Supplementary Material

Physical Exercise as a Potential Treatment for Fatigue in Parkinson's Disease? A Systematic Review and Meta-Analysis of Pharmacological and Non-Pharmacological Interventions

Supplementary Table 1. Search strategies for the databases MEDLINE, EMBASE, PsycINFO, CENTRAL, and CINAHL.

MEDLINE	
#	**Searches**
1	exp Parkinson Disease/
2	parkinson*.tw,kf.
3	or/1-2
4	exp Fatigue/
5	(fatigue* or exhaust* or weary or weariness or lassitude or letharg* or sleepy or sleepiness or drowsy or drowsiness or tired* or fatigab*).tw,kf.
6	or/4-5
7	3 and 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomi?ed.ab.
11	placebo.ab.
12	drug therapy.fs.
13	randomly.ab.
14	trial.ab.
15	groups.ab.
16	or/8-15
17	exp animals/ not humans/
18	16 not 17
19	clinical trial, phase iii/
20	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
21	(19 or 20) not 17
22	18 or 21
23	7 and 22
EMBASE	
#	**Searches**
1	exp Parkinson disease/
2	parkinson*.tw,kw.
3	or/1-2
4	exp fatigue/
5	(fatigue* or exhaust* or weary or weariness or lassitude or letharg* or sleepy or sleepiness or drowsy or drowsiness or tired* or fatigab*).tw,kw.
6	or/4-5
7	3 and 6
8	Randomized controlled trial/

9	Controlled clinical study/
10	random*.ti,ab.
11	randomization/
12	intermethod comparison/
13	placebo.ti,ab.
14	(compare or compared or comparison).ti.
15	(open adj label).ti,ab.
16	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
17	double blind procedure/
18	parallel group$1.ti,ab.
19	(crossover or cross over).ti,ab.
20	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
21	(controlled adj7 (study or design or trial)).ti,ab.
22	(volunteer or volunteers).ti,ab.
23	trial.ti.
24	or/8-23
25	phase 3 clinical trial/
26	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.
27	or/25-26
28	(animal experiment/ or Animal experiment/) not (human experiment/ or human/)
29	(24 or 27) not 28
30	7 and 29

PsycINFO

#	Query
S12	S7 AND S11
S11	(S8 OR S9 OR S10)
S10	TX randomly OR randomized OR placebo* OR double-blind
S9	TX (random* OR controlled) AND trial*
S8	SU placebo
S7	(S3 AND S6)
S6	(S4 OR S5)
S5	TX (fatigue* OR exhaust* OR weary OR weariness OR lassitude OR letharg* OR sleepy OR sleepiness OR drowsy OR drowsiness OR tired* OR fatigab*)
S4	SU Fatigue
S3	(S1 OR S2)
S2	TX parkinson*
S1	SU Parkinson Disease

CENTRAL

ID	Search
#1	MeSH descriptor: [Parkinson Disease] explode all trees
#2	parkinson*:ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Fatigue] explode all trees
#5	(fatigue* or exhaust* or weary or weariness or lassitude or letharg* or sleepy or sleepiness or drowsy or drowsiness or tired* or fatigab*):ti,ab,kw

#6	#4 or #5
#7	#3 and #6

CINAHL

#	Query
S21	S3 AND S6 AND S20
S20	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19	TX rct
S18	(MH "Placebos")
S17	(MH "Quantitative Studies")
S16	(MH "Random Assignment")
S15	(MH "Clinical Trials+")
S14	TX versus OR vs
S13	TX phase and TX (three OR III)
S12	TX "control group*"
S11	TX "treatment arm"
S10	TX (blind* OR mask*) and TX (single OR double OR triple OR treble)
S9	TX trial AND TX (control* OR comparative)
S8	"cross over"
S7	TX andom* OR factorial* OR placebo* OR assign* OR allocat* OR crossover*
S6	S4 OR S5
S5	TX (fatigue* OR exhaust* OR weary OR weariness OR lassitude OR letharg* OR sleepy OR sleepiness OR drowsy OR drowsiness OR tired* OR fatigab*)
S4	(MH "Fatigue+")
S3	S1 OR S2
S2	TX parkinson*
S1	(MH "Parkinsonian Disorders+")

Supplementary Table 2. Full list of references of included trials and reports.

