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ORIGINAL ARTICLE

Increased risk of all-cause mortality associated with domperidone use in Parkinson's patients: a population-based cohort study in the UK

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AIMS

Domperidone is used to treat gastrointestinal symptoms in patients with Parkinson's disease (PD) and is linked to an increased risk of mortality. We sought to examine the risk of all-cause mortality associated with domperidone exposure in PD.

METHODS

We conducted a cohort study using data from the Clinical Practice Research Datalink database (1987–2011). The first recorded PD diagnosis defined index date. Time-dependent Cox proportional hazards models estimated hazard ratios (HRs) of all-cause mortality associated with domperidone use. PD patients were stratified by domperidone use (current/recent/past), with never used as the referent. Current domperidone users were stratified by daily dose, domperidone duration and other anti-Parkinson's medications. A secondary analysis compared PD patients to matched (1:1) non-PD patients.

RESULTS

A total of 5114 PD patients were identified. Current use of domperidone among PD patients was associated with a two-fold increase in all-cause mortality (HR_{adj} = 2.00, 95% confidence interval [CI]: 1.64–2.45), as compared to patients never exposed to domperidone. All-cause mortality risk was highest in those starting domperidone in the previous month [HR_{adj} = 2.97, 95% CI: 2.06–4.27]. When compared to matched non-PD patients, PD was associated with a 43% increased risk of all-cause mortality, yet this increased to a 2.4-fold increased risk among PD patients currently using domperidone.

CONCLUSION

Current use of domperidone was associated with a two-fold increased mortality risk in PD patients, as compared to PD patients that never used domperidone. The risk is highest in the first month of use and does not appear to be attributable to PD alone.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There are known risks of cardiac effects and mortality associated with domperidone, but there is little data in PD patients, where domperidone is the gold standard for treating gastrointestinal (GI) symptoms.
- PD patients using domperidone may be at greater risk of all-cause mortality due to increased cardiovascular complications and cardiac abnormalities associated with the disease.

WHAT THIS STUDY ADDS

- PD patients that were currently using domperidone had a doubled risk of all-cause mortality, when compared to PD patients that never used domperidone. The risk was similar to that of non-PD patients.
- The increased risk in mortality was highest in the first 30 days of domperidone use.

Introduction

Parkinson's disease (PD) is one of the most common chronic, progressive neurodegenerative disorders. It is associated with a significant proportion of disability-adjusted life years worldwide [1]. In addition to the commonly-observed motor dysfunctions, such as muscular rigidity and tremors, patients with PD experience other complications including sleep, cognitive abnormalities and gastrointestinal (GI) disturbances [2]. Problems with GI motility can often present as weight loss, excess salivation, dysphagia, gastroparesis, slow-transit constipation and defecation dysfunction, and can significantly impact the quality of life in patients [3]. **Domperidone** is commonly used to treat GI effects, such as nausea. Unlike other **dopamine** antagonists, domperidone does not readily cross the blood–brain barrier. Thus, it has minimal neurological adverse effects and remains the gold standard for the treatment of GI symptoms in patients with PD [4].

The cardiac side-effects of domperidone in a general patient population have been well described since the early 1980s [5]. Indeed, the parenteral form was withdrawn from the market by the manufacturer in 1984, following reports of sudden death and cardiac arrests among patients receiving chemotherapy [5–7]. More recently, the oral formulation has been associated with cardiac electrophysiological abnormalities [8], and has been linked to a 1.6- to 4.7-fold increased mortality risk [9–11]. As a result of the pharmacovigilance data exemplifying cardiologic concerns, the European Medicines Agency (EMA) released a statement in 2014 restricting the daily domperidone dose to 30 mg orally or 60 mg rectally [12]. However, the risk of sudden cardiac death among high- (>30 mg day^{-1}) and low- (≤ 30 mg day^{-1}) dose domperidone users is not well established [13, 14].

Cardiovascular complications in drug-naïve PD patients are not uncommon. Patients can experience cardiovascular autonomic failures even at early stages of the disease [15, 16]. However, little is known regarding the adverse cardiac events of domperidone in patients with PD [3]. In a small clinical study of 10 PD patients, the addition of domperidone to apomorphine therapy resulted in significant increases in blood pressure within 24 h of domperidone exposure, suggesting a mechanism involving the inhibition of presynaptic **D2-receptors** at the sinus node [17]. A recent multi-database case–control study of PD patients from seven Canadian provinces and the UK Clinical Practice Research Datalink (CPRD) found evidence of an association between domperidone use (overall or based on average daily dose [≤ 30 *vs.* >30 mg day^{-1}]) or duration of use (≤ 30 *vs.* >30 days), and the risk of ventricular arrhythmia and sudden cardiac death [18]. This, along with domperidone's increased risk of adverse cardiac events and the predisposition of PD patients to cardiovascular abnormalities, emphasizes the importance of continuing to investigate the safety of domperidone among PD patients.

