



HAL
open science

Oxycodone or Higher Dose of Levodopa for the Treatment of Parkinsonian Central Pain: OXYDOPA Trial

Christine Brefel-Courbon, Estelle Harroch, Ana Marques, David Devos, Claire Thalamas, Vanessa Rousseau, Fabienne Ory-Magne, Margherita Fabbri, David Maltête, Tiphaine Rouaud, et al.

► **To cite this version:**

Christine Brefel-Courbon, Estelle Harroch, Ana Marques, David Devos, Claire Thalamas, et al.. Oxycodone or Higher Dose of Levodopa for the Treatment of Parkinsonian Central Pain: OXYDOPA Trial. *Movement Disorders*, 2024, 39 (9), pp.1533-1543. 10.1002/mds.29878 . hal-04606320

HAL Id: hal-04606320

<https://u-picardie.hal.science/hal-04606320v1>

Submitted on 24 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

RESEARCH ARTICLE

Oxycodone or Higher Dose of Levodopa for the Treatment of Parkinsonian Central Pain: OXYDOPA Trial

Christine Brefel-Courbon, MD,^{1,2*} Estelle Harroch, MSc,¹ Ana Marques, MD, PhD,³ David Devos, MD, PhD,⁴ Claire Thalamas, MD,⁵ Vanessa Rousseau, PhD,⁵ Fabienne Ory-Magne, MD,¹ Margherita Fabbri, MD, PhD,¹ David Maltête, MD, PhD,^{6,7} Tiphaine Rouaud, MD,⁸ Sophie Drapier, MD,⁹ Melissa Tir, MD, PhD,¹⁰ Stephane Thobois, MD, PhD,^{11,12} Hayet Salhi, MD,¹³ Jean Christophe Corvol, MD, PhD,¹⁴ Giovanni Castelnovo, MD,¹⁵ Ouhaïd Lagha-Boukbiza, MD,^{16,17} Frédérique Fluchère, MD,¹⁸ Solene Frismand, MD,¹⁹ Solene Ansquer, MD, PhD,²⁰ Agnes Sommet, MD, PhD,⁵ and Olivier Rascol, MD, PhD^{1,2}

¹Department of Clinical Pharmacology and Neurosciences, Parkinson Expert Centre, Centre d'Investigation Clinique CIC1436, University Hospital of Toulouse, NeuroToul COEN Centre, NS-PARK/FCRIN Network, Toulouse, France

²Toulouse Neuroimaging Centre (TONIC), UMR1214 INSERM/UT3, Toulouse, France

³Department of Neurology, CHU Clermont-Ferrand, Université Clermont-Auvergne, CNRS, IGCCN, Institut Pascal, NS-PARK/FCRIN Network, Aubière, France

⁴Department of Medical Pharmacology, Expert Centre of Parkinson's Disease, University of Lille, LiNCog, Lille Neuroscience and Cognition, Inserm, INSERM UMR-S1172, CHU de Lille LICEND COEN Center Lille NS-Park Network, Lille, France

⁵Department of Clinical Pharmacology, Methodology Data management and Statistical Analysis Unit, Centre d'Investigation Clinique CIC1436, University Hospital of Toulouse, Toulouse, France

⁶Department of Neurology, Rouen University Hospital and University of Rouen, Mont-Saint-Aignan, France

⁷INSERM U1239, Laboratory of Neuronal and Neuroendocrine Differentiation and Communication, NS-PARK/FCRIN Network, Mont-Saint-Aignan, France

⁸Department of Neurology, Nantes University Hospital, NS-PARK/FCRIN Network, Nantes, France

⁹Department of Neurology, Rennes University Hospital, CIC INSERM 1414, NS-PARK/FCRIN Network, Rennes, France

¹⁰Department of Neurology, Department of Neurosurgery, Expert Centre for Parkinson's Disease, Amiens University Hospital, EA 4559 Laboratoire de Neurosciences Fonctionnelles et Pathologie (LNFP) Université de Picardie Jules Verne, University of Picardy Jules Verne (UPJV), NS-PARK/FCRIN Network, Amiens, France

¹¹Univ Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon Sud Charles Mérieux, CNRS, Institut des Sciences Cognitives, UMR 5229, Bron, France

¹²Centre Expert Parkinson, Hôpital Neurologique "Pierre Wertheimer", Hospices Civils de Lyon, NS-PARK/FCRIN Network, Lyon, France

¹³Centre Expert Parkinson, Neurologie, and Equipe 01 NPI IMRB; CHU Henri Mondor, AP-HP, INSERM et Faculté de Santé, Université Paris-Est Créteil, Créteil, France

¹⁴Département de Neurologie, CIC Neurosciences, Sorbonne Université, Assistance Publique Hôpitaux de Paris, Paris Brain Institute (ICM), Inserm, CNRS, Hôpital Pitié-Salpêtrière, NS-PARK/FCRIN Network, Paris, France

¹⁵Department of Neurology, CHU Nîmes, Hôpital Caremeau, Nîmes, France

¹⁶Service de Neurologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

¹⁷Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, NS-PARK/FCRIN Network, Strasbourg, France

¹⁸Service de Neurologie et Pathologie du Mouvement, Aix Marseille Université, AP-HM, Hôpital de La Timone, and UMR CNRS, Marseille, France

¹⁹Neurology Department, Nancy University Hospital, Nancy, France

²⁰Service de Neurologie, Centre Expert Parkinson, CIC-INSERM 1402, CHU Poitiers, NS-PARK/FCRIN Network, Poitiers, France

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

*Correspondence to: Dr. C. Brefel-Courbon, Department of Clinical Pharmacology, Faculty of Medicine, 37 Allées Jules Guesde, 31000, Toulouse, France; E-mail: christine.brefel-courbon@univ-tlse3.fr

Relevant conflicts of interest/financial disclosures: None.

Funding agency: This work was funded by the French Ministry of Health (PHRCN-14-0044). The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Received: 19 March 2024; **Revised:** 3 May 2024; **Accepted:** 16 May 2024

Published online 8 June 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29878

ABSTRACT: Background: Among the different types of pain related to Parkinson's disease (PD), parkinsonian central pain (PCP) is the most disabling.

Objectives: We investigated the analgesic efficacy of two therapeutic strategies (opioid with oxycodone-prolonged-release (PR) and higher dose of levodopa/benserazide) compared with placebo in patients with PCP.

