The impact of fatigue on daily activity in patients with Parkinson's disease

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Chapter 7

Interventions for fatigue in Parkinson's disease: a Cochrane Review

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Abstract

Background Factors contributing to subjective fatigue in patients with idiopathic Parkinson's disease (PD) are not well known. This makes it difficult to manage fatigue effectively in PD.

Objectives To evaluate the effects of pharmacological and non-pharmacological interventions, compared to an inactive control intervention, on subjective fatigue in PD.

Search methods We searched CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, PEDro and the WHO International Clinical Trials Registry Platform Search Portal up to December 2013. References of included studies and identified review articles were screened for additional studies.

Selection criteria Randomized controlled trials (RCTs) that report on subjective fatigue in patients with PD.

Data collection and analysis Two review authors independently performed study selection, data collection and risk of bias assessments.

Main results Eleven studies were eligible for this systematic review, with a total of 1,817 patients. Three studies included only patients who experienced clinically relevant fatigue (Fatigue Severity Scale score ≥ 4 out of 7 or Multidimensional Fatigue Inventory total score > 48 out of 100), whereas all other studies did not select patients on the basis of experienced fatigue. Nine studies investigated the effects of medication (i.e. levodopa-carbidopa, memantine, rasagiline, caffeine, methylphenidate, modafinil or doxepin) on subjective fatigue. All studies were placebo controlled. We found low quality evidence that doxepin significantly reduced the impact of fatigue on ADL or fatigue severity (one study, N = 12, standardized mean difference (SMD) = -1.50, 95% confidence interval (CI) = -2.84 to -0.15). We found high quality evidence that rasagiline significantly reduced or slowed down the progression of physical aspects of fatigue (one study, N = 1,176, SMD = -0.27, 95% CI = -0.39 to -0.16, I^2 = 0%). None of the other pharmacological interventions affected subjective fatigue in PD. With regard to adverse effects, only levodopa-carbidopa showed a statistically significant increase for the risk of nausea (one study, N = 361, risk ratio (RR) = 1.85, 95% CI = 1.05 to 3.27; high quality evidence). Two studies investigated the effect of exercise on fatigue compared with usual care. We found low quality evidence that exercise did not significantly reduce the impact of fatigue on ADL or fatigue severity (two studies, N = 57, SMD = -0.45, 95% CI = -1.12 to 0.32, I^2 = 44%).

Authors' conclusions Based on the current evidence, no clear recommendations for the treatment of subjective fatigue in PD can be provided. Doxepin may reduce the impact of fatigue on ADL and fatigue severity; however, this finding has to be confirmed in high quality RCTs. Rasagiline may be effective in reducing levels of physical fatigue in PD. No evidence was found for the effectiveness of levodopa-carbidopa, memantine, caffeine, methylphenidate, modafinil or exercise. Studies are needed to investigate the effect of exercise intensity on exercise capacity and subjective fatigue. Future studies should focus on interventions that address the maladaptive behavioral or cognitive aspects of fatigue in patients with PD. Patient characteristics, such as severity and characteristics of perceived fatigue and underlying mood disorders should be considered to identify responders and non-responders when studying interventions for fatigue. The development of a core-set of self-report fatigue questionnaires with established responsiveness and known minimal important change values will facilitate the interpretation of change in fatigue scores.

Plain language summary

Treatment for fatigue in Parkinson's disease

At least one-third of patients with Parkinson's disease complain about fatigue. It is unclear what treatment is best to reduce fatigue in patients with Parkinson's disease.

We reviewed the medical literature, up to December 2013, and found eleven studies that included a total of 1,817 patients. Nine studies investigated the effects of medication (i.e. levodopa-carbidopa, memantine, rasagiline, caffeine, methylphenidate, modafinil or doxepin) on fatigue. Two studies investigated the effects of exercise on fatigue. We found no studies that investigated the effect of cognitive- behavioral therapy.

We found that doxepin (one study, 12 patients), a drug to treat depression, may reduce fatigue We found that rasagiline (one study, 1,176 patients), an anti-Parkinson drug, reduced or slowed down the progression of physical fatigue. Most drugs were safe; however, levodopa-carbidopa (one study, 361 patients) may cause nausea.

We found no evidence that exercise (two studies, 57 patients) reduces fatigue in Parkinson's disease.

Based on the current evidence, it is not clear what treatment is most effective to treat fatigue in patients with Parkinson's disease. Future studies should investigate the effect of cognitive-behavioral therapy on fatigue in patients with Parkinson's disease.

Background

Fatigue is common in patients with idiopathic Parkinson's disease (PD) and has a negative impact on health related quality of life [1-3]. Prevalence rates reported in the literature range from 32% to 50% [4, 5]. Fatigue usually refers to difficulty initiating or sustaining voluntary activity [6]. Its many facets are believed to result from a complex interplay between the underlying disease process, peripheral control systems (i.e. muscle fatigability), central control systems (i.e. subjective sense of fatigue) and environmental factors [6]. Subjective fatigue is often subdivided into physical and mental fatigue [7]. Physical fatigue involves a sense of physical exhaustion and lack of energy to perform physical tasks despite the capacity and motivation to perform the task [8]. Mental fatigue refers to the cognitive effects experienced during and after prolonged periods of cognitive activities that require sustained concentration and mental endurance [8].

Although several potential pathophysiological mechanisms for fatigue, such as reduced concentrations of cytokines, inflammation, abnormalities of the hypothalamic adrenal axis and disturbances in the basal ganglia circuits, have been suggested [6], the exact factors contributing to fatigue in patients with PD are still not well known [7]. It is unlikely that a single mechanism contributes to subjective fatigue [9], making it difficult to manage fatigue effectively in patients with PD.

Efforts to manage fatigue involve pharmacological and non-pharmacological interventions. A balanced medication regime targeting motor performance (e.g. dopaminergic agents) and mood disturbances (e.g. psychostimulants and antidepressants) combined with a rehabilitation program (e.g. exercise and cognitive-behavioral therapy) may reduce symptoms of fatigue. An 'evidence-based medicine review' about treatments for non-motor symptoms of PD [10] included three studies [11-13] that investigated the effect of methylphenidate or modafinil on fatigue. Seppi and colleagues concluded that evidence for the efficacy and safety of methylphenidate and modafinil in the treatment of fatigue in PD was insufficient [10]. In a recently published systematic review, Franssen and colleagues [14] investigated the effects of pharmacological and non-pharmacological interventions on fatigue in patients with PD. They concluded that insufficient evidence exists to support pharmacological or non-pharmacological treatment of fatigue in patients with PD [14]. Unfortunately, this systematic review included only study reports published in English or Dutch.

Objectives

To evaluate the effects of pharmacological and non-pharmacological interventions, compared with an inactive control intervention, on subjective fatigue in patients with PD.

Methods

Criteria for considering studies for this review

Types of studies

All types of randomized controlled trials (RCTs) that report on subjective fatigue as an outcome measure were eligible for inclusion. We did not restrict on the basis of publication language.

Types of participants

Patients with a clinical diagnosis of PD, as defined by the authors of the RCT.

Types of interventions

Pharmacological interventions

We included dopaminergic agents (e.g. amantadine, levodopa), psychostimulants (e.g. methylphenidate, modafinil) and antidepressants (e.g. fluoxetine, paroxetine). If further agents were identified for the treatment of fatigue in patients with PD, these were added to the systematic review.

Non-pharmacological interventions

Exercise

All physical exercise programs that focused on improvement in exercise capacity and consisted of aerobic training and/or strength training.

Cognitive-behavioral therapy

All programs that focused on the behavioral or the cognitive aspects to substitute for or alter maladaptive behavior to manage subjective fatigue.

Other non-pharmacological interventions

If other non-pharmacological interventions were identified for the treatment of fatigue in patients with PD, these were added to the systematic review.

Control intervention

All experimental interventions had to be compared with an inactive control intervention (i.e. placebo, no treatment, standard care, or a waiting list control).

Types of outcome measures

Primary outcomes

The primary outcomes for this systematic review were subjective fatigue, subjective physical fatigue and subjective mental fatigue as measured by self-report questionnaires. If possible, we categorized the theoretical construct of fatigue as 'impact of fatigue on activities in daily life (ADL)' or 'fatigue severity' [15].

We examined the numbers of adverse effects (i.e. anxiety, falls, headache, hypertension, impulse control disorders, life-threatening skin conditions, nausea, orthostatic hypotension, psychosis, suicidal ideation and tachycardia).

Secondary outcomes

The secondary outcomes include depression, disease-specific health-related quality of life (HRQOL) and sleep disturbances.

Main outcomes for summary of findings table

The following outcomes were selected for the summary of findings table: 1) subjective fatigue, subjective physical fatigue and subjective mental fatigue; 2) anxiety, falls, headache, hypertension, impulse control disorders, life-threatening skin conditions, nausea, orthostatic hypotension, psychosis, suicidal ideation and tachycardia; and 3) HRQOL.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and additional searches of MEDLINE, EMBASE, CINAHL, PsycINFO, PEDro and the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch) prospective trial register. Text words and MESH terms for PD and fatigue were combined with the Cochrane Highly Sensitive Search Strategy to identify randomized trials [16]. We searched all databases from their inception to December 2013. Details about the search strategy have been published previously [17].

Searching other resources

References of included studies and identified review articles were screened to look for additional studies.

Data collection and analysis

Selection of studies

Two review authors (RE/JV) independently screened titles and abstracts of all studies identified by the search strategy. Irrelevant studies were discarded. For the remaining studies, full text papers were obtained and two review authors (RE/JV) independently applied the a priori defined selection criteria. Disagreement was resolved by discussion. If necessary, a third review author (EvW) was consulted to make a final decision.

Data extraction and management

A form for standardized data extraction was designed and tested before two review authors (RE/JV) independently extracted data on the: 1) characteristics of the study

sample (i.e. inclusion/exclusion criteria, number of patients randomly assigned, age, sex, disease severity, disease duration and comorbid conditions); 2) experimental and control intervention (i.e. description of intervention, dosage, frequency and duration of delivery); 3) outcome measures (i.e. description of outcome measure) and 4) results (i.e. number of patients, point estimates, measures of variance and frequency counts for dichotomous variables). One review author (RE) collated and entered all data into Review Manager 5.3 (Review Manager version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Disagreement was resolved by discussion.

Assessment of risk of bias in included studies

The Cochrane Collaboration tool for assessing risk of bias [18] was used by two review authors (RE/JV) independently to investigate the risk of bias in included studies. Seven domains of study design (i.e. sequence generation, allocation concealment, blinding of participants or personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias) were scored according to pre-defined criteria [18] as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'. The domain blinding was investigated separately for different outcomes, and the domain incomplete outcome data was investigated separately for the same outcome at different time points. Disagreement was resolved by discussion. If necessary, a third review author (EvW) was consulted to make a final decision.

Measures of treatment effect

Continuous data

The treatment effect for each continuous outcome was expressed as a standardized mean difference (SMD) with 95% confidence interval (CI). We used post-intervention data to calculate the SMD [19].

Dichotomous data

The treatment effect for each dichotomous outcome was expressed as a risk ratio (RR) or as a risk difference (RD) with 95% CI.

Unit of analysis issues

Studies with multiple treatment groups

We combined data from relevant experimental intervention groups and relevant control intervention groups to create a single pair-wise comparison [19].

Dealing with missing data

If necessary, we used additional publications to obtain missing data. No statistical methods were used to impute missing data.

Assessment of heterogeneity

Heterogeneity was investigated by comparing clinical characteristics such as patient characteristics, types of interventions and outcome measures. We discussed clinical homogeneity, and based on this discussion, we decided whether pooling of data was sensible. Statistical heterogeneity was assessed by visual inspection of the forest plot. We applied the Chi^2 test for homogeneity and calculated the I^2 statistic. To increase the power of the test for homogeneity we used a p value < 0.1 for rejecting the null-hypothesis of homogeneity. Thresholds for the interpretation of the I^2 statistic were classified according the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [20].

When interpreting the results of the test for homogeneity and the I^2 statistic, we took into account the size of the studies that were included in the meta-analysis. If statistical heterogeneity was observed (Chi^2 test p value < 0.1 and I^2 statistic > 30%) we explored factors that explained heterogeneity.

Data synthesis

If studies were comparable in relation to patients, interventions and outcomes, data were combined in a meta-analysis. For continuous outcome variables a weighted SMD was calculated with a 95% CI, using the inverse variance method. For dichotomous outcomes we estimated a pooled RR or RD with a 95% CI using the Mantel-Haenszel method. When incorporating results from cluster-randomized trials or studies that presented direct estimates of effect, we used the generic inverse variance method.

We hypothesized that the individual studies that evaluated the effects of pharmacological or non-pharmacological interventions may contain different, but related, real effects per study; therefore we combined results using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analysis: 1) depressed versus non-depressed patients and 2) patients with pronounced physical fatigue versus patients with pronounced mental fatigue.