In light of the limited and conflicting evidence, the aim of our study was to examine the risk of all-cause mortality associated with domperidone exposure among PD patients.

Methods

Data source

A population-based matched cohort study using the UK Clinical Practice Research Datalink (CPRD; www.cprd.com) was conducted. The CPRD is an ongoing primary care database, including anonymized electronic medical records from UK general practitioners (GPs) since 1987. The CPRD covers over 11 million patients from over 670 practices, and currently includes patients representing approximately 7% of the UK population [19].

Data recorded in CPRD include demographic information, medication prescription details, clinical events, preventive care, diagnostic tests, specialist referrals, hospital admissions, and major outcomes [19]. Diagnoses, symptoms, referrals, lab/diagnostic tests and prescribed medications are identified. They are entered by the GP and undergo quality checks prior to entry into the CPRD database. The accuracy and completeness of CPRD data have been well validated [20, 21].

Population

A cohort of incident PD was established and defined as those with no history of PD medications (levodopa, dopamine agonists, MAO-B inhibitors, amantadine, apomorphine, anticholinergic drugs [procyclidine, trihexyphenidyl, orphenadrine, methixine, biperiden or benzatropin] or COMT inhibitors [entacapone or tolcapone]) dispensed prior to the first diagnosis of PD, with a minimum 1-year look-back period. For PD patients, the cohort entry (index) date was the date of the first PD diagnosis after the start of CPRD data collection between 1987 and 2011.

For a secondary analysis, we created a matched cohort to examine the risk of mortality with domperidone independent of PD. Each PD patient was matched (1:1) by year of

birth, sex and practice, to a patient without a history of PD in CPRD. When no match was found, this age-matching criterion was expanded stepwise, in age increments of 1 year, to a maximum of 5 years. Non-PD patients were assigned the index date of their matched PD patient and similarly had to be enrolled in the CPRD for at least one year prior, without a history of PD medications.

All patients, PD and non-PD patients were required to have a minimum of 1 year of observation following the start of valid data collection in the CPRD.

Exposure

Follow-up time began at the matched index date, and the total period of follow-up time was divided into periods of 30 days, which permitted domperidone exposure (primary exposure of interest) to be coded in a time-dependent manner. At the start of each 30-day period, we looked back to identify prescriptions for domperidone in the previous 90 days. Based on this, all patients could be classified into the following exposure groups: **current** (patient's last prescription for domperidone was within the 90 days prior to the start of a 30-day period), **recent user** (patient's last prescription was between 91 and 181 days prior to the start of a 30-day period), past users (patient's last prescription was >181 days prior to the start of the 30-day period), and **never users** (no prescriptions ever dispensed). Exposure status was determined time-dependently in the survival analysis. More specifically, all patients were classified as never users up to the point of their first domperidone prescription, at which time their exposure status would be classified as current use. From this point forward, exposure status could move between current, recent and past exposure. However, once a patient had become a current user of domperidone, they could not return to the never user category. The 90-day assessment for prescriptions was used as prescriptions in the UK can be dispensed with a duration of up to 3 months.

Current domperidone users were further stratified by use: cumulative daily dose (in past year), average daily dose (in the past 6 months), total continuous duration of domperidone use (single prescription, duration <6 months and duration of 6 months or longer, with persistence defined as <30 days between end of prescription and beginning of new prescription) and to anti-Parkinson medication use in the previous 6 months (levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine). Finally, the risk of mortality within PD patients exposed to domperidone and within non-PD patients exposed to domperidone was identified.

Outcome

The outcome of interest was all-cause mortality, identified using mortality codes from the CPRD. Patients were followed from their index date to death date, end of CPRD data collection (2011/end of study) or the date of transfer of the patient out of the practice area (as recorded in the CPRD), whichever came first.