Methods: OXYDOPA was a randomized, double-blind, double-dummy, placebo-controlled, multicenter parallel-group trial run at 15 centers within the French NS-Park network. PD patients with PCP (≥ 30 on the Visual Analogue Scale [VAS]) were randomly assigned to receive oxycodone-PR (up to 40 mg/day), levodopa/benserazide (up to 200 mg/day) or matching placebo three times a day (tid) for 8 weeks at a stable dose, in add-on to their current dopaminergic therapy. The primary endpoint was the change in average pain intensity over the previous week rated on VAS from baseline to week-10 based on modified intention-to-treat analyses.

Results: Between May 2016 and August 2020, 66 patients were randomized to oxycodone-PR ($n = 23$),

levodopa/benserazide ($n = 20$) or placebo ($n = 23$). The mean change in pain intensity was -17 ± 18.5 on oxycodone-PR, -8.3 ± 11.1 on levodopa/benserazide, and -14.3 ± 18.9 in the placebo groups. The absolute difference versus placebo was -1.54 (97.5% confidence interval [CI], -17.0 to 13.90 ; $P = 0.8$) on oxycodone-PR and $+7.79$ (97.5% CI, -4.99 to 20.58 ; $P = 0.2$) on levodopa/benserazide. Similar proportions of patients in each group experienced all-cause adverse events. Those leading to study discontinuation were most frequently observed with oxycodone-PR (39%) than levodopa/benserazide (5%) or placebo (15%).

Conclusions: The present trial failed to demonstrate the superiority of oxycodone-PR or a higher dose of levodopa in patients with PCP, while oxycodone-PR was poorly tolerated. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: levodopa; oxycodone; pain; parkinsonian central pain; Parkinson's disease

Chronic pain is reported in 60 to 85% of PD patients,¹ with a greater prevalence than in the general population²⁻⁴ and strongly impacts on patients' quality of life.⁵ Chronic pain is heterogeneous in PD patients, including specific pains (dystonia and parkinsonian central pain [PCP], which is also defined as "central neuropathic pain") and non-specific pains (musculoskeletal, radicular, and restless syndrome), presumably linked to different underlying nociceptive, neuropathic, and nociplastic mechanisms.^{6,7}

Management of pain in Parkinson's disease (PD) is usually disappointing, based on a low level of evidence because of the paucity of well-designed controlled studies, and patients often report profound dissatisfaction. Drugs generally considered to treat pain in PD include a broad spectrum of medications, including dopaminergic agents, antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants), anticonvulsants (eg, gabapentin, pregabalin), non-steroidal anti-inflammatory drugs, and opioids. Their efficacy is poorly documented, although they can induce adverse reactions and in some cases addiction.⁸⁻¹⁰ A large epidemiological study assessing analgesic prescriptions in PD patients showed that acetaminophen and opioids were the most commonly prescribed drugs, and antidepressants and anti-epileptics were also more frequently used in PD patients than in the general population.³

The different subtypes of PD pains are probably related to different pathophysiological mechanisms,¹¹ and the choice of a given analgesic should then be based on a mechanistic approach because different drugs may have

different effects on different pains. PCP is considered one of the most disabling and difficult to treat,^{6,12} with its prevalence varying from 10% to 28%.^{2,7,13} PCP may be linked to dopaminergic dysfunction within the basal ganglia, altering lateral/medial pain pathways and inhibitory modulating processes.^{6,14} Given that, abnormal pain thresholds improved by levodopa have been reported in this condition.¹⁵⁻¹⁸ Opioid systems may also be involved in PCP, where high concentrations of opiate receptors are present in the basal ganglia,¹⁹ and behavioral studies have provided functional evidence of their involvement in pain mechanisms.¹⁴ The effect of levodopa and opiates on PCP has never been specifically assessed, although one double-blind, randomized, placebo-controlled trial failed to demonstrate the superiority of oxycodone-naloxone in PD patients suffering from different types of pain.²⁰

The aim of the present trial was to compare effect versus placebo in terms of the efficacy and tolerability of two different therapeutic strategies: one based on an opiate approach (oxycodone-prolonged release [PR]) and the other one adopting a dopaminergic route (increase in levodopa/benserazide dose) in a homogeneous population of PD patients selected to suffer specifically from PCP.

Methods

Study Design and Participants

OXYDOPA was an investigator-initiated, prospective, double-blind, double-dummy, placebo-controlled, multicenter, three-arm, parallel-group randomized

controlled trial. Participants were recruited from 15 PD Expert Centers within the French NS-Park/FCRIN Network (<https://parkinson.network/>) (Amiens, Clermont-Ferrand, Créteil, Lille, Lyon, Marseille, Nancy, Nantes, Nîmes, Paris, Poitiers, Rennes, Rouen, Strasbourg, and Toulouse).

Patients were included if they were between the ages of 45 and 75 years, had a diagnosis of PD according to the Queen Square Brain Bank criteria,²¹ and suffered from PCP, defined according to the algorithm for subtypes identification and classification of chronic pain in PD.⁶ Such an algorithm allowed to exclude subjects suffering from pains considered as unspecific to PD (musculoskeletal, radicular, or restless leg syndrome) and those related to dystonia (Supplementary Fig. S1 from Marques et al).⁶ Patients had PCP for ≥ 3 months with an intensity of ≥ 30 mm on a pain Visual Analogue Scale (VAS) over the last month.

Patients had to receive a stable treatment for addressing PD for ≥ 4 weeks before randomization. Concomitant stable step-1 analgesic (non-steroidal anti-inflammatory drugs, acetaminophen) or co-analgesic (antidepressants, antiepileptics) treatment were allowed, provided that they had been initiated at least ≥ 4 weeks before randomization. Antiparkinsonian and analgesic medications were to remain stable throughout the study.

Exclusion criteria included atypical parkinsonism, cognitive impairment (score of ≤ 23 on Mini Mental State Examination), behavioral disorders (impulse control disorder, hallucinations, and delirium), intercurrent acute pain or chronic disease-causing pain (rheumatoid arthritis, ankylosing spondylitis, diabetic neuropathy, cancer, etc.) or disabling dyskinesias (items Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] 4.1 and 4.2 > 1). Patients were also excluded if they were de novo patients not receiving anti-parkinsonian medications, treated with opioid drugs, or had contraindications to oxycodone-PR.