Sensitivity analysis

Random-effects model

If a limited number of studies (< 5) was included in any meta-analysis, we used a fixed-effect model to test the robustness of the random-effects model.

Risk of bias

To test the robustness of results, three key domains of the risk of bias assessment (i.e. allocation concealment, blinding of outcome assessment and incomplete outcome data) were used to perform sensitivity analyses. Studies were excluded from the sensitivity analysis when they scored 'unclear risk of bias' or 'high risk of bias' on one of these domains.

If blinding of patients was not possible because of the nature of the intervention, we did not consider detection bias for patient-reported outcomes as a criterion for sensitivity analysis.

Quality of the evidence

The quality of the body of evidence was evaluated using the GRADE system [21]. Results of a RCT were considered as 'high quality' evidence. The quality of the evidence was decreased based on potential risk of bias of the included studies, indirectness of evidence, unexplained heterogeneity or inconsistency in results, imprecision of results or high probability of publication bias [21].

To facilitate the interpretation of the magnitude of effects, guidance was provided. A weighted SMD of 0.2 represents a small difference, 0.5 a moderate difference and 0.8 a large difference [22].

Results

Description of studies

Results of the search

The search yielded 1,136 records, of which 68 studies were retrieved in full text for further assessment. This resulted in the exclusion of another 57 studies [23-79]. Eleven studies [11-13, 80-87] were included in the systematic review (see Figure 7.1).

Included studies

The characteristics of the included studies are summarized in Appendix 7.1. Three studies [11-13] included only patients who experienced clinically relevant fatigue

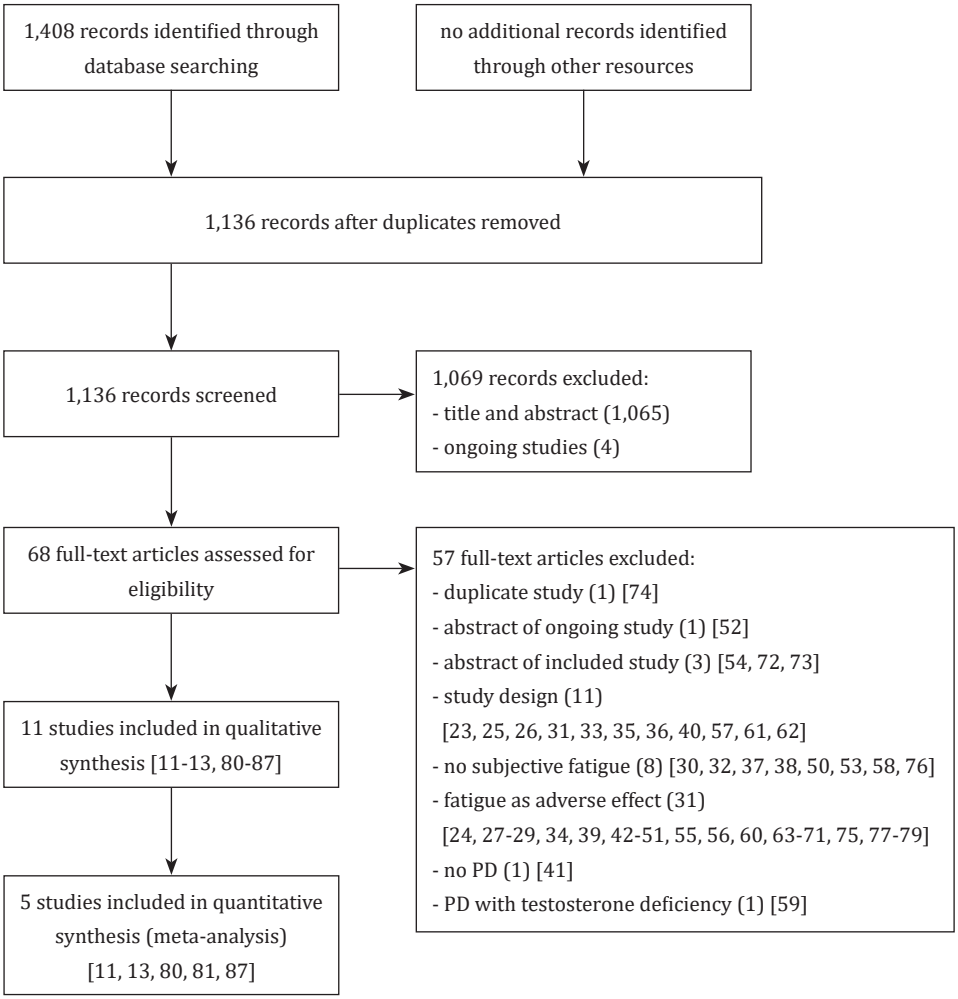

Figure 7.1 Flow diagram for study selection.

(Fatigue Severity Scale (FSS) score ≥ 4 out of 7 [12, 13] or Multidimensional Fatigue Inventory total score (MFI-total) > 48 out of 100 [11], whereas eight studies [80-87] did not select patients on the basis of experienced fatigue. Four studies [12, 13, 83, 86] excluded patients with depressive symptoms.

The effects of pharmacological interventions were investigated in nine studies. Three studies investigated the effect of dopaminergic medication (i.e. levodopa-carbidopa [86], memantine [82] and rasagiline [84]) and five studies investigated the effect of psychostimulants (i.e. caffeine [83], methylphenidate [12] and modafinil [11, 13, 81])

on subjective fatigue. One study [85] investigated the effects of antidepressants (i.e. doxepin). All studies were placebo-controlled.

Non-pharmacological interventions were investigated in two studies. One study [80] investigated the effect of home-based treadmill training, semi-supervised by a physiotherapist. The other study [87] investigated the effect of a supervised community gym-based program. Patients were supported with information and practical advice from a physiotherapist. Both studies compared the experimental intervention with usual care.

Overall, a total of 1,817 patients were included in the systematic review. Mean age ranged from 57 years [13] to 70 years [85] and mean disease severity, classified by Hoehn and Yahr stage (H&Y), ranged from 1.5 [84] to 2.6 [12]. The mean disease duration ranged from 4.0 years [11] to 8.0 years [83]; two studies [84, 86] included patients with recently diagnosed PD (mean disease duration ranged from 4.3 months [84] to 7.6 months [86].

Different self-report questionnaires were used to measure subjective fatigue. Most studies [12, 13, 81-83, 85-87] used the FSS to assess the impact of fatigue on ADL and fatigue severity. Two studies [11, 12] used the MFI to assess the impact of physical and mental fatigue on ADL, and one study [84] used the Parkinson Fatigue Scale (PFS-16) to measure the impact of physical fatigue on ADL. In most studies [80-85, 87], mean baseline levels of fatigue approached cut-off points for clinically relevant fatigue. Baseline levels of fatigue in the three studies that specifically included patients with clinically relevant fatigue [11-13] were considerably higher.

Excluded studies

Thirty-one studies [24, 27-29, 34, 39, 42-49, 51, 55, 56, 62, 63-71, 75, 77-79] were excluded because fatigue was measured as an adverse effect related to study medication and no continuous data on subjective fatigue was presented. One study that investigated the effect of rotigotine [30] was excluded because the authors used the Non-Motor Symptoms Scale (NMSS), a clinician-rated instrument, to assess fatigue. We excluded one study report [74] that summarized previously published results by Rascol and colleagues [84]. The results presented in the original publication [84] however, are included in this systematic review. Other reasons for exclusion are summarized in Figure 7.1.

Ongoing studies

Four ongoing studies (trial registration number EUCTR2007-002195-34-FR, NCT01168596, NCT01360229 and NCT01397422) were identified. Details on study design are presented in Appendix 7.2.

Risk of bias in included studies

Table 7.1 summarizes the scores for the risk of bias assessment. A detailed description about the risk of bias in the included studies is presented in Appendix 7.1.

Eight out of eleven studies [12, 13, 80-84, 87] used adequate methods for randomization and allocation concealment. One study [85] scored high risk for selection bias because allocation was not concealed. Two studies [11, 86] were not clear in describing randomization and allocation concealment and scored unclear risk for selection bias.

Except for one study [85], all studies that investigated pharmacological interventions used matched-placebo and therefore scored low risk for performance bias and detection bias for patient-reported outcomes. One study [85] did not describe blinding procedures for outcome assessors and scored unclear risk for detection bias for other outcomes.

Table 7.1 Risk of bias summary: review authors' judgements about each risk of bias item

Reference	Risk of bias item							
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Patient-reported	Blinding of outcome assessment (detection bias): Other outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Canning [80]	+	+	-	-	+	+	+	+
Lou [11]	?	?	+	+	+	-	?	+
Mendonça [12]	+	+	+	+	+	+	?	+
Ondo [81]	+	+	+	+	+	+	?	+
Ondo [82]	+	+	+	+	+	?	?	+
Postuma [83]	+	+	+	+	+	+	?	+
Rascol [84]	+	+	+	+	+	+	?	+
Rios Romenets [85]	?	-	-	-	?	+	?	+
Schifitto [86]	?	?	+	+	+	?	?	+
Tyne [13]	+	+	+	+	+	+	?	+
Winward [87]	+	+	-	-	+	+	?	+

+ Low risk of bias; ? Unclear risk of bias; - High risk of bias

Since blinding of patients and study personnel is not possible in studies that investigate exercise interventions, two studies [80, 87] scored high risk for performance bias and detection bias for patient-reported outcomes. Blinding procedures of outcome assessors were adequate; therefore, both studies [80, 87] scored low risk for detection bias for other outcomes.

One study [11] scored high risk for attrition bias as three patients (33%) in the intervention group dropped out because of an adverse effect related to study medication. These patients were not included in the statistical analyses.

Effects of interventions

The main outcomes for each intervention and the quality of the evidence are summarized in the summary of findings tables (see Appendix 7.3).

Pharmacological interventions

Levodopa-carbidopa

One study [86] investigated the effect of levodopa-carbidopa on the impact of fatigue on ADL and fatigue severity. We combined the three intervention groups to create a single pair-wise comparison for this study. After 42 weeks, no statistically significant difference was found between the combined levodopa-carbidopa group and the placebo group (N = 340, SMD = -0.22, 95% CI = -0.47 to 0.02).

Table 7.2 summarizes the risk of adverse effects. Levodopa-carbidopa significantly increased the risk for nausea (N = 361, RR = 1.85, 95% CI = 1.05 to 3.27).

Memantine

Ondo and colleagues [82] investigated the effect of memantine on the impact of fatigue on ADL and fatigue severity. After eight weeks, no difference was found between memantine and placebo (N = 36, SMD = 0.10, 95% CI = -0.56 to 0.75).

No statistically significant differences were found for the risk of adverse effects (see Table 7.2).

Memantine did not improve depression (N = 36, SMD = 0.15, 95% CI = -0.51 to 0.81), HRQOL (N = 36, SMD = 0.38, 95% CI = -0.29 to 1.04) or sleep disturbances (N = 36, SMD = 0.25, 95% CI = -0.41 to 0.91).

Table 7.2 Risk of adverse effects for pharmacological interventions

Adverse effect	Reference	N	Risk ratio (95% CI)	Favours
Levodopa-carbidopa versus placebo				
Anxiety	Schifitto [86]	361	0.46 (0.15 to 1.43)	Levodopa-carbidopa
Headache	Schifitto [86]	361	2.66 (0.82 to 8.61)	Placebo
Hypertension	Schifitto [86]	361	1.00 (0.28 to 3.60)	Inconclusive
Nausea	Schifitto [86]	361	1.85 (1.05 to 3.27)	Placebo
Memantine versus placebo				
Anxiety	Ondo [82]	40	0.33 (0.01 to 7.72)	Memantine
Hypertension	Ondo [82]	40	0.33 (0.01 to 7.72)	Memantine
Impulse control disorders	Ondo [82]	40	3.00 (0.13 to 69.52)	Placebo
Nausea	Ondo [82]	40	0.14 (0.01 to 2.60)	Memantine
Rasagiline versus placebo				
Anxiety	Rascol [84]	1,176	0.57 (0.33 to 0.99)	Rasagiline
Headache	Rascol [84]	1,176	0.80 (0.50 to 1.29)	Rasagiline
Hypertension	Rascol [84]	1,176	0.53 (0.27 to 1.06)	Rasagiline
Impulse control disorders	Rascol [84]	1,176	3.07 (0.13 to 75.26)	Placebo
Nausea	Rascol [84]	1,176	0.89 (0.49 to 1.60)	Rasagiline
Orthostatic hypotension	Rascol [84]	1,176	0.61 (0.15 to 2.56)	Rasagiline
Caffeine versus placebo				
Anxiety	Postuma [83]	61	1.03 (0.07 to 15.78)	Placebo
Headache	Postuma [83]	61	2.07 (0.20 to 21.61)	Placebo
Methylphenidate versus placebo				
Headache	Mendonça [12]	31	0.24 (0.01 to 4.62)	Methylphenidate
Hypertension	Mendonça [12]	31	6.00 (0.31 to 115.56)	Placebo
Nausea	Mendonça [12]	31	1.21 (0.08 to 17.71)	Placebo
Tachycardia	Mendonça [12]	31	0.40 (0.02 to 9.12)	Methylphenidate
Modafinil versus placebo				
Anxiety	Ondo [81]; Tyne [13]	50	3.14 (0.35 to 27.79)	Placebo
Headache	Tyne [13]	13	0.58 (0.07 to 4.95)	Modafinil
Hypertension	Tyne [13]	13	3.43 (0.16 to 71.36)	Placebo
Nausea	Ondo [81]; Tyne [13]	50	1.01 (0.11 to 8.93)	Placebo
Doxepin versus placebo				
Nausea	Rios Romenets [85]	12	3.00 (0.15 to 61.74)	Placebo
Orthostatic hypotension	Rios Romenets [85]	12	3.00 (0.15 to 61.74)	Placebo

Rasagiline

Rascol and colleagues [84] investigated the effect of rasagiline 1 mg/day and rasagiline 2 mg/day on the impact of physical fatigue on ADL. For the impact of physical fatigue on ADL, we were able to combine the two experimental groups in a meta-analysis

(see Figure 7.2) After 36 weeks, a statistical significant difference was found between rasagiline and placebo. Patients that used rasagiline experienced significant lower levels of physical fatigue when compared with patients receiving placebo (N = 1,176, SMD = -0.27, 95% CI = -0.39 to -0.16, I^2 = 0%). Sensitivity analysis using a fixed-effect model yielded the same result.

