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REVIEW ARTICLE

Impact of Pharmacotherapy on Quality of Life in Patients with Parkinson's Disease

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Abstract Quality of life (QoL) is a patient-reported outcome frequently included in Parkinson's disease (PD) clinical trials as a secondary or tertiary endpoint. However, QoL is an important variable that reflects the impact of disease and treatment from the patients' perspective. In a chronic, neurodegenerative disease such as PD, with a wide range of complex symptoms, QoL provides valuable and comprehensive information on the patients' health status. This narrative review aims to evaluate the effect of specific PD treatments currently in use on patients' QoL measured with the Parkinson's Disease Questionnaire, 39-item (PDQ-39) or 8-item (PDQ-8) version. A quantification of this effect is provided by calculation of the relative change and effect size. These two parameters allow an intuitive standardized approach to the importance of change based on its magnitude. Some high-quality studies (Level I) were found for levodopa (immediate- or extended-release formulations), levodopa with added-on catechol-*O*-methyltransferase (COMT) inhibitors, levodopa/carbidopa gel for intestinal infusion, some dopamine agonists (ropinirole, cabergoline, pergolide), and the monoamine oxidase B (MAO-B) inhibitor safinamide. As a whole, these studies found a beneficial effect of variable magnitude, weak to moderate, on patients' QoL. Studies with a lower level of evidence or not providing enough data to estimate relative change and effect size, including those for the apomorphine subcutaneous pump, also reported improvement of QoL, but the evidence was insufficient to confirm the effect. More high-quality studies focused on QoL are needed to determine the real impact of PD drug treatments for this important outcome.

Key Points

Quality of life (QoL) is a relevant outcome for clinical trials and research on Parkinson's disease (PD), and can be measured by means of questionnaires such as the Parkinson's Disease Questionnaire, 39-item (PDQ-39) or 8-item (PDQ-8) version.

The importance of change can be estimated from its magnitude, determined by formulas providing standardized values.

For some anti-PD drugs there is strong evidence demonstrating weak to moderate beneficial effect on patients' QoL, but this kind of evidence is lacking for others.

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1 Introduction

This article reviews the clinical evidence to date regarding antiparkinsonian pharmacotherapy and quality of life (QoL) in Parkinson's disease (PD). The previous review

with this objective was also published in *CNS Drugs* and dates back to 2008 [1]. An updated version is warranted since the past 6 years have seen novel therapeutic options entering the scene and an increased number of clinical trials assessing QoL. The current armamentarium for PD includes four drug classes with a diversity of mechanisms aiming to enhance the levodopa-depleted striato nigral circuits. These drugs include levodopa, catechol-*O*-methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors and oral and transdermal synthetic dopamine agonists. For advanced motor symptoms, where fluctuations and dyskinesias are not adequately controlled with the oral or transdermal options, new formulations have been developed allowing continuous medication infusions. In an attempt to standardize the available data and provide practical information for the clinician, the published trials were rated according to their level of evidence, relative change and effect size on QoL were calculated, and conclusions about efficacy were provided.

1.1 Definition of Quality of Life (QoL)

QoL is defined as a multidimensional concept combining physical, psychological, and social aspects with personal judgments about well-being and satisfaction with health [2]. This endpoint is gaining increased importance as an assessment variable in PD clinical trials due to various reasons, some related to the advances in our knowledge of PD itself, and others regarding the paradigm shift towards a patient-centered model of medicine that is currently ongoing [3]. Clinical investigation in the past decades has rendered the classical view of PD as a motor neurological disease obsolete. Clinical research has established that there are more than 30 possible non-motor symptoms that may affect the parkinsonian patient. They consist of dysautonomia (urinary urgency, constipation, sweating, orthostasis, and sexual dysfunction), mood issues (depression, anxiety), cognitive problems (from mild impairment to severe dementia), impulse control disorders, and sleep alterations [including rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, and daytime sleepiness]. Some of the symptoms (olfaction loss, depression, RBD) may be clinical biomarkers of disease progression as they may appear years before the first motor symptoms [4] and the unequivocal progression of cognitive impairment to dementia in most patients is a marker of disability [5]. This vast array of non-motor symptoms has thus redefined PD as a complex multidimensional neurodegenerative disease. It is clearly not enough for antiparkinsonian medications to demonstrate benefit on the motor aspects of the disease. In fact, a recent study in PD patients suggests that non-motor symptoms, when considered as a whole, have a higher impact on how patients judge their well-being than the classic motor issues [6, 7]. Therefore, when designing a clinical trial to evaluate the benefit of a drug on a complex chronic disease such as PD, a comprehensive variable such as QoL that gives holistic information about the patient's well-being is evidently useful. QoL is a patient-reported outcome (PRO) and PROs are highly valued in the current patient-centered healthcare paradigm, since they provide information from the patient's perspective, without intermediaries.

1.2 QoL Measures

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) recommend that PROs be included in clinical trials and measured by properly validated instruments in the corresponding condition [8, 9]. Many scales have been developed to measure QoL but only a few are disease specific and thus particularly recommended for PD patients [10]. Specific scales address health problems that are highly prevalent in the target population for which they were developed and show better responsiveness than generic measures. In PD, there are five specific scales [Parkinson's Disease Questionnaire, 39-item version (PDQ-39), Parkinson's Disease Questionnaire, 8-item version (PDQ-8), Parkinson's Impact Scale (PIMS), Parkinson's Disease Quality of Life Questionnaire (PDQL), SCales for Outcomes in Parkinson's disease—PsychoSocial (SCOPA-PS)] that have gained the qualification of 'recommended' for application in PD patients. As such, they fulfill the criteria of prior application in PD; successful clinimetric testing with established validation, reliability, and sensitivity assessments; and use by researchers other than the group that developed the scale [10]. The PDQ-39 and the shorter PDQ-8 questionnaires address eight key dimensions of health and daily activities and are the most widely used.

