number of falls were recorded. The results indicated a correlation between the level of cognitive impairment and incidence of falls. There was a significant reduction in falls after 12 months of treatment in the rivastigmine group compared to placebo (1.82 ± 1.99 falls/person/year in the rivastigmine group compared to 4.26 ± 1.63 falls/person/year in the placebo group, p < 0.01).

*Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS)*

UPDRS was a secondary outcome in 6 of the studies, none of which showed a significant difference. In the Henderson study20, MDS-UPDRS scores had a mean value of 95.5 (SD = 28.2) in the placebo group and 87.2 (SD = 29.7) in the rivastigmine group. When adjusted for baseline measures, the adjusted mean difference between groups was -3.29 and p = 0.3.

MDS-UPDRS was also recorded in the van Mierlo study16 as an indicator of disease severity. Here, the change in scores between baseline and at 6 months were compared in placebo and rivastigmine groups. There were no statistically significant differences in the score changes in part 1 (p = 0.98; Wilcoxon rank sum test), part 2 (p = 0.71; Wilcoxon rank sum test) or part 3 (p = 0.54; Wilcoxon rank sum test) of the UPDRS schedule.

In the Mamikonyan cross-over trial19, the motor score (part 3) of the UPDRS was a secondary outcome. Analysed with a linear mixed effects model which compared post-baseline scores at the end of each study phase for each treatment, no significant difference was seen (Regression co-efficient -1.24; F(1,23.75) = 0.48; p = 0.5).

In the Devos study18, the mean UPDRS part 3 score increased from 23 to 25 after 6 months of placebo treatment. The mean score for the rivastigmine group increased from 22.5 to 24.5. Covariance analysis indicated that there was no significant main effect of group on the score (F(1,25) = 0.4, p = 0.5).

There was a non-significant tendency to improvement in part 3 UPDRS score in the Reading open label trial13, with a mean baseline score of 32.3 (SD = 10.4) compared to a mean score of 29.8 (SD = 11.5) during the experimental phase. The score then worsened on withdrawal of rivastigmine to a mean of 34.8 (SD = 12.2). When analysed with the Wilcoxon signed rank scale, the difference between baseline and experimental scores were not significant (Z = 1.18, P > 0.2).

Sobow15 also measured UPDRS scores at the beginning of treatment and after 12 weeks of rivastigmine treatment. In Case 1, UPDRS score was 20 at beginning and 22 after 12 weeks. The score in Case 2 was 26 at beginning and reduced to 24 at 12 weeks. For Case 3 the score reduced from 29 to 28 and in Case 4 the score increased from 19 to 20.

*Adverse effects*

Adverse effects were discussed in 8 studies. Gastrointestinal side-effects were commonly reported in the rivastigmine group of the Henderson20 and van Mierlo16 trials. There were no between group differences reported by Mamikonyan19, but rash and an increased ‘off’ time were more common in the rivastigmine group. In the study by Devos18, there were 5 significant adverse reactions in the placebo group, compared to none in the rivastigmine group. However, overall there were more adverse events in the rivastigmine group, in particular faintness and asthenia. Di Giacopo17 reported that rivastigmine was tolerated in most patients, with only minor side effects, which were mainly related to peripheral cholinergic action. Reading13 also observed that rivastigmine was generally well tolerated, but that significant nausea was a dose-limited side-effect for some patients. There were no major adverse effects in the Sobow case series15.

**Discussion**

*Psychosis*

Symptoms of psychosis in Parkinson’s disease include hallucinations and paranoid delusional beliefs. These symptoms can have a profound impact on quality of life and carer-burden. Visual hallucinations are a common experience in Parkinson’s disease and occur on a wide-ranging spectrum from minor visual hallucinations with retained insight, which are not necessarily psychotic in nature, to distressing, well-formed images.

Three of the 9 studies primarily focused on the effects of rivastigmine on psychotic symptoms. The earlier case study15 and open label trial13 indicated that rivastigmine may be of benefit to Parkinson’s psychosis. The Reading et *al*. trial13 included patients with a diagnosis of Parkinson’s disease more than 2 years ago who experienced troublesome, recurrent hallucinations. Patients with an MMSE <10 were excluded, however it is likely that the trial included patients with mild-moderate dementia as well as MCI. In contrast, the RCT conducted by van Mierlo et *al*.16 excluded patients with an MMSE <26, which is likely to be a more appropriate threshold for excluding dementia. The trial recruited patients who had experienced minor visual hallucinations in the previous 4 weeks. Only 4/46 patients in the treatment group and 5/45 patients in the placebo group developed psychosis in the subsequent 2 years, therefore the trial was underpowered to demonstrate the primary outcome of time to develop PD psychosis. Slow recruitment to the trial led to premature termination and high attrition further affected the power of the study. The lack of a significant effect in the trial may reflect a different mechanism in the generation of minor visual hallucinations compared to frank psychotic hallucinations.