Study	Reports
Pharmacological interventions (N = 14)	
Adler 2003	Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J (2003) Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord* **18**, 287-293.
Büchele 2018	Büchele F, Hackius M, Schreglmann SR, Omlor W, Werth E, Maric A, Imbach LL, Hagele-Link S, Waldvogel D, Baumann CR (2018) Sodium oxybate for excessive daytime sleepiness and sleep disturbance in Parkinson disease: A randomized clinical trial. *JAMA Neurol* **75**, 114-118.
Lim 2015	Lim TT, Kluger BM, Rodriguez RL, Malaty IA, Palacio R, Ojo OO, Patel S, Gujrati Y, Nutter B, Swartz C, Hennessy C, Fernandez HH (2015) Rasagiline for the symptomatic treatment of fatigue in Parkinson's disease. *Mov Disord* **30**, 1825-1830. --- Lim TT, Kluger BM, Rodriguez RL, Palacio Jr. R, Gujrato Y, Nutter B, Swartz C, Hennessy C, Malaty IA, Fernandez HH (2013) Rasagiline for the symptomatic treatment of fatigue in Parkinson's disease: A 3-center, placebo-controlled, pilot study (the REST trial). *Mov Disord* **28**, S165. Patel S, Lim TT, Kluger B, Rodriguez R, Malaty I, Palacio R, Ojo O, Gujrati Y, Swartz C, Nutter B, Hennessy C, Fernandez H (2015) Re-evaluating Rasagiline for the Symptomatic Treatment of Fatigue in Parkinson's Disease: A 3-Center, Placebo-Controlled, Pilot Study (The REST PD Trial) (P1.186). *Neurology* **84**.
Lou 2009	Lou JS, Dimitrova DM, Park BS, Johnson SC, Eaton R, Arnold G, Nutt JG (2009) Using modafinil to treat fatigue in Parkinson disease: A double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* **32**, 305-310.
Mendonca 2007	Mendonca DA, Menezes K, Jog MS (2007) Methylphenidate improves fatigue scores in Parkinson disease: A randomized controlled trial. *Mov Disord* **22**, 2070-2076.
Ondo 2005	Ondo WG, Fayle R, Atassi F, Jankovic J (2005) Modafinil for daytime somnolence in Parkinson's disease: Double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry* **76**, 1636-1639.
Ondo 2011	Ondo WG, Shinawi L, Davidson A, Lai D (2011) Memantine for non-motor features of Parkinson's disease: A double-blind placebo controlled exploratory pilot trial. *Parkinsonism Relat Disord* **17**, 156-159.
Pahwa 2015	Pahwa R, Tanner CM, Hauser RA, Sethi K, Isaacson S, Truong D, Struck L, Ruby AE, McClure NL, Went GT, Stempien MJ (2015) Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). *Mov Disord* **30**, 788-795. --- Pahwa R, Tanner CM, Hauser RA, Sethi KD, Isaacson SH, Truong DD, Struck LK, Stempien MJ, WT Gent (2013) Randomized trial of extended release amantadine in Parkinson's disease patients with levodopa-induced dyskinesia (EASED study). *Mov Disord* **28**, S158.
Peball 2020	Peball M, Krismer F, Knaus HG, Djamshidian A, Werkmann M, Carbone F, Ellmerer P, Heim B, Marini K, Valent D, Goebel G, Ulmer H, Stockner H, Wenning GK, Stolz R, Krejcy K, Poewe W, Seppi K (2020) Non-Motor Symptoms in Parkinson's disease are reduced by Nabilone. *Ann Neurol* **88**, 712-722. --- EUCTR2017-000192-86-AT. Investigation of the effect of Nabilon in patients suffering from Parkinson´s Disease with non-motor symptoms (e.g.sleeping disorders,cognitive dysfunction, hallucinations, autonomic dysfunction including urinary incontinence, constipation,...). https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-000192-86-AT (first posted: 2017).
Postuma 2012	Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovich M, Filla L, Zanatta D, Rios Romenets S, Altman R, Chuang R, Shah B (2012) Caffeine for treatment of Parkinson disease: a randomized controlled trial. *Neurology* **79**, 651-658. ---

	Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovich M, Filla L, Zanatta D, Rios Romenets S, Altman R, Chuang R, Shah B (2012) Caffeine for treatment of Parkinson disease: a randomized controlled trial. Correction. *Neurology* **79**, 1744. NCT00459420. Caffeine for Excessive Daytime Somnolence in Parkinson's Disease. https://clinicaltrials.gov/show/NCT00459420 (first posted 2007). Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovich M, Filla L, Zanatta D, Rios Romenets S, Altman R, Chuang R, Shah B (2012) Caffeine for treatment of Parkinson's disease – A randomized controlled trial. *Mov Disord* **27***,* S135.
Stocchi 2014	Stocchi F; ADAGIO investigators (2014) Benefits of treatment with rasagiline for fatigue symptoms in patients with early Parkinson's disease. *Eur J Neurol* **21**, 357-360. --- Rascol O (2009) Broadening the prospects for Parkinson's disease patients with early rasagiline treatment. *Eur J Neurol* **16**, 658. Rascol O, Fitzer-Attas CJ, Hauser R, Jankovic J, Lang A, Langston JW, Melamed E, Poewe W, Stocchi F, Tolosa E, Eyal E, Weiss YM, Olanow CW (2011) A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes. *Lancet Neurol* **10**, 415-423. Rascol O, Fitzer-Attas CJ, Hauser R, Jankovic J, Lang A, Langston JW, Melamed E, Poewe W, Stocchi F, Tolosa E, Eyal E, Weiss YM, Olanow CW (2012) A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes: Correction. *Lancet Neurol* **11**, 415-423. Smith KM, Eyal E, Xie S, Weintraub D (2014) Combined rasagiline and antidepressant use in Parkinson's disease in the ADAGIO study: Effects on non-motor symptoms and tolerability. *Mov Disord* **1**, S266-S267. Smith KM, Eyal E, Xie S, Weintraub D (2015) Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: Effects on nonmotor symptoms and tolerability. *JAMA Neurol* **72**, 88-95. Stocchi F; for the ADAGIO Investigators (2009) Benefits of treatment with rasagiline in fatigue symptoms in patients with early Parkinson's disease. *Eur J Neurol* **16**, 525. Stocchi F (2010) Treatment with Rasagiline Provides Benefits in the Symptoms of Fatigue in Patients with Early Parkinson's Disease. *Mov Disord* **25**, S676.
Ricciardi 2015	Ricciardi L, De Nigris F, Specchia A, Fasano A (2015) Homotaurine in Parkinson's disease. *Neurol Sci* **36**, 1581-1587.
Schifitto 2008	Schifitto G, Friedman JH, Oakes D, Shulman L, Comella CL, Marek K, Fahn S (2008) Fatigue in levodopa-naive subjects with Parkinson disease. *Neurology* **71**, 481-485.
Tyne 2010	Tyne HL, Taylor J, Baker GA, Steiger MJ (2010) Modafinil for Parkinson's disease fatigue. *J Neurol* **257**, 452-456.
Non-pharmacological interventions (N = 16)	
Bogosian 2021	Bogosian A, Hurt CS, Hindle JV, McCracken LM, Vasconcelos e Sa DA, Axell S, Tapper K, Stevens J, Hirani PS, Salhab M, Ye W, Cubi-Molla P (2021) Acceptability and Feasibility of a Mindfulness Intervention Delivered via Videoconferencing for People with Parkinson's. *J Geriatr Psychiatry Neurol* **35**, 155-167. --- Bogosian A, Hurt CS, Vasconcelos E Sa D, Hindle J, McCracken L, Cubi-Molla P (2017) Distant delivery of a mindfulness-based intervention for people with Parkinson's disease: the study protocol of a randomised pilot trial. *Pilot Feasibility Stud* **3**, 4.
Canning 2012	Canning CG, Allen NE, Dean CM, Goh L, Fung VSC (2012) Home-based treadmill training for individuals with Parkinson's disease: A randomized controlled trial. *Clin Rehabil* **26**, 817-826. --- Canning CG, Allen NE, Dean CM, Goh L, Fung VSC (2012). Minimally-supervised treadmill training for individuals with Parkinson's disease: A randomized controlled trial. *Neurorehabil Neural Repair* **26**, 703-704.