2 Literature Search and Classification Methodology

A literature search was carried out through to 30 November 2014 using PubMed. Terms included for the search were Parkinson's Disease/PD, quality of life/QoL, health related quality of life/HRQoL, PDQ-39/PDQ-8, levodopa, entacapone, tolcapone, COMT inhibitor, dopamine agonists, pergolide, cabergoline, rotigotine, ropinirol, pramipexole, MAO-B inhibitor, selegiline, rasagiline, apomorphine, apomorphine infusion/pump, duodenal levodopa (+/− infusion/pump/gel), jejunal levodopa (+/− infusion/pump/gel), and duodopa. In addition, related references from papers and personal files were reviewed.

Criteria for inclusion of articles to this narrative review were (1) QoL was a primary or secondary variable of interest in the study; (2) QoL was measured with the PDQ-39 or PDQ-8 questionnaires; and (3) information on the QoL outcome was provided as relative change and effect size, or enough information (means and standard deviations at baseline and follow-up) was given to calculate these parameters. Exclusion criteria were (1) no fulfillment of any inclusion criterion; and (2) language other than English or Spanish.

Articles were classified and rated according to level of evidence (Table 1) [11]. Relative change [12] and effect size [13, 14] were calculated, where possible, according to the following formulae:

$$\text{Relative change} = (\text{mean}_{T2} - \text{mean}_{T1})/\text{mean}_{T1}]$$

$$\text{Effect size} = [(\text{mean}_{T2} - \text{mean}_{T1})/\text{standard deviation}_{T1}].$$

These two variables provide information on how important the change was after exposure to the tested drug. The higher the magnitude of relative change and effect size, the more likely that it will be clinically meaningful. Effect size values are standardized as follows: <0.20, negligible; 0.20–0.49, small; 0.50–0.79, moderate; and ≥ 0.80, large effect [15, 16]. The information was summarized, quantifying each intervention's impact on magnitude of change in QoL (Tables 2, 3, 4, 5, 6). Only the studies with outcomes translated to relative change and effect size are shown in the tables. Conclusions regarding efficacy were made according to the effect of each drug on QoL, as in previous studies [11], and refer only to those studies meeting the three criteria for review.

3 Impact of Pharmacotherapy on QoL

3.1 Levodopa With and Without Catechol-*O*-Methyltransferase Inhibitors

Levodopa is the usual treatment in PD, alone or in combination with other drugs, and the most effective, although its prolonged use can cause development of motor complications, such as on–off fluctuations and dyskinesias. Administration of COMT or MAO-B inhibitors along with levodopa extends its plasma half-life and permits a more continuous delivery of levodopa to the brain [17, 18], increasing 'on' time, reducing 'off' time, and allowing levodopa dose reduction [1]. More recent is the extended-release formulation of oral carbidopa–levodopa (IPX066), composed by microbeads designed to dissolve at various rates in the small bowel, allowing for sustaining therapeutic serum levodopa concentrations for longer periods [19].

Twelve studies assessing the impact of levodopa on QoL with PDQ-39/PDQ-8 and enough data to calculate effect size and relative change were identified and reviewed (Table 2). Among them, there is one Level I clinical trial reporting the effect of immediate-release oral levodopa–carbidopa on PDQ-39, in comparison with intestinal gel formulation [20]. Although oral levodopa–carbidopa was

Table 1 Criteria for levels of evidence and conclusions on efficacy (modified from Martinez-Martin and Kurtis [11])

Level of evidence	Definition
Level I	Randomized controlled trials
	Minimum sample size: 30 patients in each group
	Minimum follow-up: 3 months
Level II	Randomized studies with very small samples, short follow-up (<3 months), open-label after randomization at baseline (extension); or
	Non-randomized clinical trials, or observational controlled studies such as cohort or case-control studies
Level III	Non-controlled studies, i.e., case series
Conclusion on efficacy	**Effect on quality of life**
Efficacious	Evidence shows that the intervention has a positive effect (based on data from at least one high-quality randomized controlled trial and no conflicting data from other randomized controlled trials)
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect (based on data from any randomized controlled trial and no conflicting data from other randomized controlled trials)
Unlikely efficacious	Evidence suggests that the intervention does not have a positive effect (based on data from any randomized controlled trial and no conflicting data from other randomized controlled trials)
Non-efficacious	Evidence shows that the intervention does not have a positive effect (based on data from at least one high-quality randomized controlled trial and no conflicting data from other randomized controlled trials)
Insufficient evidence	There are no data available or available data do not provide enough evidence either for or against the use of the intervention (all the circumstances not covered by the previous statements)

Table 2 Studies on levodopa with information on relative change and effect size

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Martinez-Martin et al. [22] and Martinez-Martin and Koller [23] (transfer to controlled-release levodopa/carbidopa)	621	III	PDQ-39	3 months	Significant improvement in QoL	30	0.48
Olanow et al. [20] (immediate-release oral levodopa–carbidopa vs intestinal gel formulation)	37 + 34	I	PDQ-39	12 weeks	Pre: 38.6 ± 17.9 (–3.9)	10.1	0.22
Hauser et al. [24] [extended-release carbidopa/levodopa (IPX066) vs. immediate-release]	398	I	PDQ-39	13 weeks	Extended release: Pre: 30.6 ± 15.7 Post: 26.9 ± 15.8 (–3.7) Immediate release: Pre: 31.3 ± 17.0 Post: 29.4 ± 15.9 (–1.9)	Extended release: 12.1 Immediate release: 6.1	Extended release: 0.24 Immediate release: 0.11
Pahwa et al. [25] [extended-release carbidopa–levodopa (IPX066) vs. placebo]	381	I	PDQ-39	30 weeks	Pre: 145 mg group: 26.0 ± 16.9 (–4.4) 245 mg group: 25.2 ± 18.6 (–3.8) 390 mg group: 25.1 ± 17.1 (–6.0)	145 mg group: 16.92 245 mg group: 15.07 390 mg group: 23.90	145 mg group: 0.26 245 mg group: 0.20 390 mg group: 0.35
Koller et al. [26] (levodopa + tolcapone vs. levodopa + pergolide)	203	II	PDQ-39	12 weeks	Levodopa + pergolide: Pre: 43.9 ± 12.7 Post: 39.4 ± 12.6 (–4.5) Levodopa + tolcapone: Pre: 45.2 ± 12.0 Post: 38.1 ± 12.0 (–7.1)	Levodopa + pergolide: 10.25 Levodopa +tolcapone: 15.71	Levodopa + pergolide: 0.35 Levodopa + tolcapone: 0.59
Olanow et al. [27] (levodopa + entacapone vs. levodopa + placebo)	373	I	PDQ-39	26 weeks	Levodopa + entacapone: 30.2 ± 15.48 (–0.7) Levodopa + placebo: 30.3 ± 13.14 (1.6)	Levodopa + entacapone: 2.31 Levodopa + placebo: 5.28	Levodopa + entacapone: 0.04 Levodopa + placebo: 0.12
Deuschl et al. [28] (levodopa + entacapone vs. levodopa + cabergoline)	161	II	PDQ-39	12 weeks	Entacapone: Pre: 28.3 ± 14.7 Post: 24.9 ± 14.8 (–3.4) Cabergoline: Pre: 28.0 ± 12.7 Post: 21.7 ± 12.8 (–6.3)	Entacapone: 12.01 Cabergoline: 22.5	Entacapone: 0.23 Cabergoline: 0.50

