D.3 Pharmacological management of non-motor symptoms

D.3.1 Daytime hypersomnolence

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Movement Disorders 2003;18:287-93.
Study type	Randomised, double-blind, placebo controlled cross over study (1 week washout period)
Evidence level	1++ (low risk of bias)
Study objective	To assess the safety and efficacy of modafinil for the treatment of excessive daytime sleepiness in patients with Parkinson's disease
Number of patients	N=21 Parkinson's disease (PD) patients N=11 started on modafinil N=10 started on placebo Location: USA Site: single
Patient characteristics	27 consecutive patients with PD who admitted having excessive daytime sleepiness were questioned using the Epworth Sleepiness Scale (ESS). Patients were included if they scored ≥ 10. 21 of the 27 patients questioned met these criteria and were included in the study. Patients were not allowed to start new PD medications during the study. Inclusion criteria: ≥ 30 years of age, a Folstein Mini-Mental Status Exam score >24, and ability to complete diary forms. Mean baseline characteristics: mean age 65 years, F:M was 6:14, duration of PD 7.4 years, ESS 16.9 Of the 20 patients who completed the trial 19 had motor fluctuations
Intervention	Modafinil 200mg/d for 3 weeks
Comparison	Matching placebo for 3 weeks
Length of follow-up	Baseline, week 3, week 4 (baseline visit 2), week 7 and week 8 (1 week after discontinuation)
Outcome measures	ESS, Excessive Daytime Sleepiness Rating Scale (EDSRS), modified Fatigue Assessment Inventory (FAI), Excessive Daytime Fatigue Rating Scale (EDFRS), Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr stage

	(H&Y), Schwab and England Activities of Daily Living Scale, Timed Tapping Test, and a Clinical Global Impression of Change (CGI-C) scale
Effect size	Drug compliance was 93% ± 28% while on modafinil and 113% ± 36% on placebo ESS Demonstrated a carry-over effect (p=0.013) from period to 1 to period 2 At visit 3, before the second treatment period the modafinil group/placebo group had decreased 2.3 ± 4.2 from a baseline of 17.8 ± 4.2 The placebo/modafinil group increased 2.0 ± 2.5 from a baseline of 16.0 ± 4.2 The carry-over effect was replicated after period 2 (p=0.006) At visit 5 (end of second washout period) modafinil/placebo group had increased 0.9 ± 2.1 from 15.5 ± 4.1 at visit 3 Placebo/modafinil group decreased 3.3 ± 3.8 from 18.0 ± 5.1 at visit 3 Comparing changes from baseline- the ESS for patients treated with 200 mg/d modafinil was better (p=0.039) than placebo treated patients ESS for patients treated with modafinil was 4.4 points better than placebo (95%CI –8.6 to –0.2) Two patients had an ESS <10 while receiving modafinil The ESS scores for the placebo group went from 16.0 +/- 4.2 (mean +/- SD) to 17.0 +/- 5.1 ESS scores for the modafinil group went from 17.8 +/- 4.2 to 14.4 +/- 5.7 (P = 0.039). CGI-C Patient-rated CGI-C improved +0.75 on modafinil compared with +0.15 for placebo (p=0.07) Physician-rated CGI-C improved +0.75 on modafinil compared to +0.25 placebo (p=0.12) Improvements were reported by 7 (35%) of patients on modafinil only, 1 (5%) patient on placebo-only, 2 patients (10%) receiving both modafinil and placebo, and 10 patients (50%) reported no change on either treatment (p=0.070) No significant differences were found in any of the other secondary outcome measures of sleepiness or fatigue Modafinil did not have an effect on sleep time based on diary analysis The patient Clinical Global Impression of Change (+3 to -3) improved by 0.75 on modafinil compared with 0.15 for placebo (P = 0.07). A total of 7 of 20 (35%) of the patients reported some improvement on modafinil but not placebo Parkinson's disease scores

