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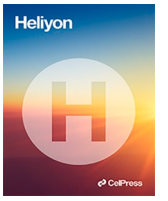

Research article

Treatment of apathy in Parkinson's disease: A bayesian network meta-analysis of randomised controlled trials

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ABSTRACT

Background: Apathy is an important but unrecognised aspect of Parkinson's disease (PD). The optimal therapeutic options for apathy remain unclear. Early recognition and treatment of apathy can reduce the significant burden of disease for patients and their caregivers. Here we conducted a meta-analysis to evaluate the comparative efficacy of different treatment modalities of apathy in PD (CRD42021292099).

Methods: We screened Medline, Embase, and PsycINFO databases for articles on therapies for apathy in PD. The outcome of interest is the reduction in apathy scores post-intervention and is measured by standardised mean differences (SMD) with 95% credible intervals (CrI). We included only randomised controlled trials examining interventions targeted at reducing apathy.

Results: Nineteen studies involving 2372 patients were included in the quantitative analysis. The network meta-analysis found pharmacotherapy to be the most efficacious treatment, significantly better than brain stimulation (SMD -0.43, 95% CrI −0.78 to −0.07), exercise-based interventions (SMD -0.66, 95% CrI −1.25 to −0.08), supplements (SMD -0.33, 95% CrI −0.67 to 0), and placebo (SMD -0.38, 95% CrI −0.56 to −0.23). Subgroup analysis of pharmacotherapy versus placebo found similar efficacy of dopamine agonists (SMD -0.36, 95% CI -0.59 to −0.12, $P = 0.003$) and alternative medications (SMD -0.42, 95% CI -0.61 to −0.23, $P < 0.001$). The remaining comparisons and subgroup analyses did not demonstrate any significant treatment effects.

Conclusion: Our meta-analysis of randomised controlled trials showed that pharmacotherapy is the most efficacious treatment option, with dopamine agonists having similar efficacy as other medications. Further research is needed to determine the optimal management strategy.

1. Introduction

Patients with Parkinson's disease (PD) experience a great deal of distressing neuropsychiatric symptoms [1]. Apathy is of particular importance owing to its early association with motor impairment [2]. Apathy is characterised by a lack of motivation with reduced

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goal-directed cognition, as well as behavioural and emotional disengagement [3]. The prevalence of apathetic disposition in PD patients is high at 29% [2] but can affect up to half of the patients [4]. Despite being vastly debilitating throughout the disease course [5], apathy unfortunately remains under-recognised.

While the progressive loss of functional autonomy occurs in PD patients due to motor disturbances, apathy is independently associated with the inability to perform activities of daily living [6,7]. Apathetic patients often experience a markedly reduced quality of life (QoL) regardless of disease stage [7]; apathy is also the symptom most frequently correlated with diminished QoL [8] and caregiver distress [9,10]. Even amongst patients with newly diagnosed PD, apathy is a major contributor to the decreased QoL [5].

The recognition of apathy as an independent substrate for treatment is key, as it allows for potential differentiated therapy. Prior literature on interventions for apathy in PD seems promising; in addition to improving neuropsychiatric (apathy included) and cognitive symptoms, they appear to improve the patient's quality of life [11,12]. Numerous randomised controlled trials (RCTs) of medications (namely cholinesterase inhibitors, dopaminergic agents, and antidepressants) have shown efficacy in improving apathy symptoms in PD [11]. Though there are limited studies on non-pharmacological interventions, exercise appears promising with preliminary evidence of improvements in functional ability, postural stability, and gait [12].

Nevertheless, the optimal strategy to manage apathy in apathy remains unclear, and there has not been a study to date that evaluated the different treatment options. Despite various RCTs on the topic, conclusions remain varied, particularly owing to limited statistical power and varying methodology. To address these gaps in knowledge, we conducted this network meta-analysis to compare the efficacy of various interventions.

2. Methods

2.1. Search strategy

This network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis (NMA) guidelines [13], and is registered with PROSPERO at CRD42021292099. We screened Medline, Embase, and PsycINFO databases for relevant articles. The search strategy involved keywords and medical subject heading (MeSH) terms synonymous with "Parkinson's disease" and "apathy". A randomised controlled trial filter was applied before exporting the search results, and references of related reviews were screened to ensure a comprehensive search. A copy of the search strategy for Medline can be found in Supplementary Material 1.

2.2. Study selection and Extraction

Each study was reviewed twice in an independent and blinded manner, and the titles and abstracts were screened before retrieving and reviewing the full texts. An independent author was involved in the resolution of disputes. Only RCTs were considered for inclusion; observational studies, reviews, meta-analyses, editorials, commentaries, conference abstracts, and non-English language articles were excluded.

