Comprehensive Examination of Therapies for Pain in Parkinson's Disease: A Systematic Review and Meta-Analysis

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Keywords

Parkinson's disease · Pain therapy · Meta-analysis

Abstract

Pain in Parkinson's disease (PD) is a debilitating symptom with a prevalence of 68%, yet is untreated 50% of the time. What is unclear, however, is which treatment is optimal for minimizing pain severity in PD. Thus, the objective of this systematic review and meta-analysis was to investigate the efficacy of a variety of novel, complimentary, and conventional treatments for pain in PD and elucidate which therapy is the most effective. A systematic search was performed using MEDLINE, PsycINFO, Embase, CINAHL, and CENTRAL databases. To identify additional articles, manual searches of reference lists of included trials were also searched. Major neurology conference proceedings occurring between January 2014 and February 2018 were also searched to identify unpublished studies that may be potentially eligible. Twenty-five randomized controlled trials that encompassed medical, surgical, and complementary therapies met our inclusion criteria and exhibited moderate quality evidence. Two

reviewers conducted assessments for study eligibility, risk of bias, data extraction, and quality of evidence rating. A conservative random-effects model was used to pool effect estimates of pain severity. The greatest reductions in pain were found with safinamide (Standardized mean difference = -4.83 , 95% CI $[-5.07$ to $-4.59]$, $p < 0.0001$), followed by cannabinoids and opioids, multidisciplinary team care, catechol-O-methyltransferase inhibitors, and electrical and Chinese therapies. Moderate effects in reducing pain were in pramipexole and surgery, while the weakest effects were in dopaminergic agonists and miscellaneous therapies. Safinamide is an important adjunct to standard parkinsonian medication for alleviating pain in PD.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition with a prevalence of 0.3% of the entire population (or 1% for people above the age of 65), and continues to increase alarmingly with associated eco-

nomic and social burden [1–3]. PD is often associated with muscle rigidity, tremors, and cognitive decline particularly in patients over 40 years of age. Pain is an extremely common non-motor symptom that is prevalent among 68–95% of PD patients [4–7]. Pain in PD has a significant impact on quality of life, evidenced by its association with higher scores of both depression and anxiety in these patients [8]. Despite the high rates of pain prevalence, between 25 and 50% of PD patients are receiving no treatment for their pain [4–6]. A notable concern in PD is the experience and severity of pain across various patient populations [9].

Pain in PD is attributable to a primary or secondary cause. Primary causes are associated with early morning dystonia or motor fluctuations compared to secondary causes that are associated with musculoskeletal pain [10]. Although various treatments exist for PD, it is unclear as to which is most effective in alleviating pain in PD. We performed a meta-analysis of randomized controlled trials (RCTs) to determine the effect of conventional, complementary or experimental therapies on pain severity in PD.

Methods

The reporting of this study is in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [11], and the protocols for reviews detailed in the Cochrane Handbook for Systematic Reviews of Interventions [12] (Appendix 1).

Identification of Studies

A systematic search was performed using MEDLINE, PsycINFO, Embase, CINAHL, and CENTRAL from the inception of the databases to February 2, 2018. To increase the sensitivity of the search, we used MeSH and Emtree headings in various combinations and supplemented with free text (Appendix 2). Reference lists of included trials were also searched to identify additional articles. Major neurology conference proceedings occurring between January 2014 and February 2018 were also searched to identify unpublished studies that may be potentially eligible.

Assessment of Eligibility

Two authors independently screened titles and abstracts which were followed by a full-text screening to determine eligibility of clinical trials. All disagreements were resolved through consensus and via arbitration by a senior author.

All studies meeting the following criteria were included:

- (1) RCTs only.
- (2) Trials assessing a continuous measure of pain severity.
- (3) Adult patients (age ≥ 18) with idiopathic PD.

No restrictions were made for language, publication date, presence of absence of co-interventions, or length of follow-up.

Assessment of Risk of Bias

The risk of bias tool in Review Manager (RevMan) by the Cochrane Collaboration was used by 2 reviewers (A.R.Q. and S.M.) to independently perform a risk of bias assessment [12]. Study authors were contacted to resolve any concerns.

Data Extraction

The extracted data from available studies included first author's last name, publication year, RCT design, scale used to calculate pain severity, therapeutic intervention, funding source, and country. Furthermore, data for treatment and control groups were extracted in terms of sample size, age, gender, disease duration, and the amount of missing or lost data in terms of participants. In the event where important data was unclear or missing, we attempted to contact study authors to retrieve such information.

Statistical Analyses

Agreement of reviewers' assessment for study eligibility was calculated using Cohen's kappa coefficient (κ), with $\kappa \geq 0.65$ being considered adequate [13]. The intraclass correlation coefficient was used to calculate reviewer agreement for the risk of bias assessment. A conservative random-effects model of DerSimonian and Laird [14] was used to pool effect estimates of pain severity using Prometa 3. Pain severity effect estimates relative to control were generated using the standardized mean difference (SMD) with 95% CIs. Negative values for pain severity represent pain reduction, while positive values represent pain augmentation. Publication bias was examined through funnel plots, as well as Egger's and Begg's tests for publication bias. All tests of significance were 2-tailed, with a significance threshold set at $p = 0.05$.

Evaluation of Heterogeneity

Heterogeneity was quantified using the I^2 statistic from the χ^2 test for heterogeneity. In accordance to the interpretation from the Cochrane Handbook, heterogeneity for I^2 values between 30 and 60% may be moderate, 50 and 90% may be substantial, while values between 75 and 100% may be considerable [12]. We hypothesized a priori that heterogeneity may be accounted for by treatment drug dosage, the particular procedure of therapy, and stage of the disease.

Sensitivity Analysis

The main analysis consisted of patients who successfully completed follow-up and were analyzed within the eligible trials. Participants with missing data were not included. To explore the effect of missing data, we conducted an a priori sensitivity analysis that used the participants enrolled as the sample sizes for all eligible trials, assuming that the pain severity scores for treatment and control groups remained the same. Furthermore, a second a priori sensitivity analysis included studies with less than 2 ratings of high-risk bias across any of the categories of the risk of bias assessment.

GRADE Quality Assessment and Summary of Findings

The GRADE quality assessment guidelines were used to analyze the quality of evidence for or against the use of treatments in PD for reducing pain [15]. Although RCTs produce the highest quality of evidence, we conducted a quality assessment, as they are still susceptible to bias, imprecision, inconsistency, and poor methodological construct.