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	Modafinil did not cause any worsening or improvement of PD signs No significant differences between modafinil and placebo treatment periods on UPDRS, H&Y, timed tapping test, or diaries Modafinil had no effect on the percentage 'on' time There was no significant carryover effect for any other measure.. There was no significant improvement or worsening of the UPDRS subscores I-III, Timed Tap test, or time on. Vital signs, electrocardiograms, and lab tests were unchanged. Modafinil was very well tolerated. Our data demonstrate that, in a small sample size, administration of 200 mg/day of modafinil was associated with few side effects and was modestly effective for the treatment of excessive daytime sleepiness in patients with PD. Adverse effects There were no clinically or statistically significant effects of modafinil compared with placebo The following treatment-emergent effects were reported by one patient each: atrial fibrillation (patient with known paroxysmal atrial fibrillation), bruise, elevated blood pressure, flu, insomnia, rectal prolapse, and skin redness One patient reported: hot flashes, gas, increased 'off' time Another patient reported: pruritic rash and sore tongue On placebo one patient reported: allergy symptoms, anxiety, back spasm, headache, and heart burn No patients described any episodes of 'sleep attacks'
Source of funding	Pharmaceutical company
Additional comments	Exams were performed when patients were in their 'on' states Modafinil and placebo tablets were identical in size, colour, and taste Methods of randomisation and allocation concealment stated Pills were counted at each visit to monitor compliance Elimination half-life of modafinil after multiple doses in 15 hours in healthy controls- no data regarding the duration of benefit that might occur after discontinuation of drug in patients with PD The sample size (n=16) was based on 80% power to detect differences of 0.75 standard deviations used the paired T-test Sample size was increased to n=21 in case of premature withdrawals 1 patient dropped out of modafinil group a few days after starting trial

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Bibliographic reference	Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002; 25:905-9.
Study type	Double-blind, randomised, placebo-controlled, cross-over study (2-week washout phase)
Evidence level	1++ (low risk of bias)
Study objective	To assess the therapeutic efficacy of modafinil in the treatment of increased daytime sleepiness in patients with Parkinson's disease
Number of patients	N=15 patients with Parkinson's disease Location: Austria Sites: single
Patient characteristics	Recruited from outpatient clinic at University Hospital Department of Neurology All patients had a score of 10 or more on Epworth Sleepiness Scale (ESS) Exclusion criteria: see paper 12 patients completed study- 9 men, 3 women; mean age 65.0, mean symptomatic PD duration 6.8 years, all patients were on levodopa therapy
Intervention	Modafinil dose was 100mg in first week and 200mg in second week
Comparison	Placebo
Length of follow-up	2 week treatment phase, 2 week washout and 2 week treatment phase
Outcome measures	ESS, maintenance of wakefulness test (MWT) sleep log and depression scale, Unified Parkinson's disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) staging, adverse effects
Effect size	ESS Modafinil improved perceived sleepiness ESS scores at baseline did not differ between treatment and placebo Subjective sleepiness improved by 0.83 $\pm$ 1.99 points with placebo and by 3.42 $\pm$ 3.90 with modafinil Analysis of variance revealed a significant interaction (p=0.011) between medication condition and ESS changes from baseline to end MWT Latency to stage 1 sleep was calculated using (MWT)

	No significant difference was found between the treatment groups at baseline (p=0.26) and at the end of the treatment phase (p=0.114) The mean changes of sleep latencies at the end versus beginning of each block were also not significantly different (p=0.139) Sleep logs Similar amounts of sleep were obtained in both treatment groups Estimated time of sleep 390 ± 80 min at baseline of placebo treatment, 360 ± 94 min at end of placebo treatment, 375 ± 86 min at baseline of modafinil treatment, and 360 ± 50min at the end of modafinil treatment (median standard deviation, p=0.3) Depression scores Beck depression scores were not statistically different between baseline and end of treatment for placebo and modafinil Side effects Modafinil: insomnia (n=1), constipation (n=1), diarrhoea (n=2), dizziness (n=1) Placebo: constipation (n=1), flatulence (n=1), diarrhoea (n=1), insomnia (n=1) In no case did side effects lead to study withdrawal
Source of funding	Pharmaceutical
Additional comments	Method of randomisation and allocation concealment stated Modafinil and placebo were prepared in identical-looking capsules 3 patients did not complete study Not intention-to-treat analysis

Study details	Participants	Methods	Results				Comments
Full citation Lou,J.-S., Dimitrova,D.M., Park,B.S., Johnson,S.C., Eaton,R., Arnold,G., Nutt,J.G., Using modafinil to treat fatigue in Parkinson's disease: A	Sample size 19 PD patients Inclusion criteria	Details: Sample of 19 PD patients from movement disorders clinic participated. Potential participants filled	Results EPSWORTH SLEEP SCALE Modafinil Placebo	baseline 8.3 (1.6) 9.8 (1.5)	month 1 6.4 (1.6) 8.9(1.5)	Month 2 6.0 (1.6) 9.0(1.5)	Overall Risk of Bias SERIOUS: very small sample size

