OXFORD

Original Article

Cardiovascular Safety of Metoclopramide Compared to Domperidone: A Population-Based Cohort Study

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Abstract

Background: Metoclopramide and domperidone are common prokinetics used to alleviate gastro-intestinal symptoms. However, both drugs may trigger ventricular arrhythmias.

Aim: We conducted this population-based study to compare the 30-day cardiovascular safety of metoclopramide versus domperidone in outpatient care.

Methods: We used health care databases to identify a cohort of patients in Ontario, Canada newly dispensed metoclopramide or domperidone. Inverse probability of treatment weighting based on propensity scores was used to balance the baseline characteristics of the two groups. All outcomes were assessed in the 30 days following drug dispensing. The primary outcome was hospital encounter with ventricular arrhythmia. The secondary outcomes were hospital encounter with cardiac arrest, all-cause mortality and cardiovascular mortality.

Results: We identified 196,544 patients, 19% of whom were prescribed metoclopramide. There was no difference in the risk of a hospital encounter with ventricular arrythmia (0.02% in both groups), or cardiac arrest (0.10% with metoclopramide and 0.08% with domperidone). However, 1.34% of patients died after starting metoclopramide compared to 0.52% of patients starting domperidone; weighted risk ratio 2.50 (95% confidence interval [CI] 2.13 to 3.03). Similarly, 0.42% of patients died of cardiovascular causes after starting metoclopramide compared to 0.19 % of patients starting domperidone; weighted risk ratio 2.00 (95% CI 1.44 to 2.77).

Conclusion: The 30-day risk for a hospital encounter with ventricular arrhythmia was low for both metoclopramide and domperidone, with no significant difference in the rate between the two drugs. The higher 30-day risk of death observed with metoclopramide compared with domperidone in this study has also been observed in other studies and warrants further investigation.

Keywords: *Cardiovascular death; Gastroparesis; Prokinetic*

Introduction

Prokinetic agents such as domperidone and metoclopramide are prescribed for the treatment of gastroparesis as well as nausea and vomiting. Domperidone, a peripherally acting dopamine antagonist, is commonly used due to its favourable neurologic side effect profile until concerns arose regarding the risk of sudden cardiac death. As a result, it has not been approved in the United States market, although it is still available and widely used in Canada (1). The increased risk of cardiac death is attributed to blockade of HERG (human ether a-go-go

related gene) channels which causes electrocardiogram QT interval prolongation and predisposes to torsades de pointes (2). Studies have shown a significantly higher risk of sudden cardiac death and ventricular arrhythmia with domperidone compared to nonuse (odds ratio [OR] 1.56 to 1.59) (3,4).

As a result of these concerns, metoclopramide has become the medication of choice for many clinicians treating gastroparesis (5). Its prokinetic effect stems primarily from the activation of serotonin receptors, with minimal dopaminergic antagonism, resulting in a theoretically lower risk of adverse cardiac events (2). In vitro studies demonstrate a significantly lower affinity of metoclopramide for the HERG channel when compared to domperidone (2); however, QT prolongation and a risk of cardiac arrest are still described with metoclopramide (6–8).

Comparisons between domperidone and metoclopramide on cardiovascular adverse events in large cohort studies have yielded varying results, from an equivalent risk (4) to an increased risk of out-of-hospital sudden cardiac death with metoclopramide compared to domperidone (OR 2.5, 95% confidence interval [CI] 1.06 to 5.88) (9). We conducted this comparative population-based study to further assess the 30-day risk of adverse cardiovascular outcomes after starting metoclopramide compared to domperidone in routine outpatient care.

METHODS

Study Design and Setting

We conducted a population-based, retrospective cohort study of residents in the province of Ontario, Canada from 2002 to 2017 using linked administrative health data. All Ontario residents have universal access to health care and in 2018 Ontario's population was 14.3 million (10). Segments of the Ontario population also have outpatient prescription drug coverage including all residents 65 years or older (~2.4 million) and those younger patients who have high drug costs relative to their income, receive disability support or social assistance. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act which does not require review by the Research Ethics Board. We have reported this study according to recommended guidelines for observational studies that use routinely collected health data (11) (see Supplementary Appendix A).