Fig. 1. PRISMA flow chart. A flowchart ultimately showing the included studies. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Results

Eligible and Included Studies

Out of 876 potentially eligible articles, 175 were duplicates and the remaining 701 titles and abstracts were screened. Subsequently, 27 full-texts were screened and 24 were ultimately eligible for our review (Fig. 1). One study pooled the results of 2 (RCTs [16]. Thus, 25 RCTs were included with a total of 1,744 patients undergoing a therapeutic intervention and 1,610 patients undergoing a control intervention. Agreement between the reviewers for study eligibility was moderately high ($\kappa = 0.724$, 95% CI [0.479–0.969], $p < 0.0001$) and the agreement for risk of bias assessment was very high (intraclass correlation coefficient = 0.856, 95% CI [0.714–0.927], $p < 0.0001$).

Study Characteristics

The mean age of study participants was 66 years in the treatment and control groups. The proportion of male patients was 61% in the treatment group and 60% in the

control group. Mean disease duration of PD was 7.9 (3.5) years and 7.2 (3.4) years in the treatment and control group respectively (Table 1, please see Appendix 3 for group-wise demographics).

The number of trials for each identifiable therapeutic intervention category was 3 for dopaminergic agonists [17–19], 2 for cannabinoids and opioids [20, 21], 3 for surgical methods [22–24], 4 for electrical or Chinese therapies [25–28], 2 for pramipexole [29, 30], 2 for safinamide [16], 1 for catechol-O-methyltransferase (COMT) inhibitors [31], 1 for multidisciplinary team care [32], and 7 for miscellaneous therapies. Miscellaneous therapies included hydrotherapy [33, 34], massage therapy [35], gym training [36], mindfulness therapy [37], vibration therapy [38], and power yoga [39] (Table 1, with further intervention details in Appendix 4).

Pain severity was reported in 8 trials using the pain subscale of the Visual Analogue Scale (VAS-P) [17, 24, 26, 27, 29, 30, 33, 35], in 8 using section 39 of the Parkinson's Disease Questionnaire-39 [16, 22, 23, 31, 32, 36, 37, 39], in 4 using the Likert pain scale [18, 19, 34, 38], in 1 using the King Parkinson's Disease Pain Scale [21], in 1 using question 1.9 of the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS Q1.9) [25], in 1 using the McGill Pain Scale [20], and in 1 trial using the Daily Pain Rating Sheet [28] (Table 1).

Risk of Bias

The risk of bias assessment through RevMan is summarized (Fig. 2). The funnel plot for pain severity was fairly symmetric (Fig. 3), with publication bias being statistically insignificant (Egger: $p = 0.776$; Begg: $p = 0.427$).

Pain Severity

The largest effects for pain severity reduction were found in safinamide (SMD = -4.83 , $p < 0.0001$), followed by cannabinoids and opioids (SMD = -2.24 , $p < 0.0001$; $I^2 = 0.00\%$, $p = 0.363$), multidisciplinary team care (SMD = -2.01 , $p < 0.0001$), and COMT inhibitors (SMD = -1.81 , $p < 0.0001$). Thereafter was a large effect from electrical and Chinese therapies with considerable heterogeneity (SMD = -0.98 , $p = 0.020$; $I^2 = 86.9\%$, $p < 0.0001$). Moderate sized effects on pain severity reduction were found for pramipexole with insignificant heterogeneity (SMD = -0.50 , $p = 0.001$; $I^2 = 69.0\%$, $p = 0.073$), followed by surgery with insignificant heterogeneity (SMD = -0.42 , $p = 0.011$; $I^2 = 26.6\%$, $p = 0.256$). Small effects for pain severity reduction were found for dopaminergic agonists with insignificant heterogeneity (SMD = -0.27 , $p < 0.0001$;

Table 1. Characteristics of eligible studies

Lead author	Year	RCT type	Therapeutic intervention	Funding source	Country	Assessment of pain severity	Sample size ¹ , n		Age*, years, mean (SD)		Gender*, men, %		Disease duration*, years, mean (SD)		Lost/missing data, n	
							treatment	control	treatment	control	treatment	control	treatment	control	treatment	control
Barone [17]	2010	Double-blind Placebo-controlled	Pramipexole	Boehringer Ingelheim	Austria, Germany, U.K., U.S., and Spain	VAS-P	139	148	67.4 (9.0)	66.6 (9.9)	43	51	4.0 (4.5)	4.0 (3.9)	5	4
Carroll [20]	2004	Double-blind Crossover-controlled	Cannabis	NR	UK	MPQ	17		67.0 (6.8)		63		14 (9.5)		2	
Cattaneo [16]	2017	Double-blind Placebo-controlled	Safinamide	Newron and Merck Sorono	21 countries	PDQ-39	440	438	60.9 (6.4)	60.8 (6.5)	72	65	8.6 (2.9)	8.6 (3.0)	58	59
Charles [22]	2014	Single-blind Comparative-controlled	Deep brain stimulation	Medtronic, awards, grants and private donations	U.S.	PDQ-39	15	14	60.0 (6.8)	60.0 (7.0)	93	87	NR	NR	0	1
Chua [25]	2017	Double-blind Placebo-controlled	Chinese medicine	PuraPharm international Ltd., federal, university grants, and corporate	Hong Kong	MDS-UPDRS	45	46	63.5 (9.7)	63.3 (8.2)	63	69	6.4 (4.2)	5.4 (3.8)	11	9
De Bie [24]	1999	Single-blind Waiting-list controlled	Unilateral pallidotomy	Prinses beatrix spierfonds	Netherlands	VAS-P	19	16	60.3 (7.5)	61.4 (8.4)	42	50	16.0 (5.2)	17.8 (5.2)	0	2
Hauser [29]	2009	Double-blind Placebo-controlled	Pardoprunox	Abbott healthcare products	Bulgaria, Serbia, and Malta	VAS-P	28	10	64.8 (6.1)	65.1 (7.8)	80	55	7.5 (3.0)	6.6 (3.2)	23	1
Jitkrisadukul [26]	2017	Double-blind Sham-controlled	Tremor's glove	University grants, awards and federal	Thailand	VAS-P	15	15	63.4 (11)	64.3 (9.5)	53	40	7.9 (4.0)	6.6 (2.6)	0	0
Kapur [38]	2012	Single-blind Sham-controlled	Vibration therapy	NR	U.S.	Likert	10	10	66.5 (9.6)	62.1 (6.7)	80	60	6.6 (3.8)	5.6 (3.6)	0	0
Lei [27]	2016	Double-blind Sham-controlled	Electroacupuncture	None	U.S.	VAS-P	10	5	69.8 (4.5)	71.0 (12)	60	40	6.2 (5.9)	5.2 (4.7)	0	0
Marck [32]	2013	Single-blind Comparative-controlled	Multidisciplinary care	Federal and corporate	Canada	PDQ-39	51	49	65.9 (8.5)	68.1 (8.8)	59	57	4.6 (3.9)	3.7 (3.5)	10	12
Ni [39]	2016	Unblind Comparative-controlled	Power yoga	None	U.S.	PDQ-39	13	10	71.2 (6.5)	74.9 (8.3)	73	50	6.9 (6.3)	5.9 (6.2)	2	2
Olanow [31]	2004	Double-blind Placebo-controlled	Entacapone	Novartis pharmaceuticals	U.S.	PDQ-39	281	274	69.8 (9.3)	70.2 (9.4)	73	69	4.4 (3.5)	4.5 (3.5)	92	103