Covariates (mortality risk factors)

The following variables were identified at baseline: sex, body mass index (BMI), smoking status and alcohol use. Read codes indicating consumption of >2 alcoholic drinks per day were assessed within the 6 months prior to baseline to determine alcohol use. A history of falls was identified in the 3–12 months before index. All other potential confounders were determined in a time-dependent manner (i.e., at the start of follow-up and at the start of each 30-day period): age, a history (ever diagnosis) of: congestive heart failure, cerebrovascular disease (including stroke), hypertension, acute myocardial infarction, ischaemic heart disease, acute or chronic renal failure, diabetes, dementia and fracture. Additionally, the following prescriptions in the 6 months prior to the start of an interval were identified: hypnotics/anxiolytics, anticonvulsants, opioids (tramadol as the least potent), non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and antipsychotics.

Statistical analysis

Time-dependent Cox proportional hazards models (SAS 9.2, PHREG procedure) were used to estimate the hazard ratios (HRs) of all-cause mortality from patients with PD and domperidone use. The total period of follow-up was divided into periods of 30 days, and the presence of risk factors was assessed at the start of each 30-day period. Potential confounders were included in the final model if they independently changed the beta-coefficient by at least 5%. Missing data on lifestyle variables (BMI, smoking status and alcohol use) were treated as separate levels using indicator variables.

The primary analysis assessed the association between all-cause mortality risk associated with domperidone use (current, recent, past or never) in PD patients. Among PD patients, current domperidone users were further stratified by the average daily dose, cumulative dose, duration of domperidone use and type of anti-Parkinson's medication. Never use of domperidone was used as the referent category, and the primary exposure of interest was current use of domperidone.

In a secondary analysis, the association between all-cause mortality risk in PD patients stratified by domperidone use (current, recent, past or never), as compared to the matched non-PD patients (reference group) was completed. Additionally, the risk of all-cause mortality associated with domperidone exposure (current, recent, past or never) among only the non-PD patients was examined.

Additionally, a sensitivity analysis (data not shown) was conducted to investigate the risk of all-cause mortality with domperidone exposure (current, recent, past, never) at different levels of disease severity (mild, moderate, severe), with matched non-PD disease patients as the reference group. Disease severity was determined by the treatment prescribed during the different stages of PD and in accordance with the National Institute for Health and Care Excellence (NICE) guidelines on PD [22]. This approach is similar to that used in a previously published study using the CPRD [23].

The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). ISAC is a non-statutory expert advisory body, established in 2006 to give advice on research-related requests to access data from the Clinical Practice Research Datalink (protocol number 15_042R).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [24], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/2018 [25].

Results

Primary analysis

Patient characteristics. Table 1 provides the baseline characteristics of the included PD patients. A total of 5114 incident PD patients were identified, with a mean age of 74.5 years (SD = 9.7), and 3.8 years of follow-up time. Approximately two-thirds of patients had a BMI within the normal range (20–30 km m^{-2}) and 66% were current alcohol users (Table 1). At baseline, 23% of patients had a history of non-skin malignancies, 21% had a history of ischaemic heart disease and 21% had a prior fracture. Within 6 months prior to the index date, prescriptions for antidepressants were identified in 22% of patients.

Risk of mortality associated with domperidone exposure. Table 2 shows that PD patients with current use of domperidone had the highest mortality risk (HR_{adj}: 2.00, 95% CI: 1.64–2.45), compared to never users. The risk attenuated as use became more distant (recent domperidone use HR_{adj}: 1.46, 95% CI: 0.96–2.88 and past domperidone use HR_{adj}: 1.17, 95% CI: 1.01–1.35) (Table 2).

When current domperidone users were further stratified by daily dose and duration of use, the highest mortality risk was observed among users receiving a moderate (15–29 mg) average daily dose (HR_{adj}: 2.16, 95% CI: 1.55–3.01) and low cumulative dose (HR_{adj}: 2.81, 95% CI: 2.07–3.81). Additionally, PD patients with less than 1 month of exposure showed an almost three-fold increased mortality risk (HR_{adj}: 2.97, 95% CI: 2.06–4.27).

Stratification by type of anti-Parkinson medication is provided in Table 3. With the exception of dopamine agonists, all current anti-Parkinson medications use in conjunction with current domperidone use was associated with a significant increased risk for mortality. The highest risk was observed among concurrent users of amantadine and domperidone, where a four-fold increase in mortality risk was observed (HR_{adj}: 4.01, 95% CI: 1.49–10.76), as compared to non-users of amantadine.

Secondary analysis

Risk of mortality among Parkinson's disease patients, compared to non-PD patients. The baseline demographics of the matched non-PD patients are provided in Appendix Table A1. While the non-PD patients were well-matched, a lower proportion of PD patients were current smokers (16% *vs.* 21%). As expected, more PD patients had cerebrovascular disease (15% PD, 10% non-PD), and were taking antidepressants (22% PD, 10% non-PD) and anxiolytics (13% PD, 8% non-PD).