We had to create a single pair-wise comparison to calculate the risk of adverse effects. Rasagiline did not significantly increase the risk for adverse effects compared to placebo (see Table 7.2).

Caffeine

One study [83] investigated the effect of caffeine on fatigue. After six weeks, no difference was found between caffeine and placebo on the impact of fatigue on ADL (N = 61, SMD = -0.29, 95% CI = -0.79 to 0.22) and on fatigue severity (N = 61, SMD = 0.19, 95% CI = -0.32 to 0.69).

No statistically significant differences were found for the risk of adverse effects (see Table 7.2).

Caffeine did not improve depression (N = 61, SMD = 0.14, 95% CI = -0.36 to 0.65) and HRQOL (N = 61, SMD = -0.06, 95% CI = -0.56 to 0.44). Two questionnaires were used

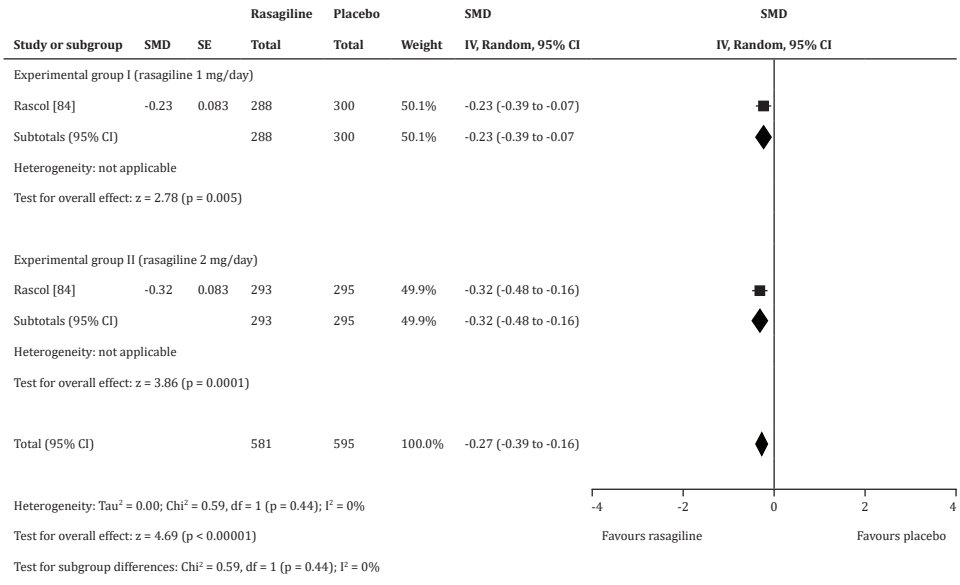

Figure 7.2 Rasagiline versus placebo, subjective impact of physical fatigue on (post-intervention).

to investigate the effect of caffeine on sleep disturbances; no differences were found between caffeine and placebo on the Epworth Sleepiness Scale (ESS) (N = 61, SMD = -0.46, 95% CI = -0.96 to 0.05) and the Pittsburgh Sleep Quality Index (PSQI) (N = 61, SMD = -0.13, 95% CI = -0.63 to 0.38).

Methylphenidate

One study [12] investigated the effect of methylphenidate on fatigue. Two self-report questionnaires were used to measure fatigue. After six weeks no statistically significant differences were found between methylphenidate and placebo on the FSS (N = 34, SMD = -0.64, 95% CI = -1.33 to 0.05) and the MFI total score (N = 34, SMD = -0.36, 95% CI = -1.04 to 0.32). The MFI subscales were used to investigate the effect of methylphenidate on the impact of physical and mental fatigue on ADL. No statistically significant differences were found for physical fatigue (N = 34, SMD = -0.48, 95% CI = -1.17 to 0.20) or mental fatigue (N = 34, SMD = 0.02, 95% CI = -0.65 to 0.70).

The risk of adverse effects did not significantly differ in patients that used methylphenidate compared with patients that received placebo (see Table 7.2).

Modafinil

Three studies [11, 13, 81] investigated the effect of modafinil on the impact of fatigue on ADL. One study presented insufficient data [13], the other two studies [11, 81] were pooled in a meta-analysis (see Figure 7.3). No statistically significant difference was found between modafinil and placebo (N = 53, SMD = -0.17, 95% CI = -0.72 to 0.37, I^2 = 0%). The subgroup analysis presented in Figure 7.3 shows that the estimate of effect for modafinil in patients with underlying depression was larger (N = 16, SMD = -0.40, 95% CI = -1.43 to 0.62) compared to non-depressed patients (N = 37, SMD = -0.08, 95% CI = -0.73 to 0.56). The robustness of the random-effects model was confirmed by sensitivity analysis; meta-analysis using a fixed effect model did not change the effect of modafinil. Sensitivity analysis in which we excluded one study because of unclear allocation concealment and high risk of attrition bias [11] reduced the effect size of modafinil (N = 37, SMD = -0.08, 95% CI = -0.73 to 0.56). In one study [11], post-treatment data showed a statistically significant difference for the impact of physical fatigue on ADL between patients that used modafinil and patients that received placebo (N = 16, SMD = -1.23, 95% CI = -2.36 to -0.11). No effect was found on the impact of mental fatigue on ADL (N = 16, SMD = 0.05, 95% CI = -0.97 to 1.06). Another study [81] investigated the effect of modafinil on fatigue severity; no statistically significant difference was found between modafinil and placebo (N = 37, SMD = -0.08, 95% CI = -0.73 to 0.56).

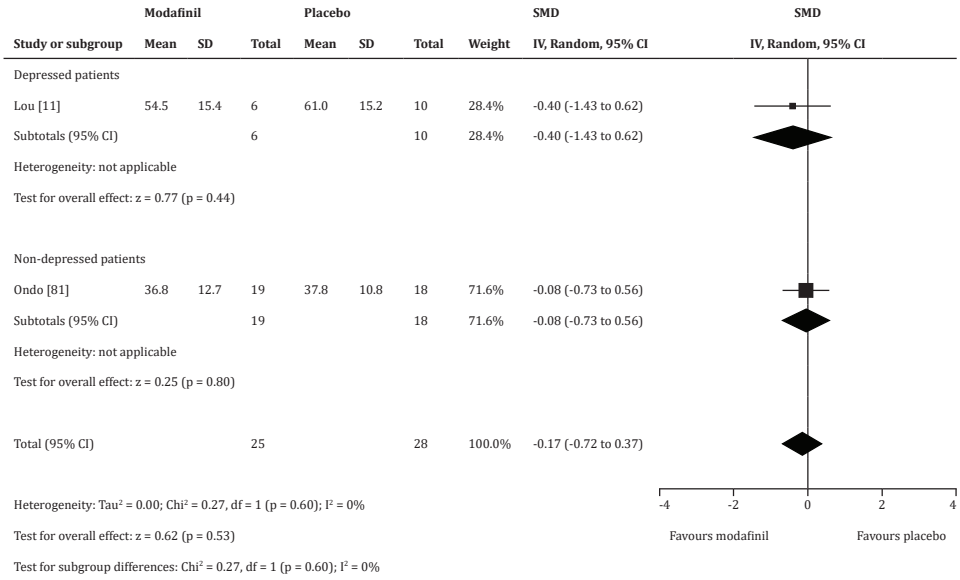

Figure 7.3 Modafinil versus placebo, subjective impact of fatigue (post-intervention).

Table 7.2 summarizes the risk of adverse effects in patients that used modafinil compared with patients that received placebo. The results of two studies [13, 81] were pooled in a meta-analysis; no statistically significant differences were found for anxiety (N = 50, RR = 3.14, 95% CI = 0.35 to 27.79, I^2 = 0%) (Figure 7.4) or nausea (N = 50, RR = 1.01, 95% CI = 0.11 to 8.93, I^2 = 0%) (Figure 7.5). Sensitivity analyses using fixed-effect models showed comparable results (RR = 3.13, 95% CI = 0.35 to 27.68, I^2 = 0% and RR = 1.04, 95% CI = 0.15 to 7.21, I^2 = 0% respectively).

Two studies [11, 81] investigated the effect of modafinil on depression and sleep disturbances. Figure 7.6 and Figure 7.7 present the results that were pooled in a meta-

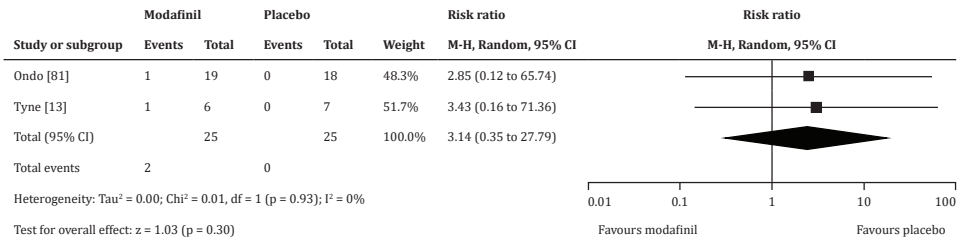

Figure 7.4 Modafinil versus placebo, anxiety (adverse effect, post-intervention).

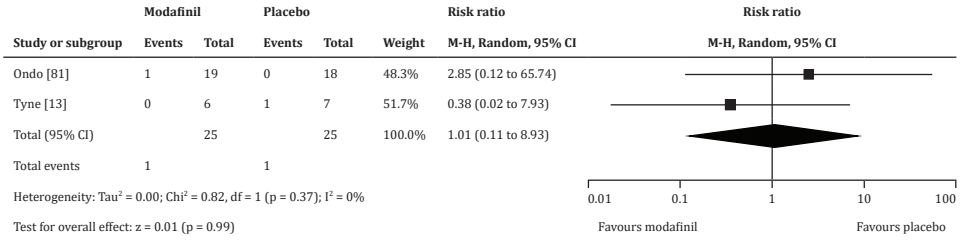

Figure 7.5 Modafinil versus placebo, nausea (adverse effect, post-intervention).

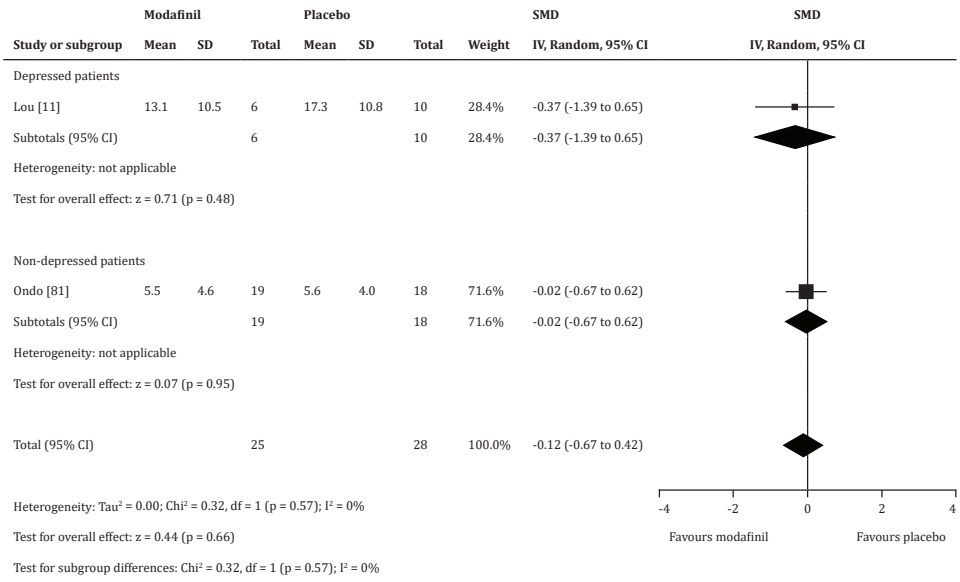

Figure 7.6 Modafinil versus placebo, depression (post-intervention).

analysis; no statistical differences were found for depression (N = 53, SMD = -0.12, 95% CI = -0.67 to 0.42, I^2 = 0%) and sleep disturbances (N = 53, SMD = -0.31, 95% CI = -0.86 to 0.24, I^2 = 0%). Subgroup analyses show that the estimates of effect for modafinil in patients with underlying depression were larger compared to patients without depressive disorders (see Figure 7.6 and Figure 7.7).

