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ORIGINAL RESEARCH ARTICLE

Evaluation of Prescription Practices of Domperidone in Parkinson's Disease: A Cross Sectional Study Among French Neurologists

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Abstract

Background Domperidone is used to treat gastrointestinal symptoms in patients with Parkinson's disease. Because of an increased risk of cardiac adverse events, the European Medicines Agency has issued recommendations restricting its use mainly in terms of age, dose, and treatment duration.

Objective The aim of this study was to investigate current prescription practices of domperidone in Parkinson's disease among French neurologists.

Methods A cross-sectional study based on a questionnaire was conducted among French neurologists from Parkinson's disease expert centers from the French NS-Park/FCRIN network, general hospitals, and private practice.

Results Among the 253 neurologists who completed the questionnaire, 86 (34%) were physicians from expert centers and 167 (66%) were from other healthcare settings; 209 (83%) were aware of recommendations restricting domperidone use. The majority of neurologists (92%) declared prescribing domperidone regardless of the age of the patients. Sixty-one percent of neurologists prescribed domperidone beyond 7 days in newly diagnosed patients, 33% in patients with orthostatic hypotension, and 79% in patients receiving continuous apomorphine treatment. They did not follow the recommendation on posology in newly diagnosed patients (7% of neurologists), patients with orthostatic hypotension (10%), and patients receiving continuous apomorphine therapy (25%). Finally, only 58% of neurologists declared taking specific precautions before prescribing domperidone.

Conclusions These findings show most French neurologists who responded to our questionnaire do not fully follow the restrictions on domperidone use, particularly in terms of treatment duration, and in patients receiving continuous apomorphine treatment. This may reflect the unmet need to prevent nausea in patients with Parkinson's disease treated with dopaminergic drugs, particularly continuous apomorphine therapy.

1 Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease after Alzheimer's disease and affects 1% of the population over 60 years of age [1]. As a consequence of population aging and life expectancy improvement, the number of patients with PD is predicted to grow

Key Points

The European Medicines Agency has issued recommendations restricting domperidone use to patients aged younger than 60 years, at doses below 30 mg/day and for a short period only; making it challenging for neurologists to prescribe domperidone for patients with Parkinson's disease.

Our results show most French neurologists who responded to our questionnaire do not fully follow the restrictions on domperidone use and specific precautions are not always taken before prescribing this medicine to patients with Parkinson's disease.

This study highlights the unmet need to prevent nausea in patients with Parkinson's disease treated with dopaminergic drugs.

Jean-Christophe Corvol and Florence Tubach contributed equally to the present work.

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substantially in future years and should affect 260,000 persons in France in 2030 [2]. The treatment of PD is based on dopamine replacement therapies (DRT). Nausea is the most frequent adverse event of DRT, occurring in 30–40% of patients at initiation of treatment [3–7]. Domperidone is an "old" antiemetic drug supposed to work by blocking dopamine D_2 receptors in the gut and the area postrema controlling vomiting [8]. As compared to other antiemetic drugs, domperidone does not readily cross the blood–brain barrier and can thus be used in PD despite its dopamine receptor antagonist properties. Domperidone has indeed shown efficacy in preventing nausea related to dopaminergic medication in PD [9]. Domperidone is also used in PD to treat orthostatic hypotension, another adverse effect of dopaminergic drugs [10].

Arrhythmias, sudden death, and cardiac arrest were reported with high intravenous domperidone doses [11, 12], this alert has led to the withdrawal of the parenteral form of the drug in 1984. More recently, two case control studies found an increased risk of sudden death associated with oral domperidone use. In these studies, the increased risk was dependent on age, dose, and the use of domperidone in combination with cytochrome P450 3A4 inhibitors [13, 14]. Following this alert, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) has issued recommendations restricting domperidone use to patients aged younger than 60 years, at doses below 30 mg/day and for a short period only (up to 7 days) [15].

Because alternative antiemetic drugs are limited in PD owing to their dopaminergic antagonist properties (other benzamides) or their similar safety profile (prolonged QT), domperidone has been prescribed as a preventive therapy in patients with PD in several countries, including France. In this population, usually aged older than 60 years, doses of 60 or 80 mg/day were commonly prescribed [9], for at least the first 2 months of the DRT escalating dose period or longer. In addition, a particular "niche" of domperidone use is patients treated with continuous subcutaneous administration of apomorphine, a second-line therapy in PD, inducing severe and prolonged nausea in many patients.

