Cardiac safety and clinical efficacy of high-dose domperidone for long-term treatment of gastroparesis symptoms

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ABSTRACT

Domperidone is an effective antiemetic used worldwide, but there have been reports of possible cardiotoxicity. Our goal was to explore the cardiac safety and clinical efficacy of long-term domperidone, titrated as high as 120 mg/day, in patients not responding or unable to tolerate other therapies for gastroparesis (GP).This retrospective cohort study was conducted at a single tertiary care academic center. We objectively assessed the safety and efficacy of domperidone through questionnaires, clinical follow-up and frequent ECGs as mandated by the Food and Drug Administration. We excluded patients with a history of dangerous arrhythmias, prolonged QTc, clinically significant electrolyte disturbances, gastrointestinal hemorrhage or obstruction, presence of a prolactinoma, pregnant or breastfeeding females, or allergy to domperidone. A total of 21 patients met the inclusion criteria for eligibility in this study (52.4% white, 42.9% Hispanic; mean age 50.1 years; 90.5% female). The mean duration of domperidone therapy was 52.3 (range 16–97) months with a mean highest dose of 80 mg/day (range 40–120 mg). Two patients (9.5%) taking 120 mg/day experienced asymptomatic meaningful QTc prolongation (>450 ms in males, >470 ms in females). One-third of patients had asymptomatic non-meaningful QTc prolongation. Palpitations or chest pain was reported in 19% of patients without ECG abnormalities or adverse cardiac events. The mean severity of vomiting and nausea was improved by 82% and 55%, respectively.Long-term treatment with high doses of domperidone (40–120 mg/day) improved GP symptoms in patients previously refractory to other medical therapies and with a satisfactory cardiovascular risk profile.

Significance of this study

What is already known about this subject?

⇒ The first-line treatment options for gastroparesis (GP) include dietary management and pharmacological agents such as antiemetics and prokinetics.
⇒ Metoclopramide is the only medication approved by the Food and Drug Administration (FDA) in the USA to treat GP.
⇒ Oral domperidone is approved in several countries outside the USA to treat refractory GP but it is not approved by the FDA.

What are the new findings?

⇒ In our study using high-dose domperidone, 57% of the study cohort actually exceeded the 50% improvement mark in their symptoms.
⇒ Most benefits were observed with reductions in vomiting, followed by nausea and abdominal pain.
⇒ No patient experienced any adverse cardiac events such as arrhythmias or high-degree nodal block.

How might these results change the focus of research or clinical practice?

⇒ Domperidone is a potential option in patients with GP who had exhausted other therapeutic options, the majority failing metoclopramide or unable to tolerate its side effects. This is a real challenge that is frequently faced by practicing gastroenterologists, and hence our data provide that high-dose domperidone has a satisfactory cardiovascular risk profile while effectively reducing symptoms of GP.

INTRODUCTION

Gastroparesis (GP) is characterized by delayed gastric emptying in the absence of mechanical obstruction.[1] It has been estimated that up to 4% of the population experience symptoms of GP.[2 3] The most important causes of GP include diabetes mellitus, and idiopathic and post-surgical vagus nerve injury.[1] GP is manifested more commonly in patients with type 1 diabetes (40%) than patients with type 2 diabetes (25%). The first-line treatment options include dietary management and pharmacological agents such as antiemetics and prokinetics.[4] Domperidone and metoclopramide are classified as prokinetics

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with dopamine D2 receptor antagonistic action, blocking dopamine's intrinsic inhibitory effect on gastrointestinal (GI) motility, which improves gastric emptying while at the same time reducing nausea mediated by dopamine receptors in the chemoreceptor trigger zone.[5]

For the past 45 years, metoclopramide is the only medication approved by the Food and Drug Administration (FDA) in the USA to treat GP. However, it comes with a black box warning to restrict its use for 3 months due to concerns about neurological side effects such as tardive dyskinesia.[6] In contrast to metoclopramide, domperidone does not have a central neurological side effect profile since it does not readily cross the blood–brain barrier.[5] Oral domperidone is approved in several countries outside the USA to treat refractory GP. However, it is not approved by the FDA, and domperidone in the USA can only be prescribed under the FDA Investigational New Drug (IND) program.[5]

