Pharmacological treatment of apathy in Parkinson's disease, review of the literature

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Abstract

Background

Apathy is a highly challenging factor in the general treatment of patients with Parkinson's disease (PD) and can present a major burden for caregivers. The objective of this study to answer the question of what is known about the current evidence-based pharmacological treatment of apathy, not combined with comorbid depression or dementia, in PD.

Methods

We searched for publications in online databases (PubMed, Embase.com, Cochrane Database of Systematic Reviews, CENTRAL and PsycInfo/Ebsco) and performed a review of the literature. Included trials were based on patients with PD, with a drug intervention and apathy as an outcome measurement. Patients with comorbid dementia, severe depression, or patients after deep brain stimulation were excluded.

Results

Out of 1767 articles, we included 10 articles with a total of 723 patients who received intervention and 311 patients who received placebo, standard care or were healthy controls. Combining the results of the studies with a focus on favourable significant outcomes and the risk of bias, we would advise rivastigmine as a treatment of apathy in patients with PD, and pramipexole or selegiline in PD patients with apathy without cognitive disturbance. An important limitation of this study is that the included studies show a broad heterogeneity.

Conclusions

Research is sparse on the topic of evidence-based pharmacological treatment for apathy in PD. Combining the results of the studies with a focus on favourable significant outcomes and the risk of bias, we would advise rivastigmine as a treatment of apathy in patients with PD, and pramipexole or selegiline in PD patients with apathy without cognitive disturbance.

Background

Apathy is defined in 1991 by Marin as a syndrome of primary motivational loss, that is loss of motivation not attributable to emotional distress, intellectual impairment or diminished level of consciousness(1). It is an important nonmotor neuropsychiatric feature of PD and has been described in the context of lack of motivation and diminished responsiveness to stimuli or reward-dependence. Apathy has been associated with depression, executive dysfunction and auto-activation failure (2), but it can also exist as an exclusive entity. Apathy is highly prevalent in PD and offers great challenge to clinicians as it contributes unfavorably to daily functioning, well-being and quality of life of the patient and caregivers(3).

Essential criteria to diagnose PD is the presence of motor parkinsonism, which is defined as bradykinesia, in combination with at least either resting tremor (4-6hz) and/or rigidity (MDS-PD criteria 2015)(4). Furthermore, the diagnosis can be confirmed by the UK brain bank criteria(5).

The prevalence rate of apathy in PD rates from 13.9–70%, the mean prevalence is 35%. One important factor contributing to the wide variability across studies is represented by different recruitment criteria and apathy assessment. Pure apathy (without comorbid depression and/ or dementia) rates ranges from 3 to 47.9% (6). Spalletta et al described in their study the neuropsychiatric profile of a cohort of 24 de novo, drug naïve PD patients and 8.3% of the cohort were apathic according to the Apathy rating Scale (7). Pedersen et al reported a prevalence rate of apathy in newly diagnosed patients with PD of 22.9%. The apathy in this study was described as “pure apathy”, referring to lack of depression or dementia(8). Apathy can be an early sign in PD. It can even occur before the PD is diagnosed(9).

Blonder et al concluded in their review that patients with PD suffering from apathy are more prone to be associated with rapid progression of motor and cognitive symptoms(10). Yahr et al even described apathy as the most disabling aspect of PD that result in inability to rapidly and easily perform the most ordinary motor activities(11). In daily life, these patients show delays in executive functions(12). This results in longer time needed for a daily meal, dressing and bathing, and other activities of daily life(13).

The objective of this study to answer the question of what is known about the current evidence-based pharmacological treatment of apathy, not combined with comorbid depression or dementia, in PD. The participants in this study are patients with PD and apathy, without comorbid depression or dementia, the intervention is pharmacological treatment of apathy, the comparison is comparison drug, regular therapy for PD or placebo, the outcome is the outcome on one of the apathy questionnaires, and the study design is further explained in the method section.

Methods

Aim

The objective of this study to answer the question of what is known about the current evidence-based pharmacological treatment of apathy, not combined with comorbid depression or dementia, in PD.