Little is known about domperidone use in PD in France in clinical practice since EMA recommendations have restricted its use. Nevertheless, because of the characteristics of patients with PD and the use of domperidone in PD, complying with the recommended restrictions on age, dose, and duration of treatment may be challenging for neurologists. Therefore, the aim of this study was to investigate the prescription practices of French neurologists regarding domperidone in PD, after the EMA recommendations restricting its use.

2 Methods

2.1 Study Design, Study Setting, and Participants

This study is the first part of a global project named "DUMP" (Domperidone use and misuse in Parkinson's Disease") registered with an ENCEPP seal EUPAS26319 (https://www.encepp.eu/encepp/viewResource.htm?id=33284) and funded by the French agency for drugs (Agence Nationale de Sécurité du Médicament). We conducted an observational cross-sectional study based on an anonymous paper or web-based questionnaire completed by neurologists between June 2018 and February 2019 across France. To ensure the representativeness of diverse practices, neurologists were recruited from PD expert centers [16] (France Parkinson Expert Centers list available at www.franceparkinson.fr/la-maladie/prise-en-charge/centres-experts-parkinson/) and public institutions (university and general hospitals) and private practices.

French neurologists were identified and contacted to participate in the survey by different methods and several e-mails sent by (1) the French Society of Neurology (www.sf-neuro.org/), which is the national society for French neurologists (four e-mails from July to October 2018), and (2) the French clinical research network for PD and movement disorders (NS-Park/FCRIN network, https://parkinson.network/) gathering the 25 French PD expert centers (three e-mails from October 2018 to January 2019). In addition, to recruit private practice neurologists, questionnaires were distributed for completion during the congress of the Association des Neurologues Libéraux de Langue Française (French liberal neurologists association, https://anllf.org/) and an online version of the questionnaire was also available on the website of this association.

In each setting, neurologists received a training note detailing how to answer the questionnaire. The study aimed at describing physician self-reported usual practices and did not involve any patient. All data were collected anonymously. In accordance with French law, no ethics committee advice was needed.

2.2 Questionnaire and Measurements

The questionnaire was conceived by a multidisciplinary team of neurologists, pharmacologists, and epidemiologists (Electronic Supplementary Material). The first part of the questionnaire collected data on the respondent: age, sex, duration of practice in years, practice location, and profiles of patients with PD in the practice. Then, data on domperidone prescribing practices (indication, dosage, duration, evaluation of contraindications, and precaution for use) were collected according to patients' profiles. The questionnaire ended with

questions about awareness of the revised recommendations endorsed by the EMA to restrict the use of domperidone, whether neurologists had changed their prescribing practice since then; whether they encountered difficulties to treat the symptoms (e.g., nausea and orthostatic hypotension) owing to the prescription restrictions of domperidone, and which therapeutic alternatives to domperidone were being used.

2.3 Statistical Methods

Categorical variables were reported as counts and percentages and quantitative variables as mean and standard deviation. For the question about "clinical situations for prescribing domperidone in patients with Parkinson's disease", neurologists had the option of multiple responses; percentages were calculated according to all marked responses.

Shapiro–Wilk (if $n > 50$) or Anderson and Darling (if $n < 50$) tests were used to evaluate each variable for normality. Comparisons of qualitative variables were performed with the Fisher's Exact or Pearson's Chi-squared test, as appropriate, while those on quantitative variables were performed with the Wilcoxon rank sum test. The level of significance was set at $p < 0.05$. All analyses were performed with the R software (Version 1.1.419).

3 Results

3.1 Participants

Overall, 253 neurologists participated in the study; 86 (34%) were physicians from PD expert centers and 167 (66%) were from other healthcare settings (public hospitals, private practices, or clinics). According to the Conseil de l'Ordre National des Médecins (French National Medical Council (www.conseil-national.medecin.fr/lordre-medecins/conseil-national-lordre/international-relations), 2362 neurologists were registered in France in 2016, of those 92 belonged to expert centers. Therefore, the participation rate was 94% ($n = 86/92$) among PD expert centers, and 7% ($n = 167/2270$) among non-expert centers.