Data Sources

Patient characteristics, prescription drug use, covariate information, and outcome data were obtained from seven health databases at the Institute for Clinical and Evaluative Sciences (ICES). The data sets (Canadian Institute for Health Information- Discharge Abstract Database, ICES-derived Physician Database, National Ambulatory Care Reporting System, Ontario Drug Benefit Database, Ontario Health Insurance Plan Database, Office of the Registrar General-Deaths and the Registered Persons Database) were linked using unique encoded identifiers and analyzed at ICES. Based on the CIHI guidelines, trained personnel in Ontario hospitals review medical charts to code diagnoses and procedures using the International Classification of Diseases (ICD) coding system. These personnel only consider physician-recorded diagnoses and do not review electrocardiograms or other results. Additional information on the specific databases is provided in Supplementary Appendix B. Information on covariate definitions are provided in Supplementary Appendix C.

The datasets we used were complete for all variables except prescriber speciality (12.9% and 11.5% in the metoclopramide and domperidone groups, respectively; missing data defined as a separate category) and estimates of neighbourhood income (0.5% and 0.3% in the metoclopramide and domperidone groups respectively, missing data recorded as the middle quintile). Losses to follow up occurred only with emigration from the province, estimated to occur at a rate of less than 0.2% per year (12).

Cohort Construction

We established a cohort of patients 19 years of age or over who were dispensed a new prescription for either domperidone or metoclopramide from an outpatient pharmacy between April 1, 2002 and February 28, 2017. The date the domperidone or metoclopramide prescription was filled served as the date of cohort entry. Patients were followed for 30 days after cohort entry (Figure 1). To make our findings generalizable to routine prescribing, we excluded people dispensed doses that were either very low (daily dose of <15 mg for domperidone or <10 mg for metoclopramide) or very high (daily dose >60 mg for either drug). To avoid the influence of prior prokinetic use on our estimates of risk, we included only 'new users' of the study drugs by excluding people with prior prescriptions for domperidone, metoclopramide or any other prokinetic drug in the prior 180 days. As we did not have access to hospital pharmacy records, people with evidence of a hospital discharge or emergency department visit within the prior 2 days were excluded (so that we excluded patients from this study who may have started their prokinetic medications in hospital). We excluded patients who were prescribed both domperidone and metoclopramide simultaneously to compare mutually exclusive groups. We restricted to the first eligible study drug prescription in those patients with multiple eligible prescriptions.

We excluded people with a prior hospital admission with cardiac arrest, ventricular arrhythmia or implantation of an implantable cardiac defibrillator in the previous 5 years as we were concerned this prior history could influence practitioner choice of the type of prokinetic prescribed (which would raise

epidemiologic concerns about confounding by indication). For similar reasons, we also excluded patients with a prescription for an antineoplastic drug in the last 180 days or a diagnosis of cancer within the past 5 years, as metoclopramide (but not domperidone) is commonly used as an antiemetic in this population. To ensure all patients in the cohort had a baseline period of recorded prescription drug use, we excluded anyone with no dispensed medications in the prior 180 days in the provincial drug plan database.

Outcomes

We assessed outcomes within 30 days of cohort entry which is consistent with the highest mortality risk time period in domperidone users (9,13) as well as the median prescription duration for each drug. Our primary outcome was a hospital encounter (either emergency department visit or hospital admission) with ventricular arrhythmia. Secondary outcomes were a

hospital encounter with cardiac arrest, all-cause mortality and cardiovascular mortality. Diagnostic codes for the primary and secondary outcomes as well as information on their validation can be found in Supplementary Appendix D (14–22). Database information on cardiovascular mortality was only available until December 2015 resulting in a reduced cohort size for this outcome.

Statistical Analysis

We used standardized differences to compare baseline characteristics between groups. This metric describes differences between group means relative to the pooled standard deviation and is considered meaningful if greater than 10% (23).