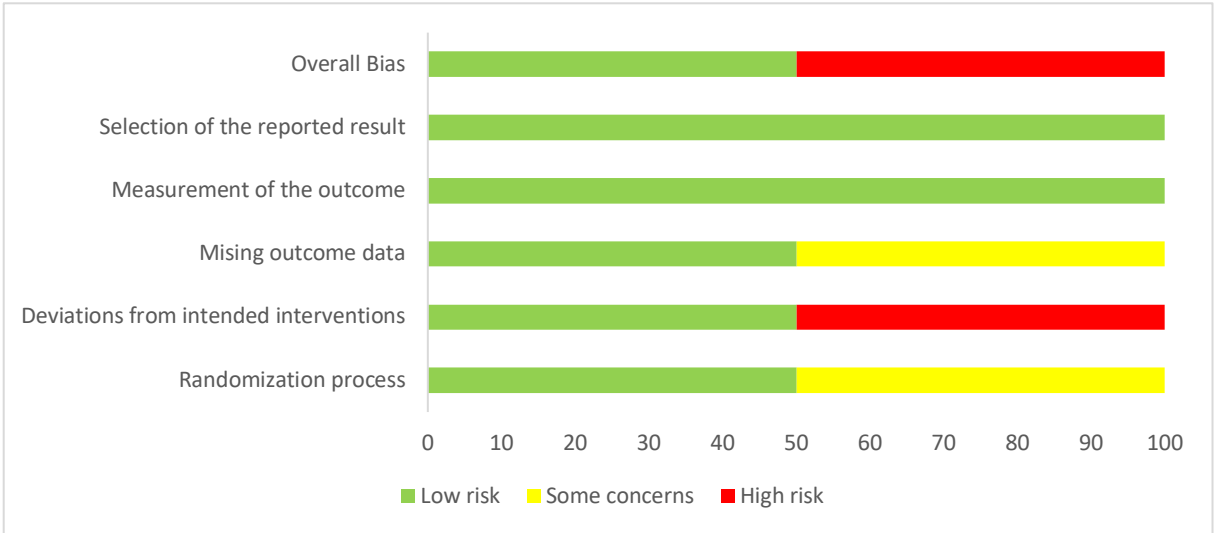
Coe 2018	Coe S, Franssen M, Collett J, Boyle D, Meaney A, Chantry R, Esser P, Izadi H, Dawes H (2018) Physical Activity, Fatigue, and Sleep in People with Parkinson's Disease: A Secondary per Protocol Analysis from an Intervention Trial. Parkinson's Dis **2018**, 1517807.
Cugusi 2015	Cugusi L, Solla P, Serpe R, Carzedda T, Piras L, Oggianu M, Gabba S, Di Blasio A, Bergamin M, Cannas A, Marrosu F, Mercuro G (2015) Effects of a Nordic Walking program on motor and non-motor symptoms, functional performance and body composition in patients with Parkinson's disease. *NeuroRehabilitation* **37**, 245-254.
Kluger 2016	Kluger BM, Rakowski D, Christian M, Cedar D, Wong B, Crawford J, Uveges K, Berk J, Abaca E, Corbin L, Garvan C (2016) Randomized, Controlled Trial of Acupuncture for Fatigue in Parkinson's Disease *Mov Disord* **31**, 1027-1032. --- McRae C, Andrews R, Kluger B (2014) Double-blind acupuncture study for the treatment of fatigue in Parkinson's disease: Qualitative perspectives. *Mov Disord* **29**, S295. McRae C, Rogers SE, Grine D, Kluger B (2016) Differences between actual and perceived treatment groups in a double-blind placebo trial of acupuncture for fatigue in Parkinson's disease. *4th World Parkinson Congress Portland, Oregon, USA.*
Kong 2018	Kong KH, Ng HL, Li W, Ng DW, Tan SI, Tay KY, Au WL, Tan LCS (2018) Acupuncture in the treatment of fatigue in Parkinson's disease: A pilot, randomized, controlled study. *Brain Behav* **8**, e00897.
Michels 2018	Michels K, Dubaz O, Hornthal E, Bega D (2018) „Dance Therapy" as a psychotherapeutic movement intervention in Parkinson's disease. *Complement Ther Med* **40**, 248-252. --- Michels K, Hornthal E, Berga D (2018) A pilot study on dance/movement therapy in Parkinson's disease (P5.074). *Neurology* **90**.
Ortiz-Rubio 2018	Ortiz-Rubio A, Cabrera-Martos I, Torres-Sánchez I, Casilda-López J, López-López L, Valenza MC (2018) Effects of a resistance training program on balance and fatigue perception in patients with Parkinson's disease: A randomized controlled trial. *Med Clin (Barc)* **150**, 460-464.
Raymackers 2019	Raymackers JM, Andrade M, Baey E, Vanneste M, Evrard F (2019) Bright light therapy with a head-mounted device for anxiety, depression sleepiness and fatigue in patients with Parkinson's disease. *Acta Neurol Belg* **119**, 607-613.
Rios Romenets 2013	Rios Romenets S, Creti L, Fichten C, Bailes S, Libman E, Pelletier A, Postuma RB (2013) Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease – a randomized study. *Parkinsonism Relat Disord* **19**, 670-675.
Solla 2019	Solla P, Cugusi L, Bertoli M, Cereatti A, Della Croce U, Pani D, Fadda L, Cannas A, Marrosu F, Defazio G, Mercuro G (2019) Sardinian Folk Dance for Individuals with Parkinson's Disease: A randomized controlled pilot trial. *J Altern Complement Med* **25**, 305-316.
Sturkenboom 2014	Sturkenboom IHWM, Graff MJL, Hendriks JCM, Veenhuizen Y, Munneke M, Bloem BR, Nijhuis-van der Sanden MW (2014) Efficacy of occupational therapy for patients with Parkinson's disease: A randomized controlled trial. *Lancet Neurol* **13**, 557-566. --- Sturkenboom IHWM, Graff MJ, Borm GF, Adang EMM, Nijhuis-van der Sanden MWG, Bloem BR, Munneke M (2013) Effectiveness of occupational therapy in Parkinson's disease: study protocol for a randomized controlled trial. *Trials* **14**, 34. Sturkenboom I, Graff M, Veehuizen Y, Hendriks J, Bloem B, Nijhuis-van der Sanden M, Munneke M (2013) The effectiveness of occupational therapy in Parkinson's disease. *J Parkinsons Dis* **3**, 157.
Videnovic 2017	Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC (2017) Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease a randomized clinical trial. *JAMA Neurol* **74**, 411-418. ---