Table 1. (continued)

Lead author	Year	RCT type	Therapeutic intervention	Funding source	Country	Assessment of pain severity	Sample size ¹ , n		Age*, years, mean (SD)		Gender*, men, %		Disease duration*, years, mean (SD)		Lost/missing data, n	
							treatment	control	treatment	control	treatment	control	treatment	control	treatment	control
Perez de la Cruz [33]	2017	Single-blind Comparative-controlled	Hydrotherapy	None	Spain	VAS-P	15	15	67.5 (9.9)	66.8 (5.3)	NR	NR	6.2 (2.5)	6.7 (3.2)	0	0
Pickut [37]	2015	Single-blind Comparative-controlled	Mindfulness therapy	NR	Belgium	PDQ-39	14	13	61.4 (11)	62.2 (6.6)	50	54	5.7 (0.81)	8.2 (1.9)	1	2
Poliakoff [36]	2013	Single-blind Waiting-list controlled	Gym training	Corporate grant	U.K.	PDQ-39	11	10	66.6 (7.3)	63.7 (8.8)	59	63	7.4 (3.9)	4.7 (3.9)	5	6
Rascol [30]	2012	Double-blind Placebo-controlled	Pardoprinox	Abbott healthcare products	Argentina, Brazil, Canada, Chile, Colombia, Latvia, Lithuania, Peru, Russia, Ukraine, and U.S.	VAS-P	140	133	62.4 (8.9)	62.1 (9.3)	54	67	6.7 (4.4)	6.6 (4.7)	10	12
Rascol [18]	2016	Double-blind Placebo-controlled	Rotigotine	UCB pharma and private donor	Germany, Poland, Slovakia, and U.S.	Likert	30	30	66.5 (12)	65.3 (14)	54	52	5.9 (3.5)	5.6 (4.7)	5	3
Rintala [28]	2010	Double-blind Sham-controlled	Cranial electrotherapy	Federal, private donation, and electromedical products international Inc	U.S.	DPRS	6	7	74.7 (7.8)	74.4 (8.3)	67	86	15 (13)	5.2 (2.4)	0	0
Skogar [35]	2013	Single-blind Comparative-controlled	Tactile touch therapy	Corporate and federal	Sweden	VAS-P	29	15	NR	NR	34	40	NR	NR	0	1
Trenkwalder [19]	2011	Double-blind Placebo-controlled	Rotigotine	Schwarz biosciences GmbH	Poland, South Africa, Hungary, U.S., Germany, U.K., Italy, New Zealand, and Finland	Likert	178	89	64.8 (9.3)	64.4 (11)	64	64	4.6 (4.2)	4.9 (4.6)	12	8
Trenkwalder [21]	2015	Double-blind Placebo-controlled	Oxycodone-naloxone	Mundipharma research	Czech Republic, Germany, Hungary, Poland, Romania, and Spain	KPPS	63	82	66.7 (8.9)	67.5 (8.1)	49	54	6.9 (5.2)	6.7 (4.2)	30	27

Table 1. (continued)

Lead author	Year	RCT type	Therapeutic intervention	Funding source	Country	Assessment of pain severity	Sample size ¹ , <i>n</i>		Age*, years, mean (SD)	Gender*, men, %		Disease duration*, years, mean (SD)		Lost/missing data, <i>n</i>		
							treatment	control		treatment	control	treatment	control	treatment	control	
Volpe [34]	2017	Single-blind Comparative-controlled	Hydrotherapy	None	Italy	Likert	13	11	70.6 (7.8)	70.0 (7.8)	60	67	9.4 (7.5)	9.0 (7.0)	2	4
Williams [23]	2010	Unblind Comparative-controlled	Deep brain stimulation	Federal	U.K.	PDQ-39	162	153	59.0 (11)	59.0 (9.8)	68	74	12 (7.5)	11 (7.3)	21	30
Totals and averages							1,744	1,610	65.6 (4.0)	65.7 (4.3)	61	60	7.9 (3.4)	7.1 (3.4)	289	288

¹ Refers to the number analyzed.
* Baseline characteristics.
NR, not reported; RCT, randomized clinical trial; PDQ-39, Parkinson's Disease Questionnaire – Section 39; VAS-P, visual analogue scale – pain; MDS-UPDRS, movement disorders society – unified Parkinson's disease rating scale; DPRS, daily pain rating scale; MPQ, McGill pain scale; KPPS, king's Parkinson's disease rating scale; Likert, Likert pain rating scale.

¹ Refers to the number analyzed.
 * Baseline characteristics.
 NR, not reported; RCT, randomized clinical trial; PDQ-39, Parkinson's Disease Questionnaire – Section 39; VAS-P, visual analogue scale – pain; MDS-UPDS, movement disorders society – unified Parkinson's disease rating scale; DPRS, daily pain rating scale; MPQ, McGill pain scale; KPPS, king's Parkinson's disease rating scale; Likert, Likert pain rating scale.

Fig. 2. Risk of bias assessment – a summative review of each risk of bias item for each included trial. “+” indicates low risk of bias, “-” indicates high risk of bias, while “?” indicates that bias is unclear.

Fig. 3. Funnel plot of standard error of SMD (d) against (d) to assess for publication bias. SMD, standardized mean difference.

$I^2 = 45.8\%$, $p = 0.158$). The smallest effect was found for miscellaneous therapies with considerable heterogeneity (SMD = -0.03 , $p = 0.947$; $I^2 = 91.6\%$, $p < 0.0001$; Fig. 4). In the GRADE quality assessment, pain severity was rated as moderate quality of evidence with respect to the need of more trials needed for certain subgroups to confirm the effect, such as for multidisciplinary team care and COMT inhibitors (Table 2).