Studies were included if they were randomised controlled trials that examined interventions for apathy in PD, with each arm comprising at least 15 patients at analysis. These studies must also report the change in apathy scores according to a validated scale; they include the Starkstein Apathy Scale, Apathy Scale, Lille Apathy Rating Scale (LARS), the apathy sub-domains of the Unified Parkinson's Disease Rating Scale (UPDRS), and the Non-Motor Symptoms Scale (NMSS). The outcome of interest is the efficacy of these interventions in improving apathy in PD, as measured by changes from the baseline apathy scores.

Data were extracted from each included study twice in an independent and blinded manner. The following variables were extracted: (1) study details—the year of publication, geographical region of study, interventions studied, and sample size; (2) baseline patient characteristics—age, gender, disease progression (as measured by the Hoehn and Yahr Scale), and presence of other neuropsychiatric conditions (such as dementia, depression, and anxiety); (3) outcome-related information—scale used to evaluate apathy, the assessor of the apathy score (such as patient, caregiver, or clinician), baseline apathy scores, follow-up duration, and apathy scores at follow-up (or changes from baseline).

2.3. Statistical analysis

All analyses were conducted in R (version 4.1.1). The Bayesian network meta-analysis was performed with the *gemtc* package. The outcome of interest (change in baseline apathy scores) was measured using standardised mean differences (SMD) and their corresponding 95% credible intervals (95% CrI). Intervention groups were defined according to the type of treatment strategy used, namely (1) pharmacotherapy, (2) brain stimulation, (3) exercise-based interventions, (4) supplements, and (5) placebo, sham, or usual care. We then performed Markov Chain Monte Carlo (MCMC) simulations using vague priors and a generalised linear model with the likelihood function for Gaussian distribution and the identity link function. Four Markov chains were utilised, and the analysis was conducted with 5000 burn-ins and 100,000 iterations. No thinning was performed.

The trace and density plots were used to assess convergence of the MCMC chains, while the deviance information criterion (DIC) was used to compare the goodness-of-fit and select between the fixed- and random-effects models, as well as between the consistency and inconsistency models. Ultimately, a random-effects model was employed due to better fit as indicated by a lower DIC score. Between-intervention pairwise comparisons are presented as a relative effects table using SMD and their corresponding 95% CrI; a negative SMD favours the column-defining intervention, while a positive SMD favours the row-defining intervention. A copy of the R

script used for the Bayesian network meta-analysis can be found in Supplementary Material 2.

Subgroup analyses were conducted by pooling the studies within each intervention class using the *meta* package in R. In addition, a further subgroup analysis was undertaken for the "pharmacotherapy" subgroup to compare the effects of dopamine agonists to alternative pharmacotherapeutic agents. The DerSimonian-Laird random-effects model was employed regardless of heterogeneity, which was primarily assessed using the I^2 index. An I^2 index of less than 25% is indicative of low heterogeneity, between 25% and 75% is representative of moderate heterogeneity, and over 75% suggests substantial heterogeneity. SMD, along with their corresponding 95% confidence intervals (CI), were presented for these analyses. $P < 0.05$ was considered statistically significant.

2.4. Risk-of-bias assessment

The revised version of the Cochrane Risk-of-Bias tool for randomised trials (RoB 2) was used to evaluate the potential for bias in our included studies [14]. The RoB 2 evaluates bias across five dimensions: (1) the randomisation process, (2) deviations from intended