The trial was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The study protocol was approved by a national Ethics Committee (CPP Sud Ouest et Outremer III, France, Number EudraCT: 2015-001523-24), and written informed consent was obtained from all participants before screening. The study was registered on the [ClinicalTrials.gov](https://clinicaltrials.gov) website, NCT02601586.

Randomization and Masking

Administration of oxycodone-PR, levodopa/benserazide, or placebo was centrally randomized with block randomization (block size of three) and stratified according to center in a 1:1:1 ratio from a list generated by the Methodology and Data Management Department at the University of Toulouse Hospital Centre

with STATA Version 11.0 software (StataCorp LP, College Station, TX, www.stata.com). The participants, trial staff, investigators, and data analysts were unaware of the trial-group assignments. To maintain masking, a double-blind, double-dummy design was used in which participants were administered a combination of one tablet and one capsule. The oxycodone-PR group received oxycodone PR tablets and capsules of the levodopa/benserazide placebo; the levodopa/benserazide group received levodopa/benserazide capsules and oxycodone-PR placebo tablets; and the placebo group received placebos of the two drugs. Levodopa/benserazide was hidden in capsules and the levodopa/benserazide placebo capsules were produced by the coordinating pharmacy (Toulouse Hospital). Levodopa/benserazide was supplied by Roche (France), oxycodone-PR tablets by Mundipharma (France) and the oxycodone-PR placebo tablets by UNITHER Bordeaux (France).

Procedure

This study evaluated the effect versus placebo on PCP intensity of two drugs (oxycodone-PR and levodopa/benserazide) administered at a stable dose for 8 weeks. The treatment period was divided into three phases: 2-week titration phase, 8-week phase of treatment at the stable dose, and 8-day withdrawal phase (Supplementary Fig. S2). The study treatment was given as an add-on therapy, with the usual anti-parkinsonian treatment and any step-1 analgesic or co-analgesic treatments for patients remaining stable throughout the trial. During the 2 week titration phase, patients attended the study clinic on days 0, 5, 10, and 15, and the dose of study drug (oxycodone-PR, levodopa/benserazide, or placebo) was started at day 0 (D0) and gradually increased in three steps every 5 days: level 1 dose (oxycodone-PR 10 mg/day twice a day [bid], levodopa/benserazide 100 mg/day bid, or placebo bid), from D1 to D5 inclusive, level 2 dose (oxycodone-PR 20 mg/day three times a day [tid] [10 mg/0 mg/10 mg], levodopa/benserazide 150 mg/day tid [50 mg/50 mg/50 mg], or placebo tid) from D6 to D10 inclusive, and level 3 dose (oxycodone-PR 40 mg/day tid [20 mg/0 mg/20 mg], levodopa/benserazide 200 mg/day tid [100 mg/50 mg/50 mg], or placebo tid) from D11 to D15 inclusive. If adverse effects occurred, it was possible to down-titrate to the previous lower level dose. Treatments were then dispensed at stable doses (from D16–D71) during the 8-week phase, although they could be reduced to the lower level dose if adverse effects occurred. Finally, there was an 8-day withdrawal phase (from D72–D79) during which the dose of the treatment was gradually decreased before discontinuation. All primary and secondary outcomes were

assessed at D0, D43, and D71. All clinical assessments were performed while patients received their usual anti-parkinsonian treatment in the *on* state. Adverse events, compliance with the study drug, use of PD drugs, and concomitant drugs were documented at each study visit. During the study, patients were allowed to take a rescue analgesic treatment (acetaminophen, maximal dosage: 3 g/day) and laxative treatment (lactulose) in the event of constipation where necessary.

Outcomes

The primary endpoint was the change in average pain intensity (as assessed by the patient for the previous week), rated on the VAS (from 0 = no pain to 100 = maximal pain) between D0 (baseline) and D71 (after 8 weeks of treatment at a stable dose). Change in maximal pain intensity over the last week rated on the VAS and the percentage of responders (30% and 50% pain relief from baseline) represented the secondary pain key endpoints. Other pain endpoints included modifications in Brief Pain Inventory, Neuropathic Pain Symptoms Inventory, short French version of McGill Pain Questionnaire, and the King's Parkinson's Disease Pain Scale between D0 and D71. Among other secondary endpoints were changes between D0 and D71 in Hospital Anxiety and Depression Scale (HADS), Parkinson's Disease Questionnaire 39 items (PDQ-39), Parkinson Fatigue Scale (PFS), Lille Apathy Rating Scale (LARS), Pittsburg Sleep Quality Index (PSQI) and non-motor and motor aspects using MDS-UPDRS part I, II, III and IV.

Statistical Analysis

As two comparisons were carried out for the main objective ("oxycodone-PR" vs. "placebo" and "levodopa/benserazide" vs. "placebo"), the α risk used to calculate the number of subjects has been adjusted to 0.025. Based on previous studies,²² we assumed an expected mean difference between active drugs and placebo of 15 mm on the VAS in terms of the change in average pain intensity after 8 weeks of treatment and a standard deviation of 13.0. With a two-sided significance level at 2.5% and a power of 90%, 19 evaluable patients per group were required. Presuming a drop-out rate of 30%, we planned for a total of 25 participants per group to be randomized with a 1:1:1 allocation rate.

We assessed the efficacy endpoints in patients who received at least one dose of the study drug and had at least one post-baseline primary efficacy data point (modified intention-to-treat [mITT]), with sensitivity analyses done for the first pain endpoints (mean and maximum VAS changes) in the per-protocol (PP) population. The safety analysis set consisted of all patients who were given at least one dose of the study medication.

Missing data on primary and secondary pain endpoints were imputed using copy mean method²³ implemented in R software.

The primary endpoint was analyzed using an adjusted linear regression model with change in average pain intensity as the response variable and treatment as the explanatory variable. Two models (oxycodone-PR vs. placebo and levodopa/benserazide vs. placebo) were performed with the following adjustment variables recorded at baseline: age, mean VAS score for the week before inclusion, center, and levodopa equivalent daily dose. The same analysis strategy was conducted for other efficacy endpoints.