Table 1

Baseline characteristics of Parkinson's Disease Patients (n = 5114)

Characteristics	*n*	%
Female	2148	42.0
Mean age in years (SD)	74.5	(9.73)
Body Mass Index		
< 20 km m^{-2}	232	4.5
20–30 km m^{-2}	3367	65.8
> 30 km m^{-2}	635	12.4
Unknown	880	17.2
Smoking status		
Never	2863	56.0
Current	825	16.1
Ex	1254	24.5
Unknown	172	3.4
Alcohol status		
Never	965	18.9
Current	3392	66.3
Ex	173	3.4
Unknown	584	11.4
Medical comorbidity history		
Any fracture	1054	20.6
Asthma	623	12.2
Chronic Obstructive Pulmonary Disease	278	5.4
Congestive heart failure	312	6.1
Diabetes Mellitus	509	10.0
Rheumatoid arthritis	86	1.7
Renal disease	87	1.7
Cerebrovascular disease	739	14.5
Inflammatory bowel disease	45	0.9
Cancer (excluding skin cancer)	1169	22.9
Dementia	279	5.4
Ischaemic heart disease	1049	20.5
Drug use in 6 months before index date[a]		
Oral glucocorticoids	212	4.1
Antidepressants	1142	22.3
Antipsychotics	322	6.3
Anxiolytics	680	13.3
Anticonvulsants	247	4.8
Bisphosphonates	249	4.9
Hormone Replacement Therapy	88	1.7

SD, standard deviation

[a]Medications stratified according to their pharmacological categories and identified using Read codes in the CPRD

Table 2

Risk of mortality among Parkinson's Disease patients, stratified by domperidone exposure and the cumulative, average daily dose and duration of domperidone use

	Events (*n*)	(%)	Age-sex adjusted HR (95% CI)[a]	Final adjusted HR (95% CI)[a]
Never domperidone use	1442	28.2	1.00 (reference)	1.00 (reference)
Past domperidone use	197	3.9	1.36 (1.18–1.58)	1.17 (1.01–1.35)
Recent domperidone use	22	0.4	1.63 (1.07–2.47)	1.46 (0.96–2.88)
Current domperidone use	102	2.0	2.41 (1.97–2.94)	2.00 (1.64–2.45)[c]
Current domperidone use, by average daily dose in past year[b]				
<15 mg domperidone	23	0.5	1.60 (1.06–2.42)	1.58 (1.04–2.39)
15–29 mg domperidone	36	0.7	2.15 (1.54–3.00)	2.16 (1.55–3.01)
≥30 mg domperidone	43	0.8	1.63 (1.20–2.21)	1.54 (1.13–2.09)
Current domperidone use, by cumulative dose in past year[b]				
<1.5 g domperidone	45	0.8	2.45 (1.82–3.30)	2.50 (1.85–3.37)[d]
1.5–6 g domperidone	46	0.6	1.45 (1.08–1.95)	1.40 (1.04–1.89)
≥6 g domperidone	11	0.6	1.47 (0.81–2.66)	1.30 (0.71–2.35)
Current domperidone use, by continuous duration of use[e]				
≤1 month	30	0.6	1.91 (1.21–3.01)	2.97 (2.06–4.27)[f]
1–6 months	28	0.5	2.92 (2.03–4.20)	1.40 (0.96–2.03)
>6 months	25	0.4	1.42 (0.97–2.07)	1.30 (0.87–1.93)
Non-continuous use	19	0.4	1.42 (0.95–2.11)	1.92 (1.22–3.02)

HR, hazard ratio, 95% CI, 95% confidence interval; PD, Parkinson's disease

Note: Current use defined as a prescription in the last 30 days, recent use defined as a prescription between 31 and 181 days, and past use defined as a prescription >181 days. Patients with no exposure to domperidone were classified as never users

[a]Fully adjusted for history of dementia and use in the previous 6 months of antidepressants, antipsychotics and anxiolytics/hypnotics

[b]In oral domperidone equivalents (1 defined daily dose equals 30 mg oral domperidone)

[c]Statistically significant difference compared with past use of PD, Wald-test ($P < 0.05$)

[d]Statistically significant difference between low cumulative dose compared with moderate or high use of domperidone, Wald-test ($P < 0.05$)

[e]≤1 months means up to 30 days, 1–6 months means 31–182 days, >6 months means >182 days, 'non-continuous use' means current user with prescription in 30 days prior, but gap since use was >30 days (eg., non-persistent)