The robustness of the random-effects models was confirmed by sensitivity analysis; meta-analyses using fixed effect models did not change the effects. Sensitivity analysis in which we excluded one study because of unclear allocation concealment and high

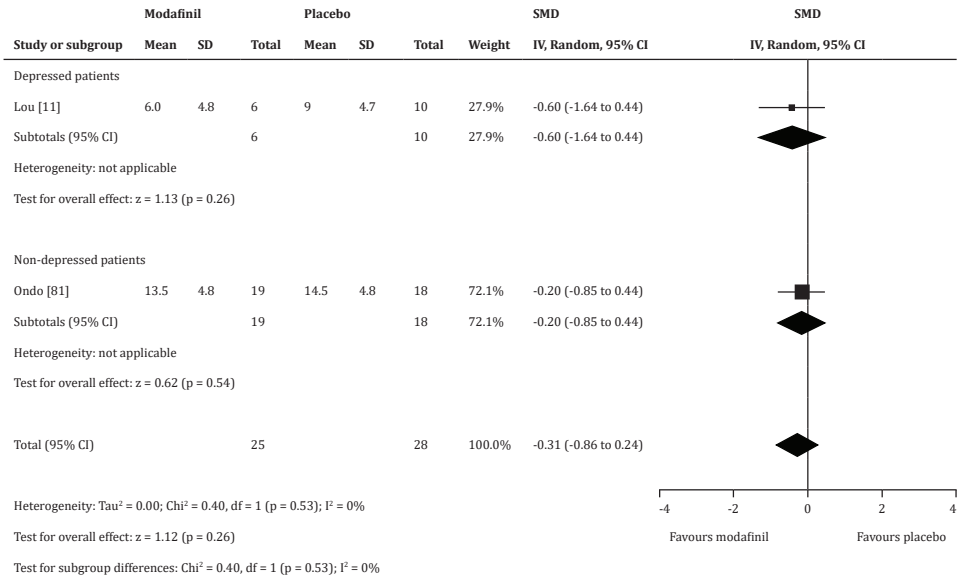

Figure 7.7 Modafinil versus placebo, sleep disturbances (post-intervention).

risk of attrition bias [11] reduced the effect sizes of modafinil for depression (N = 37, SMD = -0.02, 95% CI -0.67 to 0.62) and sleep disturbances (N = 37, SMD = -0.20, 95% CI -0.85 to 0.44).

Doxepin

One study [85] investigated the effect of doxepin on fatigue. After six weeks, a statistically significant difference was found between doxepin and placebo on the impact of fatigue on ADL and fatigue severity (N = 12, SMD = -1.50, 95% CI = -2.84 to -0.15). No statistically significant differences were found for the risk of adverse effects (see Table 7.2).

Doxepin did not improve depression (N = 12, SMD = -0.24, 95% CI = -1.38 to 0.89) and HRQOL (N = 12, SMD = -0.35, 95% = CI -1.49 to 0.79). Several questionnaires were used to investigate the effect of doxepin on sleep disturbances; a statistically significant difference was found between doxepin and placebo on the Insomnia Severity Index (ISI) (N = 12, SMD = -1.37, 95% CI = -2.69 to -0.06) but not on the total-scores of the other instruments used.

Non-pharmacological interventions

Exercise

Two studies [80, 87] investigated the effect of an exercise program on the impact of fatigue on ADL and fatigue severity. A meta-analysis (Figure 7.8) showed no statistical significant differences between exercise and usual care (N = 57, SMD = -0.45, 95% CI = -1.21 to 0.32, I^2 = 44%). Sensitivity analyses using a fixed-effect model yielded comparable results (SMD = -0.35, 95% CI = -0.88 to 0.18, I^2 = 44%).

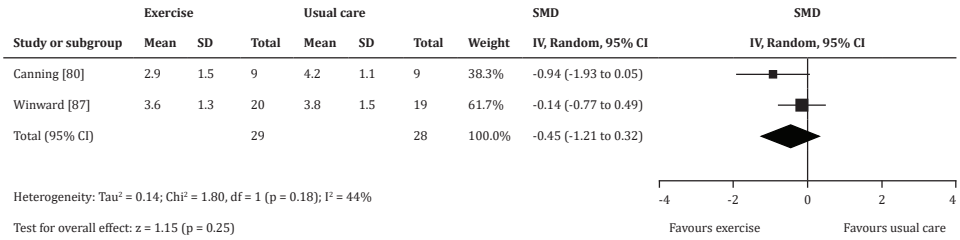

Figure 7.8 Exercise versus usual care, subjective impact of fatigue and fatigue severity (post-intervention).

One study [80] investigated possible adverse effects related to the exercise program. No adverse effects related to treadmill training were reported, including any falls during training [80].

Figure 7.9 presents the pooled results of two studies [80, 87] that investigated the effect of exercise on HRQOL. No statistically significant differences between exercise and usual care were found (N = 57, SMD = -0.08, 95% CI = -0.60 to 0.45, I^2 = 0%). Sensitivity analysis using a fixed effect model yielded the same results.

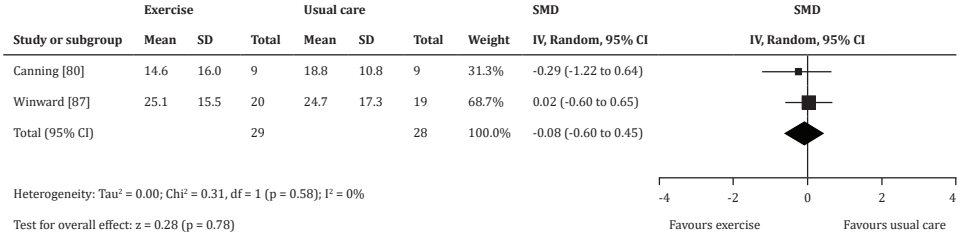

Figure 7.9 Exercise versus usual care, HRQOL (PDQ-39) (post-intervention).

Discussion

Summary of main results

The aim of the present systematic review was to evaluate the effect of pharmacological and non-pharmacological interventions on subjective fatigue in patients with PD.

We included a total of eleven studies; three of these studies included only patients who experienced clinically relevant fatigue, whereas all other studies did not select patients on the basis of experienced fatigue. Nine studies investigated the effect of medication (i.e. levodopa-carbidopa, memantine, rasagiline, caffeine, methylphenidate, modafinil and doxepin) on subjective fatigue. Only doxepin significantly reduced the impact of fatigue on ADL and fatigue severity. Post-treatment data showed statistically significant differences for the impact of physical fatigue, as measured by the PFS-16 or the MFI physical fatigue subscale, between patients that used rasagiline or modafinil compared with placebo. With regard to adverse effects, only levodopa-carbidopa showed a statistically significant increase for the risk of nausea.

Pooling the two studies that investigated the effect of exercise on subjective fatigue showed non-significant reductions of the impact of fatigue on ADL or in terms of fatigue severity.

Overall completeness and applicability of evidence

Pharmacological interventions

Although our results suggest that doxepin significantly reduces the impact of fatigue on ADL and fatigue severity in patients with PD, this finding has to be interpreted with care because the methodology used in the study by Rios Romenets and colleagues [85] shows some serious flaws. First, allocation of patients to the experimental or control group was not concealed; second, outcome assessment for patient-reported outcomes was not blinded. Therefore, it is likely that the effect found was subject to substantial bias and therefore overestimated.

One large study [84] showed that rasagiline had a small but statistically significant effect on the impact of physical fatigue on ADL. The group that received rasagiline 2 mg/day scored 0.19 points lower on the PFS-16, which represents 3.8% of the total score, compared with placebo. Patients that received rasagiline 1 mg/day scored on average 0.14 points (2.8% of total score) lower compared with placebo. These findings suggest that rasagiline may be an effective treatment to reduce symptoms of physical

fatigue in patients with PD. However, it is difficult to generalize these findings to clinical practice. First, the study was designed to investigate whether rasagiline had disease-modifying effects in patients with recently diagnosed PD (i.e. disease duration of 18 months or less from time of diagnosis). This limits the generalizability of results to patients with more advanced PD. Second, patients that received placebo showed a significant worsening of fatigue over time, whereas patients receiving rasagiline mostly maintained baseline levels of fatigue [84]. This suggests that rasagiline may reduce or slow down the progression of physical fatigue over time; however, it remains unclear if rasagiline is able to reduce the actual levels of physical fatigue in patients with PD. Preliminary results of an ongoing study (NCT01168596) showed that rasagiline 1 mg/day did not significantly reduce the impact of fatigue on ADL in moderately to severely fatigued patients with PD [52]. Future studies are needed to investigate whether rasagiline reduces actual levels of physical fatigue in patients with PD.

Our results also suggest that modafinil significantly reduces the impact of physical fatigue on ADL (N = 16, SMD = -1.23, 95% CI = -2.36 to -0.11). This finding is in conflict with the original study [11] in which the authors concluded that modafinil did not improve subjective fatigue in patients with PD. The difference found between modafinil and placebo at the end of the treatment period is likely biased by a generated imbalance at baseline. Although not statistically significant, patients that were allocated to the modafinil group reported lower physical fatigue at baseline compared with patients that were allocated to the placebo group. Lou and colleagues [11] used a mixed model that took into account both between- and within patient variances, which probably yields a more valid result than our standard post-treatment analysis. With that, it is more likely to conclude that modafinil does not significantly reduce the impact of physical fatigue on ADL.

Although no safety issues with regard to adverse effect were identified in the studies included in our systematic review, concerns have been raised that long-term use of psychostimulants (e.g. methylphenidate and modafinil) might cause drug dependency, psychotic symptoms and behavioral sensitization similar to other stimulants [10]. Rare cases of serious or life-threatening skin conditions have been reported in patients using modafinil [10]. Two 'evidence-based medicine reviews' about treatments for motor and non-motor symptoms of PD [10, 88] concluded that the safety of levodopa-carbidopa, memantine and rasagiline is acceptable. Another systematic review [89] concluded that tricyclic antidepressants, such as doxepin, could be used in patients with PD without the risk of substantial side effects.

Non-pharmacological interventions

Meta-analysis of two studies [80, 87] showed that exercise did not significantly affect the impact of fatigue on ADL and fatigue severity in patients with PD. Although both studies focused on the improvement of exercise capacity, the studies differed strongly in the achieved intensity of performed exercise. Canning and colleagues [80] planned four treadmill-training sessions a week for six weeks. Patients in this study showed excellent adherence and completed on average 94% of the prescribed sessions [80]. In the other study [87] patients were encouraged to attend five aerobic sessions and two strength sessions per week for a period of 12 weeks; however, in this study patients self-determined the number of sessions they attended, which was indeed low. Only 11 out of 20 patients achieved weekly attendance [87]. The difference in adherence to the program, and with that exercise intensity, may explain the difference in the magnitude of effect between both studies. Specific prescribed intensity [80] seems to improve the effect of an exercise program; however, this finding has to be confirmed in future studies.

Despite our broad search strategy, we identified no studies that investigated the effect of cognitive-behavioral therapy or other non-pharmacological interventions on subjective fatigue in patients with PD.

General issues studying interventions for fatigue in PD

Most studies included in our systematic review did not select patients on the basis of fatigue severity. As a result, mean baseline levels of fatigue in these studies just reached the cut-off point for clinically relevant fatigue. This may have contributed to the lack of effect for most interventions included in this systematic review and one may argue that interventions may be more beneficial in more severely fatigued patients.

Since fatigue is one of the criterion symptoms for a major depressive disorder [90] and depression may overlap with or exacerbate feelings of subjective fatigue [91], it is possible that patients with depressive disorders respond differently to treatment for fatigue than non-depressed patients. Our subgroup analysis showed a trend that modafinil was more effective in depressed patients than in patients without underlying depression; however, this result has to be interpreted with caution. First, the found effects in both subgroups were not statistically significant. Second, the subgroup analysis consisted of two studies of which one [11] scored high risk for attrition bias, which may have resulted in an overestimation of the effect of modafinil in patients with depressive disorders.

Previous research [92] suggested that physical fatigue and mental fatigue may have different etiologies and therefore may need to be managed separately. Two studies that investigated the effect of psychostimulants on physical fatigue and mental fatigue [11, 12] showed a trend towards more improvement on the impact of physical fatigue than on the impact of mental fatigue on ADL. Improvements were small and not statistically significant; however, these findings may support the hypothesis that physical fatigue and mental fatigue are independent symptoms that have to be treated differently. Unfortunately, we were not able to test this hypothesis in subgroup analyses because only one study [11] in our meta-analyses provided data on baseline levels of perceived physical and mental fatigue.