Search strategy and selection criteria.

A database search was done by C. H., I.L. and G.O. in PubMed, Embase.com, Cochrane Database of Systematic Reviews, CENTRAL and PsycInfo/Ebsco, from inception to 21 November 2019. The following terms, including synonyms and closely related words, were used as index terms or free-text words: 'Parkinson', 'Apathy', and 'pharmacotherapy'. Full search strategies for all databases are available from the authors.

Inclusion criteria were: trials based on patients with PD, with a drug intervention and apathy as an outcome measurement. Trials based on patients with Parkinson dementia or severe Parkinson depression, and patients who developed apathy after deep brain stimulation were excluded, as they may have another underlying mechanism for their apathy syndrome. Articles written in another language than English or Dutch were excluded. Articles published before 2002 were excluded, as were conference abstracts and conference papers.

All steps in the selection were made by two authors (A.V. and G.O.). If there was a difference in opinion, a consensus was made by the third author (I.L.).

Data extraction

The following data items were acquired: year, number of patients, duration of PD, questionnaire for apathy, mean age of patients, duration of follow up, intervention drug, comparison drug or placebo, outcome(s) on apathy questionnaire, outcome significant or not. Data extraction was performed independently by A.V. and G.O. If there was a difference in opinion, a decision was made by I.L.

Assessments tools

The following assessment tools were used for the screening of apathy.

Starkstein Apathy Scale (AS) (14, 15) (1992) has 14 items, and a total score from 0 to 42, scores above 14 indicated apathy. The AS can be used for screening and measures the severity of apathy. There is a version for the clinician and the caregiver. This test was tested at a group of patients with PD and has an interobserver reliability of $r = 0.81$ and test-retest reliability of $r = 0.90$. The internal validity is high (Cronbach's $\alpha = 0.76$).

Apathy Evaluation Scale (AES) (14, 16) (1991) has 18 items, and a total score from 18 to 72, scores above 38 indicated apathy. The AES can be used for screening and measures the severity of apathy. There is a version for the patient, clinician and the caregiver. The clinician observed test has an interobserver reliability of $r = 0.94$ and test-retest reliability of $r = 0.88$. The internal validity is high (Cronbach's $\alpha = 0.90$), which is higher than the patient rated and the caregiver rated version

Lille apathy rating scale (LARS) (14, 17) (2006) has 33 items, consisting to 9 domains. The LARS can be used for screening and measures the severity of apathy. There is a version for the patient, clinician and the caregiver. The LARS has an interobserver reliability of $r = 0.98$ and test-retest reliability of $r = 0.95$.

Neuropsychiatric Inventory (NPI) (14, 18) (1994) is an observational inventory concerning 12 aspects of neuropsychiatric behavior, including apathy. Each aspect will be screened first, followed by questions about the severity and frequency. The NPI can be used for screening and measures the severity of the 12 behavioral aspects. The apathy aspect has a test-retest reliability of $r = 0.68-0.74$.

Description of results

The principal outcome measure was the outcome on one of the four former mentioned apathy scales. The mean outcome, standard deviation and p-values of each study was mentioned in the result section of this study. In the combining of results of each study, p-values were compared to decide if treatment was favorable or not and visible presented in a table.

Risk of bias

Risk of bias of the included studies was assessed by using the recommended Cochrane Collaboration's Risk of Bias evaluation tool. Using this tool, two independent authors (I.L. & G.O.) scored independently six types of bias (selection bias, performance bias, detection bias, attrition bias, reporting bias and other types of bias) as low, high or unclear on potential risk of bias(19). In the results section, we report the most frequent risk of bias, which may cause limitations to this study. The risk of bias was taken into account for the recommendation of the pharmacological therapy of first choice in patients with PD and apathy.