Sensitivity Analysis

The first sensitivity analysis attempted to compensate for all missing participant data assuming the pain severity scores in control and treatment groups were the same. A -0.02 -unit reduction in pain severity was seen in cannabinoids and opioids (SMD = -2.26 vs. SMD = -2.24), while a $+0.02$ -unit increase in pain severity was seen in pardoprinox (SMD = -0.48 vs. SMD = -0.50). Surgery experienced a -0.01 -unit decrease in pain severity (SMD = -0.43 vs. SMD = -0.42). Effect sizes of all other groups did not change (Appendix 5).

To provide a more accurate and precise estimate of effect, a subsequent sensitivity analysis was conducted to exclude studies with high-risk bias concerns. Ten studies qualified for the secondary sensitivity analysis, of which 2 were dopaminergic agonists [17, 19], 1 was part of the cannabinoids and opioids class [21], 3 among the electrical and Chinese therapies [25, 27, 38], and 1 each for miscellaneous therapies [37], pardoprinox [30], safinamide [16], and COMT inhibitors [31]. Cannabinoids and opi-

oids experienced a -0.02 -unit reduction in pain severity (SMD = -2.26 vs. SMD = -2.24), electrical and Chinese therapies displayed a -0.13 -unit reduction in pain severity (SMD = -1.11 vs. SMD = -0.98), and a -0.12 -unit reduction in pain severity was seen for pardoprinox (SMD = -0.62 vs. SMD = -0.50). Miscellaneous therapies experienced a $+1.70$ -unit increase in pain severity (SMD = $+1.67$ vs. SMD = -0.03). No changes to effect sizes were seen in any of the other groups (Appendix 5).

Discussion

According to the results, the most efficacious treatment is safinamide (SMD = -4.83), followed by cannabinoids and opioids (SMD = -2.30). Safinamide is a selective, reversible monoamine-oxidase B inhibitor that reduces dopaminergic degradation and reuptake. This may make safinamide suitable for PD treatment during OFF periods, which occur as an end-of-dose worsening of the patient's response to levodopa [40]. However, it also has non-dopaminergic modes of action, including the state-dependent inhibition of voltage-gated sodium channels in the inactivated state and antilglutamatergic activity. These dopaminergic and non-dopaminergic actions may together account for its pain mitigating effects [16]. Numerous studies have shown that safinamide may be very effective at treating parkinsonian pain and is well tolerated in clinical trials [40–42]. Opioids act on opioid receptors and reduce neurotransmission. Cannabinoids control nociceptive thresholds via cannabinoid receptor agonism and may also affect tissues outside the nervous system. Both possess analgesic properties [43].

Multidisciplinary team care (SMD = -2.01), COMT inhibitors (SMD = -1.81), and electrical and Chinese therapies (SMD = -0.98) were the next most effective. The COMT inhibitor trial pertained to entacapone, which inhibits the degradation of levodopa in the peripheral nervous system. Entacapone may therefore be effective in patients with musculoskeletal pain due to motor fluctuations or rigidity [44]. A multidisciplinary team intervention offers a comprehensive approach that may address numerous patient concerns in addition to pain, though it is unclear as to which parts of the team are the most important.

Miscellaneous therapies (SMD = -0.03), dopaminergic agonists (SMD = -0.27), surgery (SMD = -0.42), and pardoprinox (SMD = -0.48) were the least effective. “Miscellaneous therapies” is an umbrella term for a

Fig. 4. A forest plot of the SMD (d) of pain severity with PD therapy subgroups by indication*. * ES = effect size (SMD - d); W, weight; SE, standard error; n_1 , sample size for treatment; n_2 , sample size for control. SMD, standardized mean difference.

grouping of therapies that lack robust, evidence-based support for their efficacy. Interestingly, mindfulness therapy, gym training, massage therapy and hydrotherapy led to greater pain severity in treated participants compared to controls. This may have been attributable to poor methodological designs such as small sample size, or due to intervention-based exercise. Pardoprunox and other dopaminergic medications were not found to be very effective in reducing pain. This may suggest that pain in PD might not be explained solely by levels of dopamine. Our findings are supported by data from Buhmann et al. [4], who found that analgesics (including opioids) and rehabilitation (a multidisciplinary treatment) were highly effective at treating pain in PD, while dopaminergic medications (unspecified which ones) were comparatively less effective.

There are several limitations in our study. There was considerable heterogeneity in the trials included for Chinese and electrical therapies ($I^2 = 86.9\%$), as well as for miscellaneous therapies ($I^2 = 91.6\%$). In addition, some studies had significant loss-to-follow up rates, which may result in attrition bias. However, our first sensitivity analysis, which compensated for missing participant data ($n = 511$), found that effect sizes changed slightly or not at all, suggesting that attrition bias is unlikely to have changed our conclusions. Furthermore, some studies had ineffective blinding, small sample sizes, and notable methodological concerns such as the use of non-validated scales for pain measurement. However, our second sensitivity analysis, which accounted for bias-compromised studies, found that effect sizes were largely unchanged. There were only a few exceptions in

Table 2. Combined GRADE and summary of findings table

Quality assessment group	no. of trials	risk of bias	inconsistency	indirectness	imprecision	other considerations	Number of patients		Effect SMD (95% CI)	Quality
							treatment	control		
Dopaminergic agonists	3	Not serious	Not serious	None	Not serious	Not serious	347	267	-0.27 (-0.38 to -0.15)***	⊕⊕⊕⊕ High
Cannabinoids and opioids	2	Not serious	Not serious	None	Serious	Not serious	80	99	-2.24 (-2.58 to -1.89)***	⊕⊕⊕⊕ Moderate
Surgery	3	Serious	Not serious	None	Not serious	Not serious	196	183	-0.42 (-0.74 to -0.10)*	⊕⊕⊕⊕ Moderate
Electrical and Chinese therapies	4	Not serious	Serious	None	Not serious	Not serious	76	73	-0.98 (-1.80 to -0.16)*	⊕⊕⊕⊕ Moderate
Miscellaneous therapies	7	Serious	Serious	None	Serious	Serious	105	84	-0.03 (-0.94 to 0.88)	⊕⊕⊕⊕ Very low
Pardoprunox	2	Not serious	Not serious	None	Not serious	Not serious	168	143	-0.50 (-0.80 to -0.19)**	⊕⊕⊕⊕ High
Safinamide	2	Not serious	Not serious	None	Not serious	Not serious	440	438	-4.38 (-5.07 to -4.59)***	⊕⊕⊕⊕ High
COMT inhibitors	1	Not serious	None	None	Not serious	Not serious	281	274	-1.81 (-1.94 to -1.67)***	⊕⊕⊕⊕ Moderate
Multidisciplinary team care	1	Serious	Not serious	None	Not serious	Not serious	51	49	-2.01 (-2.35 to -1.67)***	⊕⊕⊕⊕ Moderate
Overall	25	Not serious	Not serious	None	Not serious	Not serious ¹	1,744	1,610		⊕⊕⊕⊕ Moderate