double-blind, placebo-controlled pilot study, Clinical Neuropharmacology.32 (6) (pp 305-310), 2009.Date of Publication: November-December 2009., 305-310, 2009 Ref Id 215655 Country/ies where the study was carried out USA Study type Intervention: RCT Aim of the study To determine if modafinil improves subjective fatigue and physical fatigability Study dates Nov/Dec 2009 Source of funding National Parkinson's foundation	Diagnosis idiopathic PD with at least 2 of these 4: rigidity; tremor; bradykinesia; postural instability. All were dopa-responsive No patients had motor fluctuations. Exclusion criteria patients with other neurological disorders. Also excluded patients with medical conditions that might cause excessive fatigue i.e. heart failure, endocrine disorders, pulmonary disease, renal failure, anaemia,	out multidimensional fatigue inventory (MFI) to assess subjective fatigue. Only those who scored >48 were enrolled into study. They were then randomly assigned by the pharmacy to the treatment group or placebo. Modafinil and placebo capsules had same appearance. Study required 3 visits per participant: baseline, month 1 and month 2. Each visit, subjects performed 2 motor tasks to evaluate physical fatigability quantitatively and filled out questionnaires to evaluate their subjective fatigue, depression, and sleepiness. Patients performed motor tasks within 1-2	UPDRS baseline month month 2 modafinil 26(3) 25(3) 26(4) placebo 40(3) 39(4) 39(4) Paper reports: ESS scores tended to decrease at months 1 and 2 in Modafinil group, but not placebo ($p<0.12$). Non-significant difference between groups in ESS. Non-reported interaction effects =no significant difference between modafinil and placebo. Neither group showed a decrement in UPDRS score over the study period.	gender bias: only men in modafinil group subjects in placebo group had significantly higher (almost double modafinil group) scores in UPDRS Other information Motor tasks are irrelevant to current review as fatigue is not a primary outcome. Only Epworth sleep scale values were evaluated, in line with existing research on efficacy of modafinil on daytime hypersomnolence/EDS

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	arthritis, chronic fatigue syndrome, fibromyalgia, psychosis.	house of their last dose of antiparkinsonian medication at each visit. Interventions Modafinil: 100mg PO twice a day for 2 months. Placebo: placebo PO twice a day for 2 months.		

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Bibliographic reference	Ondo WG, Faye R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurogurg Psychiatry 2005;76:1636-1639
Study type	Randomised, double-blind, placebo controlled trial
Evidence level	1++ (low risk of bias)
Study objective	To determine whether modafinil is effective in reversing daytime sleepiness in people with PD
Number of patients	N=40 Parkinson's disease (PD) patients (37 completed the study). N=20 started on modafinil N=20 started on placebo Location: USA Site: Single
Patient characteristics	40 patients satisfying diagnostic criteria for PD between 35 and 80 years of age and who reported daytime somnolence as measured by an ES score of greater than 10. Exclusion criteria: Serious medical conditions, known narcolepsy, known sleep apnoea and pregnancy. Patients were not allowed to take prescription stimulant medications.

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	Mean baseline characteristics: 29 men/ 11 women, mean age 64.8, mean duration of PD 6.8 years, mean dopaminergic dose 8.5mg/day, 12/40 fluctuating response, UPDRS activities of daily living mean score 13.7, UPDRS mean/motor score 26.7 and mean Epworth score (ES) 15.8.
Intervention	Modafinil one 100mg upon waking and at lunch (200mg/day). After one week the dose was increased to two pills twice a day (400mg/day).
Comparison	Matching placebo administered as for intervention
Length of follow-up	Visit 1 at baseline and visit 2 at 4 weeks.
Outcome measures	ES, UPDRS activities of daily living and motor scores, Multiple sleep latency test (MSLT), SF-36, Fatigue Severity Scale (FFS), Hamilton Depression scale, change in sleepiness "much or very much improved", adverse events.
Effect size	Three patients dropped out: 2 men on placebo and 1 woman on modafinil)the latter was instructed to stop taking study medication by her local physician due to back pain). All drop-outs were prior to post drug evaluation. ES and MSLT There was no significant change in the primary endpoint, the ES score. Patients on modafinil showed an improvement of 2.7 points compared with the placebo group who improved by 1.5 points (p=0.28). MSLT results were not significantly different although the scores worsened less with modafinil (-0.16 (3.59) minutes) than with placebo (-0.70 (3.28) minutes), p=0.14. Other outcomes The UPDRS, Fatigue Severity Scale, Hamilton Depression Scale, SF-36 and global impression scores did not significantly change compared to placebo. In fluctuating subjects, there was no change in on/off time. Adverse effects Only one patient taking modafinil elected to return to the lower dose, secondary to nausea and anxiety. Other adverse events thought to be at least possibly drug related included dry mouth N=1), dizziness (N=1), and back pain (N=1).
Source of funding	Cephalon Pharmaceuticals, the makers of Provigil.
Additional comments	The authors performed a power analysis and found that they required a total of 28 participants (14 per group) to achieve a power of 0.81. Modafinil and placebo tablets were identical in size and appearance. Methods of randomisation and allocation concealment stated. The authors concluded that "Modafinil failed to significantly improve EDS in PD compared with placebo. The drug did not alter motor symptoms and was well tolerated".