We initially planned to match on a propensity score to balance the distribution of baseline characteristics between domperidone and metoclopramide users. However, our baseline analysis showed that only 19% of the cohort were new
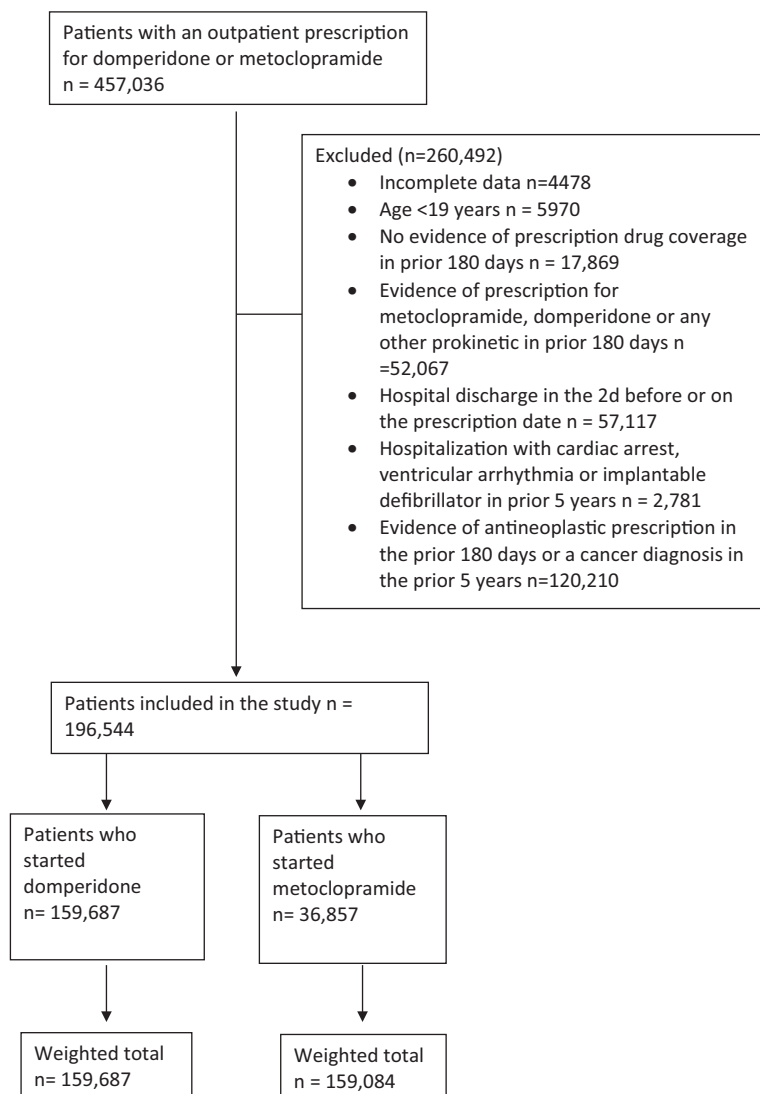

Figure 1. Cohort selection.

users of metoclopramide; in this case, matching may have led to a substantial loss of domperidone users and a loss in the precision of our estimates. This prompted our use of inverse probability of treatment weighting (IPTW) based on the propensity scores to produce a synthetic weighted sample that retained all individuals in the analysis and was well balanced on many measured baseline characteristics. IPTW weights that would estimate the average treatment effect in the treated were used as this produces results comparable to propensity score matching (24,25). To accomplish this, we produced propensity scores that reflected the probability of receiving a prescription for metoclopramide given a set of baseline characteristics. We determined propensity scores using a logistic regression model incorporating 120 prespecified baseline variables, chosen because of their possible influence on the primary outcome (Supplementary Appendix E). We then applied propensity score-based weights to patients and their outcomes to produce groups that were well balanced across all baseline characteristics except for maximum dose percentage. Metoclopramide users were compared to a referent group of domperidone users. We used modified Poisson regression models that accounted for the weights to estimate risk ratios (RR) and 95% CIs. For all outcomes we interpreted two-tailed *P* values of 0.05 or less as statistically significant. To minimize the chance of patient re-identification, cells in all tables with 5 or fewer patients are reported as '< 6'. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