In addition, χ^2 tests (or Fisher tests as appropriate) were carried out to make comparisons between treatment groups for the two secondary pain key endpoints (qualitative variable). The risk differences were calculated with 97.5% confidence interval (CI) based on Newcombe confidence limits. Statistical significance was set at 2.5% for the primary as well as the two secondary pain key endpoints and at 5% for others.

The incidence and frequency of adverse events were presented according to the classification of MedDRA version 17.1. Adverse events were catalogued by "system organ class" and "preferred term."

Statistical analysis was conducted using SAS Version 9.4. Some methods of imputations may be carried out in R.

Results

We enrolled 66 patients between May 11, 2016 and August 21, 2020. Twenty-three were assigned to receive oxycodone-PR, 20 to levodopa/benserazide, and 23 to placebo. Fourteen (61%) of 23 patients in the oxycodone-PR group, 16 (80%) of 20 patients in levodopa/benserazide group, and 15 (65%) of 23 patients in the placebo group completed the study (Fig. 1). The most common reason for discontinuing treatment was because of adverse events (nine receiving oxycodone-PR, three receiving placebo, and one receiving levodopa/benserazide). The two protocol deviations were related to changes in concomitant anti-parkinsonian treatment. One patient in the levodopa/benserazide group self-reduced his daily dose of levodopa/benserazide from D15 and another patient in the placebo group increased his daily levodopa dose from D43. Baseline demographic and clinical characteristics of the mITT analysis set were balanced between treatment groups (Table 1). During the 8 weeks of stable dosing, 57% of the patients of the oxycodone-PR group received the level 2 dose of the drug study, whereas 60% of the levodopa/benserazide group and 71% of the placebo group were given the level 3 dose. The mean daily doses of oxycodone-PR and levodopa/benserazide were 20.7 ± 5.9 mg and 183.3 ± 24.3 mg, respectively.

The primary outcome measure of change in average pain intensity from baseline to D71 decreased

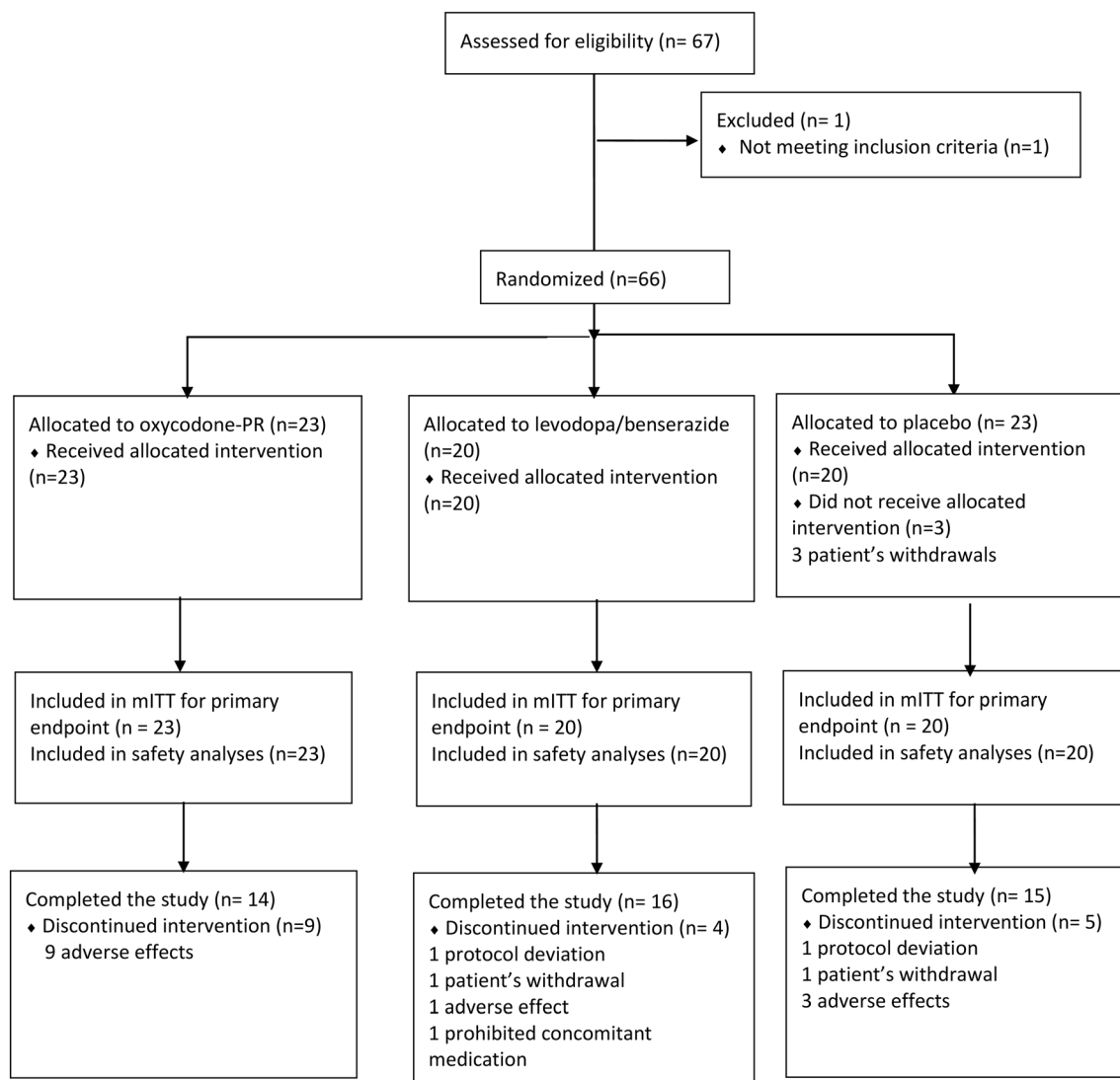


FIG. 1. Trial profile.

(ie, clinically improved) by $-17 \text{ mm} \pm 18.5$ on oxycodone-PR, $-8.3 \text{ mm} \pm 11.1$ on levodopa/benserazide and $-14.3 \text{ mm} \pm 18.9$ on the placebo (Fig. 2). The unadjusted and adjusted analyses did not reveal any significant difference between the groups (Table 2). The PP analysis yielded similar results (Supplementary Table S3). For the secondary pain outcomes, no notable differences were observed between groups in terms of mean changes from baseline to D71 except for percentage of responders (30%), which showed a significant risk difference between the oxycodone-PR and levodopa/benserazide groups in favor of oxycodone-PR (Tables 2 and 3).