Table 2 continued

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Tolosa et al. [29] (levodopa/carbidopa/entacapone vs. levodopa/carbidopa)	95	I	PDQ-39	3 months	Levodopa/carbidopa: Pre: 139.6 ± 24.8 Post: 139.4 ± 25.9 (–0.2)[a] Levodopa–entacapone: Pre: 140.1 ± 23.5 Post: 146.3 ± 24.4 (6.2)[a] (Not standardized)	Levodopa/carbidopa: 0.14 Levodopa–entacapone: 4.24	Levodopa/carbidopa: 0.008 Levodopa-entacapone: 0.26
Reichmann et al. [30] (levodopa + entacapone vs. levodopa–placebo)	270	I	PDQ-39	13 weeks	Pre: 29.0 ± 13.5 (–0.60)	2.07	0.04
Durif et al. [32] (levodopa + entacapone)	489	III	PDQ-39	8 weeks	PDQ-39 domains: Pre: ranged from 17.5 ± 20.9 (Social Support) to 55.7 ± 23.4 (Mobility) Post: ranged from 16.6 ± 20.3 (Social Support) to 49.7 ± 23.9 (Mobility) Δ: ranged from 0.9 (Social Support) to 6.0 (Mobility).	Mobility: 10.77 ADL: 10.92 Emotional Well-Being: 11.56 Stigma: 10.12 Social Support: 5.14 Cognition: 3.17 Communication: 9.87 Bodily Discomfort: 14.01	Mobility: 0.26 ADL: 0.25 Emotional Well-Being: 0.26 Stigma: 0.18 Social Support: 0.04 Cognition: 0.06 Communication: 0.15 Bodily Discomfort: 0.26
Gershanik et al. [31] (levodopa + entacapone)	374	III	PDQ-39	8 weeks (treatment) 20 weeks (extension)	Treatment: Pre: 38.4 Post: 33.5 (–4.9) Extension: 33.6 (–4.8)	Treatment: 12.76 Extension: 12.5	
Grandas et al. [34] (levodopa + entacapone)	249	III	PDQ-8	3 months (treatment)	Pre: 11.9 ± 5.4 Post: 9.3 ± 4.6 (–2.6) (Not standardized)	21.84	0.48

ADL activities of daily living, *PDQ-8* Parkinson's Disease Questionnaire, 8-item version, *PDQ-39* Parkinson's Disease Questionnaire, 39-item version, *QoL* quality of life, *SD* standard deviation

[a] Data as published by the authors

Table 3 Studies on dopamine agonists with information on relative change and effect size

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Fedorova and Chigir' [40] (pramipexole)	30	III	PDQ-39	13 months	Pre: 82.4 ± 13.3 Post: 98.1 ± 12.7[a] ($p < 0.01$)	19	1.2
Takanashi et al. [41] (pramipexole extended-release)	29	III	PDQ-39	8 weeks	Pre: 20.4 ± 13.4 Post: 19.6 (–0.8) Not significant differences	3.92	0.06
Odin et al. [44] (cabergoline)	34	III	PDQ-39	4.5 months	(6.28) Significant improvement	15.6	0.51
Deuschl et al. [28] (levodopa + entacapone vs. levodopa + cabergoline)	161	I	PDQ-39	12 weeks	Entacapone: Pre: 28.3 ± 14.7 Post: 24.9 ± 14.8 (–3.4) Cabergoline: Pre: 28.0 ± 12.7 Post: 21.7 ± 12.8 (–6.3)	Entacapone: 12.01 Cabergoline: 22.5	Entacapone: 0.23 Cabergoline: 0.50
Linazasoro, Spanish Dopamine Agonists Study Group [42] (cabergoline vs. other dopamine agonists)	128	III	PDQ-8	12 weeks	Pre: 13.3 Post: 9.9 (–3.4) (Not standardized) ($p < 0.0001$)	25.6	
Pahwa et al. [46] (add-on ropinirole prolonged-release vs. placebo)	393	I	PDQ-39	24 weeks	Pre (Δ): Mobility: 42.2 ± 25.6 (–4.9) ADL: 42.3 ± 24.4 (–5.4) Emotional Well-Being: 32.5 ± 21.7 (–4.3) Stigma: 31.2 ± 23.9 (–3.3) Social Support: 14.1 ± 19.9 (–1.5) Cognition: 25.0 ± 18.0 (–3.4) Communication: 24.7 ± 20.7 (–1.4) Bodily Discomfort: 37.7 ± 20.8 (–3.6)	Mobility: 11.61 ADL: 10.73 Emotional Well-Being: 13.23 Stigma: 10.58 Social Support: 10.63 Cognition: 13.6 Communication: 5.67 Bodily Discomfort: 9.55	Mobility: 0.19 ADL: 0.22 Emotional Well-Being: 0.20 Stigma: 0.14 Social Support: 0.07 Cognition: 0.19 Communication: 0.07 Bodily Discomfort: 0.17
Trenkwalder et al. [49] (rotigotine vs. placebo)	287	II	PDQ-8	12 weeks (follow-up: 4 weeks)	Pre: 30.8 ± 18.2 (–6.9)	22.40	0.38