[f]Statistically significant difference compared with moderate or long duration of domperidone use, Wald-test ($P < 0.05$)

The results of mortality risk comparing PD patients with the matched non-PD patients are presented in Appendix Table A2. As compared to non-PD patients, PD was associated with a 43% increased risk in all-cause mortality (HR_{adj}: 1.43, 95% CI: 1.33–1.54). However, this risk was significantly increased among PD patients with current use of domperidone (HR_{adj}: 2.40, 95% CI: 1.95–2.94), as compared to non-PD patients. Among non-PD patients, current domperidone exposure was associated with a two-fold increase in all-cause mortality risk (HR_{adj}: 2.19, 95% CI: 1.50–3.21), as compared to non-PD patients with no domperidone exposure (Appendix Table A3). This observed risk among current domperidone users is similar to the two-fold increased risk observed among PD patients, as presented in Table 2.

The results of the sensitivity analysis whereby PD patients were stratified by disease severity (mild, moderate, severe) and domperidone exposure (current, recent, past and never), showed that current domperidone use was associated with a significant increase in all-cause mortality risk among PD patients, as compared to the matched non-PD patients (data not shown). This was similar to the findings in the primary analysis.

Discussion

Our results identified a doubling of all-cause mortality risk among PD patients currently using domperidone, compared to PD patients that were never exposed to domperidone. Additionally, a similar increase in all-cause mortality was observed among PD and non-PD patients currently using domperidone. To our knowledge, this is the first population-based study to examine the risk of all-cause mortality associated with domperidone use in PD and non-PD patients.

Previous literature on domperidone that evaluated the association with sudden cardiac death (SCD) in the general

Table 3

Risk of mortality among Parkinson's Disease patients, stratified to anti-Parkinson medication use in 3-months before death date and to domperidone use

	Events (*n*)	(%)	Age-sex adjusted HR (95% CI)[a]	Final adjusted HR (95% CI)[a]
Anti-Parkinson's disease medication stratification[b,c]				
No Levodopa[c]	703	13.8	1.00 (reference)	1.00 (reference)
Current Levodopa	1060	20.7	0.90 (0.82–0.99)	0.94 (0.85–1.03)
Domperidone (never)	846	16.5	0.87 (0.79–0.96)[d]	0.91 (0.83–1.01)[d]
Domperidone (current)	78	1.5	1.59 (1.26–2.01)[d]	1.62 (1.28–2.06)[d]
No dopamine agonists	1616	31.6	1.00 (reference)	1.00 (reference)
Current dopamine agonists	147	2.9	0.77 (0.64–0.92)	0.84 (0.70–1.00)
Domperidone (never)	110	2.2	0.88 (0.72–1.07)	0.96 (0.78–1.17)
Domperidone (current)	20	0.4	1.18 (0.75–1.84)	1.22 (0.78–1.92)
No MAO-B inhibitor	1707	33.4	1.00 (reference)	1.00 (reference)
Current MAO-B inhibitor	56	1.1	0.82 (0.63–1.07)	0.87 (0.67–1.14)
Domperidone (never)	36	0.7	0.72 (0.52–1.00)[d]	0.77 (0.55–1.08)[d]
Domperidone (current)	11	0.2	2.49 (1.37–4.52)[d]	2.37 (1.30–4.31)[d]
No COMT-inhibitor	1681	32.9	1.00 (reference)	1.00 (reference)
Current COMT-inhibitor	82	1.6	1.02 (0.82–1.28)	1.14 (0.91–1.43)
Domperidone (never)	46	0.9	0.84 (0.63–1.13)[d]	0.96 (0.71–1.30)[d]
Domperidone (current)	14	0.3	2.48 (1.46–4.21)[d]	2.34 (1.37–3.98)[d]
No amantadine	1737	34.0	1.00 (reference)	1.00 (reference)
Current amantadine	26	0.5	1.22 (0.83–1.80)	1.28 (0.86–1.89)
Domperidone (never)	17	0.3	1.10 (0.68–1.77)	1.19 (0.73–1.92)
Domperidone (current)	<6	0.1	3.50 (1.31–9.37)	4.01 (1.49–10.76)