We identified 159,687 (81%) new users of domperidone and 36,857 (19%) new users of metoclopramide (see cohort selection, Figure 1). The drugs were prescribed by 18,023 different physicians and dispensed by 7,122 different pharmacies. In the unweighted cohort, new users of metoclopramide compared to domperidone were younger (mean age 63 versus 66 years old), were more likely to have a rural residence, were more likely to have a prior history of depression or anxiety, were less likely to use a statin or a proton pump inhibitor and had less hospital admissions and primary care visits in the year before cohort entry (Table 1). After weighting, the baseline characteristics between the two groups were well balanced (standardized difference less than 10%). Most prescriptions (70%) in both groups were provided by primary care physicians, with a similar number of patients in each group seeing a cardiologist. The rates of comorbid gastro-esophageal reflux disease and proton pump inhibitor co-prescriptions as well as concomitant QT prolonging medications were well balanced. The only exception was percentage of maximal dose prescribed—we set the maximum dose of domperidone as 30 mg per day and metoclopramide as 40 mg per day based on the product

monographs and the most recent guidelines from the American Journal of Gastroenterology (5,26,27). Using these definitions, the proportion of patients prescribed a maximum dose was significantly higher in the domperidone group compared to the metoclopramide group (Table 1).

Outcomes

Results for the primary outcome of hospitalization with ventricular arrhythmia and secondary outcomes are presented in Table 2.

Primary Outcome

New use of metoclopramide did not associate with an increased risk of ventricular arrhythmia compared to new use of domperidone (weighted total of 35 of 159,084 patients taking metoclopramide [0.02%] versus 32 of 159,687 patients taking domperidone [0.02%], risk difference 0.00% [95% CI −0.01 to 0.02%]).

Secondary Outcomes

Hospital Encounter With Cardiac Arrest
New use of metoclopramide was not associated with an increased risk of hospital encounter with cardiac arrest (weighted total of 162 of 159,084 metoclopramide users [0.10%] compared to 127 of 159,687 domperidone users [0.08%] risk difference 0.02% [95% CI −0.02% to 0.07%], risk ratio 1.28 [95% CI 0.81 to 2.00]).

Mortality
New use of metoclopramide compared to domperidone was associated with a higher risk of all-cause mortality and cardiovascular mortality. All-cause mortality occurred in 1,824 of 159,084 (1.15%) metoclopramide users compared to 825 of 159,687 domperidone users (0.52%) after weighting (risk difference 0.63% [95% CI 0.50 to 0.76], risk ratio 2.22 [95% CI 1.96 to 2.50]). Before IPTW, cardiovascular mortality occurred in 143 of 34,271 (0.42%) metoclopramide users and 294 of 151,235 (0.19%) domperidone users (risk ratio 2.15 95% CI 1.75 to 2.62; *P* <0.0001). After weighting, cardiovascular mortality occurred in 528 of 147,989 metoclopramide users (0.36%) compared to 294 of 151,235 domperidone users (0.19%) (risk difference 0.16% [95% CI 0.09 to 0.24], risk ratio 1.82 [95% CI 1.45 to 2.33]). These differences persisted after adjustment for the percentage of maximal dose. When examining the specific causes of cardiovascular mortality, ischemic heart disease was most common in both medications and the distribution of the causes was similar between metoclopramide and domperidone (Supplementary Appendix F).

Discussion

In this retrospective cohort study, we found low absolute rates of recorded ventricular arrhythmia and cardiac arrest