Although most studies used validated self-report questionnaires to measure fatigue, the interpretation of the magnitude of effect is difficult as measurement properties such as measurement error and responsiveness have not been investigated properly yet in patients with PD [15]. It is unclear whether measurement error and responsiveness of the used self-report questionnaires is adequate to detect clinically meaningful changes in subjective fatigue. For example, the found effect of modafinil [11] and methylphenidate [12] on the impact of fatigue measured by the MFI did not exceed the smallest detectable change (i.e. the measurement error) of this instrument in patients with PD [93]. Furthermore, different questionnaires measure different aspects or constructs of fatigue [15], which makes it difficult to compare results between studies.

Quality of the evidence

We rated the effect of rasagiline on the impact of physical fatigue on ADL as high quality evidence. With regard to adverse effects, we found high quality evidence that levodopa-carbidopa increased the risk for nausea as drug-related adverse effect. However, designating a single RCT as high quality evidence may feel uncomfortable, given that first positive study results often not held under subsequent investigation [94]. Although it is not possible to investigate consistency for these results at this point in time, automatically rating down quality is not recommended by the GRADE working group [94].

For most other outcomes, the quality of the evidence was rated ‘moderate‘ because of imprecision of results. This indicates that for these outcomes future research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate of effect. The quality of the evidence for the effect of modafinil and doxepin on the impact of fatigue on ADL ranged from low to very low. Therefore,

the evidence in favor of the effect of modafinil and doxepin on the impact of fatigue on ADL should be considered with caution, as further research is likely to change the estimate of effect.

Agreements and disagreements with other studies or reviews

Our findings are in line with a previous review by Seppi and colleagues [10]. The authors concluded that there was insufficient evidence either for, or against the effectiveness of methylphenidate and modafinil to treat subjective fatigue in patients with PD [10]. Recently, Franssen and colleagues [14] systematically reviewed the effects of pharmacological and non-pharmacological interventions on fatigue in patients with PD. All studies included in their systematic review were identified by our search strategy and considered for inclusion. However, we used slightly different criteria for study selection and excluded four studies [23, 38, 41, 50] that were incorporated in their review. Nevertheless, our conclusions are in agreement with their findings as the authors concluded that insufficient evidence exists to support pharmacological or non-pharmacological treatment of fatigue in patients with PD.

Potential biases in the review process

This systematic review has some limitations. First, as studies used different self-report questionnaires to assess fatigue, we transformed all continuous outcomes into SMD's. Unfortunately, the interpretation of the SMD is challenging as rules of thumb [22] are to a certain extent arbitrary and do not intuitively resonate with either clinicians or patients [95]. To address this limitation we planned to perform additional analyses in which we standardized continuous outcomes into minimal important change (MIC) units [17, 95] to indicate whether the observed effect is considered important by patients. However, despite an extensive literature search, we found established MIC values for only a few questionnaires. Therefore we decided to perform analyses based on SMD's only.

Second, for continuous outcomes we used post-intervention data to calculate the mean difference between the intervention group and the control group [19]. For two small studies, that included baseline measurements in their statistical analyses [11, 80], this method resulted in other estimates of effect compared to the data presented in the original publication. However, taken the clinical relevance of the effects and the quality of the evidence into account, our conclusions are largely in line with the conclusions presented in the original publications [11, 80].

Authors' conclusions

Implications for practice

Based on the current evidence, it is difficult to provide clear recommendations for the treatment of subjective fatigue in patients with PD. Doxepin may reduce the impact of fatigue on ADL and fatigue severity; however, this finding has to be confirmed in high quality RCTs. Rasagiline may be effective in reducing levels of physical fatigue in patients with PD, whereas no evidence was found for the effectiveness of levodopa-carbidopa, memantine, caffeine, methylphenidate, modafinil and exercise. As depressive disorders may modify the effect of interventions on subjective fatigue in patients with PD, treatment of fatigue should always be accompanied by assessment and treatment of underlying depression.

Implications for research

The conclusions of this systematic review are based on studies that in general were characterized by small sample size. Future studies should increase sample size to reduce the probability of a type II error, i.e. concluding that the treatment is not effective when in reality it is. Studies are needed to investigate the effect of exercise intensity on exercise capacity and subjective fatigue. Future studies should focus on programs that address the behavioral or cognitive aspects that address maladaptive behavior or coping related to fatigue in patients with PD. Patient characteristics, such as severity and characteristics of perceived fatigue and underlying mood disorders should be considered to identify responders and non-responders when studying interventions for fatigue. The development of a core-set of self-report fatigue questionnaires with established responsiveness and known MIC values will facilitate the interpretation of change in fatigue scores in patients with PD.

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Appendix 7.1 Characteristics of included studies

Table A7.1.1 Canning [80]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue or depression
Participants	Experimental group: N = 10 Age (mean (SD)) = 60.7 (5.9) Sex (male/female) = 5/5 Disease severity = not reported Disease duration in years (mean (SD)) = 6.1 (4.0) Fatigue (VAS 0-7) (mean (SD)) = 3.3 (1.6) Depression = not reported Comorbid conditions: not reported Control group: N = 10 Age (mean (SD)) = 62.9 (9.9) Sex (male/female) = 6/4 Disease severity = not reported Disease duration in years (mean (SD)) = 5.2 (4.1) Fatigue (VAS 0-7) (mean (SD)) = 3.7 (1.2) Depression = not reported Comorbid conditions: not reported
Interventions	Experimental group: Semi-supervised home-based program of 30–40 minutes of treadmill walking, four times a week for six weeks. Sessions included a 5-minute warm-up and cool-down of walking in place, sit-to-stand exercise and stretching exercises followed by treadmill walking at 50% of the average speed maintained during the pre-test 6-minute walk test. Intensity of treadmill training was progressed over the six weeks. Participants initially walked at 60% of the average speed maintained during the pre-test 6-minute walk test. Over subsequent sessions, walking speed was increased to 80% of the average 6-minute walk test speed. Additional cognitive or manual tasks during walking were introduced systematically from week 4 of training, with participants aiming to maintain stride length. Verbal and visual cues were provided to encourage participants to focus on maintaining big steps while walking. Seven sessions were supervised, in the participant's home, by a physiotherapist. All other sessions were completed independently by the participant. Control group: The control group received usual care (i.e. advice to maintain current levels of physical activity).

Table A7.1.1 Canning [80] (continued)

Study characteristics		
Outcomes	Measured at baseline (week 0), post-treatment (week 6) and follow-up (week 12) Primary outcomes: Fatigue during prior two weeks (not further specified) measured by VAS 0-7 Secondary outcomes: HRQOL measured by PDQ-39 Adverse effects: Falls	
Funding and conflict of interest	Funding: University of Sydney Research and Development Grant Conflict of interest: None declared	
Notes	Study protocol available on www.clinicaltrials.gov #NCT00261781	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'…a staff member who was not involved in the trial randomly allocated participants to the treadmill training or control group using opaque envelopes pre-prepared by one investigator...'
Allocation concealment (selection bias)	Low risk	'…using opaque envelopes pre-prepared by one investigator...'
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind patients and personnel for intervention
Blinding of outcome assessment (detection bias) Patient-reported outcomes	High risk	Not possible to blind patients for intervention
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'Efficacy outcome measures were made by an assessor blinded to group allocation…'
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up described, intention-to-treat analyses performed
Selective reporting (reporting bias)	Low risk	Presented results in accordance with study protocol (www.clinicaltrials.gov)
Other bias	Low risk	

Table A7.1.2 Lou [11]

Study characteristics	
Methods	RCT Specific inclusion criteria for fatigue (MFI-total > 48 out of 100) No specific inclusion criteria for depression
Participants	Experimental group: N = 9 Age (mean (SD)) = 64.0 (9) Sex (male/female) = 9/0 Disease severity (UPDRS-total) (mean (SD)) = 28.0 (10) Disease duration in years (mean (SD)) = 4.0 (3) Fatigue (MFI-total) (mean (SE)) = 55.8 (5.1) Depression (CES-D) (mean (SE)) = 17.1 (3.5) Comorbid conditions: not reported Control group: N = 10 Age (mean (SD)) = 69.0 (8) Sex (male/female) = 5/5 Disease severity (UPDRS-total) (mean (SD)) = 40.0 (11) Disease duration in years (mean (SD)) = 8.0 (6) Fatigue (MFI-total) (mean (SE)) = 63.5 (4.8) Depression (CES-D) (mean (SE)) = 23.6 (3.4) Comorbid conditions: not reported
Interventions	Experimental group: Patients remained on their regular medication for the duration of the study. In addition, modafinil 100 mg twice a day for two months was administered orally. Control group: Patients remained on their regular medication for the duration of the study. In addition, placebo (same schedule) was administered orally.
Outcomes	Measured at baseline (month 0), during treatment (month 1) and post-treatment (month 2) Primary outcomes: Subjective impact of fatigue on ADL measured by MFI-total Subjective impact of physical fatigue on ADL measured by MFI physical fatigue subscale Subjective impact of mental fatigue on ADL measured by MFI mental fatigue subscale Secondary outcomes: Depression measured by CES-D Sleep disturbances measured by ESS
Funding and conflict of interest	Funding: National Parkinson Foundation Conflict of interest: Not reported
Notes	

Table A7.1.2 Lou [11] (continued)

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'They were randomly assigned by the pharmacy…' No details provided
Allocation concealment (selection bias)	Unclear risk	'They were randomly assigned by the pharmacy…' No details provided
Blinding of participants and personnel (performance bias)	Low risk	'The modafinil and the placebo capsules had the same appearance.'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'The modafinil and the placebo capsules had the same appearance.'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'Double blind…'
Incomplete outcome data (attrition bias)	High risk	'Three subjects in the modafinil group reported adverse events… …subjects did not complete the study and were not included in the analysis.'
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section
Other bias	Low risk	

Table A7.1.3 Mendonça [12]

Study characteristics	
Methods	RCT Specific inclusion criteria for fatigue (FSS score ≥ 4 out of 7) Patients with active depression were excluded
Participants	Experimental group: N = 17 Age (mean (SD)) = 66.3 (7.6) Sex (% male) = 94.1 Disease severity (H&Y) (mean (SD)) = 2.4 (0.3) Disease duration in months (mean (SD)) = 72.2 (61.2) Fatigue (FSS) (mean (SD)) = 43.8 (6.7) Fatigue (MFI-total) (mean (SD)) = 51.0 (10.8) Depression = not reported Comorbid conditions: not reported Control group: N = 19 Age (mean (SD)) = 62.2 (10.0) Sex (% male) = 42.1 Disease severity (H&Y) (mean (SD)) = 2.6 (0.5) Disease duration in months (mean (SD)) = 80.6 (79.8) Fatigue (FSS) (mean (SD)) = 44.9 (6.2) Fatigue (MFI-total) (mean (SD)) = 52.5 (15.5) Depression = not reported Comorbid conditions: not reported
Interventions	Experimental group: Patients had been optimized on regular antiparkinsonian medication. The dose of medication was not changed during the study. In addition, methylphenidate 10 mg three times a day for six weeks was administered orally. Control group: Patients had been optimized on regular antiparkinsonian medication. The dose of medication was not changed during the study. In addition, placebo (same schedule) was administered orally.
Outcomes	Measured at baseline (week 0) and post-treatment (week 6) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS and MFI-total Subjective impact of physical fatigue on ADL measured by MFI physical fatigue subscale Subjective impact of mental fatigue measured on ADL by MFI mental fatigue subscale Subjective severity of fatigue measured by FSS Adverse effects: Headache, hypertension, nausea and tachycardia

Table A7.1.3 Mendonça [12] (continued)

Study characteristics		
Funding and conflict of interest	Funding: Not reported Conflict of interest: Not reported	
Notes	Authors adapted scores for FSS and MFI: FSS 7-point Likert (0-6); MFI 5-point Likert (0-4)	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Block randomization was done centrally via a computer-generated list…'
Allocation concealment (selection bias)	Low risk	'Numbered containers of study medication... ...patient and the study physician were blinded to whether the patient was receiving methylphenidate or placebo.'
Blinding of participants and personnel (performance bias)	Low risk	'To ensure blinding, the medications were identical in appearance, packaging, and labeling.'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'To ensure blinding, the medications were identical in appearance, packaging, and labeling.'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'…motor score and neurologic exam were performed by one study physician…'
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up described, intention-to-treat analyses performed
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section
Other bias	Low risk	