Among participating neurologists, mean age was 51.8 years, a majority of participants were men ($n = 149$, 59%), and the average duration of practice was 22.5 years (Table 1). Physicians from PD expert centers were younger (mean age 46.5 vs 54.6 years, $p < 0.001$) and consequently with fewer years of practice (mean duration 17.3 vs 25.1 years, $p < 0.001$).

The median number of patients with PD followed by neurologists per year was 400 in PD expert centers and 140 in non-expert centers, respectively. The patient population differed according to the type of practice (i.e., expert or non-expert centers); more patients newly diagnosed (median number 30 vs 18.5, $p < 0.001$), with severe diagnosis (median number 200 vs 30, $p < 0.001$), or receiving continuous apomorphine therapy (median number 20 vs 4, $p < 0.001$) were seen in PD expert centers annually (Table 1).

3.2 Clinical Situations for Prescribing Domperidone

The main clinical situation for prescribing domperidone to patients with PD was nausea at treatment initiation with dopamine agonists ($n = 176$, 35%), followed by nausea under continuous apomorphine infusion ($n = 91$, 18%) and all patients receiving continuous apomorphine infusions [with or without nausea] ($n = 86$, 17%) [Fig. 1]. Orthostatic hypotension represented 12% ($n = 63$) of the clinical situations for prescribing domperidone. There was no difference in the frequency of indications for domperidone between neurologists in expert or non-expert centers except that there were more neurologists who completely stopped prescribing domperidone in expert centers (6% vs 1%, $p = 0.013$).

3.3 Use and Misuse of Domperidone among Neurologists

Among participants, 83% ($n = 209$) were aware of the recommendations endorsed by the EMA to restrict the use of domperidone (93% in PD expert centers vs 78% non-expert centers; $p = 0.003$). Overall, 74.1% ($n = 186$) of the participants acknowledged having changed their prescribing habits since the safety alerts and the revision of recommendations regarding the use of domperidone; with no significant difference between expert and non-expert centers (77% vs 73%, $p = 0.49$).

Only 6% ($n = 14$) of the respondents complied with the EMA recommendation to limit the prescription of domperidone to patients below the age of 60 years (Fig. 2a). The large majority of neurologists (92%, $n = 223$) declared prescribing domperidone to all patients regardless of their age.

Seven percent of neurologists ($n = 17$) reported prescribing domperidone in newly diagnosed patients at higher doses than recommended by the EMA [i.e., above 30 mg/per day], ten percent of neurologists ($n = 25$) in patients with orthostatic hypotension and 25% ($n = 61$) in patients receiving continuous apomorphine therapy (Fig. 2c). Regarding treatment duration, the proportion of neurologists who prescribed domperidone for more than 7 days was 61% ($n = 152$) in newly diagnosed patients, 33% ($n = 82$) in patients with orthostatic hypotension, and 79%

Table 1 Characteristics of questionnaire respondents and patient population by center status

	Global	Center status		
	N = 253	PD expert centers *N* = 86	Non-expert centers *N* = 167	*P*-value
Neurologists sociodemographic data				
Age, years, mean (SD)	51.8 (9.9)	46.5 (10.9)	54.6 (8.1)	< 0.001
Male, *N* (%)	149 (58.9)	46 (53.5)	103 (61.7)	0.22
Duration of practice, years, mean (SD)	22.5 (9.8)	17.3 (40.4)	25.1 (8.3)	< 0.001
Patients profile in the practice, Med [IQR] per year				
Total patients with PD	200 [97.5–350]	400 [250–500]	140 [70–200]	< 0.001
Patients with newly diagnosed PD	20 [10–40]	30 [18.75–50]	18.5 [10–30]	< 0.001
Patients with severe PD	50 [20–150]	200 [100–350]	30 [15–56.25]	< 0.001
Patients with PD receiving continuous apomorphine therapy	5 [2–15]	20 [10–32.5]	4 [1–6]	< 0.001

IQR interquartile range, *Med* median, *PD* Parkinson's disease, *SD* standard deviation