For other secondary outcomes, the changes in HADS, LARS, FSS, PSQI, PDQ-39, and MDS-UPDRS part I, II, III, and IV between D0 and D71 were similar in each treatment group, except for sleep, which improved in the oxycodone-PR group compared to the levodopa/benserazide and placebo groups (Supplementary Table S4).

In the safety-analysis set, the incidence of all-cause adverse events was comparable between treatment groups (Supplementary Table S5). Two participants in the oxycodone-PR group experienced a serious adverse event, one pulmonary embolism (resolved after appropriate emergency treatment) and one lentigo maligna (eliminated after surgical treatment). One patient in the levodopa/benserazide group suffered a serious adverse event (malaise, somnolence, and nausea, which rapidly cleared within few hours). Another patient in the placebo group encountered a serious adverse event (worsening pain secondary to biceps brachii tendon rupture requiring opioid treatment). All these patients were withdrawn from study, although these serious adverse events were deemed by the investigator as being unlikely to be related to the study treatment.

The incidence of treatment-related adverse events was slightly higher in the oxycodone-PR group than

TABLE 1 Patient demographic and clinical characteristics at baseline

	Total (n = 63)	Oxycodone-PR group (n = 23)	Levodopa/benserazide group (n = 20)	Placebo group (n = 20)
Age, y	64.2 ± 7.4	62.3 ± 8.5	65.2 ± 6	65.6 ± 7.1
Sex				
Male	31 (49.2%)	9 (39.1%)	11 (55%)	11 (55%)
Female	32 (50.8%)	14 (60.9%)	9 (45%)	9 (45%)
Disease duration, y	6.9 ± 3.9	5.8 ± 3.1	8.4 ± 4.7	6.6 ± 3.5
BMI	26.3 ± 4.4	26 ± 4.6	26.7 ± 4.4	26.3 ± 4.3
MDS-UPDRS part I	15.6 ± 4.5	15.6 ± 4.1	15.7 ± 5.8	15.5 ± 3.5
MDS-UPDRS part II	13.4 ± 6	12.3 ± 4.1	14.7 ± 7.9	13.5 ± 5.6
MDS-UPDRS part III	21.3 ± 9.4	23 ± 10.1	21.7 ± 10.4	19.2 ± 7.4
MDS-UPDRS part IV	5.8 ± 4.5	4.7 ± 4.4	6.8 ± 5.1	6 ± 3.9
LEDD, mg/d	1094.2 ± 600.1	981.7 ± 522.2	942.1 ± 521.2	1375.9 ± 681.6
MMSE	28.7 ± 1.3	28.5 ± 1.6	28.9 ± 1.2	28.9 ± 1.1
HADS total	18.2 ± 6.1	19.3 ± 6.1	17.8 ± 6.4	17.4 ± 5.8
Anxiety	10.3 ± 3.5	11 ± 3.7	9.8 ± 3.4	9.9 ± 3.2
Depression	7.9 ± 3.9	8.3 ± 4.4	8 ± 3.6	7.5 ± 3.7
Pain				
Mean VAS (mm)	56.2 ± 18.1	60.2 ± 14	51.7 ± 20.7	56.1 ± 19.4
Maximal VAS (mm)	78 ± 14.8	82.8 ± 13.5	75.7 ± 17.3	74.8 ± 12.7
Antiparkinsonian medication				
Levodopa containing drug	58 (92.1%)	20 (87.1%)	18 (90.0%)	20 (100.0%)
COMT inhibitor	19 (30.2%)	7 (30.4%)	5 (25.0%)	7 (35.0%)
MAO-B inhibitor	28 (44.4%)	9 (39.1%)	11 (55.0%)	8 (40.0%)
Dopamine agonist	53 (84.1%)	18 (78.3%)	17 (85.0%)	18 (90.0%)
Amantadine	11 (17.5%)	3 (13.0%)	5 (25.0%)	3 (15.0%)

Data are n (%) or mean ± standard deviation. Scores on MDS-UPDRS part I range from 0–52: higher scores indicating more severe impairment in non-motor aspects of daily living. Scores on MDS-UPDRS part II range from 0–52: higher scores indicating more severe impairment in motor aspects of daily living. Scores on MDS-UPDRS part III range from 0–132: higher scores indicating more severe impairment on a clinician-conducted motor examination. Scores on MDS-UPDRS part IV range from 0–24: higher scores indicating more severe impairment in motor complications.

Abbreviations: PR, prolonged release; BMI, body mass index; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose was calculated;²⁴ MMSE, Mini Mental State Examination (score range, 0–30; ≥27 indicates normal cognition); HADS, Hospital Anxiety and Depression Scale; VAS, Visual Analogue Scale; COMT, catechol-O-methyltransferase; MOAB, monoamine oxidase B.

in the levodopa/benserazide and placebo groups (Supplementary Table S4). Nausea, constipation, vomiting, and somnolence were more prevalent in patients treated with oxycodone-PR than in individuals treated with levodopa/benserazide or placebo. By contrast, treatment-related dyskinesia was more common with levodopa/benserazide than with oxycodone-PR or placebo.

Discontinuation of the study drug because of adverse events was more frequent in the oxycodone-PR group, (somnolence [n = 4], nausea/vomiting [n = 8], or constipation [n = 3]) than in the placebo (worsening of pain [n = 1], nausea, asthenia, and constipation [n = 2]), and

levodopa/benserazide groups (dyskinesia and nausea [n = 1]) (Supplementary Table S5).