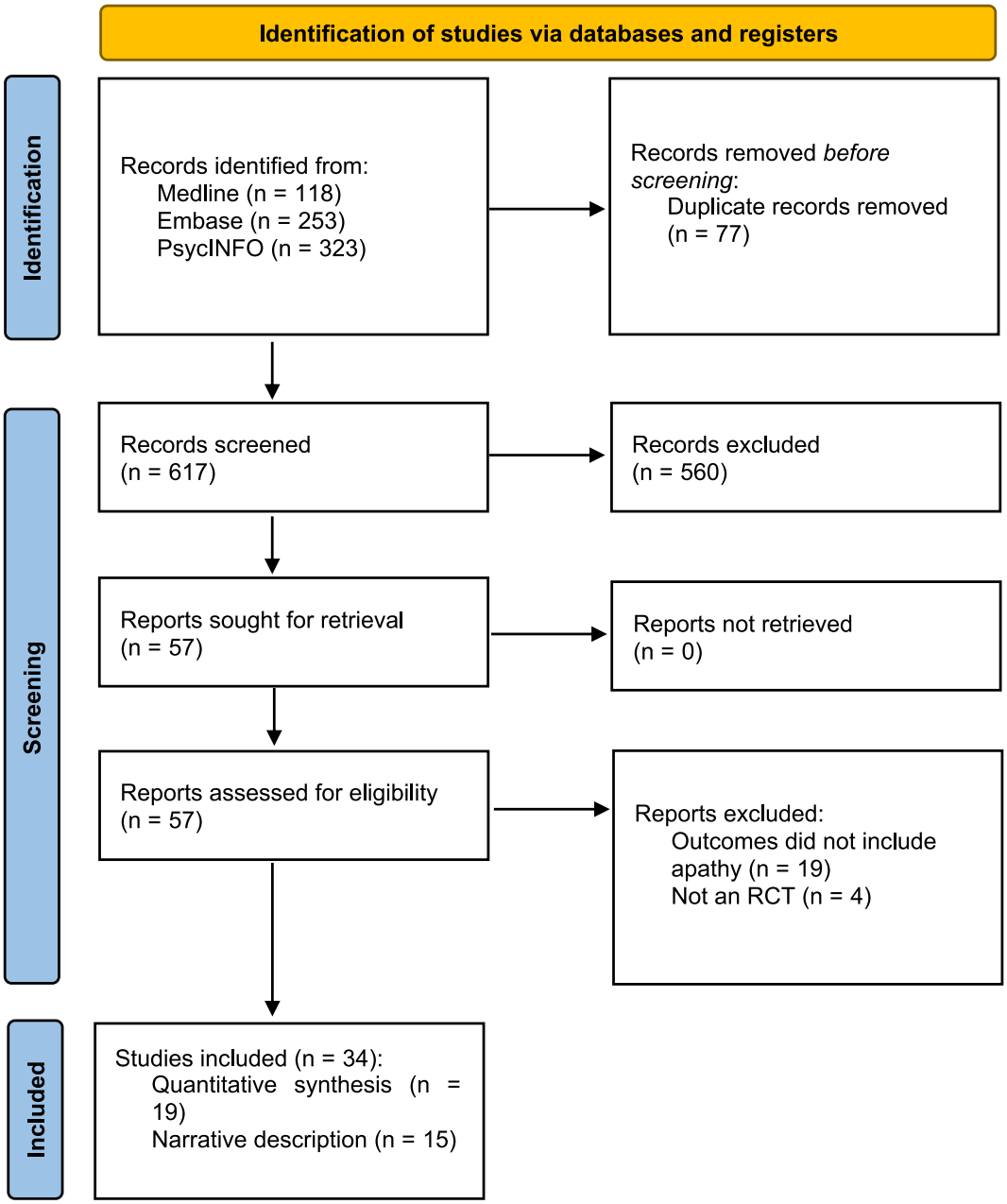

Fig. 1. Prisma Flow Diagram.

Table 1
Summary of articles included in quantitative Synthesis.