Domperidone was first developed in 1978, and the clinical efficacy of domperidone is well documented in the literature. The position statement from the American Gastroenterology Association recognizes domperidone as a treatment option for GP.[1 7] Recommended dosing is generally 30 mg by mouth daily; however, many patients find relief of GP symptoms using much higher doses of domperidone when all other medical therapies have failed. In a trial of patients with GP, domperidone at 80 mg/day dose for an average of 23 months resulted in a significant reduction in GI symptoms and hospitalizations, enhanced quality of life, and acceleration of gastric emptying to normal.[8] Another multicenter, 2-phase withdrawal study involving over 200 insulin-dependent patients with diabetes showed that domperidone at 80 mg/day provided a significant reduction in upper GI symptoms along with a significant improvement in the quality of life with a good tolerability profile.[9] Several other studies have also demonstrated the clinical efficacy of domperidone in patients with GP or GP-like symptoms.[10–13]

Concerns of QTc interval prolongation and the possibility of sudden cardiac death (SCD) have resulted in this drug being limited in the USA to restricted access under an FDA-IND protocol. Initially, there were reports of cardiotoxicity from QTc prolongation after intravenous administration of high doses.[14–16] A systematic review by Rossi and Giorgi reported 3.8 times increased odds of SCD (OR 3.8; 95% CI 1.5 to 9.7) with the use of intravenous domperidone, based on animal studies, case reports, and observational studies.[17] To put this into perspective, because of the low oral bioavailability of domperidone (13%–17%), oral doses over 1000 mg/day would correlate with the intravenous doses administered to patients when cardiotoxicity was reported.[5 18] Nevertheless, the intravenous formulation of domperidone is no longer available and therefore is no longer used in clinical practice.

In recent years, there have been studies evaluating the safety of domperidone use, especially at high doses.[19–22] However, there is a lack of data on the long-term follow-up of patients with GP on high-dose domperidone. Our center is involved in the use of domperidone under FDA-IND protocol for patients with GP who are refractory to other first-line medications. High-dose domperidone safety and efficacy need to be explored in order to provide the evidence that will guide the conscientious treatment of patients who are in need of a more robust armamentarium of medical therapy for non-responsive symptoms of GP. Our aim was to investigate the long-term safety and efficacy of high-dose domperidone (≥40 mg daily) with an emphasis on QTc prolongation effects and possible cardiac toxicity, as well as its symptomatic efficacy.

MATERIALS AND METHODS

Patient selection

This retrospective cohort study was conducted at a single tertiary care academic medical center. Patients with GP at our Gastroenterology Motility Center who were receiving chronic high-dose domperidone through the aforementioned FDA-IND compassionate use protocol over a period of 8 years from January 2013 to January 2021 were reviewed. All these patients had failed to improve or could not tolerate metoclopramide therapy or other prokinetics such as erythromycin, neostigmine, and bethanechol because of adverse events. Thus, they required another treatment, and domperidone was provided as a new therapeutic option. We defined a high dose of domperidone as 40 mg or above daily and defined chronic use as 3 months or more. Our study's inclusion criteria were adults more than 18 years of age; symptomatic patients with GP refractory to or unable to tolerate standard therapy; receiving chronic treatment with high-dose domperidone; availability of at least 1 baseline ECG with at least 1 follow-up ECG after 3 months of treatment; and able to be contacted for a follow-up telephone interview regarding symptom and side effect status. In accordance with the FDA-IND protocol, informed consent was obtained from all the patients for the administration of domperidone. Exclusion criteria include (1) history of dangerous arrhythmia(s) including ventricular tachycardia, ventricular fibrillation, or torsades de pointes; (2) clinically significant bradycardia, sinus node dysfunction, or heart block; (3) prolonged QTc (QTc >450 ms for males or >470 ms for females); and (4) clinically significant electrolyte disturbances, GI hemorrhage or obstruction, presence of a prolactinoma, pregnant or breastfeeding females, or known allergy to domperidone. Of note, patients with minor forms of ectopy, such as premature atrial contractions, were not excluded.

Assessment of safety and efficacy of domperidone

We assessed the safety and efficacy of domperidone in 2 ways: (1) administration of questionnaires (online supplemental appendix 1), and (2) review of ECGs to specifically assess for QTc prolongation and/or the development of arrhythmia(s).

1. Questionnaire implementation
   Questionnaires aimed to capture both constants and variables relating to the patient at baseline and then after a minimum of 3 months' use of high-dose domperidone through open-ended questions, multiple-choice questions, and side effect/symptom assessment questions using a 5-point Likert scale. Constants assessed included patient demographics, body mass index prior to treatment, gender, the reason for seeking domperidone, diabetic status, and the presence of symptoms. Variables analyzed included highest daily dose domperidone used, most recent daily dosage at

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the time of questionnaire administration, any GI-related hospitalizations while receiving treatment, presence or development of any cardiac problems since starting domperidone, prolactin-related side effects, changes in weight, and subjective changes in the overall condition that warranted treatment with domperidone.