COMT, catechol-O-methyltransferase; HR, hazard ratio; 95% CI, 95% confidence interval; MAO-B, monoamine oxidase B; PD, Parkinson's disease
Note: Current use defined as a prescription in the last 30 days, recent use defined as a prescription between 31 and 181 days, and past use defined as a prescription >181 days. Patients with no exposure to domperidone were classified as never users
[a]Fully adjusted for, history of dementia and use in the previous 6 months of antidepressants, antipsychotics, anxiolytics/hypnotics and PD medication not being investigated in this analysis
[b]In each analysis, non-use of the specified anti-Parkinson's medication is the reference group. Current users of the anti-Parkinson's medication are further stratified by dompidone exposure status – and compared to the never users of the anti-Parkinson's medication
[c]Among the current users of the specified anti-Parkinson's medication, all analyses were adjusted for recent and past use of domperidone
[d]Statistically significant difference between no use of domperidone versus current use of domperidone, Wald-test ($P < 0.05$)

population suggested that domperidone was associated with an increased risk of cardiac adverse events, including mortality [9–11]. Interestingly, in a study by Arana and colleagues, it was identified that the risk for sudden cardiac death was concentrated within 15 days from first domperidone exposure [26]. This finding supports our results showing an elevated risk for all-cause mortality within the first month of use. One explanation for this may be that domperidone is most frequently prescribed in short courses for the relief of GI symptoms, and therefore continued use of this medication is less likely. The observed two-fold increased risk associated with current domperidone use among PD patients, is in line with the 2.4-fold increased risk of VT/SCD observed by Renoux *et al.* [18]. However, it is noteworthy that the more general all-cause mortality outcome in our study may have permitted the inclusion of more events, thereby increasing the power of this study.

To date there are very few studies that have identified mortality risk of domperidone, based on daily dose or cumulative exposure [13, 14], yet the EMA has made recommendations for <30 mg day^{-1} oral domperidone use [12]. A population-based case–control study from the general practice database in the Netherlands (n = 15 480) found an 11-fold increase among high-dose domperidone users (>30 mg day^{-1}), compared to doses of ≤30 mg day^{-1} [13]. While our results identified an increased risk of high dose users, as compared to never users of domperidone, we did not identify that high-dose use (>30 mg day^{-1}) was statistically different that patients receiving lower doses (15–29 mg day^{-1} and <15 mg day^{-1}). The discrepancy in

findings could be due to a number of factors, including differences in the study population, categorization of high *vs*. low daily dose and included confounders. Conversely, a recent retrospective study in which 90% of patients were receiving domperidone 80–120 mg day^{-1}, showed that domperidone did not lead to higher risks of adverse cardiovascular events [14]. In addition, our findings indicate that the risk of all-cause mortality may be increased with doses of <15 mg day^{-1}, and further increased with doses of 15–29 mg day^{-1}, yet these were not statistically different from the high-dose category. To our knowledge, this is the first study to stratify by average daily dose, and the first study to examine the effects of cumulative dose of domperidone in PD. These analyses permit a more detailed assessment of domperidone effects at various doses and at cumulative exposures, simulating a more realistic representation of patient use. However, it remains unclear if the dose of domperidone influences the risk of adverse cardiac events or mortality risk, and therefore more research is likely warranted.

Risk of mortality seems to be lowest among PD patients receiving concurrent treatment with domperidone and dopamine agonists, such as levodopa [27, 28]. The neuroprotective effect of dopamine agonists is well established in the literature, as both in vivo and in vitro studies have proven that dopamine agonists scavenge free radicals and alleviate symptoms associated with the pathogenesis PD [29, 30]. The attenuation of the neurological symptoms of PD by agonists could therefore lead to a lower associated risk of mortality in patients with PD, who are treated with domperidone.

Our results indicate that PD alone is associated with a 43% mortality risk, which parallels findings in the existing literature on PD mortality [27, 28]. However, our results add to this literature by identifying that this risk is substantially increased among current users of domperidone. Moreover, we identified that domperidone use increased the risk of all-cause mortality in both PD and non-PD patients, suggesting that the increase is not attributable to PD alone. This ties closely with earlier case–control studies which showed that the risk of SCD is increased with the use of QTc-prolonging drugs, including domperidone [10, 11, 13, 31–33].

Our analysis has several strengths. First, the study utilized the CPRD database permitting a large sample size and long duration of follow-up. This allowed for the analysis of mutually exclusive exposure classifications, which might not be feasible in smaller sized studies [34]. Second, the positive predictive value of the diagnoses of PD in the CPRD ranges from 81% to 90% [35, 36], suggesting that the risk of misclassification of the disease in the database is low. Additionally, compared to the less clinically descriptive study designs that use claims data, the CPRD further provided more detailed primary care records. We were able to assess a large number of potential confounders time-dependently in the CPRD, in addition to the inclusion of baseline assessments of alcohol use, smoking status and BMI as potential confounders.