¹ COMT inhibitor and multidisciplinary team care interventions need more trials. Miscellaneous therapy studies need greater sample sizes.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$. SMD, standardized mean difference.

studies with weak efficacy, including a substantial increase in the miscellaneous therapies by a single mindfulness therapy study (SMD = +1.67 vs. SMD = -0.03). Studies with large effect sizes in pain severity did not experience changes in effect size, and hence our primary conclusions did not change. A notable limitation was that multiple subgroups such as multidisciplinary team care and COMT inhibitors were each composed of a single trial. Other subgroups such as cannabinoids and opioids, and surgery, or electrical and Chinese therapies had only 2, 3, or 4 studies, respectively. As our search was exhaustive, there is a clear paucity of RCT evidence relating to the aforementioned groups that included a measure of pain severity. Considering the Cochrane Collaboration recommends a minimum number of 10 studies in each subgroup for a subgroup effect to be considered believable [12], our results should be generalized cautiously.

Implications for Clinical Practice and Research

Our findings show that safinamide is an important adjunct to the standard parkinsonian medications for alleviating pain in PD. Analgesics in the form of opioids and cannabinoids were shown to be effective but not nearly to the same extent. Thus, they are an important consideration if a patient responds poorly to safinamide. Although analgesic therapy is effective, only one-half of PD patients with pain report having used them [5, 45]. Nègre-Pagès et al. [45] found that analgesic use was lower for patients with PD pain as opposed to non-PD pain despite greater indices of pain severity and impairment of health-related quality of life. This may have arisen from the fact that PD pain was reported less frequently and/or because dopaminergic drug adjustment may have been preferred for PD pain treatment instead of analgesics. In light of our findings, it appears that dopaminergic drug adjustment yields little benefit, whereas adjusting levels of levodopa via entacapone (or presumably any other drug that inhibits peripheral metabolism of levodopa) may be a more favorable strategy. A multidisciplinary team approach is also recommended; however, additional studies with different team compositions need to be conducted to determine which teams work best. Furthermore, more trials of high methodological quality focusing on different aspects of pain (i.e., severity, temporality, localization, etc.) as well as the pathophysiological mechanisms of pain in PD are needed to form a consensus on the effectiveness of these therapies on patient-important outcomes related to pain.

Conclusion

This systematic review and meta-analysis found that safinamide was the most efficacious among all studied therapies in reducing pain in PD. Cannabinoids and opioids, multidisciplinary team care, COMT inhibitors, and electrical and Chinese therapies all exhibited relatively lower, yet strong efficacy. Pardoprunox, surgery, and dopaminergic agonists had limited efficacy. Complementary therapies have little to no efficacy or in-

crease rather than reduce pain in PD. More trials of high methodological quality focusing on different types of pain, as well as exploring novel therapies for pain in PD are warranted.

Disclosure Statement

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Appendix 1

PRISMA Checklist

Section/topic	Number	Checklist item	Reported on page number
<i>Title</i> Title	1	Identify the report as a systematic review, meta-analysis, or both	1
<i>Abstract</i> Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
<i>Introduction</i> Rationale	3	Describe the rationale for the review in the context of what is already known	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	2
Methods Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	11–12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	2

Section/topic	Number	Checklist item	Reported on page number
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	2
<i>Results</i>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, 3, 4–6, 13–15 PICOS, follow-up period) and provide the citations	3, 4–6, 13–15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	3, 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	8, 13–15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	3, 7, 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	7, 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	7, 15
<i>Discussion</i>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	7–9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	10
<i>Funding</i>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	10

Appendix 2

Search strategy. Conducted February 25, 2018.

Medline	Embase	Cochrane	Cinahl	Psycinfo
#1. Pharmacotherap\$.mp or exp Pharmacotherapy/ or Medical therap\$.mp orexp Medical therapy/ #2. Drug therap\$.mp or exp Drug therapy/ #3. 1 or 2 #4. Dopamine agonist\$.mp or exp Dopamine agonists/ or MAO-B	#1. Pharmacotherap\$.mp or exp Pharmacotherapy/ #2. Medical therap\$.mp or exp Medical therapy/ #3. Drug therap\$.mp or exp Drug therapy/ #4. 1 or 2 or 3 #5. Dopamine agonist\$.mp or exp	#1. MeSH descriptor: [Pain treatment] explode all trees #2. MeSH descriptor: [Parkinson's disease] explode all trees #3. Parkinson's disease #4. Pain #5. Pain severity	#1. MH ("Parkinson's disease") OR MH ("Parkinson disease") OR MH ("idiopathic Parkinson's disease") #2. TX ("pain") OR TX ("pain severity") #3. (MH Pharmacotherapy) OR (MH Medical therapy) OR (MH	#1. MJ Parkinson's disease #2. TX Pain #3. MJ Psychotherap* #4. MJ Cognitive behavior?ral therapy #5. MJ Behavior?ral therapy #6. MJ Gestalt therap* #7. MJ Existential therap*