	Videnovic A, Marconi A, Kuhta T, Miskevics S, Zee P (2014) Bright Light Therapy Improves Excessive Daytime Sleepiness Associated with Parkinson's Disease (I3-2.004). *Neurology* **82**. Videnovic A, Marconi A, Kuhta T, Miskevics S, Zee P (2014) Light therapy improves excessive daytime sleepiness associated with Parkinson's disease. *Mov Disord* **29**, S299.
Walter 2019	Walter AA, Adams EV, Van Puymbroeck M, Crowe BM, Urrea-Mendoza E, Hawkins BL, Sharp J, Woschkolup K, Revilla FJ, Schmid AA (2019) Changes in Nonmotor Symptoms Following an 8-Week Yoga Intervention for People with Parkinson's Disease. *Int J Yoga Therap* **29**, 91-99. --- Urrea-Mendoza E, Van Puymbroeck M, Walter A, Hawkins BL, Woschkolup K, Park J, Sharp J, Schmid AA, Revilla FJ (2016) Effectiveness of yoga in decreasing symptoms and improving quality of life in Parkinson's disease. *Arch Phys Med Rehabil* **97**, e63-e64.
Winward 2012	Winward C, Sackley C, Meek C, Izadi H, Barker K, Wade D, Dawes H (2012) Weekly exercise does not improve fatigue levels in Parkinson's disease. *Mov Disord* **27**, 143-146.
Wu 2021	Wu PL, Lee M, Wu SL, Ho HH, Chang MH, Lin HS, Huang TT (2021) Effects of home-based exercise on motor, non-motor symptoms and health-related quality of life in Parkinson's disease patients: A randomized controlled trial. *Jpn J Nurs Sci*, e12418. --- NCT03752346. Multimodal Exercise Program on Parkinson's Disease Patients With Depression. https://clinicaltrials.gov/show/NCT03752346 (first posted 2018).

Supplementary Table 3. Sensitivity analysis.

Comparisons	Number of studies included	Random effects model	Fixed effect model
Pharmacological interventions			
Modafinil vs. Placebo	2	SMD = -0.21, 95% CI -0.74 – 0.31, $p = 0.43$	
Non-pharmacological interventions			
Exercise vs. Passive control group/Placebo	8	SMD = -0.37, 95% CI -0.69 – -0.05, $p = 0.02$	SMD = -0.40, 95% CI -0.63 – -0.18, $p = 0.0004$
Acupuncture vs. Placebo	2	SMD = 0.16, 95% CI -0.19 – 0.50, $p = 0.37$	

Supplementary Figure 1. Risk of bias 2.0 summary for pharmacological trials included in meta-analysis.



Supplementary Figure 2. Risk of bias 2.0 summary for non-pharmacological trials included in meta-analysis.