Study	Intervention(s)	Control	Follow-Up Duration	Sample Size[a]	Age (years)[a]	Female (%)[a]	Disease Duration (years)[a]	Apathy Scale	Baseline Apathy[a]	Risk of Bias
Antonini et al., 2015 [30]	Transdermal rotigotine patch[b]	Placebo	12 weeks	207/120	68 ± 9/67 ± 10	42.4/46.4	7 ± 4/5 ± 3	NMSS	14.8 ± 12.8/ 14.7 ± 12.2	Low
Athauda et al., 2018 [36]	Exenatide, self-injection at 2 mg once a week	Placebo	60 weeks	31/29	*N.R.*	*N.R.*	*N.R.*	NMSS	4.3 ± 6.7/5.4 ± 8.1	Low
Barone et al., 2015 [37]	Rasagiline, 1 mg once a day orally	Placebo	12 weeks	53/63	66 ± 9/66 ± 8	58.5/42.9	4 ± 3/5 ± 4	UDPRS	1.1 ± 0.9/1.1 ± 0.9	Low
Castrioto et al., 2020 [31]	Transdermal rotigotine patch	Placebo	6 months	26/22	57 ± 7/61 ± 8	34.6/32.8	2 ± 1/2 ± 2	LARS	−13.7 ± 6.9/-11.0 ± 6.9	Low
Chua et al., 2017 [45]	Jiawei-Liujunzi Tang, 11 g twice per day orally	Placebo	32 weeks	45/46	64 ± 10/63 ± 8	37.5/30.9	6 ± 4/5 ± 4	NMSS	65.5 ± 49.8/ 47.4 ± 35.7	Low
Chung et al., 2016 [32]	Transdermal rotigotine patch[b]	Placebo	8 weeks	149/164	66 ± 9/65 ± 8	52.2/62.2	3 ± 3/3 ± 3	AS	19.2 ± 6.1/19.0 ± 6.2	Low
Hauser et al., 2016[33,c]	**Intervention 1:** "Low-dose" transdermal rotigotine patch **Intervention 2:** "High-dose" transdermal rotigotine patch	Placebo	12 weeks	30/37/ 32	68 ± 11/70 ± 8/69 ± 12	34.1/ 34.1/45.0	5 ± 4/5 ± 4/ 4 ± 4	AS	20.1 ± 4.4/20.2 ± 4.8/19.7 ± 3.8	Low
Lhommée et al., 2018 [41]	Bilateral subthalamic stimulation with medical therapy	Medical therapy alone	2 years	120/123	53 ± 7/52 ± 6	24.0/34.1	7 ± 3/8 ± 3	SAS	9.9 ± 8.1/9.8 ± 8.2	Some concerns
Meloni et al., 2020[46,d]	5-hydroxytryptophan, 50 mg once a day for 4 weeks	Placebo	16 weeks	23	68 ± 7	30.4	10 ± 6	AS	17.4 ± 2.7	Low
Ory-Magne et al., 2014 [38]	Continuing amantadine at unchanged baseline dose	Replacing amantadine with placebo	3 months	27/29	61 ± 7/66 ± 7	*N.R.*	13 ± 8/14 ± 5	AS	1.3 ± 2.1/1.9 ± 2.3	Low
Peball et al., 2020 [47]	Continuing nabilone, up to 1 mg twice daily	Replacing nabilone with placebo	4 weeks	19/19	65 ± 8/64 ± 8	47.4/26.3	8 ± 6/7 ± 5	NMSS	8.0 ± 10.0/6.5 ± 7.7	Low
Ray Chaudhuri et al., 2013 [34]	Transdermal rotigotine patch, up to 16mg/day	Placebo	4 weeks	178/88	65 ± 9/65 ± 10	17.4/69.3	5 ± 4/5 ± 5	NMSS	7.1 ± 9.3/7.3 ± 10.0	Low
Rios Romenets et al., 2015 [43]	24 partnered tango classes, 1-h class twice per week	Self-directed exercise	12 weeks	18/15	63 ± 10/64 ± 8	33.3/53.3	6 ± 4/8 ± 5	AS	28.9 ± 7.3/26.8 ± 7.6	Some concerns
Sacheli et al., 2019 [44]	36 sessions of aerobic exercise, each session lasting from 40 to 60 min thrice a week	Stretching programme	3 months	20/15	67 ± 6/68 ± 9	35.0/40.0	4 ± 3/5 ± 4	SAS	10.7 ± 6.5/15.7 ± 6.5	Low
Schwarzschild et al., 2021 [48]	Inosine, taken orally at up to two 500 mg tablets, thrice daily	Placebo	2 years	144/149	63 ± 10/64 ± 9	55.6/45.0	1 ± 1/1 ± 1	*N.R.*	*N.R.*	Low
Shirota et al., 2013 [42]	**Intervention 1:** 1-Hz rTMS, performed weekly for 8 weeks **Intervention 2:** 10-Hz rTMS, performed weekly for 8 weeks	Sham procedure	20 weeks	34/34/ 34	69 ± 8/68 ± 8/66 ± 9	64.7/ 64.7/50.0	9 ± 7/8 ± 7/ 8 ± 4	*N.R.*	*N.R.*	Low
Smith et al., 2015 [39]	Rasagiline, taken orally at either 1 mg or 2 mg daily	Placebo	36 weeks	68/69	*N.R.*	*N.R.*	5 ± 5/4 ± 5	*N.R.*	*N.R.*	Low
Thobois et al., 2013 [35]	Piribedil, taken orally at dosages up to 300 mg daily	Placebo	12 weeks	19/18	59 ± 7/56 ± 8	47.4/38.9	12 ± 4/11 ± 3	SAS	21.1 ± 4.8/18.9 ± 4.2	Low
Weintraub et al., 2010 [40]	Atomoxetine, taken orally at either 40 mg (if a decreased dose is clinically indicated) or 80 mg daily (target dose)	Placebo	8 weeks	28/27	64 ± 10/65 ± 12	28.6/40.7	8 ± 7/6 ± 6	AS	18.1 ± 7.9/16.7 ± 4.8	Low

Abbreviations: AS, Apathy Scale; LARS, Lille Apathy Rating Scale; NMSS, Non-Motor Symptom Scale; rTMS, repetitive transcranial magnetic stimulation; SAS, Starkstein Apathy Scale. *N.R.*, not reported.

[a] Reported as (*intervention*)/(*control*) for two-arm studies, and (*intervention 1*)/(*intervention 2*)/(*control*) for three-arm studies.

[b] Titrated to optimal dose over 1–7 weeks; ≤8 mg/24 h for patients not receiving levodopa or with early-stage Parkinson's disease, and ≤16 mg/24 h for patients receiving levodopa or with late-stage Parkinson's disease.