Table 1. Select baseline characteristics

Total patients	Preweighting			Postweighting		
	Meto-clopramide	Domperidone	Standardized difference	Meto-clopramide	Domperidone	Standardized difference
	36,857	159,687		159,084 (artificially weighted N)	159,687 (artificially weighted N)	
Demographics						
Age, mean (SD)	63.1 (17.9)	65.9 (15.7)	17%	66.1 (33.3)	65.9 (15.7)	0%
Female Sex, N (%)	25,817 (70.0)	108,752 (68.1)	4%	107,826 (67.8)	108,752 (68.1)	1%
Rural residence, N (%)	6,118 (16.6)	18,176 (11.4)	15%	18,522 (11.6)	181,76 (11.4)	1%
Long-term care, N (%)	1,773 (4.8)	5,327 (3.3)	8%	5,574 (3.5)	5,327 (3.3)	1%
Prescriber information, N (%)						
General practitioner	25,981 (70.5)	112,983 (70.8)	1%	110,671 (69.6)	112,983 (70.8)	3%
Internist	703 (1.9)	3,568 (2.2)	2%	3,696 (2.3)	3,568 (2.2)	1%
Nephrologist	218 (0.6)	1,976 (1.2)	6%	2,111 (1.3)	1,976 (1.2)	1%
Cardiologist	147 (0.4)	940 (0.6)	3%	952 (0.6)	940 (0.6)	0%
Endocrinologist	79 (0.2)	486 (0.3)	2%	572 (0.4)	486 (0.3)	2%
Other	4,979 (13.5)	21,406 (13.4)	0%	22,826 (14.3)	21,406 (13.4)	3%
Missing	4,750 (12.9)	18,328 (11.5)	4%	18,256 (11.5)	18,328 (11.5)	0%
Comorbidities, N (%)						
Acute kidney injury	1,161 (3.2)	3,906 (2.4)	5%	4,369 (2.7)	3,906 (2.4)	2%
Renal disease	1,925 (5.2)	8,546 (5.4)	1%	8,985 (5.6)	8,546 (5.4)	1%
Myocardial infarction	1,322 (3.6)	4,925 (3.1)	3%	5,184 (3.3)	4,925 (3.1)	1%
Angina	6,870 (18.6)	30,189 (18.9)	1%	30,532 (19.2)	30,189 (18.9)	1%
Atrial fibrillation/flutter	1,754 (4.8)	6,283 (3.9)	4%	6,440 (4.0)	6,283 (3.9)	1%
Heart failure	4,427 (12.0)	16,973 (10.6)	4%	17,380 (10.9)	16,973 (10.6)	1%
Coronary artery disease	8,840 (24.0)	39,877 (25.0)	2%	40,246 (25.3)	39,877 (25.0)	1%
Hypertension	15,133 (41.1)	72,982 (45.7)	9%	73,353 (46.1)	72,982 (45.7)	1%
Chronic liver disease	2,575 (7.0)	9,423 (5.9)	4%	9,407 (5.9)	9,423 (5.9)	0%
GERD	1,942 (5.3)	10,310 (6.5)	5%	8,847 (5.3)	10,310 (6.5)	5%
Chronic lung disease	12,627 (34.3)	52,490 (32.9)	3%	52,433 (33.0)	52,490 (32.9)	0%
COPD	2,051 (5.6)	6,380 (4.0)	7%	6,506 (4.1)	6,380 (4.0)	1%
Diabetes	4,754 (12.9)	22,768 (14.3)	4%	23,451 (14.7)	22,768 (14.3)	1%
Hypoglycemia	341 (0.9)	1,189 (0.7)	2%	1,371 (0.9)	1,189 (0.7)	2%