Results

Literature search (Fig. 1, PRISMA flow diagram)

The search provided 1767 articles identified through database searching. Another additional 15 articles were identified through other sources. After removing duplicates, 1091 articles remained. After reading the title and abstract (performed by A.V. and G.O.), 1002 articles were excluded. After assessing the full-text of the articles, another 79 articles were excluded. In total, 10 articles remained as studies for qualitative synthesis.

A total of 3 randomized controlled trials, 2 prospective cohort studies, 2 observational studies, 1 inpatient controlled trial, 1 comparison cohort study and 1 open label study were included in this review. In total, 723 patients received intervention and 311 patients received placebo, or standard care or were healthy controls.

Appraisal of studies (Table 1)

Table 1
Data results of the included studies

Author	Study design	Participants	Participants: Duration of PD	Follow- up duration	Intervention	Comparison	Outcome	P-value
Nagayama 2019 (20)	Open label study	N = 22	6.4 (SD 4.8) years	12 weeks	Istradefylline 20 mg/day, after 4 weeks 40 mg/day		AS-score baseline: 22.8 (SD 5.0), 12 weeks follow-up 19 (SD 6.7)	P = 0.005
Houvenaghel 2018 (21)	Observational study	N = 10	11.1 (SD 4.4) years	6 months	Add-on continuous subcutaneous apomorphine infusion		AES baseline: 28.5 (SD7.2), 6 months follow-up: 30.1 (SD 9.6)	P = 0.27
Auffret 2017 (22)	Observational study	N = 12 apomorphine add-on, n = 6 control	Apomorphine group 13.8 (SD3.6) years	6 months	Apomorphine 14.8 (SD6) hours, 3.9 (SD1.7) mg/hour	Standard oral antiparkinson treatment	LARS patient baseline: -24.12 (SD 8.4), 6 months follow-up: -24.2 (SD 7.0) LARS-informant baseline: -20.7 (SD 6.1), 6 months follow-up: -24.2 (SD 7.3)	LARS patient (p = 0.72), LARS-informant: p = 0.02
Hauser 2016 (23)	Multicenter RCT	N = 41 rotigotine low dose, N = 41 rotigotine high dose, n = 40 placebo	Rotigotine low dose: 4.9 (SD 4.0) years. Rotigotine high dose: 4.8 (SD 4.3) years Placebo 3.7 (SD 3.7) years	12 weeks after titration period, 29 weeks total	Transdermal rotigotine low 7.2 (SD1.1) mg/day. Transdermal rotigotine high 9.9 (SD3.8) mg/day	Placebo	AS rotigotine low baseline: 20.1 (SD 4.4), change: -4.66 (SD 0.98) AS rotigotine high baseline: 20.2(SD 4.8), change: -4.91 (SD 0.92) AS placebo baseline: 19.7 (SD 3.8), change: -4.69 (SD 0.93)	Rotigotine low dose: p = 0.977 Rotigotine high dose: p = 0.859
Perez-Perez 2015 (24)	Prospective cross-sectional study	N = 250 pramipexole, N = 150 ropinirole, N = 115 monotherapy	Pramipexole: 7.1 (SD4.0) years. Ropinirole: 8.0 (SD5.0) years. Monotherapy: 6.9 (SD4.0) years	No follow-up	Pramipexole 1.59 (SD0.7)mg/day (with/without levodopa). Ropinirole 8.17 (SD5.3)mg/day (with or without levodopa).	Monotherapy 591+/- 370 mg/day	NPI-apathy pramipexole: 1.01 (SD 1.7) NPI-apathy ropinirole: 1.54 (SD 2.3) NPI-apathy levodopa: 1.87 (SD 2.9)	Pramipexole vs levodopa: p = 0.02 Pramipexole vs ropinirole: p = 0.06 Ropinirole vs levodopa: p = 0.45
Barone 2015 (25)	Multicenter RCT	N = 58 rasagaline, N = 65 placebo	Rasagaline: 3.7 (SD3.17) years. Placebo: 4.8 (SD3.78) years	12 weeks	Rasagaline 1 mg/day	Placebo	AS, results not mentioned in detail	No significant difference between groups