Medline	Embase	Cochrane	Cinahl	Psycinfo
inhibitor\$.mp or exp MAO-B inhibitors or COMT inhibitor\$.mp or exp COMT inhibitors #5. Pramipexole.mp or Rotigotine.mp or Transdermal patch.mp or Apomorphine. mp or Ropinirole.mp or Pergolide.mp or Bromocriptine.mp or Cabergoline.mp or Amantadine.mp or selegiline.mp or rasagiline.mp or safinamide.mp or sumanirole.mp or piribedil.mp #6. Entacapone.mp or tolcapone.mp #7. Cannabis.mp or Cannabinoid\$.mp or exp Cannabinoids/ or Opioid\$.mp or exp Opioids/ #8. Anticholinergic\$.mp or exp Anticholinergics/ or Trihexyphenidyl.mp #9. 4 or 5 or 6 or 7 or 8 #10 Psychotherap\$.mp or exp Psychotherapy/ #11. (Cognitive or Behavior?ral or Humanis\$ or Psychoanaly\$ or Holistic) therap\$.mp #12. 10 or 11 #13. exp Physical therapy or physiotherapy\$.mp #14. exp (Complementary or Alternative) medicine #15. (Exercise or massage or mindfulness\$) therap\$.mp #16. Chinese medicine.mp or Herbal treatment.mp #17. Chiropract\$.mp or Acupuncture.mp #18. Electr* therap\$.mp or Electric* stimulat*.mp #19. 13 or 14 or 15 or 16 or 17 or 18 #20. Parkinson's disease.mp or Parkinson disease.mp or exp Parkinson's disease #21. Pain.mp or exp Pain #22. randomized controlled trial.pt. #23. controlled clinical trial.pt. #24. trial.ti. #25. placebo.ab. OR sham.ab. OR standard.ab. #26. random*.ab #27. 22 or 23 or 24 or 25 or 26 #33. 20 and 21 and 27 #34. 20 and 21 and 27 and (3 or 9 or 12 or 19) #35. Limit 34 to humans	Dopamine agonists/ #6. Pramipexole.mp or Rotigotine.mp or Transdermal patch.mp or Apomorphine.mp or Ropinirole.mp or Pergolide.mp or Bromocriptine.mp or Cabergoline.mp or Amantadine.mp or Sumanirole.mp or Piribedil.mp #7. MAO-B inhibitor\$.mp or exp MAO-B inhibitors/ #8. Selegiline.mp or rasagiline.mp or safinamide.mp #9. COMT inhibitor\$.mp or exp COMT inhibitors/ #10. Entacapone.mp or tolcapone.mp #11. Cannabis.mp or Cannabinoid\$.mp or exp Cannabinoids/ #12. Opioid\$.mp or exp Opioids/ #13. Anticholinergic\$.mp or exp Anticholinergics/ or Trihexyphenidyl.mp #14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 #15. Psychotherap\$.mp or exp Psychotherapy/ #16. Cognitive therap\$.mp #17. Behavior?ral therap\$.mp #18. Humanis\$ therap\$.mp #19. Psychoanaly\$ therap\$.mp #20. Holistic therap\$.mp #21. 15 or 16 or 17 or 18 or 19 or 20 #22. Physiotherap\$.mp or Exercise therap\$.mp or exp Physical therapy/ #23. Massage therap\$.mp or Meditation. mp or Mindfulness\$ therap\$.mp #24. Chinese medicine.mp or Herbal treatment.mp #25. Chiropract\$.mp or Acupuncture.mp #26. Electr* therap\$.mp or Electric* stimulat*.mp #27. 22 or 23 or 24 or 25 or 26 #28. Parkinson's disease.mp or Parkinson disease.mp or exp Parkinson's disease #29. Pain.mp or exp Pain #30. trial.ti #31. placebo.ab or sham.ab or control.ab or standard.ab #32. random*.ab #33. randomized controlled trial/ #34. exp controlled clinical trial/ #35. 30 or 31 or 32 or 33 or 34 #36. 28 and 29 and 35 #37. 28 and 29 and 35 and (4 or 14 or 21 or 27) #38. limit 37 to human	#6. Pain score #7. Pharmacotherap\$ #8. Medical therap\$ #9. Physiotherap\$ #10. Psychotherap\$ #11. Deep brain stimulation #12. Surg\$ #13. Acupuncture #14. Massage therap\$ #15. Cognitive therap\$ #16. Exercise therap\$ #17. Holistic therap\$ #18. Psychotherap\$ #19. Multidisciplinary care #20. Chinese medicine #21. Herbal therap\$ #22. Transdermal patch #23. Cannabis #24. Marijuana #25. Rotigotine #26. Ropinirole #27. Sumanirole #28. Piribedil #29. Cannabinoid #30. Safinamide #31. Pardoprinox #32. Analges\$ #33. Selegiline #34. Rasagiline #35. Anticholinergic\$ #36. Amantadine #37. Apomorphine #38. Trihexyphenidyl #39. COMT* OR COMT Inhibitors #40. Entacapone #41. Tolcapone #42. MAO-B Inhibitor #43. Electrical stimulation #44. Mindfulness\$ AND therap\$ #45. Dopaminergic agonists #46. (#7-#42) AND #3 AND #4 #47. (#7-#42) AND #3 AND #5 #48. (#7-#42) AND #3 AND #6	Drug therapy) #4. (MH Physiotherapy) OR (MH Exercise therapy) OR (MH Rehabilitation) #5. (MH Psychotherapy) OR (MH Cognitive therapy) OR (MH Behavior?ral therapy) OR (MH Humanistic therapy) OR (MH Psychoanalytic therapy) OR (MH Holistic therapy) #6. (MH Acupuncture) OR (MH Massage therapy) OR (MH Electrical therapy) OR (MH Electrical stimulation) #7. (MH Hydrotherapy) OR (MH Water-based therapy) #8. (MH Deep brain stimulation) OR (MH Subthalamic stimulation) OR (MH Surgery) #9. (MH Multidisiplinary care) OR (MH Allied health team care) #10. (MH Herbal medicine) OR (MH Herbal therapy) OR (MH Chinese medicine) #11. (MH cannabis) OR (MH marijuana) OR (MH cannabinoid*) #12. (MH opioid) #13. (MH rasagiline) OR (MH selegiline) OR (MH MAO-B inhibitor*) OR (MAO-B) #14. (MH COMT Inhibitor*) OR (MH entacapone) OR (MH tolcapone) #15. (MH safinamide) OR (MH pardoprinox) OR (MH analges*) #16. (MH anticholinergic*) OR (MH trihexyphenidyl) #17. (MH rotigotine) OR (MH transderm* patch) OR (MH pramipexole) OR (MH apomorphine) OR OR (MH sumanirole) OR (MH piribedil) OR (MH Dopamin* agonist*) #18. (MH Randomized Controlled Trial) OR (MH Controlled clinical trial) OR (MH Controlled trial) OR (MH Clinical trial) #19. (#1) AND (#2) AND (#3-17) AND (#18)	#8. MJ Mindfulness-based therap\$ #9. MJ Holistic therap* #10. MJ Yoga #11. MJ Humanistic therap* #12. MJ Client-centred therap* #13. MJ Psychoanaly* therap* OR Psychoanaly* #14. MJ Holistic therap* #15. MJ Meditation #16. MJ Randomized controlled trial #17. MJ Controlled clinical trial #18. #1 AND #2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15) AND #16 #19. #1 AND #2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15) AND #17

Appendix 3

Group-wise summary of demographical characteristics*.