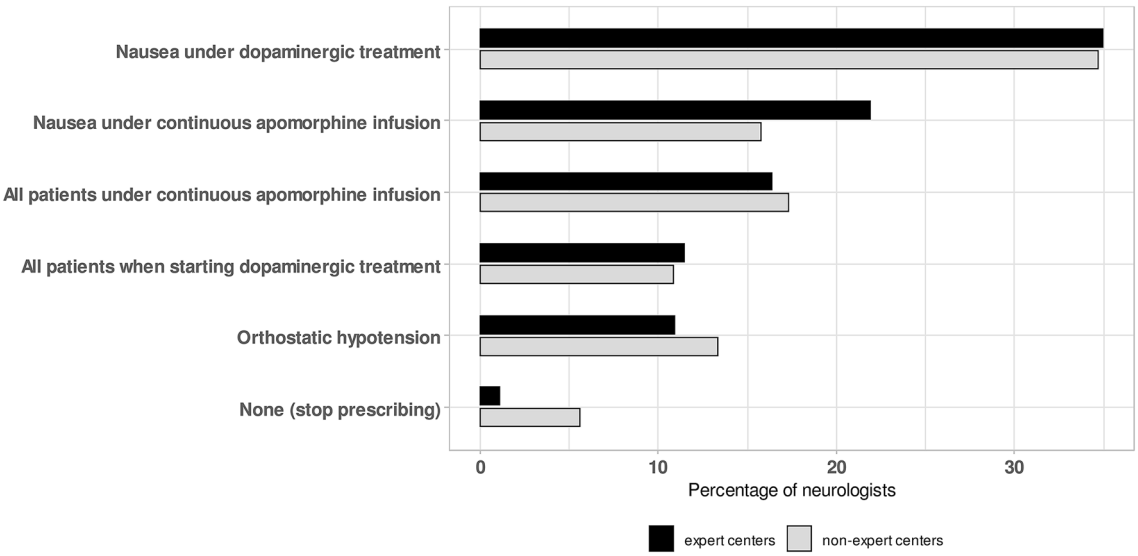

Fig. 1 Clinical situations for prescribing domperidone in patients with Parkinson's disease. For this question, neurologists had the option of multiple responses. Percentages were calculated according to all marked responses ($n = 506$)

($n = 163$) in patients receiving continuous apomorphine therapy (Fig. 2d).

3.4 Precaution for Use

Among the 253 neurologists, 144 (58%) declared taking special precautions before prescribing domperidone to patients with PD (Fig. 2b). Among them, the most frequent precaution was "searching for concomitant use of contraindicated anti-arrhythmic" ($n = 119$, 83%), followed by "searching for a personal or family history of cardiovascular diseases" ($n = 116$, 81%) and "asking for a consultation with a cardiologist whenever in doubt" ($n = 72$, 50%) [Table 2]. In expert centers, neurologists were more likely to perform or have performed an electrocardiogram before domperidone initiation than neurologists from non-expert centers (74% vs 33%, $p < 0.001$).

3.5 Alternative Therapeutics

Overall, 41% ($n = 120$) of the neurologists reported continuing to prescribe domperidone to patients with PD in the absence of a suitable alternative, despite the EMA's recommendations. Some of the neurologists declared prescribing ondansetron ($n = 20$, 7%) or metoclopramide ($n = 10$, 3%) as an alternative, and only 3% ($n = 17$) completely stopped prescribing domperidone. One third (34%, $n = 86$) of the