Discussion

The main originality of the OXYDOPA trial is that for the first time it focused on PD patients experiencing a single specific subtype of chronic pain, namely PCP. Pain is heterogeneous in PD, and different subtypes of PD pain may not share similar underlying pathophysiological mechanisms.²⁵ Consequently, these different subtypes may respond in a different manner to different analgesic

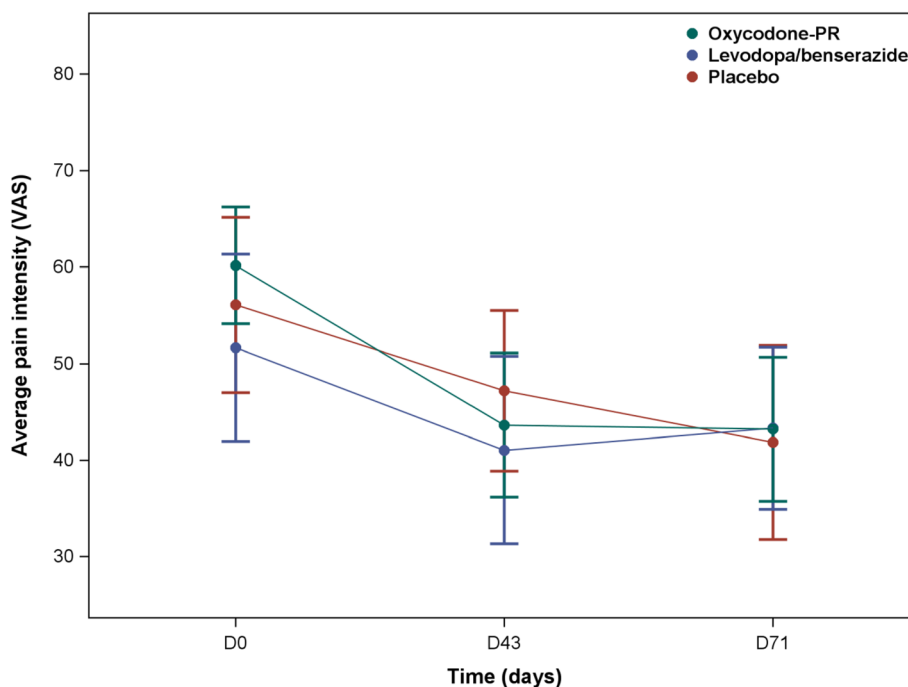


FIG. 2. Mean Visual Analogue Scale (VAS) pain scores with 95% confidence interval (CI) in modified intention-to-treat population during the study.

strategies, reducing the chances of detecting an effect in heterogeneous cohorts of patients by mixing them together. Nevertheless, the trial failed to demonstrate the superiority over placebo of two different strategies (adjunction of an opiate drug or increase in levodopa daily dose) on the severity of PCP. Such negative findings were consistent across all primary and secondary pain-related outcomes. The trial also illustrated that the placebo effect was significant and oxycodone-PR was poorly tolerated in such patients.

The observed placebo response was strong in the OXYDOPA trial, with a mean reduction of ~25% on PCP severity as assessed by the VAS (primary outcome), whereas 40% and 15% of the patients reported a moderate ($\geq 30\%$ VAS reduction) or very important ($\geq 50\%$ VAS reduction) improvement, respectively.²⁶ These results confirm the importance of the placebo effect on PCP, as well as other types of pain and other motor and non-motor symptoms in this disease.²⁷ Neuroimaging studies have shown that the placebo effect in PD is linked to dopamine release in striatal nuclei.²⁸ Moreover, in healthy volunteers, placebo analgesia correlates with the activation of mesolimbic and mesocortical dopaminergic and opioid pathways.²⁹ Both mechanisms may be relevant to account for the placebo effect observed on PCP in the present trial.

Based on preclinical and clinical findings suggesting a potential involvement of opioid systems in painful mechanisms in PD,^{20,30} the use of oxycodone-PR to treat PCP is a conceivable option, and a number of PD patients actually receive opiate medications in real life.³

Nevertheless, no beneficial effect was observed versus the placebo in this trial. A mild effect of oxycodone-PR cannot be formally excluded given that the CI contained the target effect size (-15), as the placebo effect was important and the variance larger than anticipated.³¹ Regardless of the fact that these results might be considered as statistically inconclusive, the magnitude of the difference observed between the oxycodone-PR and the placebo arms was notably small (1.54/100 mm on the VAS), far below the 10 mm usually considered as the clinically important difference between analgesic treatment and placebo.²⁶ This strongly challenges the potential clinical usefulness of this drug in this indication, especially when considering the poor tolerability of oxycodone-PR in this population. Indeed, ~40% of participants discontinued oxycodone-PR prematurely, because of well-known and expected adverse events, including somnolence and gastrointestinal side effects such as nausea, vomiting, and constipation. Only one patient could tolerate the target dosage (40 mg, level 3) during the trial, whereas the others had to be down-titrated to level 2 (57%) or level 1 because of tolerability issues. The average daily dose of oxycodone-PR (20.7 mg) was consequently lower than the 40 mg initially planned, and this may also have diminished the chances of detecting a more potent analgesic effect. The PANDA study is the only other published randomized controlled trial assessing the effect of oxycodone in PD patients suffering from chronic pain, but in this trial, oxycodone was combined in a fixed regimen with naloxone, a peripheral opiate antagonist, to minimize,

TABLE 2 Changes in primary and secondary pain endpoints between D0 and D71 (mITT)

Outcomes	Oxycodone-PR group n = 23	Levodopa/ benserazide group n = 20	Placebo group n = 20	Treatment effect adjusted**		
				Oxycodone- PR vs. placebo	Levodopa/ benserazide vs. placebo	Levodopa/ benserazide vs. oxycodone-PR
Average VAS score (mm)	-17 ± 18.5 (-26.2 to -7.7) *	-8.3 ± 11.1 (-14.4 to -2.3) *	-14.3 ± 18.9 (-24.5 to -4.0) *	-1.54 (-17.0 to 13.90) *	7.79 (-4.99 to 20.58) *	7.13 (-4.37 to 18.64) *
Maximal VAS score (mm)	-17.6 ± 21.5 (-28.4 to -6.9) *	-14.0 ± 13.4 (-21.3 to -6.7) *	-12.1 ± 22.7 (-24.4 to 0.2) *	-3.3 (-21.6 to 15.0) *	1.1 (-14.0 to 16.2) *	2.0 (-11.6 to 15.63) *
Brief Pain Inventory	-7.2 ± 10 (-11.5 to -2.8)	-2.9 ± 15.7 (-10.3 to 4.4)	-2.1 ± 12.8 (-8.1 to 3.9)	-5.0 (-12.1 to 2.0)	-0.8 (-10.0 to 8.4)	-4.2 (-3.8 to 12.2)
Total score (0-70)				P = 0.2	P = 0.9	P = 0.3
Neuropathic Pain Symptoms Inventory	-7.1 ± 12.3 (-12.4 to -1.7)	-6.9 ± 16 (-14.4 to 0.6)	-6.1 ± 13.8 (-12.6 to 0.3)	-1.0 (-9.0 to 7.1)	-0.8 (-10.4 to 8.8)	0.2 (-8.6 to 8.9)
Score total (0-100)				P = 0.8	P = 0.9	P = 0.9
McGill Pain Questionnaire	-3.9 ± 6.8 (-6.9 to -0.9)	-5.0 ± 8.7 (-9 to -0.9)	-3.7 ± 9.7 (-8.2 to 0.8)	-0.2 (-5.3 to 5.0)	-1.7 (-7.1 to 4.6)	-1.1 (-5.9 to 3.8)
Score total (0-45)				P = 0.9	P = 0.7	P = 0.7
King's Parkinson's Disease Pain Scale	-7.5 ± 13 (-13.2 to -1.9)	-10.8 ± 14 (-17.3 to -4.2)	-6.5 ± 19.5 (-15.7 to 2.6)	-3.2 (-11.5 to 5.1)	-4.2 (-15.1 to 6.6)	-1.0 (-11.1 to 9.1)
Total score				P = 0.8	P = 0.4	P = 0.4