[c] "Low-dose" was defined as ≤6 mg/24 h for early PD (those not receiving levodopa), or ≤8 mg/24 h for advanced PD (those receiving levodopa); "high-dose" was defined as ≤8 mg/24 h for early PD, or ≤16 mg/24 h for advanced PD.

[d] The study was a cross-over trial, and baseline demographics are reported as one cohort.

interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Each included study was assessed twice for their risk of bias in a blinded manner by four authors and disagreements were resolved through discussion with an independent author.

3. Results

3.1. Summary of included articles

The database search yielded 694 studies with 77 duplicates. Following eligibility assessment, 34 studies were included in the final review (Fig. 1). A total of 34 studies were included in the final review, with 15 narratively described and 19 quantitatively analysed. The 15 studies narratively described involved 467 patients. Amongst these, 7 studies compared interventions within the same class [15–21]; 7 studies had small sample sizes (at least one arm had <15 participants) [22–28]; 1 study cannot be categorised into the pre-defined intervention classes [29].

On the other hand, the 19 studies analysed quantitatively involved 2372 PD patients (Table 1). Pharmacotherapy was examined in 11 studies comprising 1514 patients [30–40]; brain stimulation in 2 studies with 345 patients [41,42]; exercise-based interventions in 2 studies with 68 patients [43,44]; and supplements in 4 studies with 445 patients [45–48]. The studies included in the quantitative analysis were generally of low risk of bias, except for 2 studies that presented some concerns due to awareness of the participants and assessors regarding the interventions [41,43].

3.2. Bayesian network meta-analysis

A total of 19 studies involving 2372 individuals with PD were included in the random-effects Bayesian network meta-analysis (Table 2). Pharmacotherapy was demonstrated to be more favourable in reducing apathy scores when compared to brain stimulation (SMD -0.43, 95% CrI −0.78 to −0.07), exercise-based interventions (SMD -0.66, 95% CrI −1.25 to −0.08), and placebo (SMD -0.38, 95% CrI −0.56 to −0.23). Pharmacotherapy was also superior to supplements with borderline statistical significance (SMD -0.33, 95% CrI −0.67 to 0).

3.3. Within-intervention subgroup analyses

3.3.1. Pharmacotherapy

A total of 11 studies, involving 1514 patients, were pooled (Fig. 2), and the analysis yielded pharmacotherapy to be effective in improving apathy scores (SMD -0.38, 95% CI -0.54 to −0.23, $P < 0.001$). The overall analysis demonstrated moderate heterogeneity at an I^2 index of 49%. Further subgroup analysis was conducted to explore differences between dopamine agonists (6 studies with 1090 patients) and alternative agents (5 studies with 424 patients), with no significant differences detected ($P = 0.682$). Alternative medications included rasagiline [37,39], exenatide [36], amantadine [38], and atomoxetine [40]. Dopamine agonists produced an SMD of −0.36 (95% CI -0.59 to −0.12, $P = 0.003$), which was comparable to alternative agents (SMD -0.42, 95% CI -0.61 to −0.23, $P < 0.001$). Interestingly, alternative agents demonstrated no heterogeneity, while dopamine agonists were markedly more heterogeneous ($I^2 = 65\%$).

3.3.2. Non-pharmacologic interventions

Two unique studies with a total of 345 patients were pooled for the brain stimulation subgroup analysis (Supplementary Fig. 1), but the analysis returned no significant results (SMD 0.04, 95% CI -0.24 to 0.33, $P = 0.757$) with moderately low levels of heterogeneity ($I^2 = 33\%$). As for exercise-based interventions (Supplementary Fig. 2), 2 studies with 68 patients similarly demonstrated no significant effects on the apathy scores (SMD 0.27, 95% CI -0.34 to 0.87, $P = 0.388$) with moderately low levels of heterogeneity ($I^2 = 36\%$). Lastly, the subgroup analysis for supplements comprised 4 studies with 445 patients (Supplementary Fig. 3) but did not demonstrate significant reductions in apathy scores (SMD -0.04, 95% CI -0.22 to 0.14, $P = 0.650$). There was no heterogeneity observed in the supplements analysis.

Table 2
Pairwise comparisons between interventions for apathy in Parkinson's disease.