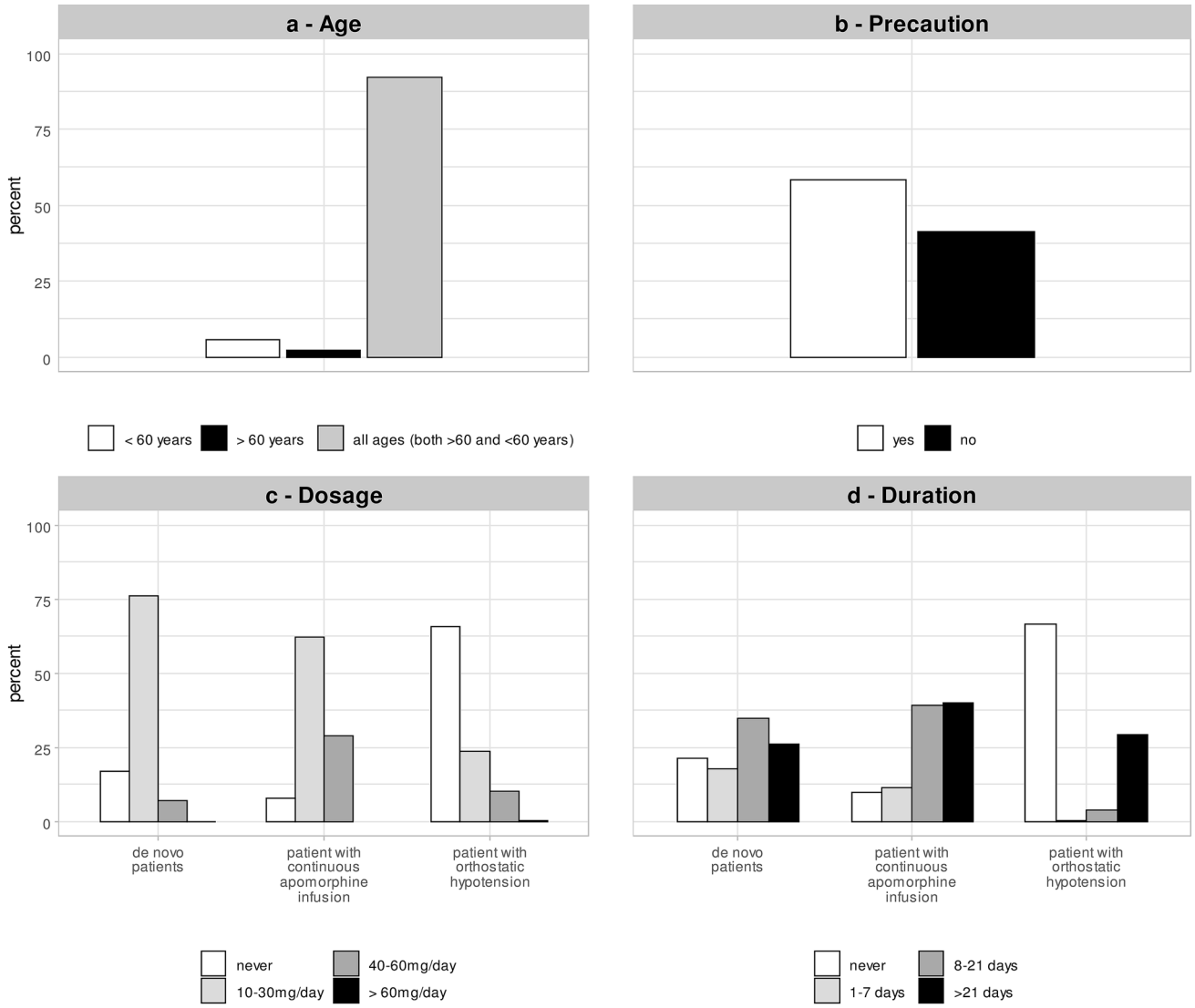

Fig. 2 Habits of domperidone prescription by neurologists in patients with Parkinson's disease: patient's age, precaution for use, dosage, and duration of treatment

participants declared having difficulties treating nausea or orthostatic hypotension in patients with PD.

4 Discussion

To our knowledge, this is the first survey on clinical practice for the use of domperidone. Our results highlight that many French neurologists are still prescribing domperidone in PD without strictly respecting the EMA's recommendations, and without taking specific precautions in more than 40% of them. This occurs despite the fact that 83% are aware of these recommendations. However, 74% declare having changed their prescribing habits. The main reasons for using domperidone were to prevent or treat nausea at dopaminergic therapy initiation in de novo patients (35%) or in patients treated with continuous apomorphine (18%). The current French guidelines recommending treatment initiation with a dopamine agonist in a patient with a young age at onset may explain the relatively high rate of domperidone use in this indication. This may be different in other countries where treatment initiation is more common with levodopa-decarboxylase inhibitor combinations. Prescription of domperidone to all patients starting dopaminergic treatment was however not systematic, representing only 11% of neurologists. Domperidone was also prescribed for orthostatic hypotension by 13% of the respondents, a relatively low rate considering the prevalence of orthostatic hypotension estimated to have a range of 30–65% in PD [17–19]. Age restriction was the least followed recommendation, with

Table 2 Precautions taken by neurologists before prescribing domperidone in patients with Parkinson's disease