Table 3 continued

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Koller et al. [26] (levodopa + pergolide vs. levodopa + tolcapone)	203	I	PDQ-39	12 weeks	Levodopa + pergolide: Pre: 43.9 ± 12.7 Post: 39.4 ± 12.6 (–4.5) Levodopa + tolcapone: Pre: 45.2 ± 12.0 Post: 38.1 ± 12.0 (–7.1)	Levodopa + pergolide: 10.25 Levodopa + tolcapone: 15.71	Levodopa + pergolide: 0.35 Levodopa +tolcapone: 0.59
Thobois et al. [50] (piribedil)	37	II	PDQ-39	12 weeks	Pre: 7.2 ± 2.5 Post: 6 ± 2.9 (–1.2) (Not standardized)	16.67	0.48

ADL activities of daily living, *PDQ-8* Parkinson's Disease Questionnaire, 8-item version, *PDQ-39* Parkinson's Disease Questionnaire, 39-item version, *QoL* quality of life, *SD* standard deviation

[a] Data as published by the authors

Table 4 Studies on monoamine oxidase B inhibitors with information on relative change and effect size

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Reichmann and Jost [57] (rasagiline)	754	III	PDQ-39	4 months	Not reported (significant improvement in both groups)	Monotherapy: 27.5 Combination: 19.0	
Müller et al. [59] (selegiline to rasagiline)	30	III	PDQ-39	4 months	Pre: 24.6 ± 2.8 Post: 22.6 ± 2.6 (2.0)	8.1	0.71
Lyons et al. [58] (orally disintegrating selegiline)	60	III	PDQ-39	12 weeks	Pre: 28.6 ± 15.3 Post: 24.4 ± 15.1 (4.2)	14.7	0.27
Borgohain et al. [62] (safinamide)	447	I	PDQ-39	6 months	100 mg/day: Pre: 229 ± 124.1 Post: not reported (–28.4) 50 mg/day: Pre: 225.0 ± 110.5 Post: not reported (–16.4) (Not standardized)[a]	100 mg/day: 12.4 50 mg/day: 7.3	100 mg/day: 0.23 50 mg/day: 0.15

PDQ-39 Parkinson's Disease Questionnaire, 39-item version, *QoL* quality of life, *SD* standard deviation

[a] Data as published by the authors

Table 5 Studies on apomorphine with information on relative change and effect size

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Martinez-Martin et al. [67] (apomorphine)	17	III	PDQ-8	12.5 ± 11.5 months	Pre: 55.7 ± 19.8 Post: 32.3 ± 21.5 (–23.3)	42.0	1.18
Martinez-Martin et al. [64] (apomorphine vs. duodopa)	43 + 44	II	PDQ-8	6 months	Pre: 49.8 ± 16.6 Post: 35.0 ± 18.0 (–14.8)	29.75	0.89

PDQ-8 Parkinson's Disease Questionnaire, 8-item version, *QoL* quality of life, *SD* standard deviation

beneficial for QoL, relative change and effect size values were higher for the intestinal gel group.

A Level II clinical trial on the effect of levodopa alone against dopamine agonists or MAO-B inhibitors on QoL [21] showed results favoring levodopa as initial treatment over levodopa-sparing therapy, both on PDQ-39 mobility and activities of daily living scores and the summary index, even though patients treated with levodopa developed more abnormal movements. Benefits, although few, persisted over the study period (7 years). A Level III study [22, 23] on 621 patients that switched from standard levodopa to controlled-release levodopa, found better QoL after 3 months of follow-up, with a relative change of 30 % and an effect size of 0.48.

The effect of IPX066 on QoL has been tested in two Level I studies. Hauser et al. [24] compared immediate-release and extended-release carbidopa–levodopa formulations in a randomized, double-blind, double-dummy study of 471 participants with motor fluctuations. The IPX066 formulation was beneficial for QoL, reaching a relative change of 12.1 % and an effect size of 0.24 in the PDQ-39 summary index, while immediate-release carbidopa–levodopa had a relative change of 6.1 % and an effect size of 0.11. In a randomized, double-blind, placebo-controlled Level I clinical trial, the impact on QoL of IPX066 at three different doses (145, 245, and 390 mg, administered three times daily) was tested [25]. Significant changes were observed in PDQ-39 summary index from baseline and compared with placebo. The relative change ranged from 15.1 % (245 mg group) to 23.9 % (390 mg), and the effect size ranged from 0.20 (245 mg) to 0.36 (390 mg).

The rest of the identified trials assessed the effects of COMT inhibitors (tolcapone, entacapone) or other drugs (e.g., pergolide) in combination with levodopa. Tolcapone as an add-on treatment to levodopa was beneficial in improving QoL in PD patients with motor fluctuations in a Level I clinical trial [26], with better response in PDQ-39 (relative change 15.7 %, effect size 0.59) than pergolide (relative change 10.3 %, effect size 0.35), and fewer adverse events. However, due to its potential hepatotoxicity, liver function must be frequently monitored if tolcapone is used.

Levodopa with entacapone has been tested in four Level I clinical trials using PDQ-39 [27–30]. In a double-blind, placebo-controlled clinical trial, Olanow et al. [27] found significant improvement in QoL with the administration of levodopa with entacapone compared with placebo, although the change was of small magnitude (relative change: 2.3 % of improvement for entacapone, 5.3 % of worsening for placebo; effect size: 0.04 improvement for entacapone, 0.12 worsening for placebo). Deuschl et al. [28] compared the effect on QoL of entacapone versus cabergoline. PDQ-39 scores significantly decreased from baseline with both drugs, but cabergoline showed a higher relative change and effect size (22.5 % and 0.50, respectively) than entacapone (12.0 % and 0.23, respectively). In a randomized, double-blind clinical trial, Tolosa et al. [29] tested the efficacy of levodopa/carbidopa/entacapone versus levodopa/carbidopa only, with better results for added on entacapone. However, in another study [30] there were no significant improvements in QoL when adding entacapone.

Other studies on entacapone (evidence Level III) [31–34] found reductions in PDQ-39 or PDQ-8 scores. For PDQ-39, relative change was 15.5 % [31] for the summary index and a range of 3.2–14.0 % for PDQ-39 domains [32]. Using PDQ-8, Onofrj et al. [33] found a mean reduction in scores of 1.8 with no significant differences by dose, while in another study [34] the mean change in PDQ-8 was −2.6, with a relative change of 21.8 % and an effect size of 0.48.