MAO-B= Monoamineoxidase-B, DA= Dopamine, AS= Apathy Scale, AES= Apathy Evaluation Scale, LARS= Lille Apathy Rating Scale, NPI= Neuropsychiatric Inventory

Author	Study design	Participants	Participants: Duration of PD	Follow-up duration	Intervention	Comparison	Outcome	P-value
Devos 2014 (26)	Multicenter RCT	N = 16 rivastigmine, N = 14 placebo	Rivastigmine: 12 years. Placebo: 13 years	18 months	Rivastigmine 9.5 mg/day, during first 6 months of study; added to stable antiparkinson medication	Placebo added to stable antiparkinson medication	LARS Rivastigmine baseline: -11.5. 6 months follow-up: -20.0. Placebo baseline: -13.3. 6 months follow-up: -13.5	p = 0.034
Spalletta 2014 (7)	Prospective cohortstudy	N = 24	1.4 (SD0.97) years	12 months	On 6 months: 67% DA, 25% levodopa, 8% both. On 12 months: 58% DA, 25% levodopa, 17% both		AS-score baseline; 8.50 (SD 5.29). At 6 months; 7.50 (SD 5.68). At 12 months 5.62 (SD 6.32).	No significant difference
Krishna 2014 (27)	Comparison cohortstudy	N = 37 MAO-B inhibitor and levodopa. N = 39 levodopa or DA. N = 43 healthy controls	MAO-B-inhibitor and levodopa: 8.61 (SD4.1) years levodopa or DA: 8.46 (SD3.8) years	No follow-up	Rasagaline 0.5-1.0 mg. Selegiline 10-20 mg. Levodopa or DA dose not mentioned	Healthy controls	AES-score MAO-inhibitor combined with levodopa group: 32.6 (SD 6.2). Only levodopa or DA group: 39.8 (SD 5.1). Healthy control group: 33.4 (SD 5.7).	MAO-B inhibitor combined with levodopa group vs only levodopa or DA group: p = 0.032
Czernecki 2002 (28)	Inpatient controlled trial	N = 23 levodopa, (N = 10 of-first, N = 13 of-first)n = 28 control	14.9 (SD1.2) years	No follow-up	Day 1 on, day 2 off. Levodopa 1115.3 mg/day	Day 1 off, day 2 on. Levodopa 1115.3 mg/day	AS-score On first. Day 1: 9.4 (SD 2.0). Day 2: 12.8 (SD 2.0). Off-first. Day 1: 14.8 (SD 2.3). Day 2: 12.3 (SD 2.1)	On-first: p = 0.068, Off-first: p < 0.0001 in favor of levodopa treatment
MAO-B= Monoamineoxidase-B, DA= Dopamine, AS= Apathy Scale, AES= Apathy Evaluation Scale, LARS= Lille Apathy Rating Scale, NPI= Neuropsychiatric Inventory								

Nagayama et al (20) performed an open label study with a new anti-parkinsonian treatment istradefylline, starting with 20 mg a day and increased at week 4 till 40 mg a day. The AS (15) was used. There was no differentiation between primary and secondary outcome measurement. The AS-score at baseline was 22.8 (SD 5.0) and at week 12: 19.6 (SD 6.7), there was a change with a significant difference of p = 0.005.

Houvenaghel et al (21) performed an observational study with continuous subcutaneous apomorphine infusion (CSAI). Although this was add-on to the standard anti parkinsonian medication, in general the standard medication could be lowered during the study. They performed the analyses on the AES. The AES-score at baseline was 28.5 (SD 7.2) and after 6 months of follow-up it was 30.1 (SD 9.6). This change did not reach a significant difference, (p = 0.27).

Auffret et al (22) compared in their observational study add-on apomorphine-infusion with standard oral antiparkinson treatment. They used the patient and informant based LARS (17) to evaluate apathy. They found that according to the informants there was a significant improvement (p = 0.02) in apathy scores; at baseline they scored - 20.7 (SD6.1) and after 6 months follow-up they scored - 24.2 (SD7.3). The patient-rated LARS did not show a significant improvement (p = 0.72); at baseline they scored - 24.12 (SD 8.4) and, after 6 months of follow-up -24.2 (SD7.0).