Symptom and side effect profiles assessed using the 5-point Likert scale ranked both severity and frequency of symptoms/side effects from 0 to 4. For symptom/side effect severity scaling, a score of 0 represented absent, 1 mild, 2 moderate, 3 severe, and 4 extremely severe. For symptom/side effect frequency scaling, a score of 0 represented absent, 1 represented once a week, 2 represented 2–3 times a week, 3 represented 4–6 times a week, and 4 represented a frequency of daily or more. These scaled measurements for frequency and severity monitored the following: abdominal pain, early satiety, bloating after meals, nausea, vomiting, constipation, diarrhea, heart palpitations, nipple tenderness, breast enlargement, nipple discharge, chest pain, muscle spasms, and restlessness.

Subjective changes in the overall condition that warranted treatment with domperidone were assessed via a line representing symptom severity numbered as negative and positive percentages (see online supplemental appendix 1—percentage selection ranged from negative 50%, indicating worsening symptoms, to positive 100%, indicating improving symptoms). If patients indicated no change, then they would select zero. If patients indicated a change, then they were asked to rank their change from −50% worse to 100% better.

2. ECG interpretation

Baseline and follow-up ECGs were reviewed and evaluated for the presence of arrhythmias and/or clinical QTc prolongation. All ECGs were serially monitored and independently reviewed by a single board-certified cardiologist (TS). The presence of any significant arrhythmia(s) or QTc prolongation was recorded for each patient along with the associated domperidone dose. All patients had the degree of QTc change assessed by comparing the baseline ECG to the most recent ECG and calculating the QTc difference between these 2 EKGs. Patients were separated into 3 categories: (1) patients with a decrease in QTc, (2) patients with a 'meaningful' asymptomatic QTc increase, defined as the QTc interval exceeding 450 ms in males or 470 ms in females, and (3) patients with a 'non-meaningful' asymptomatic QTc increase where the QTc interval remained within normal limits. Patients who had an asymptomatic 'non-meaningful' QTc increase were then stratified by the most recent domperidone dose (≥80 mg daily or <80 mg daily), and average QTc increases were compared between these groups. The most recent recorded dose of domperidone was used for all analyses of QTc intervals in order to more correctly extrapolate the correct dose being used at the time the most recent ECG was taken.

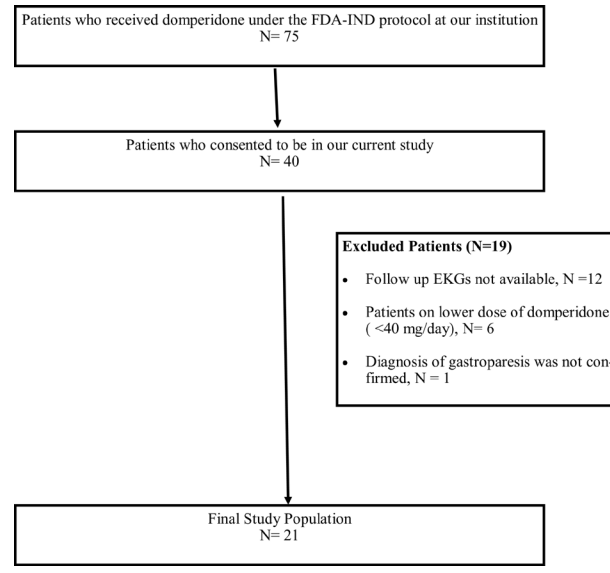

Figure 1 Flow chart of the study population. FDA-IND, Food and Drug Administration Investigational New Drug.

Statistical analysis

Data analysis was performed using IBM SPSS software V.27 (SPSS). Descriptive summary statistics are presented as means+SD for continuous variables with normal distribution, median with IQR for continuous variables with non-normal distribution, and frequencies with percentages for categorical variables.

RESULTS

Patient demographics and dosing

At the time of the study, 75 patients were enrolled in the FDA-IND compassionate use protocol for domperidone at our academic center. Among them, a total of 21 patients were on chronic high-dose domperidone use and met the inclusion criteria with at least 1 follow-up EKG and 1 follow-up interview (figure 1). The basic demographics of the study cohort are outlined in table 1.