Among neurologists who declared taking precautions ($N = 144/253$)	Center status			*P*-value
	Global $N = 144$	Expert centers $N = 50$	Non-expert centers $N = 94$	
Asking for a consultation with a cardiologist, *N* (%)				
Whenever in doubt	72 (50.0)	24 (48.0)	48 (51.1)	0.726
Each time	18 (12.5)	4 (8.0)	14 (14.9)	0.234
Systematically perform or have performed an ECG before treatment initiation	68 (47.2)	37 (74.0)	31 (33.0)	<0.001
Searching for concomitant use of contraindicated substances, *N* (%)				
Anti-arrhythmics	119 (82.6)	43 (86.0)	76 (80.9)	0.437
Antibiotics or antifungal agents	23 (16.0)	5 (10.0)	18 (19.2)	0.154
Medicines used in cancer	16 (11.1)	4 (8.0)	12 (12.2)	0.386
Antidepressants	54 (37.5)	17 (34.0)	37 (39.4)	0.527
Antihistaminics	20 (13.9)	5 (10.0)	15 (16.0)	0.325
Antipsychotics	68 (47.2)	21 (42.0)	47 (50.0)	0.360
Searching for a family history of sudden death	48 (33.3)	10 (20.0)	38 (40.4)	0.013
Searching for a personal or family history of cardiovascular diseases	116 (80.6)	38 (76.0)	78 (83.0)	0.313

Percentages were calculated among the neurologists who answered YES to the question "Do you take any precautions before prescribing domperidone in patients with Parkinson's disease?" ($N = 144/253$)

92% of neurologists prescribing domperidone regardless of age. Patients for whom the neurologists were more prone to prescribe domperidone outside of EMA restrictions were those treated with continuous subcutaneous apomorphine infusions, 25% of the neurologists prescribing domperidone at a higher dose (i.e., > 30 mg) and 79% for a longer period (i.e., beyond 7 days) than recommended.

The benefit-risk ratio of domperidone use is currently not adequately assessed in PD and should be at least moderate owing to the lack of therapeutic alternatives to treat adverse effects of DRT. Efficacy of domperidone was assessed in "old" clinical trials with small sample sizes, and a methodology that does not comply with the current gold standards [9, 10]. The evidence of efficacy is thus considered as low for nausea and orthostatic hypotension in PD and the drug is not approved in certain countries such as the USA. However, because extrapyramidal adverse effects are minimal with domperidone, off-label prescriptions in PD are understandable, particularly in the context of an apomorphine concomitant prescription [20]. Domperidone was systematically proposed in clinical trials testing subcutaneous apomorphine infusions, before and after treatment initiation (30–60 mg per day, 48 hours before and 2 weeks after treatment initiation) [21], although lower doses were proposed in more recent trials (30 mg/day starting 3 days before an apomorphine infusion) [22].

However, domperidone was associated with an increased risk of mortality in the general population, recently confirmed in the PD population, the current use of domperidone being associated with a twofold increase mortality, increasing to three-fold in the month following initiation [23]. The cause of this higher mortality in PD is not known and the increased risk in this study concerned all causes of mortality. However, the higher mortality associated with domperidone has been suggested to be related the propensity of domperidone to prolong QT and has been associated with sudden death in the general population [23]. In our study, less than 60% of the neurologists declared taking special precautions regarding this risk, and among all respondents, only a quarter of neurologists declared performing an electrocardiogram before initiating domperidone or requesting a consultation with a cardiologist. These findings highlight the need to secure domperidone prescriptions outside of safety restrictions for patients with PD, by systematically recommending consultation with a cardiologist and/or an electrocardiogram before initiating treatment.

Alternatives to domperidone are very limited in PD. In our study, alternative anti-emetic drugs were prescribed by 3–7% of neurologists only, and 30% of them declared having difficulties in treating nausea and orthostatic hypotension. Indeed, other benzamides or neuroleptics are not accurate alternatives in PD because they cross the blood–brain barrier and worsen parkinsonian symptoms by blocking dopamine receptors in the central nervous system. Trimethobenzamide is the only drug that has shown efficacy in treating nausea in PD, but is only available in the USA [24]. More importantly, all antiemetic drugs, including benzamides (of which trimethobenzamide) and setrons, are associated with an increased risk of prolonged QT similar to domperidone. Further studies would be needed to compare the safety profile of these potential alternatives to domperidone in the PD population. Non-pharmacological intervention such as hypnosis for preventing or treating nausea may also be evaluated in

PD, but it is probably not appropriate for long-term treatment such as continuous infusions of apomorphine. An EMA statement did not explicitly mention that PD is a disorder where the balance between the advantages and disadvantages of dopamine therapy might be rather different from that which applies in other disorders. Thus, French neurologists' appreciation in this regard and clinical common sense may contribute to explain their continued use of domperidone.