Hauser et al (23) performed a multicenter RCT in which they compared transdermal low and high doses rotigotine with placebo. The AS (15) was used in this study as a primary outcome measurement. They found that the placebo group scored at baseline 19.7 (SD 3.8), with a change at follow-up of -4.69 (SD 0.93). The low dose rotigotine group scored 20.1 (SD 4.4), with a change of -4.66 (SD 0.98) at follow-up ($p = 0.977$). The high dose rotigotine group scores 20.2 (SD 4.8) at baseline, with a change of -4.91 (SD 0.92) at follow-up ($p = 0.859$). Neither low dose nor high dose rotigotine was associated with relevant improvement versus placebo.

Perez-Perez et al (24) performed a cross-sectional study in which there was no follow-up. The NPI (18) apathy subscale was used to evaluate apathy. They found that the pramipexole group scored 1.01 (SD 1.7) on the NPI-aphathy subscale. The ropinirole group scored 1.54 (SD 2.3) in the NPI-aphathy subscale. The levodopa group scored 1.87 (SD 2.9) on the NPI-subscale. There was a significant difference in favor of pramipexole of $p = 0.02$ between pramipexole and levodopa. There was a trend to significant difference in favor of pramipexole of $p = 0.06$ between pramipexole and ropinirol. There was no significant difference between the ropinirole and levodopa group ($p = 0.45$).

Barone et al (25) compared in their multicenter RCT rasagiline 1 mg a day with a placebo group. The AS (15) was used as a secondary outcome measurement and it showed that there was no significant difference between the groups. Further details were not mentioned.

Devos et al (26) performed a multicenter RCT in patients with apathy in which they compared rivastigmine 9.5 mg a day with placebo. The LARS was used to evaluate apathy which was a primary outcome measurement in this study. They found that the rivastigmine group scored - 11.5 at baseline and - 20.0 after 6 months of treatment. The placebo group scored - 13.3 at baseline and - 13.5 after 6 months. A lower score indicates a better score. There was a significant difference with $p = 0.034$ between the rivastigmine and the placebo group. At the start of the study, both groups had apathy in 100% of the patients. After 6 months, 83% of the patients in the placebo group had apathy compared to 37% of the rivastigmine group.

Spalletta et al (7) performed a prospective cohort study of 24 de novo PD patients. At 6 months of therapy, 67% used DA, 25% used levodopa and 8% used both. At 12 months of therapy, 58% used DA, 25% used levodopa and 17% used both. The AS was used at inclusion, 6 months and 12 months of therapy. There was no differentiation between primary or secondary outcome measurement. At inclusion the AS-score was 8.50 (SD 5.29), at 6 months 7.50 (SD 5.68) and at 12 months 5.62 (SD 6.32). There was no significant difference in AS-score between any of the timepoints of measurement.

Krishna et al (27) performed a comparison cohort study. A group of 37 patients used a mono-amine oxidase B inhibitor (MAO-B inhibitor) (rasagiline or selegiline) combined with levodopa. The second group consisted of 39 patients and used only levodopa or a DA. The healthy control group consisted of 43 persons. The AES was used. The AES-score for the MAO-B-inhibitor combined with levodopa group was 32.6 (SD 6.2), for the only levodopa or DA group was 39.8 (SD 5.1) and for the healthy control group was 33.4 (SD 5.7). There was a significant difference between de MAO-B-inhibitor combined with levodopa group and the only levodopa or DA group of $p = 0.032$. They suggested a beneficial effect of the MAO-B-inhibitor on apathy-scores.