In summary, there are few high-quality studies on the efficacy of levodopa (immediate- or extended-release formulations) or levodopa with COMT inhibitors (entacapone/tolcapone) in improving the QoL of PD patients. Evidence demonstrates that levodopa is efficacious to induce beneficial changes of small magnitude in QoL and that they are likely maintained over time.

Table 6 Studies on levodopa/carbidopa intestinal gel with information on relative change and effect size

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Antonini et al. [84] (levodopa–carbidopa gel infusion)	18	III	PDQ-39	24 months	Pre: 59.5 ± 14.4 Post: 42.2 ± 10.3 (10.3)	17.31	1.20
Isacson et al. [69] (levodopa–carbidopa gel infusion)	12	III	PDQ-39	6 months	Pre: 24.3 ± 7.8 Post: 26.5 ± 14.8 (2.2)	9.05	0.28
Honig et al. [85] (levodopa–carbidopa gel infusion)	22	III	PDQ-8	6 months	Pre: 44.2 ± 18.4 Post: 20.7 ± 12.0 (–23.5)	53.2	1.28
Puente et al. [86] (levodopa–carbidopa gel infusion)	9	III	PDQ-39	18 months	Pre: 73.2 ± 11.7 Post: 45.7 ± 21.7 (–27.5)	38.0	2.39
Santos-García et al. [74] (levodopa–carbidopa gel infusion)	11	III	PDQ-39	3–31 months	Pre: 88.6 ± 17.9 Post: not reported (–42.5)	48.0	2.37
Meppelink et al. [70] (levodopa–carbidopa gel infusion)	15	III	PDQ-8	6 months	Drug-naïve group: Pre: 10.7 ± 3.1 Post: 7.1 ± 4.9 (–3.6) Previous users: Pre: 9.1 ± 6.5 Post: 8.3 ± 5.4 (–0.8)	Drug-naïve group: 33.6 Previous users: 8.8	Drug-naïve group: 1.16 Previous users: 0.12
Fasano et al. [71] (levodopa–carbidopa gel infusion)	12	III	PDQ-8	6–52 months (mean 24.9)	Pre: 18.1 ± 6.6 Post: 16.7 ± 6.0 (–1.4)	7.7	0.21
Pålhagen et al. [87] (levodopa–carbidopa gel infusion)	25	III	PDQ-39	12 months	Pre: 33.6 ± 10.8 Post: 28.8 ± 12.8 (–4.8)	14.3	0.44
Santos-García et al. [75] (levodopa–carbidopa gel infusion)	9	III	PDQ-39	6 months, 25.3 months	Pre: 55.6 ± 11.5 Post (6 months): 29.7 ± 8.6 (–25.9) Post (end of follow-up): 34.8 ± 11.2 (–20.8)	6 months: 46.6 End of follow-up: 37.4	6 months: 2.25 End of follow-up: 1.80
Santos-García et al. [73] (levodopa–carbidopa gel infusion)	7	III	PDQ-39	23–42 (mean 31.4) months	Pre: 53.7 ± 11.9 Post: 33.6 ± 12.8 (–20.1)	37.4	1.69
Foltynie et al. [88] (levodopa–carbidopa gel infusion)	11	III	PDQ-39	3–12 months	Pre: 49.7 ± 10.4 Post (3 months): 35.8 ± 13.3 (–13.9) Post (latest follow-up): 38.7 ± 11.2 (–11.0)	3 months: 28.0 Latest follow-up: 22.1	3 months: 1.33 Latest follow-up: 1.06
Zibetti et al. [76] (levodopa–carbidopa gel infusion)	17	III	PDQ-39	36.2 ± 11.5 months (mean)	Pre: 59.2 ± 18.7 Post: 43.1 ± 13.9 (–16.1)	27.2	0.89

Table 6 continued

References (drug)	*n*	Level of evidence	QoL scale	Length of follow-up	Pre–post mean ± SD (Δ) effect on QoL	Relative change (%)	Effect size
Cáceres-Redondo et al. [89] (levodopa–carbidopa gel infusion)	29	III	PDQ-39	24 months	Pre: 84.2 ± 18.7 Post: 74.3 ± 21.3 (–9.9)	13.3	0.46
Martinez-Martin et al. [64] (apomorphine vs. levodopa–carbidopa gel infusion)	43 + 44	III	PDQ-8	6 months	Pre: 48.6 ± 14.6 Post: 32.0 ± 14.9 (–16.6)	34.2	1.14
Olanow et al. [20] (levodopa–carbidopa gel infusion vs. immediate-release oral levodopa–carbidopa)	37 + 34	I	PDQ-39	12 weeks	Pre: 35.1 ± 18.0 (–10.9)	31.0	0.61
Sensi et al. [90] (levodopa–carbidopa gel infusion)	17	III	PDQ-8	24 months	Pre: 43.3 ± 13.7 Post: 29.9 ± 17.0 (–13.4)	30.9	0.98

PDQ-8 Parkinson's Disease Questionnaire, 8-item version, *PDQ-39* Parkinson's Disease Questionnaire, 39-item version, *QoL* quality of life, *SD* standard deviation

3.2 Dopamine Agonists

Dopamine agonists can be administered either as monotherapy or as adjunctive treatment along with levodopa or other antiparkinsonian drugs. They have a longer half-life than levodopa, which may result in less pulsatile stimulation of dopamine receptors, reducing the emergence of motor complications [35]. However, intake of dopamine agonists is associated with a higher incidence of non-motor complications, such as nausea, hypotension, somnolence and sudden onset sleep attacks, impulse control disorders, and dysautonomic symptoms. Identified studies fulfilling the inclusion criteria have assessed the effect of the following dopamine agonists on QoL: pramipexole, cabergoline, ropinirole, rotigotine, pergolide, and piribedil (Table 3).