The strength of our study is the relatively large number and the different varieties of neurologists from private or public practice who responded to the questionnaire. Some limitations have also to be acknowledged. Although the participation rate of neurologists from expert centers was high and probably representative of PD specialists, the participation rate among non-expert centers was low and probably less representative. Neurologists from expert centers are more often exposed to the management of patients with more severe disease or patients receiving continuous apomorphine therapy, and therefore, their opinions were particularly important in this study as they could encounter daily dilemmas regarding domperidone restriction or prescription [16]. However, neurologists from non-expert centers who responded followed a relatively high number of patients with PD, and their responses were globally concordant with expert centers, the differences being mainly due to differences in patients' profiles rather than variations in clinical practice and prescribing habits. Another limitation is related to the design of this observational study based on self-reported questionnaires known to overestimate acceptable answers. In our case, anonymity should have reduced the social desirability bias.

5 Conclusions

French neurologists treating patients with PD encounter difficulties in complying with EMA recommendations, given the characteristics of these patients and the lack of therapeutic alternatives. However, precautions are not sufficiently taken when introducing domperidone treatment, probably owing to the lack of specific recommendations for this population of patients. These findings underline the unmet need to prevent nausea in patients with PD treated with dopaminergic drugs, particularly continuous apomorphine therapy.

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Declarations

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Conflict of interest The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. Competing financial interests unrelated to the present work: Louise-Laure Mariani received research support grants from INSERM, JNLF, and The L'Oreal Foundation; received speech honoraria from CSL, Sanofi-Genzyme, Lundbeck, and Teva; was a consultant for Alzprotect, Bionure, and Digitsole; and received travel funding from the Movement Disorders Society, ANAINF, Merck, Merz, Medtronic, Teva, and AbbVie, outside the submitted work. Olivier Rascol served as a member of advisory boards for AbbVie, Adamas, Acorda, Addex, AlzProtect, Apopharma, Astrazeneca, Bial, Biogen, Britannia, Buckwang, Clevexel, INC Reasearch, Lundbeck, Lupin, Merck, MundiPharma, Neuratris, Neuroderm, Novartis, ONO Pharma, Orion Pharma, Osmotica, Oxford Biomedica, Parexel, Pfizer, Prexton Therapeutics, Quintiles, Sanofi, Servier, Sunovion, Théranexus, Takeda, Teva, UCB, Watermark, Research, XenoPort, XO, and Zambon and received a grant from Agence Nationale de la Recherche (ANR), CHU de Toulouse, France-Parkinson, INSERM-DHOS Recherche Clinique Translationnelle, MJFox Foundation, Programme Hospitalier de Recherche Clinique, and the European Commission (FP7, H2020) as well as a grant to participate in a symposium and contribute to the review of an article IPMDS, outside the submitted work. Jean-Denis Turc received an honorarium from Abbvie for a symposium outside the submitted work. Jean-Christophe Corvol served as a member of advisory boards for UCB, Biogen, Prevail Therapeutic, Idorsia, Sanofi, Ever Pharma, Denali, BrainEver, and Theranexus, and received an unrestricted grant from the Michael J. Fox Foundation outside the present work. Florence Tubach is head of the Centre de Pharmacoépidémiologie (Cephepi) of the Assistance Publique – Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière Hospital, both these structures have received research funding, grants, and fees for consultant activities from a large number of pharmaceutical companies that have contributed indiscriminately to the salaries of its employees. Florence Tubach did not receive any personal remuneration from these companies.

Ethics approval This is an observational study that did not involve any patients. All data were collected anonymously. In accordance with French law, no ethical approval is required.

Availability of Data and Material The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Authors Contributions L-LM, OR, J-DT, ML-M, J-CC, and FT contributed to the study conception and design. Analyses were performed by HA and DL. The first draft of the manuscript was written by DL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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