Third, to correct for the commonly observed time-dependent bias in cohort studies, we used time-dependent classification of exposure and confounders. Finally, we used a new-user study design for both PD diagnosis and PD medications, in order to mitigate limitations often associated with observational studies such as selection bias [36].

We identified that the greatest risk of mortality in PD patients is within the first month of domperidone use. The results of this finding might have been diluted if a prevalent-user design was used, which includes a different timeframe for follow-up, thereby increasing probability of only including patients who survive the first month of use.

Our study shares limitations inherent with population-based cohort studies, such as selection biases. While PD patients were well matched to their non-PD patients, we note that the PD patients had higher baseline rates of cerebrovascular disease (15% *vs*. 10%), ischaemic heart disease (21% *vs*. 19%) and dementia (5% *vs*. 2%). They were also more likely to have used antidepressants (22% *vs*. 10%), antipsychotics (6% *vs*. 2%), anxiolytics (13% *vs*. 8%) and anticonvulsants (5% *vs*. 2%), 6 months prior to the index date. Thus, these patients were sicker at baseline, potentially predisposing them to increased complications and premature mortality. However, we observed that while PD alone was associated with increased all-cause mortality risk compared to non-PD patients, this risk was substantially increased among domperidone users. Additionally, we conducted analyses within PD patients only.

The CPRD database is a longitudinal primary care database, and therefore there is the potential for missing data. Indeed, the CPRD does not contain pharmacy claims and dispensing information. Thus, it is possible that some patients did not fill these prescriptions after their respective GP visits, resulting in some misclassification of exposure status. Moreover, there is the potential for misclassification of the start and end of therapy, based on when patients filled the prescription. This could partially explain why a lingering effect was observed in recent or past users, despite a hypothesis that risk would return to baseline following discontinuation. Similarly, products purchased over-the-counter and those dispensed while a patient is hospitalized are not captured in the CPRD, resulting in the possibility of residual confounding.

While the CPRD permits adjustments for a large number of confounders, we cannot rule out the potential for residual confounding, and acknowledge the potential for confounding by indication in this population. Indeed, PD severity may influence prescribing of domperidone, with more severe patients receiving domperidone. In our analysis, we identified that past users of domperidone had an elevated risk of mortality, which was not observed in the non-PD patients. This may be evidence that higher risk/sicker PD patients received domperidone. In a sensitivity analysis (data not shown), PD patients were stratified by disease severity (mild, moderate, severe) and by domperidone exposure (current, recent, past, never), and compared to the matched non-PD patients. These results were similar to the primary analysis, with current domperidone use showing a significant increased all-cause mortality risk among PD patients at all disease severities (mild, moderate and severe). However, we note that even this stratification cannot fully elucidate the effect of disease severity on mortality risk, as some patients may be misclassified. Finally,

the primary outcome of interest was all-cause mortality. As we did not further stratify by death from specific causes, it is possible our results underestimate the true cardiovascular mortality risk associated with domperidone users. Additionally, products purchased over-the-counter, and those dispensed while a patient is hospitalized, are not captured in the CPRD, resulting in the possibility of residual confounding.

Conclusion

Domperidone is one of the first options for treating GI symptoms in PD patients, yet the scientific understanding of the risk of mortality associated with domperidone use in this high-risk patient group is very limited. In our population-based study, current domperidone use was associated with a doubled risk of mortality in PD patients, which was highest at the start of domperidone treatment. Interestingly, our secondary analyses identified that the doubled risk of all-cause mortality was similar between patients with and without PD. Moreover, when comparing PD patients to non-PD patients, the risk of all-cause mortality was only moderately increased among never users of domperidone, but substantially increased among current users of domperidone. Thus, we believe these results suggest that the elevated mortality risk in PD is likely not attributable to PD alone.

Competing Interests

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Contributors

F.dV. and H.G.M.L. initiated the study. M.S. led the literature review and wrote the first draft of the manuscript. S.P. and J.H.M.D. led all statistical analysis. F.dV., S.P., J.H.M.D. and A.M.B. were responsible for the study design. All authors provided input on the interpretation of data and critically revised the manuscript for important intellectual content. All authors reviewed the final version of the manuscript to be published and provided their approval. F.dV. and A.M.B. supervised the study and are the guarantors.