Czernecki et al (28) tested 23 patients during their on and off state (10 patients on-first, 13 patients off-first) and compared them with a control group of 28 patients. The AS was used to evaluate apathy. They found that the "on-first" group scored 9.4 (SD 2.0) on the first day of measurement and 12.8 (SD 2.0) on the second day of measurement, with a significant difference of $p = 0.068$. The "off-first" group scored 14.8 (SD 2.3) on the first day of measurement and 12.3 (SD 2.1) on the second day of measurement, with a significant difference of $p = 0.012$. They concluded that apathy is less severe under levodopa treatment, whatever the group of patients and the order of assessment.

Risk of bias assessment (Table 2)

Table 2
Risk of bias

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Nagayama 2019(20)	High risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias
Houvenaghel 2018 (21)	High risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Possibility that the beneficial effect measured on self-report questionnaires was induced by placebo or care effects
Auffret 2017 (22)	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Small sample size
Hauser 2016 (23)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Funded by UCB Pharma, some authors are salaried employees of UCB Pharma, and receive stock options from their employment.
Perez-Perez 2015 (24)	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	A non-randomized, cross-sectional study, in which it can not be guaranteed that patients were selected to certain DA or levodopa in monotherapy depending of their neuropsychiatric profile
Barone 2015 (25)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Funded by Lundbeck Italia SpA. Almost all authors' institutions,, received grants from Lundbeck Italia for participating in the study
Devos 2014 (26)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Small sample size, the required sample size was estimated to be 30 participants per group
Spalletta 2014 (7)	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Small sample size
Krishna 2014 (27)	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Small sample size, no follow up study
Czernecki 2002 (28)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear: not mentioned

By using the recommended Cochrane guidance, we found that most studies had a high risk of bias by selection bias based on their type of study, like cohort studies and observational studies. Some studies are small or funded by the pharmaceutical industry. Due to these biases the findings are not always applicable to the general population of PD patients with apathy.

Discussion

This review concerns the topic of evidence based pharmacological treatment of apathy in PD. Although several studies are done, it is hard to draw strict conclusions about the best evidence-based pharmacological treatment. Overall, there was a substantial heterogeneity with respect to study design, analysis, domain, interventions, and outcome measures in the selected studies. We tried to neutralize this by strictly defining the in- and exclusion criteria for the selection of the articles. Nevertheless, in some studies, standard oral anti-parkinsonian medication was the comparative treatment and in other studies, the intervention treatment was given as an add-on to the standard oral anti-parkinsonian medication.

Based on the findings in this review, one could say with caution that rivastigmine(26), pramipexole(24), istradefylline(20), and selegiline combined with levodopa(27) are better in the treatment of apathy in PD than monotherapy with levodopa, DA or placebo (Table 3). These studies show significant outcomes in favor of the intervention treatment. Other treatment like apomorphine(21, 22), rasagiline(25, 27), and levodopa (7, 28) have contradictory results and therefore inconclusive.

Table 3
outcomes of the studies.

Favorable treatment	Unfavorable treatment	P-value	Author
Istradefylline	None	p = 0.005	Nagayama 2019 (20)
Apomorphine	Standard care	p = 0.02	Auffret 2017 (22)
Pramipexole	Levodopa	p = 0.02	Perez-Perez 2015 (24)
Rivastigmine	Placebo	p = 0.034	Devos 2014 (26)
Rasagiline/ selegiline & Levodopa	Levodopa or DA	p = 0.032	Krishna 2014 (27)
Levodopa (OFF-first)	12 hours without levodopa before levodopa	p < 0.0001	Czernecki 2002 (28)
Trend to favorable treatment	Trend to unfavorable treatment		
Pramipexole	Ropinirole	p = 0.06	Perez-Perez 2015 (24)
Levodopa (ON-first)	12 hours without levodopa after levodopa	p = 0.068	Czernecki 2002 (28)
Comparative treatment	Comparative treatment		
Apomorphine	None	p = 0.27	Houvenaghel 2018 (21)
Apomorphine	Standard care	p = 0.72	Auffret 2017 (22)
Rotigotine low dose	Placebo	p = 0.977	Hauser 2016 (23)
Rotigotine high dose	Placebo	p = 0.859	Hauser 2016 (23)
Ropinirole	Levodopa	p = 0.45	Perez-Perez 2015 (24)
Rasagiline	Placebo	No significant difference	Barone 2015 (25)
DA, levodopa or both	None	No significant difference	Spalletta 2014 (7)