Note: Data are mean ± SD (95% CI) or mean ± SD (97.5% CI*).

**Adjustment variables: age at inclusion, mean VAS score for the week before inclusion, center, and LEDD at baseline.

Abbreviations: D0, day 0; D71, day 71; mITT, modified intention-to-treat; CI, confidence interval; PR, prolonged release; VAS, Visual Analogue Scale; SD, standard deviation; LEDD, levodopa equivalent daily dose.

TABLE 3 Percentage of responders (30% and 50% pain relief) between D0 and D71 in the mITT population

Outcomes	Oxycodone-PR group n = 23	Levodopa/ benserazide group n = 20	Placebo group n = 20	Risk difference (97.5% CI)**		
				Oxycodone- PR vs. placebo	Levodopa/ benserazide vs. placebo	Levodopa/ benserazide vs. oxycodone-PR
% of responders (30%)	52.2% (29.5%–74.2%)	15% (3.1%–38.9%)	40% (18.3%–65.1%)	12.2% (–20.1 to 41.0) P = 0.42	–25.0% (–51.2 to 6.7) P = 0.07	–37.2% (–60.4 to –4.6) P = 0.01
% of responders (50%)	13% (2.7%–34.5%)	5% (0.1%–25.4%)	15% (3.1%–38.9%)	–2.0% (–28.1 to 22.7) P = 1*	–10.0% (–34.9 to 14.7) P = 0.60*	–8.0% (–30.8 to 16.1) P = 0.61*

Note: Bold values represent significant risk difference.

*Exact Fisher test.

**97.5% CIs for the risk difference are based on Newcombe confidence limits.

Abbreviations: D0, day 0; D71, day 71; mITT, modified intention-to-treat; PR, prolonged release; CI, confidence interval.

gastrointestinal side-effects.²⁰ The rate of premature discontinuations was lower in the PANDA trial than in the present one, although adverse events were also frequently observed, and the study failed to meet its primary efficacy outcome on pain scoring. Taken together, the small and uncertain effect of oxycodone-PR on PCP, combined with its poor tolerability and the current concerns related to the risk of addiction as faced in the opioid crisis in the United States,¹⁰ robustly challenge the concept that oxycodone may have a positive benefit–risk ratio to manage PCP in clinical practice.

There was clearly no efficacy on the severity of PCP in the group of patients receiving a higher dose of levodopa/benserazide. In reality, the reduction in pain severity and the percentage of responders were lower than in the placebo group. However, several data support the hypothesis that increasing the dosage of dopaminergic medications could improve PCP and this strategy is also sometimes considered in clinical practice. Pain thresholds improve following an acute challenge of levodopa in PD patients with or without PCP.^{15–17,32} A small number of trials have also suggested that adding a dopamine agonist or a monoamine oxidase B inhibitor, may improve pain in PD patients.^{8,33,34} However, such data are based on secondary endpoints or exploratory post hoc analyses. Moreover, these trials involved patients suffering from heterogeneous types of pain, frequently related to motor fluctuations, and may have, therefore, benefited indirectly from some motor improvement. It is also possible that non-dopaminergic mechanisms, especially noradrenergic/serotonergic or ion channel ones may have been involved.^{34,35} The patients in the OXYDOPA trial were already taking levodopa at baseline to manage motor symptoms. One cannot then exclude the hypothesis that some analgesic effect of the drug might already have been present when initiating the trial and was not subsequently enhanced when increasing the dose. There was, however, no trend to support this hypothesis and the placebo response turned out to be greater than the effect of a higher dose of levodopa/benserazide. It is also possible to speculate that a greater increase in levodopa/benserazide daily dosage might have provided a greater analgesic effect. However, 45% of the patients randomized to receive a supplement of 200 mg/d of levodopa/benserazide reported dyskinesia as an adverse event and 30% required down titration below the planned 200 mg dosage. This suggests that a larger increase in the levodopa/benserazide daily dose to manage PCP is unlikely to be acceptable for many patients in clinical practice.

The strengths of OXYDOPA are its robust design (randomized, double-blind, placebo-controlled), and the choice of a population focusing on one single subtype of PD pain. The trial also has several limitations. First, the number of patients enrolled in each arm was slightly less than planned, because the decision to stop recruitment was taken because of feasibility concerns in

the context of the coronavirus disease pandemic in 2020. This may have reduced the power of the trial. There were a number of dropouts, which is a common observation in clinical trials on chronic pain,³⁶ which was largely related to the poor tolerability of oxycodone-PR. The duration of the trial was limited to 8 weeks at stable dose, but given our knowledge of the clinical responses to levodopa/benserazide and oxycodone-PR, it is improbable that longer follow-up would have provided more positive results. Higher doses than the tested ones might have provided different results, but as mentioned previously, it is unlikely that patients would have tolerated them. Finally, although the study was run in a double-blind design, we did not formally assess the level of masking, and the greater frequency of adverse events in both active arms may have compromised the blinding. If so, this potential bias may have inflated rather than reduced the treatment effect on both active treatments versus placebo, further questioning the value of the observed differences.