Table A7.1.4 Ondo [81]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue or depression
Participants	Experimental group: N = 20 Age (mean (SD)) = 64.4 (10.4) Sex (male/female) = 13/7 Disease severity = not reported Disease duration in years (mean (SD)) = 6.5 (5.5) Fatigue (FSS) (mean (SD)) = 37.6 (14.1) Depression (HDS) (mean (SD)) = 6.5 (5.0) Comorbid conditions: not reported Control group: N = 20 Age (mean (SD)) = 65.1 (12.3) Sex (male/female) = 13/7 Disease severity = not reported Disease duration in years (mean (SD)) = 7.0 (4.6) Fatigue (FSS) (mean (SD)) = 36.8 (12.8) Depression (HDS) (mean (SD)) = 7.2 (5.2) Comorbid conditions: not reported
Interventions	Experimental group: Modafinil 100 mg twice a day for one week administered orally. After one week, the dose was increased to 200 mg twice a day. One week later, patients were asked by phone interview about adverse effects. If a patient had experienced adverse effects at the higher dose, they were allowed to decrease the medication to the previous dose. Patients continued at either 200 mg/day or 400 mg/day until the second visit, four weeks after baseline. Control group: Placebo (same schedule) was administered orally.
Outcomes	Measured at baseline (week 0) and post-treatment (week 4) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Adverse effects: Anxiety, nausea Secondary outcomes: Depression measured by HDS Sleep disturbances measured by ESS
Funding and conflict of interest	Funding: Cephalon Pharmaceuticals Conflict of interest: Ondo spoke for Cephalon Pharmaceuticals on several occasions approximately two years previously
Notes	

Table A7.1.4 Ondo [81] (continued)

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'...subjects were randomised by a computerised randomisation code...'
Allocation concealment (selection bias)	Low risk	'...drug and the placebo, which matched the drug in taste and appearance... ...coordinator who was shielded from the subjects and not otherwise involved in the study in any way.'
Blinding of participants and personnel (performance bias)	Low risk	'...placebo, which matched the drug in taste and appearance...'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'...placebo, which matched the drug in taste and appearance...'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'The rating physician was blinded to reports of adverse events and dosing.'
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up described
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section
Other bias	Low risk	

Table A7.1.5 Ondo [82]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue or depression
Participants	Experimental group: N = 20 Age (mean (SD)) = 69.2 (7.9) Sex (male/female) = 12/8 Disease severity (H&Y) (mean (SD)) = 2.5 (0.5) Disease duration = not reported Fatigue (FSS) (mean (SD)) = 37.6 (14.2) Depression (HDS) (mean (SD)) = 10.7 (5.0) Comorbid conditions (number of patients): anxiety (N = 2); arthritis (N = 4); cholesterol (N = 3); depression (N = 6); gastroenterological (N = 4); hypertension (N = 8); thyroid (N = 2) Control group: N = 20 Age (mean (SD)) = 68.9 (8.4) Sex (male/female) = 12/8 Disease severity (H&Y) (mean (SD)) = 2.3 (0.4) Disease duration = not reported Fatigue (FSS) (mean (SD)) = 37.2 (14.3) Depression (HDS) (mean (SD)) = 10.1 (5.0) Comorbid conditions (number of patients): anxiety (N = 4); arthritis (N = 5); cholesterol (N = 6); depression (N = 10); gastroenterological (N = 5); hypertension (N = 10); thyroid (N = 2)
Interventions	Experimental group: Patients were not allowed to change other antiparkinsonian medication during the study. In addition, memantine dosing began at 5 mg/day and increased to 10 mg twice a day in weekly increments. Memantine was administered orally for eight weeks. Control group: Patients were not allowed to change other antiparkinsonian medication during the study. In addition, placebo (same schedule) was administered orally.
Outcomes	Measured at baseline (week 0) and post-treatment (week 8) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Adverse effects: Anxiety, hypertension, impulse control disorders, nausea Secondary outcomes: Depression measured by HDS HRQOL measured by PDQ-39 Sleep disturbances measured by ESS
Funding and conflict of interest	Funding: Forest Research Institute, sponsors had the right to review the manuscript prior to submission but had no role in study execution

Table A7.1.5 Ondo [82] (continued)

Study characteristics		
	Conflict of interest: Ondo initiated grant from Forest Pharmaceuticals for study execution	
Notes	Study protocol available on www.clinicaltrials.gov #NCT00646204	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'...a computerized random number generator...'
Allocation concealment (selection bias)	Low risk	'...by a coordinator not otherwise involved in the study.'
Blinding of participants and personnel (performance bias)	Low risk	Placebo was used; in addition, personnel was blinded (www.clinicaltrials.gov)
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	Outcome assessor was blinded (www.clinicaltrials.gov)
Incomplete outcome data (attrition bias)	Unclear risk	'All four subjects who dropped were in the drug group.' 'We re-performed the 'on treatment analysis' in addition to the 'last observation carry forward analysis'. Results... ...were consistent.'
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section, no details on pre-specified outcomes in study protocol (www.clinicaltrials.gov)
Other bias	Low risk	

Table A7.1.6 Postuma [83]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue Patients with depression were excluded (BDI score ≥ 15)
Participants	Experimental group: N = 30 Age (mean (SD)) = 65.2 (8.3) Sex (% male) = 83 Disease severity (UPDRS-total) (mean (SD)) = 41.2 (13.1) Disease duration in years (mean (SD)) = 7.8 (3.5) Fatigue (FSS) (mean (SD)) = 39.9 (12.2) Depression (BDI) (mean (SD)) = 10.3 (6.1) Comorbid conditions: not reported Control group: N = 31 Age (mean (SD)) = 67.8 (11.2) Sex (% male) = 61 Disease severity (UPDRS-total) (mean (SD)) = 42.0 (17.5) Disease duration in years (mean (SD)) = 8.0 (4.8) Fatigue (FSS) (mean (SD)) = 39.5 (14.9) Depression (BDI) (mean (SD)) = 11.5 (4.7) Comorbid conditions: not reported
Interventions	Experimental group: Patients were not allowed to change other antiparkinsonian medication during the study and were instructed to continue habitual caffeine intake. In addition, caffeine dosing began at 100 mg twice a day. After three weeks dose increased to 200mg twice a day. Caffeine was administered orally for six weeks. Control group: Patients were not allowed to change other antiparkinsonian medication during the study and were instructed to continue habitual caffeine intake. In addition, placebo (same schedule) was administered orally.
Outcomes	Measured at baseline (week 0), during treatment (week 3) and post-treatment (week 6) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS, SF-36-V

Table A7.1.6 Postuma [83] (continued)

Study characteristics		
	Adverse effects: Anxiety, headache Secondary outcomes: Depression measured by BDI HRQOL measured by PDQ-39 Sleep disturbances measured by ESS, PSQI	
Funding and conflict of interest	Funding: Grants from the Canadian Institute of Health Research, the Webster Foundation and the Drummond Foundation Conflict of interest: None declared	
Notes	Study protocol available on www.clinicaltrials.gov #NCT00459420	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'...performed by study statisticians by use of PROCPLAN in SAS software and Clistat software.'
Allocation concealment (selection bias)	Low risk	'The randomization list was given to both central research pharmacies... ...not involved in outcome assessment... ...individual pill pack for each patient, with only the identifying code.'
Blinding of participants and personnel (performance bias)	Low risk	'Caffeine and placebo tablets were encapsulated to be indistinguishable in appearance; caffeine powder or lactose were placed into identical capsules.'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'All patients and examiners were blinded to treatment assignment.'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'All patients and examiners were blinded to treatment assignment.'
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up and protocol violations described '...patients were analyzed in the primary intention-to-treat analysis.'
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section, except for palpitations
Other bias	Low risk	

Table A7.1.7 Rascol [84]

Study characteristics	
Methods	RCT (delayed-start design, only first period data used) No specific inclusion criteria for fatigue or depression
Participants	Experimental group I (Rasagiline 1 mg/day): N = 288 Age (mean (SD)) = 62.4 (9.7) Sex (% male) = 60.8 Disease severity (H&Y) (mean (SD)) = 1.5 (0.5) Disease duration in months (mean (SD)) = 4.6 (4.7) Fatigue (PFS-16) (mean (SD)) = 2.2 (0.9) Depression (BDI) (mean (SD)) = 3.6 (3.1) Comorbid conditions: not reported Experimental group II (Rasagiline 2 mg/day): N = 293 Age (mean (SD)) = 62.3 (9.6) Sex (% male) = 59.7 Disease severity (H&Y) (mean (SD)) = 1.5 (0.5) Disease duration in months (mean (SD)) = 4.6 (4.6) Fatigue (PFS-16) (mean (SD)) = 2.2 (0.9) Depression (BDI) (mean (SD)) = 3.5 (3.1) Comorbid conditions: not reported Control group I (Placebo 1 mg/day): N = 300 Age (mean (SD)) = 61.9 (9.7) Sex (% male) = 62.0 Disease severity (H&Y) (mean (SD)) = 1.5 (0.5) Disease duration in months (mean (SD)) = 4.3 (4.6) Fatigue (PFS-16) (mean (SD)) = 2.2 (0.9) Depression (BDI) (mean (SD)) = 3.4 (3.2) Comorbid conditions: not reported Control group II (Placebo 2 mg/day): N = 295 Age (mean (SD)) = 62.4 (9.7) Sex (% male) = 61.7 Disease severity (H&Y) (mean (SD)) = 1.5 (0.5) Disease duration in months (mean (SD)) = 4.6 (4.6) Fatigue (PFS-16) (mean (SD)) = 2.2 (0.9) Depression (BDI) (mean (SD)) = 3.4 (3.2) Comorbid conditions: not reported
Interventions	Experimental group I (Rasagiline 1 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, rasagiline 1 mg/day was administered orally for 36 weeks. Experimental group II (Rasagiline 2 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, rasagiline 1 mg/day was administered orally for 36 weeks. Control group I (Placebo 1 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, placebo 1 mg/day (same schedule) was administered orally.

Table A7.1.7 Rascol [84] (continued)

Study characteristics		
	Control group II (Placebo 2 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, placebo 2 mg/day (same schedule) was administered orally.	
Outcomes	Measured at baseline (week 0) and post-treatment period 1 (week 36) Primary outcomes: Subjective impact of physical fatigue on ADL measured by PFS-16 Adverse effects: Anxiety, headache, hypertension, impulse control disorders, nausea, orthostatic hypotension	
Funding and conflict of interest	Funding: Teva Pharmaceutical Industries, H Lundbeck A/S Conflict of interest: The sponsor participated in study design and execution and provided funding for editorial and formatting assistance under direction of the authors; the authors had full access to all data and were responsible for study design, interpretation of data, writing of the report and decision to submit for publication	
Notes	Study protocol available on www.clinicaltrials.gov #NCT00256204 Additional publications used for data collection (Olanow, Mov Dis 2008;23:2194-201; Olanow, N Engl J Med 2009;361:1268-78; Stocchi, Eur J Neurol 2014;21:357-60)	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'…randomized… …based on a computer generated randomization scheme with blocks stratified by center...'
Allocation concealment (selection bias)	Low risk	'...participants and all personnel at study sites were masked to allocation...'
Blinding of participants and personnel (performance bias)	Low risk	'...participants and all personnel at study sites were masked to allocation...'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'...participants and all personnel at study sites were masked to allocation...'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'...participants and all personnel at study sites were masked to allocation...'
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up described
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section, no details on pre-specified outcomes in study protocol (www.clinicaltrials.gov)
Other bias	Low risk	

Table A7.1.8 Rios Romenets [85]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue or depression
Participants	Experimental group: N = 6 Age (mean (SD)) = 65.3 (10.5) Sex (% male) = 50.0 Disease severity (UPDRS-total) (mean (SD)) = 30.9 (7.6) Disease duration in years (mean (SD)) = 4.8 (3.6) Fatigue (FSS) (mean (SD)) = 46.5 (10.9) Depression (BDI) (mean (SD)) = 12.0 (7.5) Comorbid conditions: not reported Control group: N = 6 Age (mean (SD)) = 69.5 (10.5) Sex (% male) = 83.0 Disease severity (UPDRS-total) (mean (SD)) = 32.8 (14.5) Disease duration in years (mean (SD)) = 5.2 (4.4) Fatigue (FSS) (mean (SD)) = 34.0 (16.6) Depression (BDI) (mean (SD)) = 8.2 (3.7) Comorbid conditions: not reported
Interventions	Experimental group: Doxepin 10 mg/day was administered orally (at bedtime) for 6 weeks. Control group: The control group received 30 minutes of light therapy below the threshold required for active treatment. No placebo capsules were given.
Outcomes	Measured at baseline (week 0), post-treatment (week 6) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Adverse effects: Nausea, orthostatic hypotension Secondary outcomes: Depression measured by BDI HRQOL measured by PDQ-39 Sleep disturbances measured by ESS, ISI, PDSS, PSQI, SCOPA Sleep
Funding and conflict of interest	Funding: Grants from the Parkinson Society of Canada, the Canadian Institute of Health Research, the Fonds de la recherche en santé du Québec Conflict of interest: None declared
Notes	Study protocol available on www.clinicaltrials.gov #NCT01489982

Table A7.1.8 Rios Romenets [85] (continued)