Pharmacotherapy	0.43 (0.07–0.78)[a]	0.66 (0.08–1.25)[a]	0.33 (0–0.67)[a]	0.38 (0.23–0.56)[a]
−0.43 (−0.78 to −0.07)[a]	**Brain Stimulation**	0.23 (−0.40 to 0.89)	−0.10 (−0.52 to 0.35)	−0.05 (−0.35 to 0.29)
−0.66 (−1.25 to −0.08)[a]	−0.23 (−0.89 to 0.40)	**Exercise-Based Interventions**	−0.33 (−0.96 to 0.29)	−0.28 (−0.84 to 0.28)
−0.33 (−0.67 to 0)[a]	0.10 (−0.35 to 0.52)	0.33 (−0.29 to 0.96)	**Supplements**	0.05 (−0.23 to 0.35)
−0.38 (−0.56 to −0.23)[a]	0.05 (−0.29 to 0.35)	0.28 (−0.28 to 0.84)	−0.05 (−0.35 to 0.23)	**Placebo/Sham/Usual Care**

Each pairwise comparison is presented as SMD (95% CrI) by comparing the column-defining intervention to the row-defining intervention. A negative SMD favours the column-defining intervention, while a positive SMD favours the row-defining intervention.

[a] These pairwise comparisons are statistically significant as the 95% CrI does not include zero.

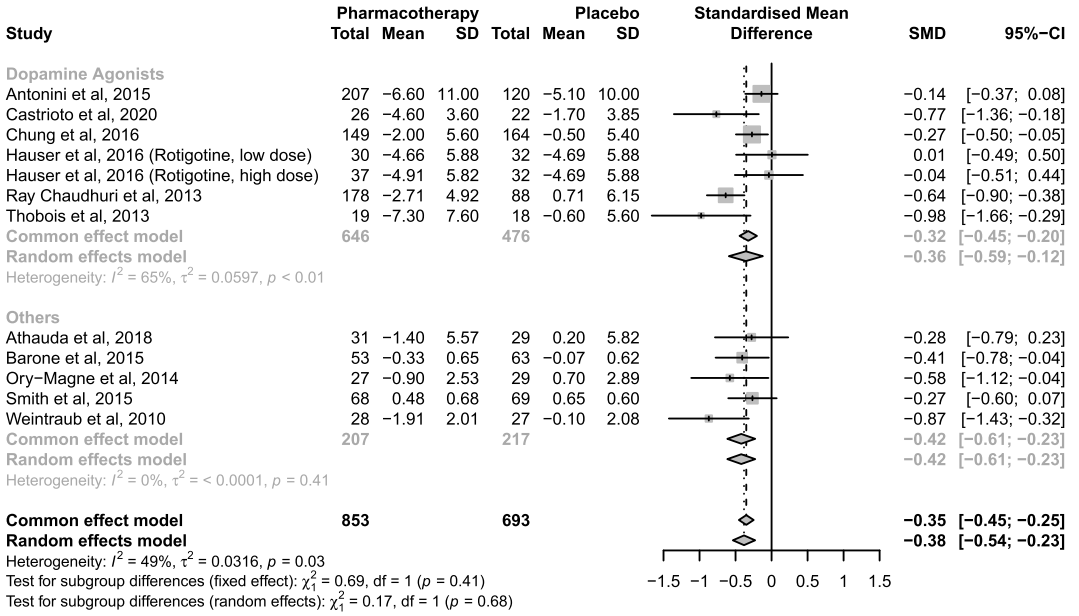

Fig. 2. Forest plot for subgroup analysis of pharmacotherapy.

3.4. Qualitative Synthesis

A total of 15 studies involving 467 PD patients were analysed qualitatively as they were unable to be included in the quantitative meta-analysis. Of these, 4 were on pharmacologic agents [19,21,23,24], 4 on brain stimulation [15,17,18,25], 4 on exercise-based programmes [16,20,22,28], 2 on psychological interventions [27,29], and 1 on docosahexaenoic acid (DHA) supplementation [26].

3.4.1. Pharmacotherapy

Devos et al. [23] and Jang et al. [24] demonstrated rivastigmine and recombinant human erythropoietin (rhEPO), respectively, to be superior to placebo; Picillo et al. [19] concluded the use of dopamine agonist monotherapy (either pramipexole or ropinirole) to be better at improving apathy in PD patients following deep brain stimulation (DBS) of the subthalamic nucleus (STN); Takahashi et al. [21] compared duloxetine (a serotonin-norepinephrine reuptake inhibitor) with paroxetine and escitalopram (selective serotonin reuptake inhibitors) but found no significant differences.

3.4.2. Brain stimulation

Amongst the studies included, 3 focused on DBS [15,17,18] and 1 on repetitive transcranial magnetic stimulation [25]. Hidding et al. [15] compared the DBS of both the subthalamic nucleus and substantia nigra with that of the subthalamic nucleus alone; Merello et al. [17] compared bilateral DBS with bilateral subthalamotomy; Okun et al. [18] compared unilateral DBS of the subthalamic nucleus with the globus pallidus internus; Maruo et al. [25] examined the efficacy of rTMS with a sham procedure as control. None of these studies, however, found significant differences.