By using the Cochrane Collaboration's Risk of Bias evaluation tool, we found that most studies had a high risk of bias because of selection bias based on the type of study, like cohort studies and observational studies. Due to these biases the findings may be difficult to generalise to a regular population of PD patients with apathy. The studies with the lowest risk of bias were the multicentre RCT's which investigated rivastigmine(26), rasagiline(25), and rotigotine(23), yet these studies were funded by the pharmaceutical industry or did have small sample sizes. Combining the results of the studies with a focus on favorable significant outcomes and the risk of bias, we would advise rivastigmine as a treatment of apathy in patients with PD.

Based on the comorbidity of each patient, one should tailor the treatment for apathy to that unique patient. Rivastigmine can cause gastro-intestinal side effects like nausea and vomiting(29), although it can have beneficial effects on dementia and cognition (30). Istradefylline is a relatively new treatment for PD symptoms and not yet approved in Europe. A proven side effect of istradefylline on short term is aggravation of dyskinesia, however more studies should be performed on the long term side effects in PD(31). Pramipexole can cause side effects like sleep attacks, somnolence, visual and auditory hallucinations, and impulse control disorders. On the other hand it is mentioned as a good option for treating a depression in PD (32), so those patients with both apathy and depression may benefit from pramipexole. Selegiline is mainly prescribed in the early stages of PD (33). It can cause side effects like nausea, vomiting, sleeplessness, dry mouth, orthostatic hypotension, dyskinesia(34), and hallucinations(35).

If there is apathy and cognitive impairments as comorbidity in PD, a first step in the treatment is to stop anti-cholinergic medication as this may worsen cognitive impairment(36). Also DA and MAO-B inhibitors could worsen the cognition in patients. Other causes of cognitive disturbance in PD, such as delirium, should be investigated and treated. However, if apathy and cognitive disturbances or dementia are comorbid in PD then the findings of this review support rivastigmine as an add-on treatment. Because there is limited experience in using rivastigmine for the indication of apathy in PD, one should refer to a movement disorder specialist.

In patients with apathy and possible depression it is important to distinguish and diagnose a comorbid depression as this is a treatable disorder in PD. Depressive patients have a depressed mood, sad and negative feelings, feelings of guilt, suicidal thoughts, negative thoughts, are pessimistic, and have a lot of self-criticism. These symptoms are not present in patients with only apathy(2). First line treatment would be to start antidepressant medication, however pramipexole as add-on could be considered in patients with both apathy and (persisting) depression(24, 32).

Treating PD with more than just monotherapy might result in better improvement of PD and concurrent neuropsychiatric symptoms such as apathy. The findings of this review indeed support the use of "add-on medication" in the treatment of apathy(22, 26, 27). Current data suggest that improving the underlying PD might be the most effective way to treat apathy in PD. This is also seen in other non-motor symptoms of PD, such as pain, hallucinations, anxiety and depression, which show improvement with better treatment of PD. In case of apathy in PD, one should tailor the non-pharmacological interventions, like establishments of daily schedules to keep the patient engaged (37), psychotherapy, and occupational therapy (38).

One should keep in mind that not only medical treatment, but probably the combination with non-pharmacological options is the best way to treat apathy in PD.

Strengths and limitations

Although research is sparse on evidence-based pharmacological treatment of apathy in PD we tried to give an extensive and complete update of the research done in this field. The latest update known in the literature was done until December 2016 and published recently (39), therefore missing publications after 2016. We performed an extensive search until November 2019, therefore adding to the existing literature. We searched for studies that assessed apathy as both as a primary outcome measurement. By doing so we included as many studies as possible about evidence-based pharmacological treatment for apathy in PD in order to get a complete overview of the existing data. Therefore, also negative findings were included in this review in order to preclude a publication bias. Another strength of this review is that we assessed the risk of bias. This showed that almost all studies had some high risk of bias, as based on their type of study, pharmaceutical influence, and small sample sizes.