Table 1. Continued

Total patients	Preweighting			Postweighting		
	Meto-clopramide	Domperidone	Standardized difference	Meto-clopramide	Domperidone	Standardized difference
	36,857	159,687		159,084 (artificially weighted *N*)	159,687 (artificially weighted *N*)	
Thyroid disease	4,249 (11.5)	19,257 (12.1)	2%	19,329 (12.2)	19,257 (12.1)	0%
Bipolar disorder	2,551 (6.9)	8,181 (5.1)	8%	8,531 (5.4)	8,181 (5.1)	1%
Depression or Anxiety	7,119 (19.3)	24,446 (15.3)	**11%**	24,721 (15.5)	24,446 (15.3)	1%
Dementia	3,295 (8.9)	12,797 (8.0)	3%	13,384 (8.4)	12,797 (8.0)	1%
Schizophrenia	1,964 (5.3)	6,796 (4.3)	5%	7,209 (4.5)	6,796 (4.3)	1%
Medication use at the time of enrolment, *N* (%)						
ACE inhibitors	6,706 (18.2)	30,341 (19.0)	2%	30,276 (19.0)	30,341 (19.0)	0%
ARBs	4,087 (11.1)	23,037 (14.4)	**10%**	23,178 (14.6)	23,037 (14.4)	1%
Alpha blockers	708 (1.9)	3,371 (2.1)	1%	3,270 (2.1)	3,371 (2.1)	0%
Beta blockers	6,434 (17.5)	29,478 (18.5)	3%	29,759 (18.7)	29,478 (18.5)	1%
CCBs	6,324 (17.2)	30,929 (19.4)	6%	30,842 (19.4)	30,929 (19.4)	0%
Loop diuretics	3,264 (8.9)	12,515 (7.8)	4%	12,728 (8.0)	12,515 (7.8)	1%
Potassium-sparing diuretics	1,508 (4.1)	5,667 (3.5)	3%	5,698 (3.6)	5,667 (3.5)	1%
Thiazide diuretics	3,420 (9.3)	16,185 (10.1)	3%	15,934 (10.0)	16,185 (10.1)	0%
Acetylsalicyclic acid	1,742 (4.7)	8,300 (5.2)	2%	8,204 (5.2)	8,300 (5.2)	0%
Antiplatelet	1,352 (3.7)	5,712 (3.6)	1%	5,916 (3.7)	5,712 (3.6)	1%
Anticoagulants	1,843 (5.0)	6,872 (4.3)	3%	7,055 (4.4)	6,872 (4.3)	0%
Statins	8,657 (23.5)	45,840 (28.7)	**12%**	46,529 (29.2)	45,840 (28.7)	1%
Ezetimibe	563 (1.5)	3,178 (2.0)	4%	3,216 (2.0)	3,178 (2.0)	0%
Antilipemics	9,160 (24.9)	48,399 (30.3)	**12%**	49,121 (30.9)	48,399 (30.3)	1%
Oral antiglycemic	4,012 (10.9)	19,420 (12.2)	4%	19,913 (12.5)	19,420 (12.2)	1%
Antiarrhythmic	358 (1.0)	997 (0.6)	4%	1,097 (0.7)	997 (0.6)	1%
TCA	1,574 (4.3)	6,855 (4.3)	0%	6,739 (4.2)	6,855 (4.3)	0%
Antipsychotics	1,079 (2.9)	4,152 (2.6)	2%	4,341 (2.7)	4,152 (2.6)	1%
Benzodiazepine	5,635 (15.3)	25,530 (16.0)	2%	25,769 (16.2)	25,530 (16.0)	1%
Antiemetic	585 (1.6)	1,615 (1.0)	5%	1,655 (1.0)	1,615 (1.0)	0%
H2RAs	2,671 (7.2)	12,597 (7.9)	3%	12,313 (7.7)	12,597 (7.9)	1%
Proton pump inhibitors	10,179 (27.6)	54,693 (34.3)	**15%**	55,432 (34.8)	54,693 (34.3)	1%
Corticosteroids	6,880 (18.7)	34,967 (21.9)	8%	35,117 (22.1)	34,967 (21.9)	0%

Table 1. Continued

Total patients	Preweighting			Postweighting		
	Meto-clopramide 36,857	Domperidone 159,687	Standardized difference	Meto-clopramide (artificially weighted N) 159,084	Domperidone (artificially weighted N) 159,687	Standardized difference
NSAIDs	4,868 (13.2)	22,531 (14.1)	3%	22,678 (14.3)	22,531 (14.1)	1%
Opioids	6,290 (17.1)	23,293 (14.6)	7%	23,331 (14.7)	23,293 (14.6)	0%
Antibiotic	7,269 (19.7)	34,725 (21.7)	5%	35,059 (22.0)	34,725 (21.7)	1%
Thyroid replacement	3,864 (10.5)	18,220 (11.4)	3%	18,612 (11.7)	18,220 (11.4)	1%
QT prolonging drugs	5,240 (14.2)	23,906 (15.0)	2%	23,989 (15.1)	23,906 (15.0)	0%
Estimates of general comorbidity, mean (SD)						
Charlson comorbidity index	0.48 (1.16)	0.38 (1.04)	9%	0.4 (2.15)	0.38 (1.04)	1%
John Hopkins ACG	9.16 (3.81)	8.93 (3.58)	6%	8.98 (7.51)	8.93 (3.58)	1%
Number of unique prescriptions	5.37 (5.9)	5.84 (5.7)	8%	5.91 (11.88)	5.84 (5.7)	1%
Number of hospitalizations last year	0.44 (1.03)	0.3 (0.78)	**15%**	0.33 (1.72)	0.3 (0.78)	2%
Family physician visits last year	15.04 (15.27)	13.11 (12.13)	**14%**	13.35 (25.76)	13.11 (12.13)	1%
Estimates of cardiac comorbidity, N (%)						
Cardiologist visits	13,193 (35.8)	60,417 (37.8)	4%	59,249 (37.2)	60,417 (37.8)	1%
Coronary angiogram	876 (2.4)	3,694 (2.3)	1%	3,980 (2.5)	3,694 (2.3)	1%
Coronary revascularization	422 (1.1)	1,667 (1.0)	1%	1,785 (1.1)	1,667 (1.0)	1%
Echocardiography	5,926 (16.1)	28,299 (17.7)	4%	28,989 (18.2)	28,299 (17.7)	1%
Electrocardiography	18,923 (51.3)	83,812 (52.5)	2%	84,253 (53.0)	83,812 (52.5)	1%
Study drug dose						
Dose >30 mg, N (%)	11,467 (31.1)	64,928 (40.7)	**20%**	63,724 (40.1)	64,928 (40.7)	1%
Maximum dose percentage						
<50%	6,732 (18.3)	0 (0.0)	**67%**	26,167 (16.4)	0 (0.0)	**63%**
50–<100%	21,320 (57.8)	29,810 (18.7)	**88%**	84,728 (53.3)	29,810 (18.7)	**77%**
100–<150%	8,550 (23.2)	125,106 (78.3)	**132%**	46,807 (29.4)	125,106 (78.3)	**113%**
≥150%	255 (0.7)	4,771 (3.0)	**17%**	1,382 (0.9)	4,771 (3.0)	**15%**