The uncertainty around rivastigmine as a treatment for psychosis in Parkinson’s disease is reflected in evidence-based recommendations. An individual research recommendation from the National Institute for Clinical Excellence (NICE) highlighted the question of whether rivastigmine is an effective treatment for psychosis in Parkinson’s disease22. However, due to lack of definitive evidence, NICE do not currently recommend the use of rivastigmine in Parkinson’s disease in patients without dementia.

Elucidating the mechanism that drives psychosis in Parkinson’s disease will be key to determining the most appropriate treatment. There is increasing evidence that visual hallucinations in Parkinson’s disease are the manifestation of large-scale brain network imbalance. Measures of white matter integrity and cortical thickness were used to compare patients with Parkinson’s disease who hallucinated with those who did not23. The brains of patients who hallucinated were found to have more white matter loss in posterior connections and in thalamic nuclei, in particular, the mediodorsal nucleus. This result indicates that the ability of the thalamus to control sensory input may become dysfunctional in Parkinson’s disease, potentially leading to perceptual abnormalities. The changes in white matter structure occurred prior to reduction in cortical thickness and thalamic volume. Therefore, connectivity imbalance may occur at an earlier stage of Parkinson’s disease, before any detectable brain atrophy.

A number of models have been suggested by which visual hallucinations occur in Parkinson’s disease and are described by Muller et al24. The most recently postulated model is the dysfunction of the attentional control networks25. In this model there is an inability to activate the dorsal attention network, which directs voluntary attention to visual stimuli, and an overreliance on the default mode network, which is associated with a brain-state of resting wakefulness. Deficits in the cholinergic system have been suggested to influence this model26.

There is also evidence that cholinergic system dysfunction is responsible for visual hallucination in some patients with Parkinson’s disease27. The pedunculopontine nucleus (PPN) is part of the cholinergic system and mainly innervates the thalamus. Degeneration at this site has previously been implicated in visual hallucinations in Parkinson’s disease due to disturbances in ascending cholinergic input to visual pathways28. When the density of the PPN was compared between patients with Parkinson’s disease who had visual hallucination and those without, there was a higher degree of PPN atrophy in patients with visual hallucinations29. The key sites of central acetylcholine activity are illustrated in Figure 2.

**Figure 2**

**Figure 2** demonstrates the key sites of acetylcholine activity in the brain. The pedunculopontine nucleus in the brainstem is a modulator of thalamic activity. The nucleus basalis of Meynert in the basal forebrain projects to frontal and prefrontal regions as well as the hippocampus.

*REM Behaviour Disorder (RBD)*

The PPN has also been implicated in RBD30. A number of neurochemical systems are likely to interact to create the phenomenon of RBD, but it is possible that depletion of the cholinergic system at key sites including the PPN and the laterodorsal tegmental nucleus in the brainstem31 is a component. Indeed, the only study in this review which investigated rivastigmine’s effects on RBD17 showed a significant reduction in episodes, indicating that cholinergic deficit contributes to the phenomenon of RBD.

*Apathy*

Clinically, apathy is seen in a reduction of voluntary goal-directed behaviours and is typically associated with a loss of motivation and emotionality. It may be observed secondary to depression or cognitive impairment, but in Parkinson’s disease, apathy can also occur in the absence of these features32. Pathology within several neuronal circuits has been implicated in the production of apathy, in particular loss of connectivity between the basal ganglia, prefrontal cortex and striatum. Additionally, cholinergic degeneration in the basal forebrain has been associated with apathy in Parkinson’s disease33. The findings of Devos et *al*.18, in which rivastigmine reduced levels of apathy support the hypothesis that cholinergic deficit contributes to apathy in Parkinson’s disease. The result was not replicated when assessed as a secondary outcome19, but this may be due to differences in inclusion and exclusion criteria.

*Cognition*

Cognitive impairment is common in Parkinson’s disease, even at an early stage34. Cognitive domains typically impaired early in the disease course include executive functions, memory, visuospatial processing, psychomotor speed and attention35. The form of cognitive impairment has been suggested to have two categories: a dopaminergic deficit resulting in executive dysfunction and a dopamine-independent deficit involving attentional and visuospatial ability36.