Table 1 Summary of the demographic data for 21 patients with gastroparesis (GP) receiving chronic high doses of domperidone therapy

Demographics	n=21 (%)
Mean age (SD)	50.1 (16.58)
Median age (IQR)	47 (35, 68.5)
Female	19 (90.5)
Mean body mass index (SD)	26.47 (8.37)
Race	
White	11 (52.4)
Hispanic	9 (42.9)
Pacific Islander	1 (4.8)
Etiology	
Diabetes	14 (66.7)
Idiopathic	7 (33.3)
Mean current domperidone dose (SD)	67.62 (24.27)
Mean highest domperidone dose (SD)	80 (20.98)
Mean duration of domperidone treatment (SD)	52.33 (22.16)

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Table 2 Severity of symptoms before and after treatment with high-dose domperidone

Symptom	Pretreatment average severity	Post-treatment average severity	Percentage decrease	P value
Abdominal pain	3.14 (1.15)	1.62 (1.40)	48.41	<0.001
Early satiety	3.19 (1.08)	1.48 (1.47)	53.61	<0.001
Bloating	2.86 (1.39)	1.76 (1.30)	38.46	0.004
Nausea	3 (1.23)	1.33 (1.28)	55.67	<0.001
Vomiting	2.67 (1.77)	0.48 (0.87)	82.02	<0.001
Constipation	1.52 (1.78)	1 (1.34)	34.21	0.149
Diarrhea	1.33 (1.53)	0.86 (1.32)	35.34	0.125

Symptom severity was graded on a 5-point Likert scale ranging from 0 to 4 (0—absent; 1—mild; 2—moderate; 3—severe; 4—extremely severe).

The mean age of the cohort was 50.1 (range 25–76) years, with 90.5% (n=19) females. The ethnicity among our patient population included 52.4% white, 42.9% Hispanic, and 4.8% Pacific Islander. In terms of etiology of GP, 66.7% of the patients had diabetes and 33.3% were categorized as idiopathic GP. The mean duration of treatment was 52.3 (range 16–97) months. At the time of the study, the mean dose of the domperidone is 67.6 mg (range 40–120 mg), with a mean highest dose of 80 mg (range 40–120 mg).

Treatment response

Tables 2 and 3 demonstrate a change in patients' symptom severity and frequency post-treatment. There was a significant improvement in the severity of all GP symptoms among the patient cohort who were treated with a high dose of domperidone. Mean symptom improvement for all 21 patients was reported at 54.8%. Symptom improvement ranged from 30% to 100%, with no patients reporting worsening of symptoms on domperidone. In fact, 54% of the cohort reported a positive symptoms response of >50% during their treatment. The symptom that improved the most was vomiting, with a reduction of 82% in mean severity and 76% in mean frequency. Nausea was the second most improved symptom with a reduction of 55% in mean severity and 52% in mean frequency. Abdominal pain was also significantly improved, with a 48% improvement in the severity and 58% in frequency. The least but still significant improvement was seen with bloating, a 38% reduction in severity, and a 22% reduction in frequency.

QTc variation from baseline to post-domperidone therapy

A total of 101 ECGs were performed during the course of this study for all participants (including 21 baseline ECGs). All patients had 1 baseline ECG and at least 1 follow-up ECG within the first year of treatment, with 15 patients having ≥1 follow-up ECG throughout the study (figure 2). There was a median of 4 follow-up ECGs per patient over the course of this study (IQR 1–6). At 120 mg/day, 2 patients (9.5%) had asymptomatic prolongation of their QTc interval (>450 ms in males, >470 ms in females) without adverse cardiac effects such as arrhythmia(s), high-degree block, myocardial infarction, cardiac-related hospital admissions or SCD (table 4). The first patient endorsed a treatment response of 30% improvement, and the drug was subsequently discontinued (QTc max of 491 ms). The second patient rated symptomatic improvement at 95% when the domperidone dose was lowered to 80 mg with subsequent resolution of QTc prolongation and without recurrence of QTc changes during 20 more months of treatment. No patient experienced any adverse cardiac events (ie, arrhythmia(s), high-degree block).