ACE, angiotensin covertering enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; H2RA, histamine-2 recptor antagonists; NSAID, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressant.

Bold values indicate standard differences >10%.

Table 2. Primary and secondary outcomes

Outcome	Exposure	Events (unweighted)		Events (weighted)		Risk difference, % (95% CI)	Unadjusted risk ratio (95% CI)	P-value	Adjusted risk ratio (95% CI)[a]	P-value
		N	n (%)	N	N (%)					
Hospital Encounter with ventricular arrythmia	DOM	159,687	32 (0.02)	159,687	32 (0.02)	0.00 (−0.01 to 0.02)	1.09 (0.50–2.38)	0.84	0.84 (0.44–1.61)	0.59
	MET	36,857	11 (0.03)	159,084	35 (0.02)					
Hospital Encounter with cardiac arrest	DOM	159,687	127 (0.08)	159,687	127 (0.08)	0.02 (−0.02 to 0.07)	1.28 (0.82–0.20)	0.27	1.37 (0.78–2.44)	0.28
	MET	36,857	35 (0.09)	159,084	162 (0.10)					
All-cause mortality	DOM	159,687	825 (0.52)	159,687	825 (0.52)	0.63 (0.50–0.76)	2.22 (1.96–2.50)	<0.0001	2.50 (2.13–3.03)	<0.0001
	MET	36,857	495 (1.34)	159,084	1,824 (1.15)					
Cardiac mortality	DOM	151,235	294 (0.19)	151,235	294 (0.19)	0.16 (0.09–0.24)	1.82 (1.45–2.33)	<0.0001	2.00 (1.45–2.78)	<0.0001
	MET	34,271	143 (0.42)	147,989	528 (0.36)					

DOM, Domperidone; MET, Metoclopramide; N, Number of patients in cohort; n, Number of events.
[a]Risk ratio adjusted for the percentage of maximum dose prescribed.

in the 30 days following new prescriptions for domperidone or metoclopramide, and no significant between-group differences in these outcomes. However, we found the risks of all-cause and cardiovascular mortality were significantly higher among new users of metoclopramide compared to domperidone.

Despite guidelines recommending metoclopramide for the treatment of gastroparesis, (5) our study and others have raised concerns over its relative safety. A recent population-based case–control study showed an increased risk of sudden cardiac death with metoclopramide compared to proton pump inhibitors or domperidone (9). Similar findings were described in a meta analysis of nine case–control or crossover studies which showed a higher risk of ventricular arrhythmia or cardiovascular mortality in patients taking metoclopramide compared to domperidone (OR 1.56; 95% CI 1.43 to 1.72) (28). Although we did not find differences in the risks of the specific outcomes of hospital encounters for ventricular arrhythmia or cardiac arrest, the increased risk of all-cause and cardiovascular mortality among metoclopramide users may suggest our lack of differences observed in the former two outcomes may be limited by their low incidence and the insensitivity of their administrative code definitions (29).