In the study by Possin et *al*.14 functional brain imaging was used to assess patients with cognitive impairment in Parkinson’s disease and healthy controls. Six patients with PDD and six with PD-MCI were included in the study. At baseline, patients demonstrated reduced spontaneous activity in a number of brain regions, including those involved in motor control, attention, executive functions and episodic memory. After 3 months of treatment with rivastigmine, these deficits were reduced. Increased activity in the left precentral gyri and inferior frontal gyri were associated with improvements in controlled attention. This result is important in not only indicating the brain areas impaired, but also the specific cognitive effects of rivastigmine treatment.

Seven studies used measures of cognitive impairment as a secondary outcome, however there was a high degree of heterogeneity in the inclusion criteria. Li et *al*.21 found an improvement in MoCA score, but it is worth noting that patients with PDD were included in the study. It would be of interest to know whether the improvement in cognition was observed in the patients with PD-MCI alone. There were no significant improvements in the secondary measures of cognition in the other studies. Specific tools may be required to detect cognitive impairment in non-demented Parkinson’s disease patients. There are a number of rating scales that have been validated for use in Parkinson’s disease, including MMSE and MoCA37. However, scales such as the Parkinson’s disease-Cognitive Rating Scale38 that have been specifically developed to test cognitive function in Parkinson’s disease may be more useful.

Another source of heterogeneity between the studies relates to the dose of rivastigmine administered. An aspired dose of 9.5 mg/day transdermal patch or 12 mg/day oral was given in the Mamikonyan19, Van Mierlo16, Henderson20, Devos18 and Reading13 studies. However, a lower dose of 4.6 mg/day patch or 6 mg/day was administered if the patient showed poor tolerance. Li21 and Di Giacopo17 both conducted studies at the lower dose of 6 mg/day oral and 4.6 mg transdermally, respectively. The different dosing regimens may indicate that some patients in these studies were underdosed and consequently efficacy was reduced.

*Gait and Falls*

An improvement in attention may be a factor in the positive results observed in the Henderson study20. Henderson et *al*. found an improvement in gait stability and a reduction in falls frequency after treatment with rivastigmine. There is evidence that cholinergic deficit results in gait instability39. Additionally, increased attention is required to compensate for gait instability to prevent falling. Therefore, falls in patients with Parkinson’s disease may be a manifestation of both impaired attention and gait instability.

*Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS)*

The principal purpose of using UPDRS in six studies was to ensure that rivastigmine did not adversely affect motor symptoms of Parkinson’s disease. None of the studies showed a significant difference, indicating that rivastigmine is not associated with a decline in Parkinson’s disease symptoms.

*Adverse Effects*

Adverse effects of rivastigmine did not seem to be a significant feature in any of the trials, although gastrointestinal side effects were commonly reported.

**Conclusion**

This review has collated evidence of the use of rivastigmine for neuropsychiatric symptoms in Parkinson’s disease, particularly focusing on symptoms prior to the development of dementia. The available studies do not provide a clear consensus, but there is evidence to support the benefit of rivastigmine for apathy, RBD, falls and psychosis. At a theoretical level, cholinergic dysfunction leading to large-scale brain network imbalance may occur early in the disorder, which supports the use of rivastigmine for these symptoms at a pre-dementia stage. The evidence reviewed also indicates that rivastigmine is safe and well tolerated in patients with Parkinson’s disease. A further randomised controlled trial using a range of neuropsychiatric outcomes could provide clarity on any benefit of rivastigmine in early Parkinson’s disease.

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**References**

1. Bosboom JL, Stoffers D, Wolters ECh. The role of acetylcholine and dopamine in dementia and psychosis in Parkinson's disease. J Neural Transm Suppl. 2003(65):185-95.

2. Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. Mov Disord. 2011;26(6):1022-31.

3. Emre M. Dementia associated with Parkinson's disease. Lancet Neurol. 2003;2(4):229-37.

4. Kandiah N, Pai MC, Senanarong V, Looi I, Ampil E, Park KW, et al. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clin Interv Aging. 2017;12:697-707.

5. Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Lenzi GL, Meco G. Donepezil in the treatment of hallucinations and delusions in Parkinson’s disease. Neurol Sci. 2002;23:41-3.

6. Stuart S, Morris R, Giritharan A, Quinn J, Nutt JG, Mancini M. Prefrontal cortex activity and gait in Parkinson’s disease with cholinergic and dopaminergic therapy. Mov disord. 2020;35(11):2019-27.

7. Linazasoro G, Lasa A, Van Blercom N. Efficacy and safety of donepezil in the treatment of executive dysfunction in Parkinson disease: a pilot study. Clin Neuropharmacol. 2005;28(4):176-8.

8. Grace J, Amick MM, Friedman JH. A double-blind comparison of galantamine hydrobromide ER and placebo in Parkinson disease. J Neurol Neurosurg Psychiatry. 2009;80(1):18-23.

9. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000;356(9247):2031-6.

10. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004;351(24):2509-18.

11. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

12. National Heart LaBI. Study Quality Assessment Tools 2014 [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

13. Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Mov Disord. 2001;16(6):1171-4.

14. Possin KL, Kang GA, Guo C, Fine EM, Trujillo AJ, Racine CA, et al. Rivastigmine is associated with restoration of left frontal brain activity in Parkinson's disease. Mov Disord. 2013;28(10):1384-90.

15. Sobow T. Parkinson's disease-related visual hallucinations unresponsive to atypical antipsychotics treated with cholinesterase inhibitors: a case series. Neurol Neurochir Pol. 2007;41(3):276-9.

16. van Mierlo TJM, Foncke EMJ, Post B, Schmand BA, Bloem BR, van Harten B, et al. Rivastigmine for minor visual hallucinations in Parkinson's disease: A randomized controlled trial with 24 months follow-up. Brain Behav. 2021;11(8):e2257.

17. Di Giacopo R, Fasano A, Quaranta D, Della Marca G, Bove F, Bentivoglio AR. Rivastigmine as alternative treatment for refractory REM behavior disorder in Parkinson's disease. Mov Disord. 2012;27(4):559-61.

18. Devos D, Moreau C, Maltête D, Lefaucheur R, Kreisler A, Eusebio A, et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. J Neurol Neurosurg Psychiatry. 2014;85(6):668-74.

19. Mamikonyan E, Xie SX, Melvin E, Weintraub D. Rivastigmine for mild cognitive impairment in Parkinson disease: a placebo-controlled study. Mov Disord. 2015;30(7):912-8.

20. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(3):249-58.

21. Li Z, Yu Z, Zhang J, Wang J, Sun C, Wang P. Impact of Rivastigmine on Cognitive Dysfunction and Falling in Parkinson's Disease Patients. Eur Neurol. 2015;74(1-2):86-91.

22. Excellence NIFC. NICE guideline NG71 - Parkinson's disease in adults. 2017.

23. Zarkali A, McColgan P, Leyland LA, Lees AJ, Weil RS. Longitudinal thalamic white and grey matter changes associated with visual hallucinations in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2022;93(2):169-79.

24. Muller AJ, Shine JM, Halliday GM, Lewis SJ. Visual hallucinations in Parkinson's disease: theoretical models. Mov Disord. 2014;29(13):1591-8.

25. Shine JM, Halliday GM, Naismith SL, Lewis SJ. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? Mov Disord. 2011;26(12):2154-9.

26. Russo M, Carrarini C, Dono F, Rispoli MG, Di Pietro M, Di Stefano V, et al. The Pharmacology of Visual Hallucinations in Synucleinopathies. Front Pharmacol. 2019;10:1379.

27. Manganelli F, Vitale C, Santangelo G, Pisciotta C, Iodice R, Cozzolino A, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. Brain. 2009;132(Pt 9):2350-5.

28. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain. 1998;121 ( Pt 10):1819-40.

29. Janzen J, van 't Ent D, Lemstra AW, Berendse HW, Barkhof F, Foncke EM. The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study. J Neurol. 2012;259(1):147-54.

30. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130(Pt 11):2770-88.

31. Benarroch EE, Schmeichel AM, Parisi JE. Depletion of mesopontine cholinergic and sparing of raphe neurons in multiple system atrophy. Neurology. 2002;59(6):944-6.

32. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex. 2006;16(7):916-28.

33. Sperling SA, Druzgal J, Blair JC, Flanigan JL, Stohlman SL, Barrett MJ. Cholinergic nucleus 4 grey matter density is associated with apathy in Parkinson's disease. Clin Neuropsychol. 2022:1-19.

34. Pfeiffer HC, Løkkegaard A, Zoetmulder M, Friberg L, Werdelin L. Cognitive impairment in early-stage non-demented Parkinson's disease patients. Acta Neurol Scand. 2014;129(5):307-18.

35. Barone P, Aarsland D, Burn D, Emre M, Kulisevsky J, Weintraub D. Cognitive impairment in nondemented Parkinson's disease. Mov Disord. 2011;26(14):2483-95.

36. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. Neurodegener Dis. 2013;11(2):79-92.

37. Kulisevsky J, Pagonabarraga J. Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov Disord. 2009;24(8):1103-10.

38. Kalbe E, Calabrese P, Kohn N, Hilker R, Riedel O, Wittchen HU, et al. Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. Parkinsonism Relat Disord. 2008;14(2):93-101.

39. Bohnen NI, Müller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology. 2009;73(20):1670-6.