The difference between baseline QTc and the most recent post-treatment QTc for all patients revealed an average of 2.7 ms decrease in QTc interval. This was after excluding the 2 patients mentioned above, who were found to have a prolonged QTc. An asymptomatic 'non-meaningful' increase in QTc was observed in 7 patients taking an average daily dose of 71.4 mg of domperidone. They had a mean increase of 23.2 ms in the QTc interval when assessing the difference from baseline. When stratifying differences in QTc for these

Table 3 Frequency of symptoms before and after treatment with high-dose domperidone

Symptom	Pretreatment average frequency	Post-treatment average frequency	Percentage decrease	P value
Abdominal pain	3.33 (1.19)	1.38 (1.36)	58.56	<0.001
Early satiety	3.43 (1.12)	1.71 (1.71)	50.15	<0.001
Bloating	2.90 (1.45)	2.24 (1.48)	22.76	0.095
Nausea	3.14 (1.32)	1.52 (1.50)	51.59	<0.001
Vomiting	2.19 (1.72)	0.52 (1.03)	76.26	<0.001
Constipation	1.62 (1.72)	0.90 (1.22)	44.44	0.052
Diarrhea	1 (1.18)	0.81 (1.25)	19	0.463

Symptom frequency was graded on a 5-point Likert scale ranging from 0 to 4 (0=absent; 1=once a week; 2=two to three times a week; 3=four to six times a week; 4=daily or more).

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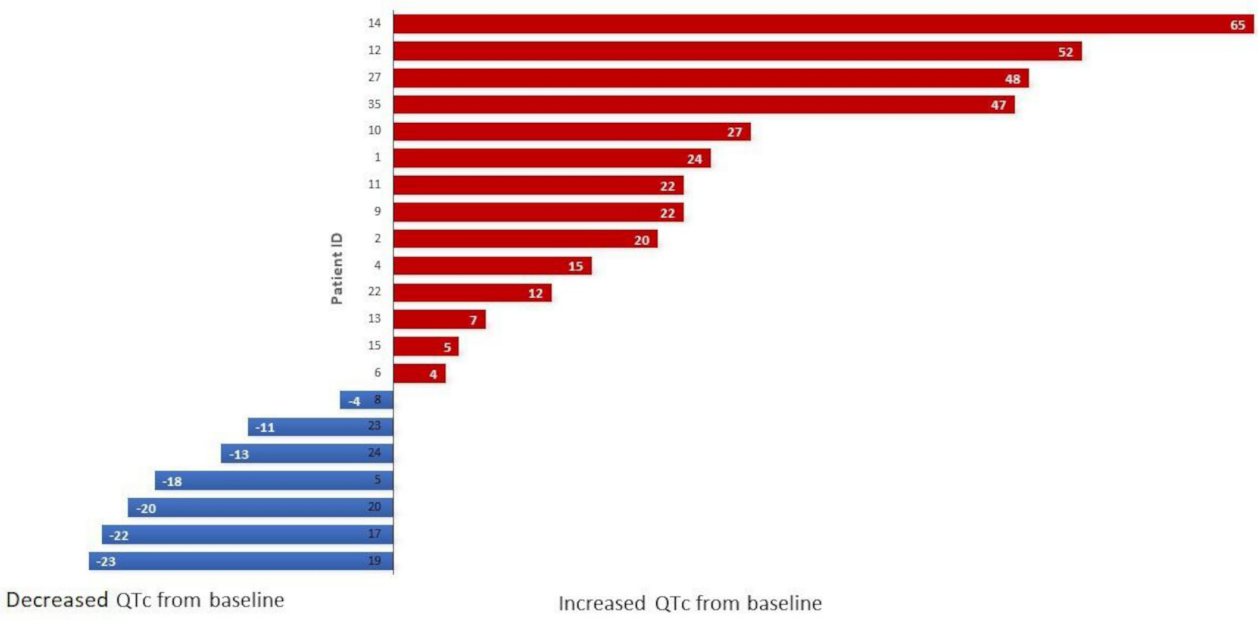

Figure 2 Bar chart depicting individual patients for baseline QTc against the largest QTc that occurred on the treatment period.

7 patients by the most recent domperidone dose of either <80 mg or ≥80 mg, we found that patients who were taking daily doses of <80 mg (n=3) had an average increase in an interval of 15.3 ms at an average dose of 46.6 mg. Patients taking ≥80 mg (n=4) had an average increase of 29.2 ms at an average dose of 90 mg. The greatest QTc difference noted in a single patient was an asymptomatic increase of 52 ms from baseline to most recent ECG in a female patient taking 80 mg (most recent QTc measured 466 ms). The majority of the patients in this study (n=12, 57.1%) were not found to have any increase in QTc and actually had an average decrease in QTc of 19.7 ms while taking a mean dose of 58 mg of domperidone (range 40–120 mg).