Pramipexole is an oral, non-ergotamine-derived dopamine agonist that has demonstrated efficacy in improving motor function, reducing disability and 'off' periods and increasing 'on' time without dyskinesias [36, 37]. Two Level I studies on pramipexole were retrieved, one using PDQ-39 [38] and other using PDQ-8 [39]. In the first one, the efficacy of pramipexole was compared with rotigotine and placebo in 506 patients with advanced PD in a randomized, double-blind, controlled clinical trial [38]. QoL results favored the treatment groups over placebo, with no significant differences between pramipexole and rotigotine. The mean change in the PDQ-39 summary index was −5.1 for pramipexole and −4.7 for rotigotine at follow-up (6 months), with similar incidence of adverse events. In the second study, a 15-week, multicenter, randomized, double-blind study, early PD patients were administered pramipexole or rasagiline [39]. PDQ-8 scores significantly improved from baseline to endpoint in the pramipexole group, while remaining stable in the rasagiline group. Neither of these studies offers enough information to calculate magnitude of change. From Level III studies with pramipexole [40, 41], Fedorova and Chigir' [40] found a relative change of 19 % and an effect size of 1.2 in PDQ-39. Takanashi et al. [41] did not find significant differences in PDQ-39 at follow-up in patients switched from standard pramipexole to the extended-release formulation.

Cabergoline is an ergot-derived dopamine agonist that can be administered as monotherapy in the early phase of PD or in combination with levodopa in more advanced phases. A Level I study has found a positive effect on QoL of cabergoline [28], with better responsiveness statistics than entacapone. Level III studies on cabergoline [42–44] also reported significant improvements on QoL, maintained after 2 years of follow-up [43], with better results than pramipexole [42], and with a relative change of 15.6 % and an effect size of 0.51 in PDQ-39 [44].

Ropinirole is another oral non-ergot dopamine agonist. In one study, when compared with levodopa as initial

treatment, it did not produce significant changes in QoL [45]. However, the prolonged-release formulation has demonstrated efficacy in reducing motor impairment and improving PDQ-39 domains combined with levodopa in a Level I study of advanced PD patients [46].

Rotigotine is a non-ergot dopamine agonist formulated in a silicone-based transdermal patch allowing for continuous delivery of the drug. Transdermal patches increase 'on' time without dyskinesias, with mild adverse effects, and they appear to be useful as monotherapy in early stages of PD [47]. In the large, randomized Level I study mentioned earlier, rotigotine was as effective as pramipexole in improving QoL [38]. Using PDQ-8, two studies have identified a greater benefit on QoL with rotigotine than with placebo [48, 49], with a relative change of 22.4 % and an effect size of 0.38 [49].

Pergolide has been tested in a Level I study with 203 patients, as add-on to levodopa, in comparison with tolcapone [26]. Although pergolide had positive effects on QoL (relative change 10.25 %; effect size 0.35), data favored tolcapone (relative change 15.7 %; effect size 0.59).

Piribedil has been used either as monotherapy in early PD or in combination with levodopa. A small placebo-controlled, randomized, double-blinded clinical trial of piribedil versus placebo in PD patients with apathy has found an improvement in QoL, with a relative change of 16.7 % and an effect size of 0.48 in PDQ-39 using piribedil [50].

A large, open-label, pragmatic clinical trial has tested the efficacy of dopamine agonists against MAO-B inhibitors on QoL [21], with results favoring MAO-B inhibitors.

In summary, there is Level I evidence demonstrating that some dopamine agonists (cabergoline, ropinirole prolonged-release, pergolide) are efficacious in improving the QoL of PD patients. Conclusions cannot be drawn with respect to other dopamine agonists because the published clinical trials studies did not use PDQ-39 or PDQ-8, are Level II or III, or do not offer information on relative change and effect size (Table 3).

3.3 Monoamine Oxidase-B Inhibitors

Selective MAO-B inhibitors prolong the effect of dopamine by preventing removal of synaptic dopamine and increasing dopamine release. Rasagiline is an irreversible, second-generation MAO-B inhibitor that is well-tolerated, safe, and has good outcomes on motor symptoms and prevention of motor complications [51]. It may be used as monotherapy to delay the need for levodopa, or as adjunct therapy with levodopa.

Very few studies have quantified the impact of rasagiline on QoL (Table 4), and some of them have used QoL measures other than PDQ-39 or PDQ-8 [51–55]. An observational study of 545 patients who started rasagiline showed a 20.1 % improvement in PDQ-39 scores after 4 months (effect size was not available) [56]. Furthermore, this patient series was increased to 754 patients, and a higher relative change was found for the group on rasagiline as monotherapy versus combined therapy [30, 57]. A more recent, 15-week, double-blind, randomized trial found non-significant differences in PDQ-8 scores when comparing rasagiline and pramipexole, although there was lower incidence of gastrointestinal and sleep disorders in the rasagiline group [39].

Selegiline was the first selective MAO-B inhibitor developed for PD treatment. An open-label clinical trial followed 60 patients for 12 weeks after initiating orally disintegrating selegiline while decreasing dopamine agonist dosages [58]. Although significant, the QoL benefit was small in magnitude (relative change 14.7 %; effect size 0.13). In addition, the MAO-B inhibitor decreased excessive daytime sleepiness, pedal edema, hallucinations, and impulse control disorders while maintaining treatment efficacy.

A study comparing these two MAO-B inhibitors, rasagiline and selegiline, showed non-significant differences (relative change 8.1 %) in QoL scores in 30 patients who changed from selegiline to rasagiline, after a 4-month follow-up [59]. This might have been due to the small sample size and lack of statistical power, since the magnitude of change was actually moderate (effect size 0.71). These results contrast with those from a previous German study, which showed a 22.2 % improvement in PDQ-39 scores in 29 patients who changed from selegiline to rasagiline [56].

A recent study compared the effect of combination therapy (levodopa combined with rasagiline or selegiline) with levodopa or dopamine agonist monotherapy [60]. Results on PDQ-39 favored the groups on combined therapy, but there was no information available on the magnitude of change. A large-scale study compared 460 patients on MAO-B inhibitors with 632 on dopamine agonists, for 7 years [21]. PDQ-39 differences were statistically better QoL for patients on MAO-B inhibitors (no information on effect size or relative change).

Safinamide is a MAO-B inhibitor that improves dopaminergic transmission and has an anti-glutamatergic effect that might reduce dyskinesias. Its effects on motor symptoms have been documented [61], but there are very few studies on how safinamide treatment may benefit QoL. A randomized, controlled, large-sample trial compared safinamine with placebo, for a 6- and 24-month period [62, 63]. QoL results were better for the group on safinamide, with significant QoL improvement over time, both at 6 and 24 months. At 6-month follow-up, there was a 7.3–12.4 %

relative change and an effect size of 0.15–0.23, with better results for higher doses of safinamide (100 mg/day) [62]. Even though the improvement remained significant at 24 months, there was no information available about relative change or effect size at that long-term follow-up [63].

In summary, there is little information about the impact of MAO-B inhibitors on QoL. Effect size ranged between 0.15 and 0.23 for safinamide in a Level I trial [62]. Other MAO-B inhibitors produced a small to moderate beneficial effect (0.13–0.71) on QoL in Level III studies. Studies suggest that MAO-B inhibitors are efficacious in improving PD patients' QoL, but evidence was insufficient for selegiline and rasagiline according to the criteria in this review.

3.4 Treatment for Advanced Parkinson's Disease

3.4.1 Apomorphine

Apomorphine is a dopamine agonist that can be administered either by a ready-loaded disposable pen for injection or as continuous infusion via an electronic driver or pump using a pre-filled syringe. In this way, a more continuous stimulation of dopamine receptors is achieved. Apomorphine infusions reduce both 'off' periods and dyskinesias, increase 'on' time, and have a beneficial effect on a number of non-motor symptoms in advanced PD [64].

Four trials that assessed the effect of continuous apomorphine infusions on QoL were found [64–67], and were published between 2001 and 2014. Two furnished information about effect size and relative change [64, 67] (Table 5). Two studies provided Level III evidence [65, 67] and two provided Level II evidence [64, 66]. Sample sizes ranged between four [66] and 43 patients [64]. The shortest follow-up was 3 weeks [66] and the longest 12.5 months [67]. QoL improvement was reported by all studies, although in one of them QoL improvement was only observed in 50 % of the sample [65].

One study compared 17 PD patients on apomorphine infusions with a control group of patients with similar characteristics but who were on conventional oral therapy [67]. Both groups were followed for a mean period of 12.5 ± 11.5 months. While the group on apomorphine significantly improved its QoL (PDQ-8) by 42 %, and had an effect size of 1.18, the control group showed worsening.

In a small sample of four patients who underwent a 3-week crossover trial, the effect of apomorphine on combination therapy with levodopa was compared with levodopa/carbidopa intestinal gel as monotherapy, and results favored the latter arm [66]. A study compared the effect of apomorphine versus levodopa/carbidopa intestinal gel on QoL, and patients in levodopa/carbidopa intestinal gel showed a slightly higher QoL improvement than patients on apomorphine [64]. The apomorphine group showed a relative change of 30 % and effect size of 0.89.

Overall, there is a lack of Level I randomized and controlled trials analyzing the effect of apomorphine on QoL. The reviewed small-sample studies show a moderate relative change (42–30 %), with large effect sizes (0.89–1.23), thus suggesting that evidence is insufficient to confirm or reject that apomorphine is efficacious for improving the QoL of PD patients.

3.4.2 Levodopa/Carbidopa Intestinal Gel

Levodopa/carbidopa gel for intestinal infusion (LCGI) is delivered directly to the duodenum or upper jejunum through a percutaneous endoscopic gastrojejunostomy tube, connected to a portable infusion pump. It has a positive effect on motor fluctuations [66, 68], reducing 'off' time, improving motor function, and decreasing the severity of non-motor symptoms by allowing more continuous dopaminergic stimulation [64]. However, it is an invasive procedure with potential complications, and requires training to set up and administer the infusions [1].

Seventeen studies that quantify the effect of LCGI on the QoL of PD patients were identified and reviewed (Table 6). All studies compared baseline with follow-up results, and three used a control group made up of patients on conventional treatment [69], on LCGI combined with apomorphine [66], or on immediate-release oral levodopa–carbidopa [20]. One trial compared LCGI-naïve patients with previous users, finding a moderate QoL improvement in LCGI-naïve patients [70]. Almost all studies were open-label, non-controlled, and the most common design was case series follow-up, thus providing Level III evidence. Only one trial reached the criteria for Level I [20] qualification, and another for Level II [66]. Sample sizes ranged from nine to 43 patients, with follow-up periods of up to 4 years [71]. Overall, the relative change in PDQ-39 summary index or PDQ-8 ranged between 7.7 and 53.2 %, with a mean of 29.2 %, and the mean effect size was large (1.14; range: 0.12–2.39). The variability of relative change and effect size results does not seem to be associated with the length of the follow-up period, and is probably due to sample characteristics.

The DIREQT (Duodopa Infusion: Randomised Efficacy and Quality of Life Trial) [66, 69, 72] was a randomized, open-label, crossover trial. Two groups of 12 patients were compared. The first group was on conventional therapy for 3 weeks and crossed over to LCGI as monotherapy for another 3 weeks. The second group received treatment in the opposite order. Follow-up lasted 6 months, with QoL evaluations [PDQ-39 and 15-Dimension QoL (15D-QoL)] every 3 weeks. At the end of the first 6-week trial, better

QoL was found in the LCGI treatment arm, with statistical difference for the 15D questionnaire and all PDQ-39 dimensions, except Social Support [72]. The relative change for patients on LCGI at the 6-month follow-up was 27 % compared to the conventional treatment baseline [69]. In a subsample of four patients who used apomorphine in the comparator arm, there were better QoL results with LCGI than with apomorphine [66].

Follow-up for longer than 2 years has been reported on small samples of patients on LCGI [71, 73–76]. All PDQ-39 subscales, except Social Support, showed significant differences. In terms of QoL, LCGI benefits were durable, with a relative change ranging from 7.7 to 37.4 % and very variable effect sizes (0.21–2.37; mean 1.51). A recent study described a 24 % change in QoL scores (effect size 0.89) after a 3-year follow-up period [76].

The largest patient series on LCGI was followed for 54 weeks in an open-label international study [77]. At baseline, there were 192 patients, of whom 61 provided PDQ-39 data after 54 weeks of treatment. There were significant changes in QoL, but information on relative change or effect size is not available. Although LCGI is well-tolerated, procedural and device complications were frequent and 31.1 % of patients experienced serious adverse effects.