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Appendix A

Table A1

Baseline demographics of Parkinson's disease patients and matched non-Parkinson's disease patients

	Parkinson's disease patients (n = 5114)	Non-Parkinson's disease patients (n = 5114)
Female (%)	42.0	42.0
Mean age in years (SD)	74.5 (9.73)	74.5 (9.73)
Body Mass Index (%)		
< 20 km m^{-2}	4.5	3.9
20–30 km m^{-2}	65.8	62.6
> 30 km m^{-2}	12.4	14.2
Unknown	17.2	19.3
Smoking status (%)		
Never	56.0	46.7
Current	16.1	21.1
Ex	24.5	27.7
Unknown	3.4	4.5

(continues)

Table A1

(Continued)

	Parkinson's disease patients (n = 5114)	Non-Parkinson's disease patients (n = 5114)
Alcohol status (%)		
Never	18.9	16.9
Current	66.3	67.7
Ex	3.4	3.1
Unknown	11.4	12.4
Medical comorbidity history (%)		
Any fracture	20.6	19.2
Asthma	12.2	12.7
Chronic Obstructive Pulmonary Disease	5.4	7.2
Congestive heart failure	6.1	5.9
Diabetes Mellitus	10.0	10.3
Rheumatoid arthritis	1.7	2.0
Renal disease	1.7	1.8
Cerebrovascular disease	14.5	10.0
Inflammatory bowel disease	0.9	1.0
Cancer (excluding skin cancer)	22.9	22.0
Dementia	5.4	2.2
Ischaemic heart disease	20.5	19.0
Drug use in 6 months before index date[a] (%)		
Oral glucocorticoids	4.1	4.2
Antidepressants	22.3	9.6
Antipsychotics	6.3	2.1
Anxiolytics	13.3	8.3
Anticonvulsants	4.8	2.2
Bisphosphonates	4.9	4.3
Hormone Replacement Therapy	1.7	1.5

All numbers are proportions or mean and standard deviation, as indicated. SD, standard deviation

[a]Medications stratified according to their pharmacological categories and identified using Read codes in the CPRD

Table A2

Risk of mortality in Parkinson's disease patients by use of domperidone, compared to matched non-Parkinson's disease patients

	Events (*n*)	(%)	Age-sex adjusted HR (95% CI)[a]	Final adjusted HR (95% CI)[a]
Non-Parkinson's Disease (matched)	1310	25.6	1.00 (reference)	1.00 (reference)
Parkinson's Disease	1763	34.5	1.73 (1.61–1.86)	1.43 (1.33–1.54)
Never use of domperidone	1442	28.2	1.67 (1.55–1.80)	1.40 (1.29–1.51)
Any use of domperidone				
Past use (>6 months)	197	3.9	1.72 (1.48–2.00)	1.39 (1.19–1.62)
Recent use (3–6 months)	22	0.4	2.06 (1.35–3.14)	1.73 (1.14–2.65)
Current use (<3 months)	102	2.0	3.05 (2.49–3.74)[b]	2.40 (1.95–2.94)[b]

HR, hazard ratio; 95% CI, 95% confidence interval
Note: Current use defined as a prescription in the last 30 days, recent use defined as a prescription between 31 and 181 days, and past use defined as a prescription >181 days. Patients with no exposure to domperidone were classified as never users
[a]Fully adjusted for history of dementia and use in the previous 6 months of antidepressants, antipsychotics and anxiolytics/hypnotics
[b]Statistically significant difference compared with no domperidone use and with past domperidone use Wald-test ($P < 0.05$)
[c]Statistically significant difference compared with no domperidone use Wald-test ($P < 0.05$)
[d]Male PD patients are compared with male non-PD patients and female PD patients with female non-PD patients. Fully adjusted model includes the variables listed in (a), in addition to recent and past use of domperidone

Table A3

Risk of mortality among non-Parkinson's disease patients exposed to domperidone use, as compared to non-Parkinson's disease patients never exposed to domperidone

Domperidone exposure	Events (*n*)	(%)	Final adjusted HR (95% CI)[a]
Never	1185	23.2	1.00 (reference)
Past use	85	1.7	0.94 (0.76–1.17)
Recent use	13	0.3	2.78 (1.61–4.79)[b]
Current use	27	0.5	2.19 (1.50–3.21)[b]

HR, hazard ratio; 95% CI, 95% confidence interval
Note: Current use defined as a prescription in the last 30 days, recent use defined as a prescription between 31 and 181 days, and past use defined as a prescription >181 days. Patients with no exposure to domperidone were classified as never users
[a]Fully adjusted for history of dementia and use of the following in the previous 6 months: antidepressants, antipsychotics and anxiolytics/hypnotics
[b]Statistically significant difference compared with past use of PD, Wald-test ($P < 0.05$)