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomization was done with a block design…' No details provided
Allocation concealment (selection bias)	High risk	'…treatment assignment was not otherwise blinded.'
Blinding of participants and personnel (performance bias)	High risk	'…placebo intervention was 30 min of light therapy… …(no placebo capsules were given).'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	High risk	'…placebo intervention was 30 min of light therapy… …(no placebo capsules were given).'
Blinding of outcome assessment (detection bias) Other outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up described
Selective reporting (reporting bias)	Unclear risk	Most results in accordance with study protocol, no detailed data presented for SCOPA Sleep and labeling of primary and secondary outcomes not consistent with study protocol (www.clinicaltrials.gov)
Other bias	Low risk	

Table A7.1.9 Schifitto [86]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue Patients with major depression were excluded
Participants	Experimental group I (levodopa-carbidopa 150/37.5 mg/day): N = 92 Age (mean (SD)) = 64.3 (10.6) Sex (% male) = 63.0 Disease severity (H&Y) (mean (SD)) = 1.9 (0.6) Disease duration in months (mean (SD)) = 5.7 (6.1) Fatigue = not reported Depression = not reported Comorbid conditions: not reported Experimental group II (levodopa-carbidopa 300/75 mg/day): N = 88 Age (mean (SD)) = 63.8 (12.1) Sex (% male) = 67.0 Disease severity (H&Y) (mean (SD)) = 1.8 (0.5) Disease duration in months (mean (SD)) = 7.6 (7.5) Fatigue = not reported Depression = not reported Comorbid conditions: not reported Experimental group III (levodopa-carbidopa 600/150 mg/day): N = 91 Age (mean (SD)) = 65.2 (10.7) Sex (% male) = 68.0 Disease severity (H&Y) (mean (SD)) = 1.9 (0.6) Disease duration in months (mean (SD)) = 6.0 (6.1) Fatigue = not reported Depression = not reported Comorbid conditions: not reported Control group: N = 90 Age (mean (SD)) = 64.9 (10.3) Sex (% male) = 72.0 Disease severity (H&Y) (mean (SD)) = 1.8 (0.5) Disease duration in months (mean (SD)) = 5.3 (5.6) Fatigue = not reported Depression = not reported Comorbid conditions: not reported
Interventions	Experimental group I (levodopa-carbidopa 150/37.5 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, levodopa-carbidopa 50 mg and 12.5 mg three times a day was administered orally (with titration to full dose occurring over nine weeks) for 40 weeks. After 40 weeks, patients underwent a three day period of step-down withdrawal from study drug and a two week washout period.

Table A7.1.9 Schifitto [86] (continued)

Study characteristics		
	Experimental group II (levodopa-carbidopa 300/75 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, levodopa-carbidopa 100 mg and 25 mg three times a day was administered orally (with titration to full dose occurring over nine weeks) for 40 weeks. After 40 weeks, patients underwent a three day period of step-down withdrawal from study drug and a two week washout period. Experimental group III (levodopa-carbidopa 600/150 mg/day): No other antiparkinsonian medication was permitted during the study. In addition, levodopa-carbidopa 200 mg and 50 mg three times a day was administered orally (with titration to full dose occurring over nine weeks) for 40 weeks. After 40 weeks, patients underwent a three day period of step-down withdrawal from study drug and a two week washout period. Control group: No other antiparkinsonian medication was permitted during the study. In addition, placebo was administered orally.	
Outcomes	Measured at baseline (week 0), weeks 3, 9, 24, 40, and post-treatment (week 42) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Adverse effects: Anxiety, headache, hypertension, nausea	
Funding and conflict of interest	Funding: National Institute of Neurological Disorders and Stroke, Department of Defense, General Clinical Research Center of the National Center for Research Resources, National Institutes of Health, Teva Pharmaceutical Industries Conflict of interest: Fahn, Oakes, Shoulson, Kieburtz, Lang, Tanner and Marek served as unpaid consultant to Teva Pharmaceutical Industries. Olanow served as paid consultant to Teva Pharmaceutical Industries	
Notes	Additional publication used for data collection (Fahn, N Engl J Med 2004;351:2498-508)	
Risk of bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Low risk	Placebo was used; in addition, personnel was blinded

Table A7.1.9 Schifitto [86] (continued)

Risk of bias	Author's judgement	Support for judgement
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'The primary rater, who was also blinded to the treatment assignment...'
Incomplete outcome data (attrition bias)	Unclear risk	Lost to follow-up described, per-protocol analyses performed
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section
Other bias	Low risk	

Table A7.1.10 Tyne [13]

Study characteristics	
Methods	RCT Specific inclusion criteria for fatigue (FSS score ≥ 4 out of 7) Patients with active depression were excluded
Participants	Experimental group: N = 6 Age (mean (range)) = 57 (49 to 64) Sex = not reported Disease severity (H&Y) (mean (range)) = 2.5 (1 to 3) Disease duration = not reported Fatigue (FSS) (median (range)) = 6.1 (2) Depression = not reported Comorbid conditions: not reported Control group: N = 7 Age (mean (range)) = 61 (51 to 74) Sex = not reported Disease severity (H&Y) (mean (range)) = 2.0 (1 to 2.5) Disease duration = not reported Fatigue (FSS) (median (range)) = 5.4 (3) Depression = not reported Comorbid conditions: not reported
Interventions	Experimental group: Modafinil, single dose daily, began at 100 mg/day and increased to 400 mg/day in the first four weeks. The maximum dose tolerated was administered orally for a subsequent five weeks. Control group: Placebo was administered orally.
Outcomes	Measured at baseline (week 0), week 4, and post-treatment (week 9) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Adverse effects: Anxiety, headache, hypertension, nausea
Funding and conflict of interest	Funding: Cephalon Pharmaceuticals Conflict of interest: Cephalon Pharmaceuticals provided an unrestricted educational grant, but were not involved in the trial, procedures or assessing outcomes
Notes	

Table A7.1.10 Tyne [13] (continued)

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization was performed by pulling the two treatment groups from a hat.'
Allocation concealment (selection bias)	Low risk	'The code was kept in sealed envelopes in the pharmacy.'
Blinding of participants and personnel (performance bias)	Low risk	'Modafinil was over-encapsulated and a matching placebo... ...same capsules.' '...once all participants had completed all assessments... ...were identified.'
Blinding of outcome assessment (detection bias) Patient-reported outcomes	Low risk	'Modafinil was over-encapsulated and a matching placebo... ...same capsules.'
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'...once all participants had completed all assessments... ...were identified.'
Incomplete outcome data (attrition bias)	Low risk	'During the trial, one patient was withdrawn, however they completed the final assessments at this time.'
Selective reporting (reporting bias)	Unclear risk	Presented results in accordance with methods section
Other bias	Low risk	

Table A7.1.11 Winward [87]

Study characteristics	
Methods	RCT No specific inclusion criteria for fatigue or depression
Participants	Experimental group: N = 20 Age (mean (SD)) = 63.4 (6.7) Sex (male/female) = 15/5 Disease severity = not reported Disease duration in years (mean (SD)) = 5.9 (4.4) Fatigue (FSS) (mean (SD)) = 4.0 (1.5) Depression = not reported Comorbid conditions: not reported Control group: N = 19 Age (mean (SD)) = 64.9 (9.6) Sex (male/female) = 16/3 Disease severity = not reported Disease duration in years (mean (SD)) = 5.7 (4.2) Fatigue (FSS) (mean (SD)) = 4.2 (1.5) Depression = not reported Comorbid conditions: not reported
Interventions	Experimental group: Supervised community gym-based program. Patients determined the number of sessions they attended (median (range) = 12.5 (1 to 31)). Exercise sessions lasted 30-45 minutes, including aerobic sessions, muscle strength and flexibility exercises for 12 weeks. Patients were supported with information and practical advice from a physiotherapist. Patients were asked to continue their usual doses of antiparkinsonian medication. Control group: The control group received usual care. Patients were asked to continue their usual doses of antiparkinsonian medication.
Outcomes	Measured at baseline (week 0) and post-treatment (week 12) Primary outcomes: Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Secondary outcomes: HRQOL measured by PDQ-39
Funding and conflict of interest	Funding: Long-term Neurological Conditions Department of Health UK, Thames Valley Primary Care Trust, National Institute for Health Research, Parkinson's Disease Society, University of Birmingham UK Conflict of interest: None declared
Notes	Study protocol available on http://public.ukcrn.org.uk #4121 Additional publication used for data collection (Elsworth, Clin Rehabil 2011;25:588-98)

Table A7.1.11 Winward [87] (continued)

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Randomization was achieved by computer-generated random block sizes...'
Allocation concealment (selection bias)	Low risk	'Allocation and block size were concealed from the assessor and study coordinator. A study physiotherapist revealed group allocation to the participants.'
Blinding of participants and personnel (performance bias)	High risk	Not possible to blind patients and personnel for intervention
Blinding of outcome assessment (detection bias) Patient-reported outcomes	High risk	Not possible to blind patients for intervention
Blinding of outcome assessment (detection bias) Other outcomes	Low risk	'...an assessor blinded to group allocation...'
Incomplete outcome data (attrition bias)	Low risk	No lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Not all pre-specified outcomes from primary study are reported
Other bias	Low risk	

Appendix 7.2 Characteristics of ongoing studies

Table A7.2.1 EUCTR2007-002195-34-FR

Study characteristics	
Study name	Evaluation of the effect of 6 months treatment with DC158AM on fatigue in patients with Parkinson's disease. Multicenter, randomised, double-blind, placebo-controlled study in parallel groups
Participants	Patients with PD
Interventions	Experimental group: DC158AM Control group: Placebo
Outcomes	Primary outcomes (with regard to this systematic review): Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS Safety and tolerability of the product
Starting date	February 2008 (first enrollment)
Contact information	Not reported
Notes	Study protocol available on http://apps.who.int/trialsearch #EUCTR2007-002195-34-FR

Table A7.2.2 NCT01168596

Study characteristics	
Study name	Rasagiline for the symptomatic treatment of fatigue in Parkinson's disease (REST)
Participants	Patients with PD
Interventions	Experimental group: Rasagiline Control group: Placebo
Outcomes	Primary outcomes (with regard to this systematic review): Subjective impact of fatigue on ADL measured by MFIS Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS
Starting date	December 2009 (first enrollment)
Contact information	Malaty I, University of Florida, Gainesville
Notes	May 2012 final data collection Preliminary results (poster session) presented in Lim [50] Study protocol available on www.clinicaltrials.gov #NCT01168596

Table A7.2.3 NCT01360229

Study characteristics	
Study name	Acupuncture for fatigue in Parkinson's disease
Participants	Patients with PD
Interventions	Experimental group: Acupuncture Control group: Sham acupuncture
Outcomes	Primary outcomes (with regard to this systematic review): Subjective impact of fatigue on ADL by MFIS
Starting date	August 2010 (first enrollment)
Contact information	Kluger B, University of Colorado, Denver
Notes	August 2015 final data collection Study protocol available on www.clinicaltrials.gov #NCT01360229

Table A7.2.4 NCT01397422

Study characteristics	
Study name	Extended release amantadine safety and efficacy study in levodopa-induced dyskinesia (EASED study)
Participants	Patients with PD and levodopa induced dyskinesia
Interventions	Experimental groups: Low dose, mid-dose or high dose amantadine extended release (ADS-5102) Control group: Placebo
Outcomes	Primary outcomes (with regard to this systematic review): Subjective impact of fatigue on ADL measured by FSS Subjective severity of fatigue measured by FSS
Starting date	July 2011 (first enrollment)
Contact information	Not reported
Notes	May 2013 final data collection Study protocol available on www.clinicaltrials.gov #NCT01397422

Appendix 7.3 Summary of findings tables

Table A7.3.1 Summary of findings table levodopa-carbidopa

Patient or population: patients with Parkinson's disease
Settings: clinical, Northern America
Intervention: levodopa-carbidopa
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk levodopa-carbidopa				
Subjective impact of fatigue on ADL, fatigue severity		The mean impact of fatigue and fatigue severity in the intervention group was 0.22 standard deviations lower (-0.47 to 0.02)		340 (1 study, single pair-wise comparison)	⊕⊕⊕⊖ moderate[a]	Small effect favours levodopa-carbidopa Not statistically significant
Anxiety (adverse effect)	56 per 1,000	26 per 1,000 (8 to 79)	RR 0.46 (0.15 to 1.43)	361 (1 study, single pair-wise comparison)	⊕⊕⊕⊖ moderate[a]	Levodopa-carbidopa does not increase risk for anxiety Not statistically significant
Headache (adverse effect)	33 per 1,000	89 per 1,000 (27 to 287)	RR 2.66 (0.82 to 8.61)	361 (1 study, single pair-wise comparison)	⊕⊕⊕⊖ moderate[a]	Levodopa-carbidopa does increase risk for headache Not statistically significant