Group	Age, years, mean (SD)		Gender, Male, %		Disease duration, years, mean (SD)	
	treatment	control	treatment	control	treatment	control
A – Dopaminergic Agonists	66.2 (1.3)	65.4 (1.1)	54	56	4.8 (0.97)	4.8 (0.80)
B – Cannabinoids & Opioids	66.9 (0.2)	67.2 (0.4)	56	59	10.5 (5.0)	10.4 (5.2)
C – Surgery	59.8 (0.68)	60.1 (1.2)	68	70	14.0 (2.8)	14.4 (4.8)

Group	Age, years, mean (SD)		Gender, Male, %		Disease duration, years, mean (SD)	
	treatment	control	treatment	control	treatment	control
D – Electrical & Chinese Therapies	67.9 (5.5)	68.2 (5.3)	61	59	8.9 (4.2)	5.6 (0.67)
E – Miscellaneous Therapies	67.3 (3.5)	66.6 (5.1)	59	56	7.0 (1.3)	6.7 (1.6)
F – Pardoprunox	63.6 (1.7)	63.6 (2.1)	67	61	7.1 (0.57)	6.6 (0.0)
G – Safinamide	60.9 (6.4)	60.8 (6.5)	72	65	8.6 (2.9)	8.6 (3.0)
H – COMT Inhibitors	69.8 (9.3)	70.2 (9.4)	73	69	4.4 (3.5)	4.5 (3.5)
I – Multidisciplinary Team Care	65.9 (8.5)	68.1 (8.8)	59	57	4.6 (3.9)	3.7 (3.5)

* Reported at base-line.

Appendix 4

Details of therapeutic intervention and control groups with standardized mean difference (d) and 95% confidence intervals for pain severity in the included trials.

First author	Year	Therapeutic intervention	Treatment details	Control details	d (95% CI)	Treatment phase duration, weeks	Follow-up phase duration, weeks
Barone [17]	2010	Pramipexole	Titrated dosage Increasing dose (0.125 mg/day -> 0.25 mg/day -> 0.5 mg/day -> 1.0 mg/day) after every 1 week until antidepressant effect achieved; max 5 weeks Remaining 7 weeks: maintenance treatment at one of above doses 3× day. Tapered off for max. 5 days	Identically appearing placebo with same procedure as shown in treatment details	-0.19 (-0.31 to -0.07)	12	2
Carroll [20]	2004	Cannabis	Titrated dosage. Body-weight dependent dose; max. 0.25 mg/kg THC, 2×/day	Identically appearing placebo capsules containing synthetic oil vesicle, 2×/day	-2.02 (-2.60 to -1.43)	1) 4 2) 4	2
Cattaneo [16]	2017	Safinamide	100 mg/day	Identically appearing placebo with same procedure as shown in treatment details	-4.83 (-5.07 to -4.59)	24	Study 016: 18 SETTLE: 4
Charles [22]	2014	Deep brain stimulation	24-month treatment phase Receive bilateral subthalamic nucleus stimulation AND optimal drug therapy	Drugs for standard PD care with individualized regimens for dosage, frequency and duration – examples: carbidopa/levodopa, pramipexole, ropinirole and selegiline	-0.25 (-0.98 to 0.48)	(Surgical procedure) 104	1) 52 2) 78 3) 104
Chua [25]	2017	Chinese medicine	32-week treatment phase Active herbal treatment 11 g, 2×/day	Identically appearing placebo granules	-1.13 (-1.39 to -0.87)	32	6
de Bie [24]	1999	Unilateral pallidotomy	Receive surgical treatment within 1 month Assessment after 6 months	Receive surgical treatment after 6 months (delayed)	-0.93 (-1.63 to -0.23)	Within 4 or 5 (1 month) (Surgical procedure)	26
Hauser [29]	2009	Pardoprunox	7-week treatment phase with 1 of 2 titration schemes differentiated at day 16: Group 1 – 6 mg/day increments for 7 day each from 6 mg/day start to max. 42 mg/day. Group 2 – 6 mg/day increments for 3 day each from 9 mg/day start to max. 36 mg/day, THEN 6 mg/day increments for 3 day each from 12 mg/day start to max. 42 mg/day. 4 days of down-titration 1-week follow-up	Identically appearing placebo with same procedure as in treatment details	-0.30 (-0.62 to 0.03)	7	1

First author	Year	Therapeutic intervention	Treatment details	Control details	d (95% CI)	Treatment phase duration, weeks	Follow-up phase duration, weeks
Jitkrisadukul [26]	2017	Tremor's glove	Resting hand-tremor suppressing medical device comprised of an electrical muscle stimulation (EMS) module and a tremor detection module. Sensor sampling rate is 100 Hz/10 s 30-min testing sessions for participants	"Sham glove" – visually identical and weight-wise the same as the treatment, except no EMS module	-2.35 (-3.28 to -1.42)	4 or 5 (1 month)	4 or 5 (1 month)
Kapur [38]	2012	Vibration therapy	CD player with a 150 W amplifier connected to vibration transducers on lounge chair mattress; CD frequencies ranged between 30–500 Hz for 30 min/day	"No vibration" – CD player disconnected from vibration transducers	-0.60 (-1.50 to 0.30)	4 or 5 (1 month)	1 day
Lei [27]	2016	Electroacupuncture	Scalp and body acupuncture with electrical stimulation. Electrical stimulation intensity level = between 3.5 and 4.5	Insertion of needles less than 4 mm just under the skin at non-acupuncture points (scalp, neck, shoulder, upper and lower extremities); no needle manipulation. Electrical stimulation intensity level = 0	-0.06 (-0.57 to 0.44)	3	3
Marck [32]	2013	Multidisciplinary care	Ongoing individualized care by movement disorders specialist allied with PD nurse and social worker	Usual care provided by the general neurologist	-2.01 (-2.35 to -1.67)	34.76 (8 months)	34.76 (8 months)
Ni [39]	2016	Power yoga	Progressively more challenging yoga procedure of performing fast transition of pose sequences, with each position held for a maximum of 3 breaths	Usual care from their general neurologist + non-exercise health education classes on changing your lifestyle, pharmacotherapy, therapy and exercise, nutrition and long-term care	-1.89 (-2.57 to -1.21)	13.03 (3 months)	Within 2
Olanow [31]	2004	Entacapone	200 mg for 26 weeks and gradually withdrawn over 2 weeks	Identically appearing placebo with same procedure as shown in treatment details	-1.81 (-1.94 to -1.67)	28	2
Perez de la Cruz [33]	2017	Hydrotherapy	A 45-minute Aquatic Ai Chi program comprised of 19 possible movements, followed by a calming down activity	10-min Warm-up exercises, 25-min strength training and aerobic exercises, followed by a 10-min cooling down period	-1.18 (-1.95 to -0.40)	10	4 or 5 (1 month)
Pickut [37]	2015	Mindfulness therapy	A 2.5-h session of meditation, yoga and body scan closely following mindfulness-based stress reduction	Usual care from a movement disorders specialist/neurologist when needed	1.67 (0.79 to 2.54)	8	8
Poliakoff [36]	2013	Gym training	Biweekly program 1 h weekly training in studio – gait, agility, some cardiovascular exercise and use of external stimuli (e.g., music); teamwork encouraged. 1 hour weekly training in gym – various cardiovascular activities (e.g., treadmill) emphasizing sustained physical activity	Wait-listed to receive the same program as the treatment group but starting 10 weeks later	0.09 (-0.34 to 0.52)	10	20
Rascol [30]	2012	Pardoprunox	Titration dosage Starting dose individual-based, but end at 12 mg/day by 3 weeks. Between weeks 3-7 – individual dose adjustments up to optimal maintenance dose of 42 mg/day	Identically appearing placebo following same titrating procedure as the treatment	-0.62 (-0.75 to -0.49)	7	1
Rascol [18]	2016	Rotigotine	Transdermal patch Titrated dose over 1-7 weeks starting and incrementing by 4 mg/24 h and incrementing until max. 16 mg/24 h reached	Identically appearing placebo patch with same titrating regimen as the treatment	-0.24 (-0.50 to 0.01)	7	4 (28 days)
Rintala [28]	2010	Cranial electrotherapy	Application of small amount of electrical current (100 microamperes) through the head via ear-clip electrodes for 40 min/day	Application of an identical appearing and assembled sham device that provided no electrical current stimulation for 40 min/day	-0.48 (-1.59 to 0.62)	6	6
Skogar [35]	2013	Tactile touch therapy	10 sessions of Massage therapy using a whole body tactile stimulation method + room immersed with lavender aroma + playing specific, distress-oriented music	Specific distress-oriented music played without the tactile stimulation method	1.44 (0.75 to 2.13)	11	1. 11 2. 14 3. 21 4. 34

First author	Year	Therapeutic intervention	Treatment details	Control details	d (95% CI)	Treatment phase duration, weeks	Follow-up phase duration, weeks
Trenkwalder [19]	2011	Rotigotine	Titrated dosage Start: 2 mg/24 h, with 2 mg/24 h increments to Max: 16 mg/24 h. Max. dose maintained for 4-weeks	Identically appearing placebo with same procedure as shown in treatment details	-0.36 (-0.48 to 0.23)	12	4 or 5 (1 month)
Trenkwalder [21]	2015	Oxycodone-naloxone	Oxycodone 2× 5 mg/24 h Naloxone 2× 2.5 mg/24 h Incremented only if pain not adequately controlled Max. Oxycodone: 2× 20 mg/24 h Max. Naloxone: 2× 10 mg/24 h	Identically appearing placebo given 2×/24 h	-2.35 (-2.78 to -1.93)	16	1-1.4 (7-10 days)
Volpe [34]	2017	Hydrotherapy	5 60-min sessions per week of a training program for correcting postural deformities within a therapeutic swimming pool	Similar procedure as in treatment, but non-water based therapeutic environment	0.28 (-0.55 to -0.10)	8	8.69 (2 months)
Williams [23]	2010	Deep brain stimulation	Stimulation or lesioning of either the subthalamic nucleus or globus pallidus pars interna (Whichever is standard during time of surgery) + Medical therapy – 10 mg apomorphine, dopaminergic agonists (e.g., 3.3 mg rotigotine), MAO-B inhibitors (e.g., 10 mg selegiline), COMT inhibitors (e.g., 133 mg entacapone), 100 mg amantadine, 100 mg levodopa and other PD-treating medications	Medical therapy only	-0.33 (-0.55 to -0.10)	(Surgical procedure)	52.14 (1 year)

Appendix 5

Sensitivity analysis of missing data and lower biased studies for the outcome of pain severity.

Analysis type	Therapeutic intervention	SMD or overall SMD (95% CI), <i>p</i> value
Sensitivity analysis type I Includes all patients enrolled in the study, regardless of whether they were successfully followed. (<i>n</i> = 3,929)	Dopaminergic agonists Cannabinoids and opioids Surgery Electrical and Chinese therapies Miscellaneous therapies Pardoprunox Safinamide COMT inhibitors Multidisciplinary team care	-0.27 (-0.27 to -0.38), <i>p</i> < 0.0001 -2.26 (-2.56 to -1.95), <i>p</i> < 0.0001 -0.43 (-0.76 to -0.09), <i>p</i> = 0.012 -0.98 (-1.79 to -0.16), <i>p</i> = 0.019 -0.03 (-0.91 to 0.85), <i>p</i> = 0.947 -0.48 (-0.79 to -0.17), <i>p</i> = 0.003 -4.83 (-5.05 to -4.61), <i>p</i> < 0.0001 -1.81 (-1.92 to -1.69), <i>p</i> < 0.0001 -2.01 (-2.32 to -1.70), <i>p</i> < 0.0001
Sensitivity analysis type II Includes all studies with less than 2 high risk concerns on the risk of bias assessment. (<i>n</i> = 2,568)	Dopaminergic agonists Cannabinoids and opioids Electrical and Chinese therapies Miscellaneous therapies Pardoprunox Safinamide COMT inhibitors	-0.27 (-0.43 to -0.11), <i>p</i> = 0.001 -2.35 (-2.78 to -1.93), <i>p</i> < 0.0001 -1.11 (-2.09 to -0.13), <i>p</i> = 0.027 1.67 (0.79 to 2.54), <i>p</i> < 0.0001 -0.62 (-0.75 to -0.49), <i>p</i> < 0.0001 -4.83 (-5.07 to -4.59), <i>p</i> < 0.0001 -1.81 (-1.94 to -1.67), <i>p</i> < 0.0001
Original analysis – complete case analysis Includes all patients who were successfully followed. (<i>n</i> = 3,354)	Dopaminergic agonists Cannabinoids and opioids Surgery Electrical and Chinese therapies Miscellaneous therapies Pardoprunox Safinamide COMT inhibitors Multidisciplinary team care	-0.27 (-0.38 to -0.15), <i>p</i> < 0.0001 -2.24 (-2.58 to -1.89), <i>p</i> < 0.0001 -0.42 (-0.74 to -0.10), <i>p</i> = 0.011 -0.98 (-1.80 to -0.16), <i>p</i> = 0.020 -0.03 (-0.94 to 0.88), <i>p</i> = 0.947 -0.50 (-0.80 to -0.19), <i>p</i> = 0.001 -4.83 (-5.07 to -4.59), <i>p</i> < 0.0001 -1.81 (-1.94 to -1.67), <i>p</i> < 0.0001 -2.01 (-2.35 to -1.67), <i>p</i> < 0.0001

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