The only study that provided Level I evidence followed patients for 12 weeks, in a randomized, double-blind/dummy/titration trial, comparing LCGI with immediate-release oral levodopa–carbidopa [20]. QoL improvement was around three times greater for the LCGI group (relative change 31 vs. 10 %; effect size 0.61 vs. 0.22) than for patients on oral therapy.

Despite the large number of studies that include QoL measures as an outcome of LCGI, there is only one Level I evidence study [20] showing that this treatment is efficacious in improving QoL. However, all of the other studies point towards a possible benefit and the magnitude of change for some of them was relatively large.

4 Discussion

This narrative review considered the studies and clinical trials with specific PD treatment drugs in which QoL, measured with a recognized instrument, was analyzed as a primary or secondary outcome. The review was restricted to studies that used the PDQ-39 or PDQ-8 as QoL measures and that provided QoL results as relative change and effect size, or furnished enough data to allow calculation of these parameters.

All drugs analyzed showed, as a whole, a beneficial effect on the QoL of PD patients, although the degree of evidence and the magnitude of improvement varied widely. A part of the change variability may be due to the characteristics of the studies, but it is also possible that there is a 'class effect' related to the drug and its method of administration. This statement is suggested by the results of this review, as the highest values of change were reached by drugs given in continuous infusions in advanced PD.

Both relative change and effect size derive from the difference in scores pre- and post-intervention and allow an approach to the importance of change, as supported by logic: a large change will probably be more important than a small one. According to de Vet et al. [78], a "minimally important change" (MIC), which "concerns change within patients", is determined in groups of patients and applied at an individual level. The MIC value can be investigated by either "anchor-based" or "distribution-based" methods. Distribution-based methods, as the effect size, lack information directly provided by patients or compared to other measures used as an anchor, whereas anchor-based methods include a criterion of MIC derived from patients or clinicians. As a consequence, anchor-based methods are preferred to determine the MIC and distribution-based methods are considered supportive.

However, anchor-based methods are not free of potential inconveniences (e.g., selection of inappropriate anchor; defective memory for precise pre vs. post comparison; uncontrolled patients' subjective judgment; possible need for multi-anchor approach) [79, 80]. On the other hand, distribution-based methods offer a way of interpretation through standardized values that can be proposed as MIC. In the absence of information directly provided by patients, the distribution-based methods can be illustrative and allow comparisons, approaching the significance of change from an objective perspective.

Threshold values for clinically important minimal changes have been proposed for the two calculated parameters applied in this review. Relative changes of $\geq$10 % of the measure range are probably clinically meaningful, as was found after applying a variety of methods to a diverse range of instruments used in different studies [81, 82]. Since both PDQ-39 and PDQ-8 summary indexes are scored from 0 to 100, this 'rule of the thumb' means that a change of 10 % in the questionnaire score may be considered an MIC. For the effect size, and according to the standard values by Cohen [15], a change of 0.20 indicates a small effect and can serve as the threshold for a minimal clinically important change [16, 83]. Following these considerations, only the outcomes of Level I studies of evidence are summarized in this review.

Three Level I studies on levodopa with entacapone, with 3–6 months' follow-up, found relative changes lower than 5 % and effect size ranging from 0.04 to 0.26. These results indicate a slight beneficial effect on patients' QoL [27, 29, 30]. Two studies with an extended-release levodopa

formulation (IPX066) and follow-up of 3 and 6 months, respectively, showed relative changes of 12–24 % and effect sizes of 0.20–0.35, pointing to a weak beneficial effect on QoL [24, 25] (Table 2). According to these results, levodopa with entacapone is efficacious in improving patients QoL, but at a low level. Conclusions are similar for the extended-release formulation, with the magnitude of change being somewhat higher, but still at the interval indicative of a small change.

Considering the dopamine agonists, PDQ-39 was used in three Level I studies with cabergoline, ropinirole, and pergolide (Table 3). Follow-up ranged from 12 to 24 weeks; the relative changes ranged from 10.25 % with pergolide and 10.7 % with ropinirole to 22.5 % with cabergoline; the effect sizes ranged from 0.16 with ropinirole to 0.50 with cabergoline. Most values were above the 0.20 threshold, suggesting that these dopamine agonists, particularly cabergoline, are efficacious in inducing a small improvement in the QoL of PD patients.

For MAO-B inhibitors, there is only one Level I study with safinamide, a selective and reversible MAO-B inhibitor with anti-glutamatergic effects. The follow-up was 6 months and the 100 mg daily dose produced a higher benefit than the 50 mg dose. The relative change values were 12.4 and 7.3 % for 100 and 50 mg, respectively, whereas the effect sizes were 0.23 and 0.15 (Table 4). Only the 100 mg dose was efficacious in producing a change over the limit value for a small change.

For advanced non-oral therapies including continuous infusions of apomorphine and LCGI, only one Level I study (LCGI) [20] with the requirements to be included in this review was found. Most trials had small sample sizes and longer follow-up periods (as a whole, 6 months to 2 years) (Tables 5, 6) than studies with other drugs. All of them showed QoL improvement, with moderate to high effect sizes. The evidence level is appropriate to confirm the efficacy of LCGI in improving the QoL of PD patients with advanced disease, but still insufficient for apomorphine.

The main limitations of this review are related to the restrictive selection of QoL measures and the literature search limited to PubMed. Nonetheless, PDQ-39 and PDQ-8 are the most widely used instruments for assessment of QoL in PD, and PubMed collects the huge majority of articles on clinical trials and observational studies of drug treatments.

5 Conclusions

The conclusions that can be drawn from this review are that (1) some pharmacological treatments for PD (levodopa immediate- and extended-release formulations, levodopa with COMT inhibitors, ropinirole, cabergoline, pergolide, safinamide, and LCGI) have been demonstrated to be efficacious in improving patients' QoL; (2) the magnitude of the effect for those with a high level of evidence is small, except for LCGI which is moderate; and (3) there is a lack of high-quality studies focused on QoL as a variable of interest in clinical trials. Furthermore, for some modalities of treatments there is inconsistent evidence on their effect on QoL, an outcome apparently considered trivial as no further clinical trials are designed to clarify the impact. This fact contrasts with the importance that QoL has for patients, clearly deserving more attention and research efforts.

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