Hypertension (adverse effect)	33 per 1,000	33 per 1,000 (9 to 120)	RR 1.00 (0.28 to 3.60)	361 (1 study, single pair-wise comparison)	⊕⊕⊕⊖ moderate[a]	Levodopa-carbidopa does not increase risk for hypertension Not statistically significant
Nausea (adverse effect)	133 per 1,000	247 per 1,000 (140 to 436)	RR 1.85 (1.05 to 3.27)	361 (1 study, single pair-wise comparison)	⊕⊕⊕⊕ high	Levodopa-carbidopa does increase risk for nausea Statistically significant

[a]*Imprecision of result*

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.2 Summary of findings table memantine

Patient or population: patients with Parkinson's disease
Settings: clinical, Northern America
Intervention: memantine
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk memantine				
Subjective impact of fatigue on ADL, fatigue severity		The mean subjective impact of fatigue in the intervention group was 0.10 standard deviations higher (-0.56 to 0.75)		36 (1 study)	⊕⊕⊕⊖ moderate[a]	No effect Not statistically significant
Anxiety (adverse effect)	50 per 1,000	17 per 1,000 (0 to 386)	RR 0.33 (0.01 to 7.72)	40 (1 study)	⊕⊕⊕⊖ moderate[a]	Memantine does not increase risk for anxiety Not statistically significant
Hypertension (adverse effect)	50 per 1,000	17 per 1,000 (0 to 386)	RR 0.33 (0.01 to 7.72)	40 (1 study)	⊕⊕⊕⊖ moderate[a]	Memantine does not increase risk for hypertension Not statistically significant

Impulse control disorders (adverse effect)	0 per 1,000	50 per 1,000 (0 to 180)[b]	RR 3.00 (0.13 to 69.52)	40 (1 study)	⊕⊕⊕⊖ moderate[a]	Memantine does increase risk for impulse control disorders Not statistically significant
Nausea (adverse effect)	150 per 1,000	21 per 1,000 (1 to 390)	RR 0.14 (0.01 to 2.60)	40 (1 study)	⊕⊕⊕⊖ moderate[a]	Memantine does not increase risk for nausea Not statistically significant
HRQOL		The mean HRQOL in the intervention group was 0.38 standard deviations lower (-0.29 to 1.04)[c]		36 (1 study)	⊕⊕⊕⊖ moderate[a]	Small effect favours placebo Not statistically significant

[a]Imprecision of result; [b]Absolute effect derived from risk difference (RD); [c]Positive SMD (0.38) in results section indicates worse HRQOL score on PDQ-39
High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.3 Summary of findings table rasagiline

Patient or population: patients with Parkinson's disease
Settings: clinical, Europe and Northern America
Intervention: rasagiline
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk rasagiline				
Subjective impact of physical fatigue on ADL		The mean subjective impact of physical fatigue in the intervention group was 0.27 standard deviations lower (-0.39 to -0.16)		1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊕ high	Small effect favours rasagiline Statistically significant
Anxiety (adverse effect)	57 per 1,000	33 per 1,000 (19 to 57)	RR 0.57 (0.33 to 0.99)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊕ high	Rasagiline does not increase risk for anxiety Statistically significant
Headache (adverse effect)	62 per 1,000	50 per 1,000 (31 to 80)	RR 0.80 (0.50 to 1.29)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊖ moderate[a]	Rasagiline does not increase risk for headache Not statistically significant
Hypertension (adverse effect)	39 per 1,000	20 per 1,000 (10 to 41)	RR 0.53 (0.27 to 1.06)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊖ moderate[a]	Rasagiline does not increase risk for hypertension Not statistically significant

Impulse control disorders (adverse effect)	0 per 1,000	2 per 1,000 (0 to 10)[b]	RR 3.07 (0.13 to 75.26)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊖ moderate[a]	Rasagiline does not increase risk for impulse control disorders Not statistically significant
Nausea (adverse effect)	39 per 1,000	34 per 1,000 (19 to 62)	RR 0.89 (0.49 to 1.60)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊖ moderate[a]	Rasagiline does not increase risk for nausea Not statistically significant
Orthostatic hypotension (adverse effect)	8 per 1,000	5 per 1,000 (1 to 22)	RR 0.61 (0.15 to 2.56)	1,176 (1 study, 2 independent comparisons)	⊕⊕⊕⊖ moderate[a]	Rasagiline does not increase risk for orthostatic hypotension Not statistically significant

[a]Imprecision of result; [b]Absolute effect derived from risk difference (RD)

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.4 Summary of findings table caffeine

Patient or population: patients with Parkinson's disease
Settings: clinical, Northern America
Intervention: caffeine
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk caffeine				
Subjective impact of fatigue on ADL, fatigue severity		The mean subjective impact of fatigue in the intervention group was 0.29 standard deviations lower (-0.79 to 0.22)		61 (1 study)	⊕⊕⊕⊖ moderate[a]	Small effect favours caffeine Not statistically significant
Subjective fatigue severity		The mean subjective fatigue severity in the intervention group was 0.19 standard deviations lower (-0.32 to 0.69)		61 (1 study)	⊕⊕⊕⊖ moderate[a]	No effect Not statistically significant
Anxiety (adverse effect)	32 per 1,000	33 per 1,000 (2 to 509)	RR 1.03 (0.07 to 15.78)	61 (1 study)	⊕⊕⊕⊖ moderate[a]	Caffeine does increase risk for anxiety Not statistically significant

Headache (adverse effect)	32 per 1,000	67 per 1,000 (6 to 697)	RR 2.07 (0.20 to 21.61)	61 (1 study)	⊕⊕⊕⊖ moderate[a]	Caffeine does increase risk for headache Not statistically significant
HRQOL		The mean HRQOL in the intervention group was 0.06 standard deviations higher (-0.56 to 0.44)[b]		61 (1 study)	⊕⊕⊕⊖ moderate[a]	No effect Not statistically significant

[a]Imprecision of result; [b]Negative SMD (-0.06) in results section indicates better HRQOL score on PDQ-39

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.5 Summary of findings table methylphenidate

Patient or population: patients with Parkinson's disease
Settings: clinical, Northern America
Intervention: methylphenidate
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk methylphenidate				
Subjective impact of fatigue on ADL, fatigue severity		The mean subjective impact of fatigue in the intervention group was 0.64 standard deviations lower (-1.33 to 0.05)		34 (1 study)	⊕⊕⊕⊖ moderate[a]	Moderate effect favours methylphenidate Not statistically significant
Subjective impact of physical fatigue on ADL		The mean subjective impact of physical fatigue in the intervention group was 0.48 standard deviations lower (-1.17 to 0.20)		34 (1 study)	⊕⊕⊕⊖ moderate[a]	Small effect favours methylphenidate Not statistically significant
Subjective impact of mental fatigue on ADL		The mean subjective impact of mental fatigue in the intervention group was 0.02 standard deviations higher (-0.65 to 0.70)		34 (1 study)	⊕⊕⊕⊖ moderate[a]	No effect Not statistically significant

Headache (adverse effect)	118 per 1,000	28 per 1,000 (1 to 544)	RR 0.24 (0.01 to 4.62)	31 (1 study)	⊕⊕⊕⊖ moderate[a]	Methylphenidate does not increase risk for headache Not statistically significant
Hypertension (adverse effect)	0 per 1,000	140 per 1,000 (0 to 350)[b]	RR 6.00 (0.31 to 115.56)	31 (1 study)	⊕⊕⊕⊖ moderate[a]	Methylphenidate does increase risk for hypertension Not statistically significant
Nausea (adverse effect)	59 per 1,000	71 per 1,000 (5 to 1,000)	RR 1.21 (0.08 to 17.71)	31 (1 study)	⊕⊕⊕⊖ moderate[a]	Methylphenidate does increase risk for nausea Not statistically significant
Tachycardia (adverse effect)	59 per 1,000	24 per 1,000 (1 to 536)	RR 0.40 (0.02 to 9.12)	31 (1 study)	⊕⊕⊕⊖ moderate[a]	Methylphenidate does not increase risk for tachycardia Not statistically significant

[a]*Imprecision of result;* [b]*Absolute effect derived from risk difference (RD)*

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.6 Summary of findings table modafinil

Patient or population: patients with Parkinson's disease
Settings: clinical, Europe and Northern America
Intervention: modafinil
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk modafinil				
Subjective impact of fatigue on ADL		The mean subjective impact of fatigue in the intervention group was 0.17 standard deviations lower (-0.72 to 0.37)		53 (2 studies)	⊕⊕⊖⊖ low[a,b]	No effect Not statistically significant
Subjective impact of physical fatigue on ADL		The mean subjective impact of physical fatigue in the intervention group was 1.23 standard deviations lower (-2.36 to -0.11)		16 (1 study)	⊕⊖⊖⊖ very low[a,c]	Large effect favours modafinil Statistically significant
Subjective impact of mental fatigue on ADL		The mean subjective impact of mental fatigue in the intervention group was 0.05 standard deviations higher (-0.97 to 1.06)		16 (1 study)	⊕⊖⊖⊖ very low[a,b]	No effect Not statistically significant

Subjective fatigue severity		The mean subjective fatigue severity in the intervention group was 0.08 standard deviations lower (-0.73 to 0.56)		37 (1 study)	⊕⊕⊕⊖ moderate[b]	No effect Not statistically significant
Anxiety (adverse effect)	0 per 1,000	70 per 1,000 (0 to 190)[d]	RR 3.14 (0.35 to 27.79)	50 (2 studies)	⊕⊕⊕⊖ moderate[b]	Modafinil does increase risk for anxiety Not statistically significant
Headache (adverse effect)	286 per 1,000	166 per 1,000 (20 to 1,000)	RR 0.58 (0.07 to 4.95)	13 (1 study)	⊕⊕⊕⊖ moderate[b]	Modafinil does not increase risk for headache Not statistically significant
Hypertension (adverse effect)	0 per 1,000	170 per 1,000 (0 to 510)[d]	RR 3.43 (0.16 to 71.36)	13 (1 study)	⊕⊕⊕⊖ moderate[b]	Modafinil does increase risk for hypertension Not statistically significant
Nausea (adverse effect)	40 per 1,000 Moderate 71 per 1,000	40 per 1,000 (4 to 357) 72 per 1,000 (8 to 634)	RR 1.01 (0.11 to 8.93)	50 (2 studies)	⊕⊕⊕⊖ moderate[b]	Modafinil does increase risk for nausea Not statistically significant

[a]Lou [11] scored 'unclear risk' for selection bias and 'high risk' for attrition bias; [b]Imprecision of result; [c]Estimate of effect likely biased by imbalance at baseline; [d]Absolute effect derived from risk difference (RD)

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.7 Summary of findings table doxepin

Patient or population: patients with Parkinson's disease
Settings: clinical, Northern America
Intervention: doxepin
Comparison: placebo

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk placebo	Corresponding risk doxepin				
Subjective impact of fatigue on ADL, fatigue severity		The change in mean subjective impact of fatigue in the intervention group was 1.50 standard deviations higher (-2.84 to -0.15)		12 (1 study)	⊕⊕⊖⊖ low[a]	Large effect favours doxepin Statistically significant
Nausea (adverse effect)	0 per 1,000	170 per 1,000 (0 to 530)[b]	RR 3.00 (0.15 to 61.74)	12 (1 study)	⊕⊖⊖⊖ very low[a,c]	Doxepin does increase risk for nausea Not statistically significant
Orthostatic hypotension (adverse effect)	0 per 1,000	170 per 1,000 (0 to 530)[b]	RR 3.00 (0.15 to 61.74)	12 (1 study)	⊕⊖⊖⊖ very low[a,c]	Doxepin does increase risk for orthostatic hypotension Not statistically significant
HRQOL		The change in mean HRQOL in the intervention group was 0.35 standard deviations higher (-1.49 to 0.79)[d]			⊕⊖⊖⊖ very low[a,c]	Small effect favours doxepin Not statistically significant

[a]Rios Romenets [85] scored 'high risk' for selection bias, 'high risk' for performance bias and 'high risk' for detection bias; [b]Absolute effect derived from risk difference (RD); [c]Imprecision of result; [d]Negative SMD (-0.35) in results section indicates better HRQOL score on PDQ-39

High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate

Table A7.3.8 Summary of findings table exercise

Patient or population: patients with Parkinson's disease
Settings: community, Australia, Europe
Intervention: exercise
Comparison: usual care

Outcomes	Illustrative comparitive risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk usual care	Corresponding risk erxercise				
Subjective impact of fatigue on ADL, fatigue severity		The mean subjective impact of fatigue in the intervention group was 0.45 standard deviations lower (-1.21 to 0.32)		57 (2 studies)	⊕⊕⊖⊖ low[a,b]	Small effect favours exercise Not statistically significant
HRQOL		The mean HRQOL in the intervention group was 0.08 standard deviations higher (-0.60 to 0.45)[c]		57 (2 studies)	⊕⊕⊖⊖ low[a,b]	No effect Not statistically significant

[a]Blinding for assessment of fatigue (patient-reported) not possible; [b]Imprecision of result; [c]Negative SMD (-0.08) in results section indicates better HRQOL score on PDQ-39
High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate