Clinical Parkinsonism & Related Disorders 4 (2021) 100096

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Non-pharmacologic interventions to treat apathy in Parkinson's disease: A realist review

Bria Mele [a,b,*], Zahinoor Ismail [a,b,c,d,e,f], Zahra Goodarzi [a,e,f,g], Tamara Pringsheim [a,d,e], Grace Lew [h], Jayna Holroyd–Leduc [a,g,i]

[a] Department of Community Health Sciences, University of Calgary, 3D10, 3280 Hospital Drive NW, Calgary, Alberta T2N 4Z6, Canada
[b] Cumming School of Medicine, University of Calgary, Health Sciences Centre, Foothills Campus, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada
[c] Department of Psychiatry, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[d] Department of Clinical Neuroscience, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[e] Hotchkiss Brain Institute, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[f] O'Brien Institute for Public Health, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[g] Department of Medicine, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[h] Faculty of Health Sciences, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta T2N 4N1, Canada
[i] Alberta Health Services, Foothills Medical Centre, South Tower, Room 1104, 1403–29 St. NW, Calgary, Alberta, T2N 2T9, Canada

ARTICLE INFO

Keywords:
Parkinson's disease
Apathy
Treatment
Non-pharmacological treatment

ABSTRACT

Introduction: There is a diverse body of evidence investigating non-pharmacological treatment options for apathy in Parkinson's disease (PD). We aimed to better understand the context and mechanisms by which non-pharmacological interventions may improve apathy in persons with PD.
Methods: We conducted a realist review of the body of evidence investigating treatment options for apathy in PD. Study authors used findings from a preceding scoping review to identify initial program theory. We then update the scoping review, which was originally conducted in 2017. Two authors independently reviewed and extracted data from studies that discussed non-pharmacological treatment options for apathy in PD. Any data concerning context, mechanisms, and outcomes of interventions for apathy in PD were extracted, synthesized, and analyzed.
Results: Our review included nine studies. We categorized studies into two categories, exercise and mindfulness. There were seven exercise interventions included. Exercise interventions evaluated group exercise compared to individual exercise, aerobic exercise, dance, Nordic walking, and an equine program. There were two mindfulness interventions.
Conclusion: Exercise interventions work best for persons with PD and apathy who are not significantly physically or cognitively impaired, and who have access to transportation, adapted programs, and specialized coaches. Exercise may improve apathy through goal-directed behaviour change and engagement in social interactions. Mindfulness interventions work best for persons with PD and apathy who are not significantly cognitively impaired, have caregiver support, and may improve apathy by targeting the emotional, cognitive, and goal-directed domains that define apathy.

Contents

* Corresponding author.
E-mail address: bria.mele@ucalgary.ca (B. Mele).

https://doi.org/10.1016/j.prdoa.2021.100096
Received 14 October 2020; Revised 1 March 2021; Accepted 10 May 2021
Available online 25 May 2021

1. Introduction

Apathy presents in 40% of persons with PD [1]. Defining features of apathy include lack of interest, initiative, and emotional reactivity [2]. Apathy in PD results in decreased quality of life for persons with PD and increased caregiver burden [3–5]. Proposed mechanisms that underly apathy include depletion of dopaminergic and cholinergic neurons in the lateral prefrontal cortex, and depletion of dopamine neurons in the mesocorticolimbic pathway [6]. Decreased activity levels in the supplementary motor area, lesions in the basal ganglia and thalamus, and lesions in the lateral prefrontal cortex have also been implicated as underlying mechanisms of apathy [6,7].

There is no single recommended treatment for apathy in Parkinson's disease (PD). Health care providers report pharmacologic interventions can work in *some* persons with apathy and PD, however not all patients are keen to initiate medications due to risk of adverse effects [8]. Pramipexole, a dopamine agonist improves mood and motivation in some persons with PD [9], but has important adverse effects, including impulse control disorders, and may precipitate hallucinations and cognitive impairment in older persons. Rivastigmine, a cholinesterase inhibitor, is reported to decrease apathy and caregiver burden [10]. However, cholinesterase inhibitors, like rivastigmine and galantamine have side effects, and it is unclear if the benefits outweigh the risks [10–12]. Persons with PD and apathy report they prefer non-pharmacologic interventions, but feel these options are not often available to them [8].

Barriers to utilizing non-pharmacologic interventions to treat apathy include a lack of evidence concerning best treatment options and lack of treatment guidelines [8]. Examples of non-pharmacologic interventions for persons with apathy and PD include a Nordic walking program, which was regularly adapted to individual participant needs [13]. The Nordic walking program involves specialized coaches and adapted exercises, developed specifically for PD populations [13]. There is also a mindfulness program designed for use in PD populations, which involves a variety of weekly sessions, activities and a retreat, all guided by specialized coaches [14]. Overall, non-pharmacologic interventions for apathy in PD offer complex multicomponent interventions [15]. Research is needed to explore contextual factors and mechanisms related to non-pharmacologic interventions that target apathy in PD, to increase the evidence base for best treatment options and improve availability for persons with apathy and PD.

Given the limited evidence and complexity of non-pharmacologic interventions for persons with apathy and PD, the objective of this realist review was to understand what components of non-pharmacologic interventions work, for whom, and in what circumstances. We also aimed to produce recommendations to guide clinical practice and future intervention development. Realist reviews are a review method that stress the process of explanation and propose explanatory strategies to inform scientific knowledge [16]. Realist reviews aim to predict intervention outcomes according to the mechanisms and contexts in which interventions work with the goal of informing policy and clinical decision-making [16,17].

2. Methods

2.1. Study design

Our realist review employed the steps described by Pawson and colleagues [18], including: i) articulating rough programme theories to be explored; ii) searching for relevant evidence; iii) appraising the quality of evidence; iv) extracting data; and v) synthesizing the evidence. Rough program theory is the process of understanding assumptions of how interventions work and their impact [18]. Realist review methods depend on the assumption that context (C) and mechanism (M) influence outcome (O). Pawson and colleagues define this assumption the CMO configuration [16]. Researchers can use the CMO configuration to guide the synthesis stage of a realist review. We also used the Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES II) to guide study development and reporting [19] (Appendix 1). Given no human subjects were involved in this realist review, ethical approval was deemed unnecessary.

2.2. Search processes

The initial scoping search, as informed by an earlier scoping review of the literature on apathy in PD [20], was originally searched from inception to January 2019. Any study classified as a non-pharmacologic intervention for persons with apathy in PD informed the development of a rough programme theory. After a rough programme theory was developed, the search was updated from January 29, 2019 to May 20, 2020. The databases searched included MEDLINE, EMBASE, PsychINFO, CINHAL, Cochrane Central Register of Control Trials, and Cochrane Database of Systematic Reviews. The two main search clusters were PD and apathy. Search terms were combined within each cluster using "or", which were then these combined using "and". The search strategy was developed with two experienced research librarians, as per the Peer Review for Electronic Search Strategies [21].

2.3. Selection and appraisal of documents

All study designs were included if they used a non-pharmacologic intervention to treat apathy in PD, either as a primary or secondary outcome, and were published in the English language. Initial treatment studies were identified by a previous scoping review on apathy in PD [20]. Two authors independently screened titles and abstracts for the initial scoping search (B.M., Z.G.) and the updated search (B.M., G.L.). At the abstract stage, any abstract that discussed the treatment of apathy in PD was included. Two authors independently screened full text articles for the initial scoping search (B.M., Z.G.) and the updated search (B.M., G.L.). At the full text stage, any article that discussed

the treatment of apathy in PD with a non-pharmacologic intervention was included.

The quality appraisal of included studies was adapted from Booth and colleagues [22], which takes into consideration whether included studies address the theory being tested and whether included studies support conclusions drawn by the researchers [18] (Appendix 2). Two authors (B.M., G.L.) assessed quality of data.

2.4. Data extraction

Two data extraction forms were used, the first extraction form was focused on extraction of study and patient demographic information. The second extraction form was focused on extraction of contextual information surrounding the intervention, the mechanisms of the intervention, and the outcomes of the intervention. One author conducted data extraction (B.M.) and a second author validated data extraction (G.L.). Initial data extraction influenced development of rough programme theory, and subsequent data extraction substantiated, refined, or refuted the rough programme theory. Data was extracted and coded in Excel.

2.5. Analysis and synthesis process

Extracted data was combined to generate CMO configurations for each included study. We considered two aspects of mechanism, including the resource mechanism and reasoning mechanism [23]. Differentiating between the resource mechanism and reasoning mechanism helped further distinguish between the context in which the intervention is taking place, and the resources and reasoning behind the intervention [23]. CMO configurations were used to generate mid-range theories, which subsequently informed the rough programme theory. Mid-range theories describe the contexts and mechanisms that result in improvements in the outcome of interest. Consultation with all study authors was used to refine rough programme theory, prior to

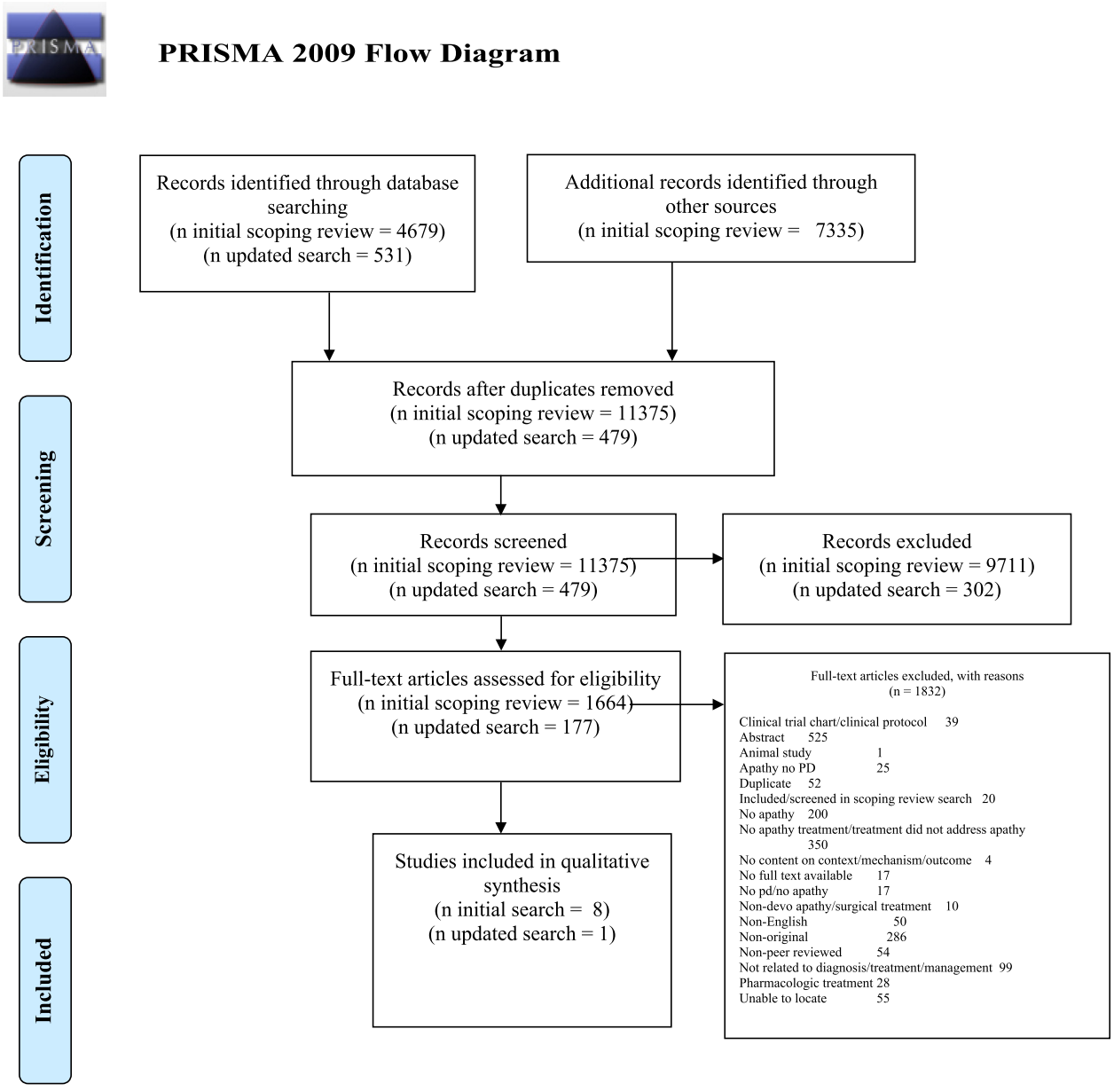

Fig. 1. PRISMA flow diagram.

Table 1
Included study characteristics.

Citation	Type of Intervention	Study Design	Apathy as Primary or Secondary Outcome	Mean Age	Variance Age	N PD	N trtmnt (start)	N control (start)	N trtmnt (end)	N control (end)	Apathy tool	Apathy score trtmnt (start)	Apathy score trtmnt (end)	Hoehn and Yahr Score
Butterfield et al., (2017)	Mindfulness	Before/After	Primary	66	10.7	34	34	27 spouses/family members included	27	23 spouses/family members	Apathy Evaluation Scale and Lille Apathy Rating Scale	42.1 (6.0)	36.1 (8.3)*	.
Cash et al., (2016)	Mindfulness	Before/After	Primary	65.64	7.62	34	34	18 caregivers	29	10 caregivers	Apathy Scale	10.5 (1.1)	9.29 (1.2)**	.
Cugusi et al., (2015)	Exercise	RCT	Partial primary	67.3	7.8	20	10	10	10	10	Apathy Scale	22.8 (14.7)	16.5 (11.9)*	.
Hashimoto et al., (2015)	Exercise	Quasi randomized, between group design	Partial primary	67.9 (dance) 62.7 (exercise) 69.7 (control)	7 (dance), 14.9 (exercise), 4.0 (control)	59	19 (dance)	21 (exercise) 19 (control)	15	17 (exercise) 14 (control)	Apathy Scale	14.7 (5.1)	10.2 (4.7)*	2, 2, 2
King et al., (2015)	Exercise	RCT	Secondary	64.2	7.3	58	17 (home). 21 (indiv), 20 class	.	17 (home). 21 (indiv), 20 class	.	Lille Apathy Rating Scale	Home: 24.1 (5.3) Indiv: 22.1 (5.3) Class: 23.9 (5.3)	Home: 24.5 (3.8)** Indiv: 24.3 (4.8)* Class: 24.4 (7.0)**	2.4
Peppe et al., (2018)	Exercise	Before/After	Partial primary	49 (median)	44–54 (range)	3	3	.	3	.	Apathy Evaluation Scale	35 (median)	29 (median) ***	.
Romenets et al., (2015)	Exercise	RCT	Secondary	64.3 (control) 63.2 (tango)	8.1 (control), 9.9 (tango)	33	18	15	18	15	Apathy Scale	28.9 (7.3)	31.3 (4.5)**	.
Sacheli et al., (2019)	Exercise	RCT	Secondary	66.67 (aerobic) 67.85 (control)	5.98 (aerobic) 8.50 (control)	35	20	15	18	15	Apathy Scale	10.65 (6.50)	12.88 (7.55)**	1 to 3
Sajatovic et al., (2017)	Exercise	RCT	Secondary	70	7.9	30	15	15	12	12	Apathy Scale	16.8 (4.0)	16.9 (4.3)**	< =3

* Statistically significant change in apathy levels.
** No statistically significant change in apathy levels.
*** Significance not reported.

Table 2
Context, mechanism, outcome configurations with mid range theories.

Reference	Mechanism(resource) + Context → Mechanism(reasoning) = Outcome
Butterfield, L. C., Cimino, C. R., Salazar, R., Sanchez-Ramos, J., Bowers, D., & Okun, M. S. (2017). The Parkinson's Active Living (PAL) Program: a behavioral intervention targeting apathy in Parkinson's disease. Journal of geriatric psychiatry and neurology, 30(1), 11–25.	Persons with PD (C^1) and elevated apathy levels (C^2), who participate in the Parkinson's active living program, a form of behavioural activation therapy aimed at goal setting ($M^{resource1}$), with a program coach who is a paraprofessional, trained interventionist ($M^{resource2}$) and with a family member or caregiver (C^3) may experience reduced apathy levels (O^1). The Parkinson's active living program ($M^{resource1}$) may reduce apathy levels (O^1) in persons with PD (C^1) meeting all other contextual descriptions, by focusing on foundational skills of activity planning, scheduling, and monitoring, which is favorable for patients with PD while facilitating self-management skills and patient independence ($M^{reasoning1}$). The Parkinson's active living program ($M^{resource1}$) may reduce apathy levels (O^1) in persons with PD (C^1) meeting all other contextual descriptions, through the following six elements ($M^{reasoning2}$): (1) baseline assessment of the target outcome variable (ie, apathy) and level of activity engagement, (2) weekly evaluation and monitoring of activities, (3) identifying activities, (4) creating an activity hierarchy, (5) charting progress using existing activity logs, and (6) planning rewards for meeting goals. The Parkinson's active living program ($M^{resource1}$) may reduce apathy levels (O^1) in persons with PD (C^1) meeting all other contextual descriptions, by using the term 'program' rather than 'intervention', explaining the term 'apathy' to avoid negative connotation, and emphasizing the difference between initiating an activity and persisting to complete an activity during psychoeducation in the planning session ($M^{reasoning3}$). The Parkinson's active living program ($M^{resource1}$) may reduce apathy levels (O^1) in persons with PD (C^1) meeting all other contextual descriptions, by delivering most of the treatment by telephone ($M^{resource3}$), a manual for use by program coaches ($M^{resource4}$), and a workbook ($M^{resource5}$) for persons with PD (C^1) – given transportation and access is a common barrier to treatment ($M^{reasoning4}$) faced by persons with PD (C^1). Persons with PD (C^1) meeting all other contextual descriptions, who dislike scheduling (C^4) may not complete the Parkinson's active living program (O^2), given not all personalities fit the program ($M^{reasoning5}$). Persons with PD (C^1) meeting all other contextual descriptions, who fear disappointing program coach ($M^{reasoning6}$), have disinterest in the program($M^{reasoning7}$), are not stimulated by goals ($M^{reasoning8}$), or have negative involvement of spouse/caregivers ($M^{reasoning9}$) may not complete the Parkinson's active living program (O^2). *Mid-Range Theory:* *Non-exercise-based interventions do not require physical functionality* *Expert coaching* *Goal setting* *Caregiver support* *Cognitively stimulating activities* *Explaining reasoning behind intervention components and using positive language*
Cash, T. V., Ekouevi, V. S., Kilbourn, C., & Lageman, S. K. (2016). Pilot study of a mindfulness-based group intervention for individuals with Parkinson's disease and their caregivers. Mindfulness, 7(2), 361–371.	Persons with PD (C^1) and no dementia (C^2), who participate in a mindfulness-based stress reduction program ($M^{resource1}$), with their caregiver, if possible (C^3) and a mindfulness trained program administrator ($Mr^{esource2}$) may experience slight but not statistically significant improvements in apathy, if they also have transportation to a clinic ($M^{resource3}$) with space for group gatherings ($M^{resource4}$). Persons with PD (C^1) meeting all other contextual descriptions, may not complete the mindfulness-based stress reduction program ($M^{resource1}$), if they prioritize participation in other medical treatments over attendance at mindfulness-based group sessions, reflecting an emphasis on primary medical providers to treat physical aspects of the disorder, in lieu of addressing equally important emotional and cognitive symptoms ($M^{reasoning1}$). *Mid-Range Theory:* *Non-exercise-based interventions do not require physical functionality* *Expert coaching* *Transportation to activity* *Space for activity in clinic* *Personality to align with activity*
Cugusi, L., Solla, P., Serpe, R., Carzedda, T., Piras, L., Oggianu, M., … & Marrosu, F. (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(2), 245–254.	Persons with PD (C^1), an H&Y score between I and II (C^2), stable medication use (C^3), and no debilitating conditions/vision impairment (C^4) who participate in a Nordic walking program ($M^{resource1}$), with adapted physical activity professionals ($M^{resource2}$) in a metropolitan area (C^5) may experience reduced apathy levels (O^1). Persons with PD (C^1), meeting all other contextual descriptions above, who participate in a Nordic walking program ($M^{resource1}$) with adapted physical activity professionals ($M^{resource2}$) in a metropolitan area (C^5) may experience feelings of improved autonomy and safety during walking (O^2). Nordic walking programs ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions above, if the program is designed to be a full body workout combining the simplicity and accessibility of walking with upper body conditioning ensuring higher energy expenditure compared to classic walking ($M^{reasoning1}$). Persons with PD (C^1) meeting all other contextual descriptions above, who maintain regular PD care ($M^{resource3}$) may not experience reduced apathy levels (O^3), without also experiencing improved autonomy and safety during walking (O^4).

(*continued on next page*)

Table 2 (*continued*)

Reference	Mechanism(resource) + Context → Mechanism(reasoning) = Outcome
Mid-Range Theory: *Physical functionality* *Well maintained drug regimen* *Adapted exercises* *Expert coaching*	
Hashimoto, H., Takabatake, S., Miyaguchi, H., Nakanishi, H., & Naitou, Y. (2015). Effects of dance on motor functions, cognitive functions, and mental symptoms of Parkinson's disease: a quasi-randomized pilot trial. Complementary therapies in medicine, 23(2), 210–219.	Persons with PD (C^1), living at home (C^2), capable of independent walking (C^3), who are able to dance for 1 h (C^4) who participate in a PD adapted dance program ($M^{resource1}$), may experience reduced apathy levels (O^1). Persons with PD (C^1) meeting all other contextual descriptions above, who participate in an at home exercise program ($M^{resource2}$) presented by book or video ($M^{resource3}$), may not experience reduced apathy levels (O^2). A PD adapted dance program ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions above by targeting cognitive function, requiring patients to plan and execute imagined movements, follow music and signals, remember repeated actions, and be aware of their own body ($M^{reasoning1}$). A PD adapted dance program ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions by providing a social activity performed with others; as the movements change the patients might be dancing alone, in pairs, or in small groups, and the resulting interactions strengthen the feeling of unity among patients. Dance provides enjoyment through mutual understanding and shared emotion between other dancers with the same health problems, and also improves mood, relieves anxiety, and increases motivation. ($M^{reasoning2}$). A PD adapted dance program ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions by working on emotions, encouraging the dancers to express their feelings, increasing motivation, and providing enjoyment through greater ease of movement ($M^{reasoning3}$). A PD adapted dance program ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions, through its use of music, dance induces pleasurable feelings ($M^{reasoning4}$).
Mid-Range Theory: *Physical functionality* *Cognitively stimulating activities* *Individual/self-driven activities less effective* *Socialization important element of activities* *Music induces positive feelings/emotions* *Activities targeting emotions*	
King, L. A., Wilhelm, J., Chen, Y., Blehm, R., Nutt, J., Chen, Z., … & Horak, F. B. (2015). Does group, individual or home exercise best improve mobility for people with Parkinson's disease?. Journal of neurologic physical therapy: JNPT, 39(4), 204.	Persons with PD (C^1), who can walk on their own (C^2), require no activites of daily living assistance (C^3), exercise less that ten hours per week (C^4), and have no cognitive impairment (C^5), who participate in an individual workout program ($M^{resource1}$) with a physiotherapist ($M^{resource2}$) may experience reduced apathy levels (O^1). Individual workout programs ($M^{resource1}$) may reduce apathy (O^1) in persons with PD (C^1) meeting all other contextual descriptions above if the workout program is designed to target postural, biochemical constraints, stability, and gait coordination ($M^{reasoning1}$), through activities such as tai chi, boxing, lunges, kayaking, agility course, Pilates ($M^{resource3}$). Persons with PD (C^1), meeting all other contextual descriptions above who participate in an individual workout program ($M^{resource1}$) with a physiotherapist ($M^{resource2}$) may experience reduced apathy levels (O^1), if they also have transportation to the clinic ($M^{resource6}$). Persons with PD (C^1), meeting all other contextual descriptions above who participate in a group exercise program ($M^{resource4}$) with a physiotherapist ($M^{resource2}$) may not experience reduced apathy levels (O^2). Persons with PD (C^1), meeting all other contextual descriptions above who participate in an unsupervised at home workout program ($M^{resource5}$) may not experience reduced apathy levels (O^2).
Mid-Range Theory: *Physical functionality* *Minimal cognitive impairment* *Adapted exercises* *Individual/self-driven activities less effective* *Variety of activities/exercises* *Expert coaching* *Transportation to activity*	
Peppe, A., Costa, A., Cerino, S., Caltagirone, C., Alleva, E., Borgi, M., & Cirulli, F. (2018). Targeting gait and life quality in persons with Parkinson's disease: Potential benefits of Equine-Assisted Interventions. Parkinsonism & related disorders, 47, 94–95.	Persons with rigid-akinetic idiopathic PD (C^1) that were not hospitalized (C^2), had an H&Y score of 2 (C^3), and no previous experience with horses (C^4), who participate in equine assisted interventions consisting of education on horse management, horseback riding, exercises on a horse, and an on ground session ($M^{resource1}$) in a non-medicalized environment (C5) may experience reduced apathy levels. Equine assisted interventions ($M^{resource1}$) in a non-medicalized environment (C^5) reduce apathy levels in persons with PD (C^1) meeting all other contextual descriptions above by providing the affective and emotional input resulting from human-animal interaction ($M^{reasoning1}$).

Table 2 (*continued*)

Reference	Mechanism(resource) + Context → Mechanism(reasoning) = Outcome
Mid-Range Theory: *Physical functionality* *Specialized equipment* *Non-medicalized environment* *Activities targeting emotion*	
Romenets, S. R., Anang, J., Fereshtehnejad, S. M., Pelletier, A., & Postuma, R. (2015). Tango for treatment of motor and non-motor manifestations in Parkinson's disease: a randomized control study. Complementary Therapies in Medicine, 23(2), 175–184.	No significant improvements in apathy (O^1) were observed in persons with PD (C^1), with an H&Y score of I-III (C^2), that could stand for 30 mins/walk without assistive devices for > = 3 m(C^3), with no more than three falls in the last 12 months(C^4), with no dementia(C^5), no hearing or vision complications (C^6), and no changes in dopaminergic therapy in the last three months (C^7) who participated in a partnered tango class ($M^{resource1}$) with a professional tango instructor ($M^{resource2}$). Persons with PD (C^1), meeting all other contextual descriptions above may report greater satisfaction (O^2) from a partnered tango class ($M^{resource1}$) with a professional tango instructor ($M^{resource2}$) versus normal pharmacological treatment plus an exercise pamphlet from PD Canada ($M^{resource3}$).
Mid-Range Theory: *Physical functionality* *Minimal cognitive impairment* *Well maintained drug regimen* *Satisfaction with group activities*	
Sacheli, M. A., Neva, J. L., Lakhani, B., Murray, D. K., Vafai, N., Shahinfard, E., … & McKenzie, J. (2019). Exercise increases caudate dopamine release and ventral striatal activation in Parkinson's disease. Movement Disorders, 34(12), 1891–1900.	No significant improvements in apathy (O^1) were observed in persons with PD (C^1) without significant cognitive impairment (C^2), depression (C^3), cardiovascular or respiratory disease (C^4), significant osteoporosis/arthritis (C^5), or contraindications to MRI (C^6) who participate in aerobic exercise in the form of cycling ($M^{resource1}$). No significant improvements in apathy (O^2) were observed in persons with PD (C^1) meeting all other contextual descriptions above who participate in a PD adapted stretching program ($M^{resource2}$). Aerobic exercise in the form of cycling ($M^{resource1}$) may enhance dopaminergic function and reward-related responsivity in nigrostriatal projections and mesolimbic projections ($M^{resoning1}$), which may improve apathy (O^2).
Mid-Range Theory: *Physical functionality* *Specialized equipment* *Activities targeting dopamine*	
Sajatovic, M., Ridgel, A. L., Walter, E. M., Tatsuoka, C. M., Colón-Zimmermann, K., Ramsey, R. K., … & Walter, B. L. (2017). A randomized trial of individual versus group-format exercise and self-management in individuals with Parkinson's disease and comorbid depression. Patient preference and adherence, 11, 965.	No significant improvements in apathy (O^1) were observed in persons with PD (C^1), with an H&Y score of I-III (C^2), who could walk independently(C^3), had been on stable PD medication for > = 2 weeks and had been on antidepressant medication (if applicable) for > = 4 weeks (C^4), with a diagnosis of depression (C^5), an MMSE score of >24 (C^6), without cardiovascular disease (C^7), a low fall risk (C^8), and no other uncontrolled diseases (C^9) who took part in peer support and guided group exercise meetings ($M^{resource1}$) with a nurse educator ($M^{resource2}$), peer-educator that also had PD and depression ($M^{resource3}$), and personal trainer ($M^{resource4}$). Persons with PD (C^1), meeting all other contextual descriptions above may report social elements of groups activities are an important factor to an intervention (O^2) compared to an individualized self-paced exercise programs ($M^{resource5}$), with both programs taking place at a gym ($M^{resource6}$), with a personal trainer ($M^{resource4}$).
Mid-Range Theory: *Physical functionality* *Well maintained drug regimen* *Satisfaction with group activities* *Individual/self-driven activities less effective* *Socialization important element of activities*	

conducting the second round of searching. Data from the second round of included studies were used to substantiate, refine, or refute the rough programme theory. A final round of consultation with all study authors took place prior to final presentation of refined programme theory. Refined programme theory describes the relationship between mid-range theories and how these relationships produced understandings of what improves the outcome of interest, under what circumstances, and why.

3. Results

3.1. Document flow

The initial scoping review search yielded 1664 studies and the updated search conducted May 20, 2020, yielded an additional 479 studies [20]. In total, nine studies were included in our final synthesis. No included studies were considered to have poor enough quality to exclude (Fig. 1).

3.2. Document characteristics

The study designs of the nine included studies included five randomized control trials (RCTs) [13,24–27], one quasi-randomized between group design [28], and three before and after (pre-post) studies [14,29,30]. Three apathy screening tools, including the Apathy Evaluation Scale (AES), Apathy Scale (AS), and Lille Apathy Rating Scale were used to screen apathy across the nine included studies (Table 1) [31–33].

We categorized studies into two types of interventions, either exercise or mindfulness. We considered any study where the primary intervention involved physical movement as an exercise intervention. We considered any study where the primary intervention involved participants consciously bringing awareness to themselves or the moment as a mindfulness intervention [34].There were seven exercise interventions included (Table 1). Overall, exercise interventions evaluated group exercise compared to individual exercise [24,26], as well as aerobic exercise [27], dance [25,28], Nordic walking [13], and an equine

program [29]. Three of the exercise interventions assessed apathy as one of many primary outcomes, and were coded as partial primary outcomes (Table 1) [13,28,29], while four exercise interventions assessed apathy as a secondary outcome [24–27]. Four of the seven exercise interventions reported significant improvements in apathy [13,24,28,29]. Descriptions of the improvements are listed in Table 1. One exercise intervention was not powered to detect changes in apathy levels [25], while two exercise interventions yielded no significant improvement in apathy [26,27]. There were two mindfulness interventions [14,30]. Both of the mindfulness interventions assessed apathy as the only primary outcome [14,30]. Butterfield and colleagues reported a significant decrease in apathy levels, while Cash and colleagues reported a non-significant improvement in apathy levels (Table 1) [14,30].

3.3. Exercise – Context, mechanism, outcome configurations

From the seven included exercise interventions, we generated 21 CMO configurations focused on explaining what exercise interventions, worked for whom, under what circumstances, and why (Table 2). When group exercise with a physiotherapist was compared to individual exercise with a physiotherapist or to individual exercise alone at home, apathy was most markedly improved in PD populations, minimal physical and cognitive impairment, who participated in the individual exercise intervention with a physiotherapist [24]. Further mechanisms that facilitated improvements in apathy, as a part of an individual exercise intervention, included transportation to the workout and a workout program that targeted posture, stability, and gait [24]. Self-efficacy, which acts as a major determinant to continuing an exercise programs, was most significantly improved in the individual exercise groups as well, possibly suggesting a relationship between improvements in self-efficacy and improvements in apathy [24]. In contrast, another comparison of individual exercise programs to group exercise programs in persons with PD and minimal physical or cognitive impairment found no improvements in apathy in either group [26]. However, all participants in the group exercise program reported a preferred aspect of treatment was the social element of group exercise compared to an individual self-paced program [26].

When aerobic exercise with a stationary bike was compared to a PD adapted stretching group, in persons with PD and minimal physical or cognitive impairment, there was no improvement in apathy [27]. However imaging of the brains of persons in the aerobic exercise group found increased dopamine realise in nigrostriatal projections and mesolimbic projections, which may in turn facilitate improvements in apathy [27]. Thus, while no significant improvements in apathy were observed, a possible mechanism to explain how aerobic exercise can improve apathy was identified.

Dance interventions involved two types of dance, a PD adapted dance program and a tango program. The PD adapted dance program was compared to an at home PD exercise program, and usual care [28]. Significant improvements in apathy were observed in persons with PD, with minimal physical and cognitive impairment, who participated in the PD adapted dance program [28]. Hashimoto and colleagues were the only included study that reported on the effect size of the intervention (Cohen's effect size = 0.78), indicating a medium to large effect size in the dance group [28]. Mechanisms associated with improvements in apathy through a PD adapted dance program include taking part in a social activity, working on emotions to express feelings through dance, greater ease of movement through dance, and music inducing pleasurable feelings (Table 2). The tango program was compared with a self-directed at home exercise program [25]. No improvements in apathy were observed in either group, which may in part be explained by the fact the study was not powered to recognize changes in apathy. However, persons with PD reported greater satisfaction from a partnered tango class with a professional tango instructor, compared to persons who participated in the self-directed at home exercise program [25].

A Nordic walking program was compared to usual PD care, and reported significant improvements in apathy for persons with PD and minimal physical or cognitive impairment [13]. Nordic walking involves walking with specially designed poles and engages the trunk and upper limbs during walking. The Nordic walking program took place in a metropolitan area, with adapted physical activity professionals. Mechanisms associated with improvements in apathy due to the Nordic walking program include the use of full body exercises, which improved feelings of autonomy and safety during walking [13].

An equine assisted intervention, which involved learning about horse management, horseback riding, and horse grooming resulted in decreased apathy levels [29]. All participants had PD and minimal physical and cognitive impairment. A key mechanism that may have led to the improvements of apathy was the non-medicalized environment [29]. The affective and emotional relationship that comes from human and animal interactions may have also attributed to decreased apathy levels.

3.4. Mindfulness – Context, mechanism, outcome configurations

From the two included mindfulness studies, we generated nine CMO configurations focused on explaining what mindfulness interventions, worked for whom, under what circumstances, and why (Table 2). The Parkinson's active living (PAL) program reduced apathy in persons with PD [30]. The PAL program focuses on behavioural activation therapy. The PAL program uses program coaches that are paraprofessional and trained as interventionists, and encourages the involvement of caregivers [30]. The program focuses on providing foundational skills in activity planning, scheduling, and monitoring to encourage self-management and independence. Further mechanisms that may lead to the improvements in apathy include providing treatment by telephone, to prevent transportation barriers. Semantics may also play an important role in the success of the PAL program, as the use of the term *program* instead of *intervention* has a more positive connotation [30]. Personality may also play a role in the success of mindfulness interventions at improving apathy, given some persons may dislike scheduling or persons may be too concerned with disappointing program coaches to focus on the intervention [30]. The other included mindfulness study found a mindfulness-based stress reduction program yielded non-statistically significant improvements in apathy among persons with PD and no cognitive impairment [14]. Mindfulness interventions may not be completed by persons that prioritize physical components of PD over emotional and cognitive symptoms [14].

3.5. Mid-range theory

We generated mid-range theories by looking at patterns and themes that arose across the 30 CMO configurations (Table 2). Mid-range theories describe the contexts and mechanisms that result in improvements in apathy, specifically in relation to the different non-pharmacologic interventions included in our review. Where improvements in apathy were not reported, we considered CMO components that may have contributed to overall satisfaction or dissatisfaction with interventions, or that may have contributed to limiting success of the intervention. One contextual factor that contributed to improvements in apathy included functionality; exercise interventions involved persons with PD with minimal physical impairment, a Hoehn and Yahr score between I and III (balance impairment, mild to moderate disease, physically independent), no cardiovascular disease, and well-managed dopaminergic treatment regiments (Fig. 2). Another contextual factor that contributed to improvements in apathy through exercise and mindfulness interventions was minimal cognitive impairment (Fig. 2). Sixteen mechanisms contributed to the improvements of

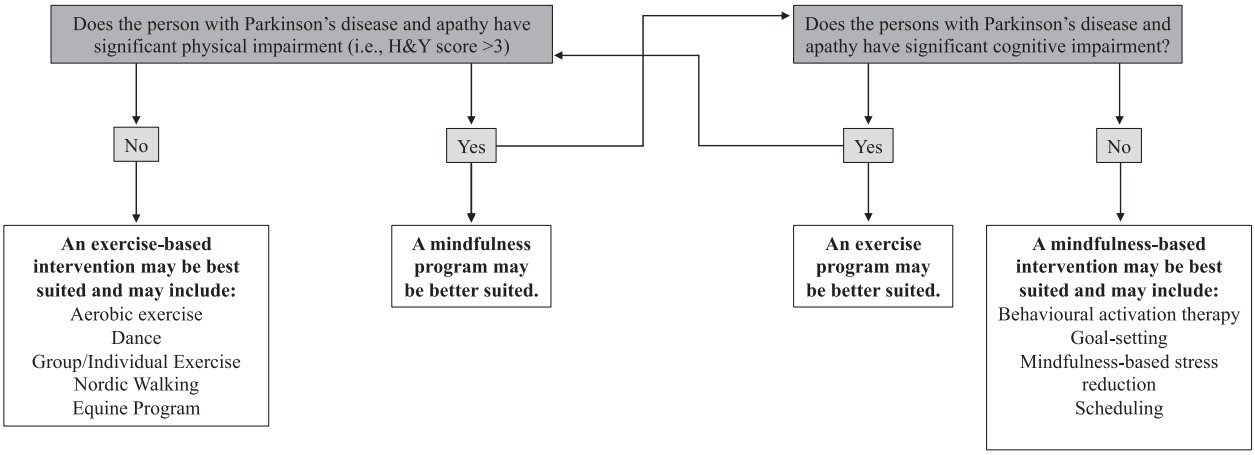

Fig. 2. Choosing a non-pharmacologic intervention to treat apathy in PD populations.

apathy (Table 2). Resource mechanisms that improved apathy were transportation to interventions and caregiver support. Reasoning mechanisms include application of physically and mentally adapted exercises, programs and coaches to help improve apathy in persons with PD. The use of non-medicalized settings and music were also key mechanisms.

3.6. Refined program theory

Our refined program theory considered the relationship between mid-range theories and how these relationships produced understandings of what non-pharmacologic interventions improve apathy in persons with PD, under what circumstances, and why. We generated five program theories: (i) persons with overall physical and cognitive functionality are best suited to take part in exercise interventions and persons with minimal cognitive impairment are best suited to take part in mindfulness interventions; (ii) transportation and caregiver support participation in non-home based non-pharmacologic interventions; (iii) mindfulness interventions for persons with PD and apathy should target emotions, cognitive stimulation, and goal setting; (iv) group activities and socialization are seen as fundamental components of exercise interventions; and (v) exercise interventions for persons with PD and apathy should consider use of expert coaching, physically adapted programs, equipment and non-medicalized facilities where possible.

4. Discussion

Our review identified nine studies that used non-pharmacologic interventions to treat apathy in PD as either a primary or secondary outcome. Two types of non-pharmacologic intervention were identified: exercise and mindfulness. Overall, successful non-pharmacologic interventions for apathy in PD involve a variety of contextual factors, resource mechanisms, and reasoning mechanisms. Understandings of what interventions, work for whom, under what circumstances, and why will help clinicians better understand non-pharmacologic treatments available for persons with PD and apathy.

Exercise interventions depend on physical function, which limits their application across PD populations. No persons with a Hoehn and Yahr (H&Y) score above 3 (balance impairment, mild to moderate disease, physically independent) were included in any of the exercise interventions. A recent systematic review of exercise interventions for persons with PD, similar to the exercise interventions included in this review, reported an average H&Y score of 2.2 (95% CI = 0.22) across 15 randomized control trails and no study with a mean population H&Y score above 2.5 [35]. Another study identifying unmet needs of persons with PD and cognitive impairment, reported there are few exercise interventions for persons with PD dementia [36]. Future research should focus on the development of exercise interventions for persons with physical and cognitive impairment, which may also provide insights into the appropriate intensity of exercise required to generated improvements in apathy.

Mindfulness interventions depend on cognitive function, which limits their application across PD populations. There are few studies that assess cognitive interventions, such as mindfulness, in persons with advanced cognitive impairment [36]. Future research should explore cognitive interventions to manage apathy among person with cognitive impairment.

Caregiver involvement and support can be a key determinant of the success of non-pharmacologic interventions. Persons with more severe physical or cognitive impairment who are unable to drive may be even more reliant on caregivers and/or public transportation [37]. Accessibility to non-home based non-pharmacologic interventions may be determined by geographical location, in that larger city centers may have more access to programs and public transportation versus rural locations [13,38]. Future research should consider focusing on non-pharmacologic apathy interventions that involve and support caregivers. More studies are also needed to investigate effectiveness of remote, home-based, non-pharmacologic interventions.

Diagnostic criteria for apathy describe three apathy dimensions, including diminished cognitive activity and goal-directed behaviour, diminished emotion, and diminished engagement in social interactions [39]. Our program theory demonstrates mindfulness programs that target emotions, cognition, and goal setting may improve apathy. Our program theory also demonstrates exercise programs with a socialization and/or group component may improve apathy. Clinicians should consider non-pharmacologic interventions that target apathy dimensions, as this is a key mechanism in improving apathy in persons with PD. Future research should investigate whether a combination of mindfulness and exercise would improve apathy with a stronger effect than either intervention on its own.

If a clinician is considering an exercise intervention, they should consider programs that include expert coaching, adapted programs for persons with PD, access to equipment, and non-medicalized facilities to practice exercise. While this program theory highlights some of the key mechanisms that help facilitate exercise interventions that decrease levels of apathy in persons with PD, accessibility to these programs and resources may be a significant barrier to participation [8].

The three studies that did not report improvements in apathy, still reported benefits. Tango dancing did not improve apathy in persons with PD [25]. However, persons in the tango dancing group had greater treatment satisfaction than those in the control group [25].

Greater satisfaction in the tango group may have been related to social interaction, which targets the diminished engagement in social interactions domain of apathy [39]. No improvements in apathy were reported in persons with PD that took part in peer-supported group exercise. However, persons in the peer-supported group exercise reported the social element of the intervention was important, also targeting the diminished engagement in social interactions domain of apathy [26,39]. Aerobic exercise in the form of stationary cycling yielded no improvements in apathy, although there were increased levels of dopaminergic function and reward-related responsivity in nigrostriatal and mesolimbic projections, a biological mechanisms that could yield improvements in apathy [27]. Future research may therefore investigate if increased intensities or duration of aerobic exercise yield higher levels of dopaminergic function, resulting in improvements in apathy. Researchers may also consider more consistently reporting effect sizes of non-pharmacologic interventions, as only one included study presented details on effect size [28].

5. Strengths and limitations

Strengths of our realist review include the systematic search strategy we used to ensure identification of relevant literature on the non-pharmacologic treatment of apathy in PD. However we did not conduct an extensive assessment of study quality or risk of bias. All study authors reviewed CMO configurations throughout the research process, making sure a variety of perspectives from different specialities were considered. While we did not directly involve patient stakeholders in this review, preceding research involving PD populations with apathy and their caregivers identified that non-pharmacologic treatments are a priority area [8]. Limitations of included studies include the possibility that there was selection bias, in that those with severe apathy, physically, or cognitive impairment may not have been included in studies. Another limitation to consider is the subjective interpretation of our refined program theory and its dependence upon the nine studies identified. Future research is required to validate our findings. Researchers may also wish to directly test our refined program theory.

6. Conclusion

Our realist review provides a theory driven account of available non-pharmacologic interventions to treat apathy in persons with PD. Across nine included studies, exercise and mindfulness intervention were identified. Exercise interventions work best for persons with PD and apathy who are not significantly physically or cognitively impaired, and who have access to transportation, adapted programs, and specialized coaches. Exercise may improve apathy through goal-directed behaviour cxhange and engagement in social interactions. Mindfulness interventions work best for persons with PD and apathy who are not significantly cognitively impaired, have caregiver support, and may improve apathy by targeting the emotional, cognitive, and goal-directed domains that define apathy.

Acknowledgement

This study did not receive any direct funding. Dr. Mele is funded through the UCalgary Brenda Strafford Foundation Chair in Geriatric Medicine and Alberta Innovates Graduate Scholarship. Dr. Holroyd-Leduc is the holder of the UCalgary Brenda Strafford Foundation Chair in Geriatric Medicine.

References

[1] M.G.H.E. den Brok, J.W. van Dalen, W.A. van Gool, E.P. Moll van Charante, R.M.A. de Bie, E. Richard, Apathy in Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 30 (2015) 759–769, https://doi.org/10.1002/mds.26208.

[2] R.S. Marin, Apathy: a neuropsychiatric syndrome, J. Neuropsychiatry Clin. Neurosci. 3 (1991) 243–254, https://doi.org/10.1176/jnp.3.3.243.

[3] J. Benito-León, E. Cubo, C. Coronell, on behalf of the ANIMO Study Group, Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: The ANIMO study, Mov. Disord. 27 (2) (2012) 211–218, https://doi.org/10.1002/mds.23872.

[4] I. Leiknes, O.-B. Tysnes, D. Aarsland, J.P. Larsen, Caregiver distress associated with neuropsychiatric problems in patients with early Parkinson's disease: the Norwegian ParkWest study, Acta Neurol. Scand. 122 (2010) 418–424, https://doi.org/10.1111/j.1600-0404.2010.01332.x.

[5] I. Leroi, V. Harbishettar, M. Andrews, K. McDonald, E.J. Byrne, A. Burns, Carer burden in apathy and impulse control disorders in Parkinson's disease, Int. J. Geriatr. Psychiatry 27 (2) (2012) 160–166, https://doi.org/10.1002/gps.2704.

[6] J. Pagonabarraga, J. Kulisevsky, A.P. Strafella, P. Krack, Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment, Lancet Neurol. 14 (2015) 518–531, https://doi.org/10.1016/S1474-4422(15)00019-8.

[7] A. Castrioto, S. Thobois, S. Carnicella, A. Maillet, P. Krack, Emotional manifestations of PD: neurobiological basis, Mov. Disord. 31 (8) (2016) 1103–1113, https://doi.org/10.1002/mds.v31.810.1002/mds.26587.

[8] B. Mele, Z. Goodarzi, H.M. Hanson, J. Holroyd-Leduc, Barriers and facilitators to diagnosing and managing apathy in Parkinson's disease: a qualitative study, BMC Neurol. 19 (2019) 101, https://doi.org/10.1186/s12883-019-1329-z.

[9] A.F.G. Leentjens, J. Koester, B. Fruh, D.T.S. Shephard, P. Barone, J.J.G. Houben, The effect of pramipexole on mood and motivational symptoms in parkinson's disease: a meta-analysis of placebo-controlled studies, Clin. Ther. 31 (2009) 89–98, https://doi.org/10.1016/j.clinthera.2009.01.012.

[10] D. Devos, C. Moreau, D. Maltete, R. Lefaucheur, A. Kreisler, A. Eusebio, G. Defer, T. Ouk, J.-P. Azulay, P. Krystkowiak, T. Witjas, M. Delliaux, A. Destee, A. Duhamel, R. Bordet, L. Defebvre, K. Dujardin, Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial, J. Neurol. Neurosurg. Psychiatry 85 (6) (2014) 668–674, https://doi.org/10.1136/jnnp-2013-306439.

[11] R. Moretti, P. Caruso, M. Dal Ben, Rivastigmine as a symptomatic treatment for apathy in Parkinson's dementia complex: new aspects for this riddle, Parkinson's Disease. (2017), https://doi.org/10.1155/2017/6219851.

[12] I.V. Litvinenko, M.M. Odinak, V.I. Mogil'naya, A.Y. Emelin, Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial), Neurosci. Behav. Physiol. 38 (9) (2008) 937–945, https://doi.org/10.1007/s11055-008-9077-3.

[13] L. Cugusi, P. Solla, R. Serpe, T. Carzedda, L. Piras, M. Oggianu, S. Gabba, A. Di Blasio, M. Bergamin, A. Cannas, F. Marrosu, G. Mercuro, 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 (2) (2015) 245–254, https://doi.org/10.3233/NRE-151257.

[14] T.V. Cash, V.S. Ekouevi, C. Kilbourn, S.K. Lageman, Pilot study of a mindfulness-based group intervention for individuals with Parkinson's disease and their caregivers, Mindfulness 7 (2) (2016) 361–371, https://doi.org/10.1007/s12671-015-0452-1.

[15] P. Craig, P. Dieppe, S. Macintyre, S. Michie, I. Nazareth, M. Petticrew, Developing and evaluating complex interventions: the new Medical Research Council guidance, BMJ 337 (2008), https://doi.org/10.1136/bmj.a1655 a1655.

[16] R. Pawson, N. Tilley, Realistic Evaluation, 1 edition, Sage Publications, London ; Thoxusand Oaks, Calif, 1997.

[17] M. Kastner, J. Antony, C. Soobiah, S.E. Straus, A.C. Tricco, Conceptual recommendations for selecting the most appropriate knowledge synthesis method to answer research questions related to complex evidence, J. Clin. Epidemiol. 73 (2016) 43–49, https://doi.org/10.1016/j.jclinepi.2015.11.022.

[18] R. Pawson, T. Greenhalgh, G. Harvey, K. Walshe, Realist review – a new method of systematic review designed for complex policy interventions, J. Health Services Res. Policy 10 (1_suppl) (2005) 21–34, https://doi.org/10.1258/1355819054308530.

[19] G. Wong, G. Westhorp, A. Manzano, J. Greenhalgh, J. Jagosh, T. Greenhalgh, RAMESES II reporting standards for realist evaluations, BMC Med. 14 (2016) 96, https://doi.org/10.1186/s12916-016-0643-1.

[20] B. Mele, S. Van, J. Holroyd-Leduc, Z. Ismail, T. Pringsheim, Z. Goodarzi, Diagnosis, treatment and management of apathy in Parkinson's disease: a scoping review, BMJ Open 10 (9) (2020) e037632, https://doi.org/10.1136/bmjopen-2020-037632.

[21] J. McGowan, M. Sampson, D.M. Salzwedel, E. Cogo, V. Foerster, C. Lefebvre, PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement, J Clin Epidemiol. 75 (2016) 40–46. 10.1016/j.jclinepi.2016.01.021.

[22] V. Booth, R. Harwood, J.E. Hancox, V. Hood-Moore, T. Masud, P. Logan, Motivation as a mechanism underpinning exercise-based falls prevention programmes for older adults with cognitive impairment: a realist review, BMJ Open. 9 (2019) e024982. 10.1136/bmjopen-2018-024982.

[23] S.M. Dalkin, J. Greenhalgh, D. Jones, B. Cunningham, M. Lhussier, What's in a mechanism? Development of a key concept in realist evaluation, Implementation Sci. 10 (2015) 49, https://doi.org/10.1186/s13012-015-0237-x.

[24] L.A. King, J. Wilhelm, Y. Chen, R. Blehm, J. Nutt, Z. Chen, A. Serdar, F.B. Horak, Effects of group, individual, and home exercise in persons with Parkinson disease: a randomized clinical trial, J. Neurol. Phys. Ther. 39 (2015) 204–212, https://doi.org/10.1097/NPT.0000000000000101.

[25] Silvia Rios Romenets, Julius Anang, Seyed-Mohammad Fereshtehnejad, Amelie Pelletier, Ronald Postuma, Tango for treatment of motor and non-motor manifestations in Parkinson's disease: a randomized control study, Complement. Ther. Med. 23 (2) (2015) 175–184, https://doi.org/10.1016/j.ctim.2015.01.015.

[26] M. Sajatovic, A.L. Ridgel, E.M. Walter, C.M. Tatsuoka, K. Colón-Zimmermann, R.K. Ramsey, E. Welter, S.A. Gunzler, C.M. Whitney, B.L. Walter, A randomized trial of individual vexrsus group-format exercise and self-management in individuals with Parkinson's disease and comorbid depression, Patient Prefer. Adherence 11 (2017) 965–973, https://doi.org/10.2147/PPA.S135551.

[27] Matthew A. Sacheli, Jason L. Neva, Bimal Lakhani, Danielle K. Murray, Nasim Vafai, Elham Shahinfard, Carolyn English, Siobhan McCormick, Katie Dinelle, Nicole Neilson, Jessamyn McKenzie, Michael Schulzer, Don C. McKenzie, Silke Appel-Cresswell, Martin J. McKeown, Lara A. Boyd, Vesna Sossi, A. Jon Stoessl, Exercise increases caudate dopamine release and ventral striatal activation in Parkinson's disease, Movement Disorders 34 (12) (2019) 1891–1900, https://doi.org/10.1002/mds.v34.1210.1002/mds.27865.

[28] Hiroko Hashimoto, Shinichi Takabatake, Hideki Miyaguchi, Hajime Nakanishi, Yasuo Naitou, Effects of dance on motor functions, cognitive functions, and mental symptoms of Parkinson's disease: a quasi-randomized pilot trial, Complement. Ther. Med. 23 (2) (2015) 210–219, https://doi.org/10.1016/j.ctim.2015.01.010.

[29] A. Peppe, A. Costa, S. Cerino, C. Caltagirone, E. Alleva, M. Borgi, F. Cirulli, Targeting gait and life quality in persons with Parkinson's disease: Potential benefits of Equine-Assisted Interventions, Parkinsonism Relat. Disord. 47 (2018) 94–95, https://doi.org/10.1016/j.parkreldis.2017.12.003.

[30] London C. Butterfield, Cynthia R. Cimino, Robert Salazar, Juan Sanchez-Ramos, Dawn Bowers, Michael S. Okun, The Parkinson's Active Living (PAL) Program, J. Geriatr. Psychiatry Neurol. 30 (1) (2017) 11–25, https://doi.org/10.1177/0891988716673467.

[31] Robert S. Marin, Ruth C. Biedrzycki, Sekip Firinciogullari, Reliability and validity of the apathy evaluation scale, Psychiatry Res. 38 (2) (1991) 143–162, https://doi.org/10.1016/0165-1781(91)90040-V.

[32] S.E. Starkstein, H.S. Mayberg, T.J. Preziosi, P. Andrezejewski, R. Leiguarda, R.G. Robinson, Reliability, validity, and clinical correlates of apathy in Parkinson's disease, J. Neuropsychiatry Clin. Neurosci. 4 (1992) 134–139, https://doi.org/10.1176/jnp.4.2.134.

[33] P. Sockeel, K. Dujardin, D. Devos, C. Denève, A. Destée, L. Defebvre, The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 77 (2006) 579–584, https://doi.org/10.1136/jnnp.2005.075929.

[34] Shauna L. Shapiro, Linda E. Carlson, John A. Astin, Benedict Freedman, Mechanisms of mindfulness, J. Clin. Psychol. 62 (3) (2006) 373–386, https://doi.org/10.1002/(ISSN)1097-467910.1002/jclp.v62:310.1002/jclp.20237.

[35] Anders Uhrbrand, Egon Stenager, Martin Sloth Pedersen, Ulrik Dalgas, Parkinson's disease and intensive exercise therapy – a systematic review and meta-analysis of randomized controlled trials, J. Neurol. Sci. 353 (1-2) (2015) 9–19, https://doi.org/10.1016/j.jns.2015.04.004.

[36] J.G. Goldman, B.A. Vernaleo, R. Camicioli, N. Dahodwala, R.D. Dobkin, T. Ellis, J. E. Gxalvin, C. Marras, J. Edwards, J. Fields, R. Golden, J. Karlawish, B. Levin, L. Shulman, G. Smith, C. Tangney, C.A. Thomas, A.I. Tröster, E.Y. Uc, N. Coyan, C. Ellman, M. Ellman, C. Hoffman, S. Hoffman, D. Simmonds, Cognitive impairment in Parkinson's disease: a report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health, NPJ Parkinsons Dis. 4 (2018), https://doi.org/10.1038/s41531-018-0055-3.

[37] R. Singh, B. Pentland, J. Hunter, F. Provan, Parkinson's disease and driving ability, J. Neurol. Neurosurg. Psychiatry 78 (2007) 363–366, https://doi.org/10.1136/jnnp.2006.103440.

[38] S.-E. Soh, J.L. McGinley, J.J. Watts, R. Iansek, M.E. Morris, Rural living and health-related quality of life in Australians with Parkinson's disease, Rural Remote Health 12 (2012) 1–9 (accessed July 8, 2020) http://dro.deakin.edu.au/view/DU:30054599.

[39] P. Robert, K.L. Lanctôt, L. Agüera-Ortiz, P. Aalten, F. Bremond, M. Defrancesco, C. Hanon, R. David, B. Dubois, K. Dujardin, M. Husain, A. König, R. Levy, V. Mantua, D. Meulien, D. Miller, H.J. Moebius, J. Rasmussen, G. Robert, M. Ruthirakuhan, F. Stella, J. Yesavage, R. Zeghari, V. Manera, Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group, European Psychiatry. 54 (2018) 71–76. x10.1016/j.eurpsy.2018.07.008.