An important limitation is that the studies show a broad heterogeneity. This may possibly be the cause why results of different studies are in conflict with each other and conclusions are not easily to drawn. Furthermore, we notice that apathy is a neuropsychiatric symptom that can be easily missed, or not be the focus of trials.

Implications for further research

Apathy in PD is a challenging problem, however by good treatment it can improve the prognosis and quality of life of patients and their caregivers. Further research needs to be done in this field. The first, and most important, step for further research is that apathy should get more attention in guidelines (40, 41) and in research. Not only more research needs to be done, but research with good methodological strategy, like RCT's, needs to be performed to prevent high risk of bias. Data out of these RCT's should be collected to come to "big data" meta-analyses. This will lead to better protocol and guidelines in the medical treatment of apathy in patients with PD. If apathy is treated in patients with PD, there will be likely more adherence to treatment for other symptoms of PD in the individual patient.

Implications for practice

It seems very important to achieve better clinical recognition of apathy in PD. This is especially the case when the patient does not improve as expected on the prescribed pharmacological treatment, or when caregivers complain on the adherence of treatment in patients. There are non-pharmacological options in the treatment of apathy in PD, like psychotherapy, and occupational therapy (38), but medical treatment could also play an important role in the treatment of apathy in PD. Few conclusions can be drawn from this review, but we suggest with caution that rivastigmine, pramipexole, istradefylline, and selegiline combined with levodopa is better in the treatment of apathy in PD than monotherapy with levodopa, DA or placebo. Combining the results of the studies with a focus on favourable significant outcomes and the risk of bias, we would advise rivastigmine as a treatment of apathy in patients with PD. One should keep in mind that every patient has different comorbidity and experience different side effects, so we should tailor the treatment of apathy in PD to every unique patient.

Conclusion

Research is sparse on the topic of evidence-based pharmacological treatment for apathy in PD. We suggest with caution that rivastigmine, pramipexole, istradefylline, and selegiline combined with levodopa is better in the treatment of apathy in PD than monotherapy with levodopa, DA or placebo. Combining the results of the studies with a focus on favourable significant outcomes and the risk of bias, we would advise rivastigmine as a treatment of apathy in patients with PD, and pramipexole or selegiline in PD patients with apathy without cognitive disturbance. One should keep in mind that every patient has different comorbidity and experience different side effects, so we should tailor the treatment of apathy in PD to every unique patient. More attention is needed for apathy in PD, not only to optimize pharmacological treatment and non-pharmacological interventions for patients, but also in starting with better recognition of apathy in clinical practice and more attention for apathy in PD guidelines.

List Of Abbreviations

PD Parkinson's disease

DA Dopamine agonist

AS Apathy Scale

AES Apathy evaluation scale

LARS Lille apathy rating scale

NPI Neuropsychiatric inventory

MAO-B Mono-amine oxidase B inhibitor

Declarations

- Ethics approval and consent to participate: not applicable, this study does not involve human participants, human data or human tissue
- Consent for publication: not applicable, this study does not include any individual person's data
- Availability of data and materials: All data generated or analysed during this study are included in this published article
- Competing interests: "The authors declare that they have no competing interests"
- Funding: There are no sources of funding for the research reported
- Authors' contributions:
 - O. is expected to have made substantial contributions to the design of the work, the analysis and interpretation of the data, have drafted the work, and substantively revised it. She approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.
 - V. is expected to have made substantial contributions to the design of the work, the analysis and interpretation of the data, and substantively revised the work. She approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.
 - d.H. is expected to have made substantial contributions to the acquisition of the data, and substantively revised the work. She approved the submitted version. She approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.
 - L. is expected to have made substantial contributions to the design of the work, the analysis and interpretation of the data, and substantively revised it. She approved. She approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.
- All authors have read and approved the manuscript
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Figures

Figure 1

PRISMA flow diagram

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