3.4.3. Exercise-based interventions

Cugusi et al. [22] found Nordic walking to be better than conventional care; King et al. [16] compared between individual-, home-, and class-based exercise programs, with individual-based exercise being the only group to significantly reduce apathy; Sajatovic et al. [20] similarly compared group-based with self-directed exercise but found no significant differences; Solla et al. [28] compared Sardinian folk dance with usual care—while there was a non-significant decrease in apathy scores for the dance group, there was a significant increase in the usual care group, resulting in the dance group having significantly better apathy scores.

3.4.4. Others

The remaining studies, of which 2 were on psychological strategies and 1 on DHA supplementation, did not find significant differences between the investigated interventions. As for psychological interventions, Peña et al. [29] compared cognitive training with occupational activities as control, while Santos et al. [27] compared post-DBS (of the subthalamic nucleus) psychoeducation and usual care. Lastly, Pomponi et al. [26] examined the effects of DHA supplementation with placebo as control.

4. Discussion

In this random-effects Bayesian network meta-analysis involving a total of 19 studies comprising of 2372 individuals with PD, we

demonstrated that pharmacotherapy is effective against apathy in PD when compared with placebo. Among pharmacotherapeutic agents, dopamine agonists showed similar efficacy when compared with other medications. Even if we removed the 3 largest studies [30,32,34], the efficacy for pharmacotherapy relative to placebo remains similar. Moreover, the network meta-analysis yielded pharmacotherapy to be favourable to the other analysed intervention classes as well, though these intervention classes included fewer patients and could potentially be underpowered.

Apathy remains an extremely common affliction, especially in subjects recently diagnosed with PD, and importantly is a major determinant of the quality of life for PD patients [5]. The effects of apathy are varied but are mainly relating to deficits in motivation as manifested across 3 distinct domains: cognitive, emotional, and behavioural [49]. As such, his can lead to a reduced ability to perform activities of daily living and an increased risk of social isolation. Importantly, perhaps as a result of cognitive amotivation, PD patients with apathy are at an increased risk of cognitive impairment and even dementia [50]. A potential hypothesis underlying this association is the impaired attention observed in apathetic PD patients, which could represent a prodromal phase of dementia [51]. The impaired attention seen in such individuals, however, could also have a neurobiological basis, since there is a paucity of dopamine which is crucial to generate motivation and maintain attention [49]. Lastly, the presence of apathy in PD patients is also associated with caregiver distress and burden, regardless of cognitive status [10,52]. As mentioned above, PD patients with apathy face challenges with performing activities of daily living due to a lack of motivation, which then places additional stress on the caregivers, and hence resulting in frustration and eventually burnout [10]. Therefore, in view of its prevalence and its deleterious effects on PD patients' quality of life, apathy is an important clinical substrate that should be concurrently managed along motor and other nonmotor symptoms.

That said, apathy is a difficult symptom to manage in PD patients, as well-studied treatment options are currently limited. Our meta-analysis demonstrated that pharmacologic therapies have significant beneficial effects on apathy in PD patients, with no difference between dopaminergic agonists (such as rotigotine and piribedil) and other drug classes (including monoamine oxidase inhibitors and selective norepinephrine reuptake inhibitors). Whilst the role of these agents in managing the motor symptoms of PD remain disputed, these medications could be useful adjuncts for managing the nonmotor aspect of PD [53]. However, while these medications may result in substantial improvements in apathy scores (and even other mood-related comorbidities), there may be challenges implementing such treatment regimens in clinical practice. Many of the studied medications are neurotropic agents which require transition across the blood-brain barrier and then interact with various receptors within the central nervous system. Such medications are also prone to drug-drug interactions, which range from altered pharmacokinetics to potentially life-threatening ones such as serotonin syndrome and sedation [54,55]. Furthermore, polypharmacy is highly prevalent in PD as patients tend to have multiple medical comorbidities. Pharmacotherapeutic options for apathy must hence be systematically studied in future research to understand their risk profiles and potential interactions.

Despite having limited RCTs performed, exercise-based interventions are especially promising given its potential to decrease PD risk and possibly even have disease-modifying effects [56]. For example, higher levels of physical activity were linked with lower risk of developing PD [57], and even amongst PD patients, physical activity appears to improve symptom severity, function, and quality of life [56]. Moreover, a recent meta-analysis found that the COVID-19 pandemic itself (not infection) has been associated with decreased physical activity levels and worsening PD symptoms in over 50% of patients, potentially suggesting a protective or disease-modifying effect of exercise on PD [58]. However, most of the evidence linking exercise and its neuroprotective effect in PD are from observational studies and animal models. Well-designed RCTs looking at the effects of exercise remain scarce, most likely because of the long duration of follow-up needed to detect a significant effect size. That said, with the mounting evidence supporting the benefits of exercise, treatment regimens involving various types of exercise (such as aerobic and resistance training) represents a promising frontier, not to mention an excellent safety profile unlike medications and invasive brain stimulation.