Several mechanisms may explain the increased mortality risk observed with metoclopramide. In a randomized controlled trial, metoclopramide compared to placebo increased QT variance which can increase risk of torsades the pointes (7). It was also one of the three most common medications shown to be responsible for a number of cases of QT prolongation and torsades de pointes in a prospective cohort study of all cases of torsade de pointes seen in Berlin in a 3-year period (4 of 35 confirmed cases of drug induced torsades de pointes) (30). In an international post market safety surveillance study, metoclopramide was linked to higher risk of myocardial infarction versus nonuse (OR 2.6 [95% CI 2.2 to 3.1]), more so than when domperidone was compared to nonuse (OR 1.6 [95% CI 1.4 to 1.8]), where in both cases, the proposed mechanism was QT prolongation (31). Metoclopramide may also predispose patients with pre-existing heart failure to exacerbations by blocking renal dopamine release and inhibiting natriuresis which could contribute to non-arrhythmia-related cardiovascular deaths (32).

Our study has several strengths. The cohort was large, and we captured data on the routine use of both domperidone and metoclopramide in the outpatient setting. The two exposure groups were well balanced after weighting, except for dose percentages, which would have favoured no difference between groups.

There are also several limitations. While the two groups were well balanced with respect to measured baseline characteristics after inverse probability of treatment weighting, the potential from bias residual confounding remains a concern. We do not know if unmeasured characteristics were balanced between

two groups, and measurement limitations may have led some baseline characteristics being misclassified. While IPTW was chosen in order to retain the entire domperidone population and the power that comes with a large sample size, it does further introduce the possibility of unmeasured confounding. We only know which medications were dispensed, and not what was taken. Given this was a retrospective rather than prospective study, and without independent outcome adjudication, we were unable to confirm the accuracy of coding for ventricular arrhythmia and cardiac arrest. The known insensitivity of these codes may have favoured nondifferential misclassification of the outcomes, thereby biasing our findings toward no difference between groups. Additionally, there is the potential for confounding by indication. While domperidone and metoclopramide are both indicated for the treatment of gastroparesis, metoclopramide is also used in the palliative setting as first line antiemetic (33). While patients with malignancy were excluded from the analysis, it is possible that preferential use of metoclopramide as an antiemetic in the nonmalignant palliative care setting may have contributed to the increased association with mortality. However, the prescription rates of other antiemetics in the metoclopramide group were low (1.6% before weighting, 1.0% after weighting) making this less likely. Additionally, a contraindication bias may have influenced our findings. The cardiac risks of domperidone have been well described (34) and as a result, it is possible that clinicians prescribed metoclopramide to patients who they deemed at high risk of cardiac arrhythmia. To reduce concerns about this bias we excluded from study those patients with a documented history of ventricular arrythmia, cardiac arrest or implantable cardiac defibrillator. We also observed no between-group differences in baseline measured cardiovascular disease, risk factors or prescription of antiarrhythmic or QT prolonging medications that would support an indication bias (Table 1).

In conclusion, in this study, we did not find a significant difference in the risk of hospital encounter with ventricular arrythmia in metoclopramide compared to domperidone users. However, metoclopramide use was associated with a significant increase in all-cause and cardiac mortality over domperidone, which challenges the commonly held belief that domperidone is the higher risk prokinetic. Further studies are needed to confirm and to elucidate the underlying mechanisms for these findings.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

ACKNOWLEDGEMENTS

Funding

Conflict of Interest

None declared by any author.

Author Contributions

A.C.: Planning of the study, interpreting the data and drafting the manuscript. A.X.G.: Planning of the study, interpretation of the data and editing of the manuscript. E.M.: Planning of the study, collecting/interpreting the data and editing the manuscript. F.M.-T.: Planning of the study, interpreting the data and editing the manuscript. M.W.: Study oversight, planning of the study, interpreting the data and editing the manuscript. All authors approved the final version of this article including the authorship list.

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