In conclusion, improving the severity of PCP remains a challenge in the management of patients with PD. Our findings do not support the hypothesis that adding oxycodone-PR or increasing the daily dose of levodopa/benserazide should be viewed as promising strategies to alleviate this type of pain. Alternative mechanism-based approaches are yet to be evaluated, such as for example, noradrenaline and serotonin reuptake inhibitors, gabapentin, and pregabalin as well as non-pharmacological interventions.³⁷ It is possible that other types of pain than PCP, observed in PD sufferers may respond better to oxycodone-PR or an increase in levodopa/benserazide doses and this should be tested properly in future trials. ■

Acknowledgments: We thank the staff at the Clinical Investigation Centre and the staff working in the Research Unit at the University of Toulouse Hospital Centre (CHU) and all PD patients involved in the trial. This study was funded by the French Ministry of Health (PHRCN-14-0044). The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Data Availability Statement

Data available on request from the authors.

References

1. Broen MP, Braaksma MM, Patijn J, et al. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. *Mov Disord* 2012;27:480–484.
2. Beiske AG, Loge JH, Rønningen A, et al. Pain in Parkinson's disease: prevalence and characteristics. *Pain* 2009;141:173–177.
3. Brefel-Courbon C, Grolleau S, Thalamas C, et al. Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. *Pain* 2009;141:14–18.
4. Buhmann C, Wrobel N, Grashorn W, et al. Pain in Parkinson disease: a cross-sectional survey of its prevalence, specifics, and therapy. *J Neurol* 2017;264:758–769.
5. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. *Parkinsonism Relat Disord* 2004;10:129–136.
6. Marques A, Attal N, Bouhassira D, et al. How to diagnose parkinsonian central pain? *Parkinsonism Relat Disord* 2019;64:50–53.
7. Mylius V, Perez Lloret S, Cury R, et al. The Parkinson disease pain classification system: results from an international mechanism-based classification approach. *Pain* 2021;162:1201–1210.
8. Buhmann C, Kassubek J, Jost WH. Management of Pain in Parkinson's disease. *J Parkinsons Dis* 2020;10:S37–S48.
9. Edinoff A, Sathivadivel N, McBride T, et al. Chronic pain treatment strategies in Parkinson's disease. *Neurol Int* 2020;12:61–76.
10. Gottlieb S, Woodcock J. Marshaling FDA benefit-risk expertise to address the current opioid abuse epidemic. *JAMA* 2017;318:421–422.
11. Bouhassira D, Attal N. Translational neuropathic pain research: a clinical perspective. *Neuroscience* 2016;338:27–35.
12. Marques A, Brefel-Courbon C. Chronic pain in Parkinson's disease: clinical and pathophysiological aspects. *Rev Neurol* 2021;177:394–399.
13. Ghosh P, Imbriani P, Caputi N, et al. A dual Centre study of pain in Parkinson's disease and its relationship with other non-motor symptoms. *J Parkinsons Dis* 2020;10:1817–1825.
14. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. *Pain* 1995;60:3–38.
15. Brefel-Courbon C, Payoux P, Thalamas C, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord* 2005;20:1557–1563.
16. Brefel-Courbon C, Ory-Magne F, Thalamas C, et al. Nociceptive brain activation in patients with neuropathic pain related to Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:548–552.
17. Gerdelat-Mas A, Simonetta-Moreau M, Thalamas C, et al. Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. *J Neurol Neurosurg Psychiatry* 2007;78:1140–1142.
18. Schestatsky P, Kumru H, Valls-Solé J, et al. Neurophysiologic study of central pain in patients with Parkinson disease. *Neurology* 2007;69:2162–2169.
19. Borsook D, Upadhyay J, Chudler EH, et al. A key role of the basal ganglia in pain and analgesia—insights gained through human functional imaging. *Mol Pain* 2010;6:27.
20. Trenkwalder C, Chaudhuri KR, Martinez-Martin P, et al. Prolonged-release oxycodone-naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): a double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 2015;14:1161–1170.
21. Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
22. Nebe A, Ebersbach G. Pain intensity on and off levodopa in patients with Parkinson's disease. *Mov Disord* 2009;24:1233–1237.
23. Genolini C, Lacombe A, Écochard R, et al. CopyMean: a new method to predict monotone missing values in longitudinal studies. *Comput Methods Programs Biomed* 2016;132:29–44.
24. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649–2653.
25. Edwards RR, Dworkin RH, Turk DC, et al. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016;157:1851–1871.
26. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009;146:238–244.
27. Witek N, Stebbins GT, Goetz CG. What influences placebo and nocebo responses in Parkinson's disease? *Mov Disord* 2018;33:1204–1212.
28. Quattrone A, Barbagallo G, Cerasa A, Stoessl AJ. Neurobiology of placebo effect in Parkinson's disease: what we have learned and where we are going. *Mov Disord* 2018;33:1213–1227.
29. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008;65:220–231.
30. Blanchet PJ, Brefel-Courbon C. Chronic pain and pain processing in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;87:200–206.

31. Tuttle AH, Tohyama S, Ramsay T, et al. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. *Pain* 2015;156:2616–2626.
32. Thompson T, Gallop K, Correll CU, et al. Pain perception in Parkinson's disease: a systematic review and meta-analysis of experimental studies. *Ageing Res Rev* 2017;35:74–86.
33. Rascol O, Zesiewicz T, Chaudhuri KR, et al. A randomized controlled exploratory pilot study to evaluate the effect of Rotigotine transdermal patch on Parkinson's disease-associated chronic pain. *J Clin Pharmacol* 2016;56:852–861.
34. Grigoriou S, Martínez-Martín P, Chaudhuri KR, et al. Effects of safinamide on pain in patients with fluctuating Parkinson's disease. *Brain Behav* 2021;11:e2336.
35. Dellapina E, Gerdelat-Mas A, Ory-Magne F, et al. Apomorphine effect on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord* 2011;26:153–157.
36. Kim Y. Missing data handling in chronic pain trials. *J Biopharm Stat* 2011;21:311–325.
37. Huissoud M, Boussac M, Joineau K, et al. The effectiveness and safety of non-pharmacological intervention for pain management in Parkinson's disease: a systematic review. *Rev Neurol* 2023. <https://doi.org/10.1016/j.neurol.2023.04.010>

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.