Non-invasive brain stimulation is an interesting up-and-coming treatment option of mood-related symptoms across both psychiatric and neurological disorders. Like exercise, the safety profile of non-invasive brain stimulation is excellent with minimal (if any) clinically significant side effects. Examples of such stimulation include transcranial direct current simulation, transcranial alternating current simulation, and transcranial magnetic simulation [59]. Though the evidence supporting its use remains limited in PD, it has been systematically studied in other psychiatric and neurological disorders and has demonstrated promising results [60,61]. However, the efficacy of such stimulation is patient-dependent and variable, and intensive treatment regimens (daily sessions of stimulation) are frequently required to produce a clinically significant effect. Two separate meta-analyses have also failed to find an improvement in motor function in PD patients post-stimulation [62,63]. These factors may hence limit the feasibility of implementing non-invasive brain stimulation in clinical practice. That said, this represents a novel approach with potential to become a useful adjunct in our armamentarium for managing PD. Furthermore, the use of such stimulation techniques could also provide useful and much needed insights into the connectomics and neural circuity within the brain.

Future directions for research include performing studies for non-European populations, development of a sensitive screening tool and a specific diagnostic tool for apathy in PD, as well as the study of biomarkers associated with or predictive of patients with apathy. Firstly, the findings presented here may have limited generalisability in Asian, African, and other non-European populations. Only 3 out of the 19 studies included in the quantitative analysis were based in countries outside of Europe or North America [32,42,45]; amongst the 15 included in the qualitative analysis, only 4 were not European or North American studies [17,21,24,25]. This suggests that the body of literature surrounding treatments of PD-specific apathy is predominated by American and European populations and may limit the generalisability of our findings to Asian and other demographics. Secondly, the development of a sensitive tool to assess PD-specific apathetic behaviour is needed; a systematic review by Carrozzino [64] has advocated for the use of rating scales that are both psychometrically robust and clinically validated. The findings of the same review also suggest that multiple scales ought to be used when diagnosing and monitoring apathy in PD patients; for example, while the SAS is valid for excluding the presence of apathy

and the LARS for diagnosis, the Neurasthenia Scale is better used for measuring severity. It is important for standardised tools to be used for future research, which would improve comparability and minimise methodology-related heterogeneity. Lastly, biomarkers of apathy in PD patients are important as they could serve as useful tools that complement rating scales in the definition of the apathy phenotype. Brainstem raphe signal alterations on transcranial sonography [65] and nucleus accumbens atrophy on magnetic resonance imaging [66] have been described in apathy patients. The identification of these biomarkers is promising since they could serve to identify patients experiencing apathy and allow for early differentiated management strategies.

5. Strengths and limitations

This is the first network meta-analysis comparing interventions for apathy in PD, which unfortunately remain underdiagnosed and undertreated. We analysed a total of 19 studies quantitatively, and further described 15 narratively. In addition, we performed subgroups analyses where meaningful and appropriate. Our findings highlighted that numerous agents can be used to manage apathy once diagnosed. Furthermore, this paper identified gaps in knowledge, namely in non-pharmacological interventions, which would warrant future RCTs with sufficient sample size and adequate follow-up.

Nonetheless, this study suffers from several limitations. There exists heterogeneity within the defined intervention classes that may arise from methodological or demographic differences across the included studies. Most studies are conducted in European or American populations, and this can limit the generalisability of the findings to other ethnic populations. Another key limitation is that SMD lacks clinical interpretability, and this could potentially limit the utility of our findings.

6. Conclusion

Among pharmacotherapeutic agents, dopamine agonists and other medications showed similar efficacy when compared with other medications. The network meta-analysis also demonstrated that pharmacotherapy was significantly better than deep brain stimulation, exercise-based interventions, supplements, and placebo. There is a need for larger clinical trials with long-term follow-up for the various non-pharmacologic interventions. Future research is also needed to determine the optimal management strategy for apathy in PD patients.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Consent for publication

All authors consent to the publication of this manuscript and related materials.

Ethics Approval and consent to participate

Not applicable.

CRediT authorship contribution statement

Aaron Shengting Mai: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yi Siang Lee:** Conceptualization. **Jung Hahn Yong:** Data curation. **Dillon Christopher Yong Jie Teo:** Data curation. **Yi-Min Wan:** Writing – review & editing, Supervision, Methodology. **Eng-King Tan:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26107.

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