Prolactin-related events and 'other' reported effects

Table 5 demonstrates prolactin-related events, as well as 'other' reported effects, not including QTc prolongation and/or ECG abnormalities. A total of 14 patients reported either prolactin-related events or 'other' reported effects during therapy. Seven patients noted prolactin-related side effects, including breast tenderness (n=2), breast enlargement (n=1), nipple discharge (n=1), and menstrual irregularities (n=4). Seven patients noted 'other' reported side effects, including the following: heart palpitations (n=4), chest pain (n=1), spasms of the voluntary muscles (n=4), and restlessness (n=4). The symptoms of chest pain and palpitations occurred in 19% of patients (n=4) without QTc prolongation or other significant ECG abnormalities. Additionally, there were no cardiac-related events, hospital admissions, or deaths in any of the patients who participated in this study. None of the symptoms reported led to the discontinuation of domperidone.

DISCUSSION

This study evaluated the efficacy and safety of high-dose domperidone in patients with GP in the setting of long-term follow-up. All patients in the study had improvement of their symptoms with a mean improvement of 54.8%, and specifically 57% of the study cohort actually exceeded the 50% improvement mark in their symptoms. Most benefits were observed with reductions in vomiting followed by nausea and abdominal pain. No patient reported worsening symptoms while on domperidone. Only 2 patients (9.5%) were found to have meaningful QTc prolongation, both taking domperidone 120 mg/day. However, no patient experienced any adverse cardiac events such as arrhythmias or high-degree nodal block. The mean highest dose of domperidone is 80 mg/day, and the mean follow-up period of the study cohort is 52 months (4.4 years).

There has been a reasonable amount of research with domperidone regarding its efficacy at conventional doses.[10–13] Gastric emptying studies, both pre-domperidone and post-domperidone treatment, have also shown improvement.[23] There have also been studies focused on subjective improvement in patient symptoms, assessed by questionnaires where the reduction in nausea, vomiting, and feelings of fullness have been the most responsive.[22] Similarly, in our study, we also observed that vomiting and nausea were the most improved symptoms in our study cohort. The shortcomings of the earlier studies using domperidone are that the doses used are conventional at 30 mg daily, with very few doses ranging up to 80 mg daily.

Clinicians managing patients taking domperidone may be hesitant to increase the dose due to the aforementioned concerns of adverse cardiac events and demonstration of effects on the QTc interval.[24] In our study, 9.5% had significant QTc prolongation, but they were asymptomatic and did not have any arrhythmias. About one-third of the patients were noted to have an asymptomatic 'non-meaningful' increase in QTc. The majority of the patients (57.1%) did not have any QTc prolongation. In a phase I randomized placebo-controlled study with 44 healthy volunteers, the use of domperidone at 80 mg/day caused prolongation of the mean QTc interval up to 10 ms without

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Table 4 EKG characteristics of patients who experienced QTc prolongation with corresponding domperidone doses (prolonged QTc values in bold)

Patients	Sex	Baseline QTc	All follow-up QTc	Most recent dose (mg)	Highest dose (mg)	Symptom % change	Prolactin-related side effects	Other adverse effects reported	ECG arrhythmias
Patient A	F	467	**491**	120	120	30% Better	No	Restlessness	None
Patient B	F	455	464-**477**-**482**-426-392-446-429-464	80	120	95% Better	No	Muscle spasms	None

clinically relevant effects.[25] Ortiz *et al* found that 15% of patients who were taking domperidone up to 120 mg/day had an asymptomatic prolongation of the QTc interval at follow-up, 3 had palpitations without ECG changes while no ventricular arrhythmia (VA) or SCD was reported.[26] A Canadian study revealed that among 122,333 patients receiving a domperidone prescription, there were only 18 reports (0.9 per 10,000) of serious adverse cardiac events with no evidence of SCD.[27] Buffery and Strother determined that the use of high-dose domperidone (80 mg/day) was not associated with QTc prolongation in healthy volunteers and concluded that their analysis does not support the theory that domperidone presents unacceptable risks.[18] Predisposing factors for increased risk of QTc prolongation and VA or SCD have been older age, female sex, heart failure with low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, bradycardia, electrolyte abnormalities such as hypokalemia and hypomagnesemia as well as polypharmacy.[16 28 29] The most recent cohort study by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Consortium assessed the effect of domperidone therapy on GP symptoms (n=181), and they reported no adverse cardiac events or unexplained deaths.[30]

On the other hand, there have been some studies that have associated domperidone use with increased risk of VA and SCD. A case–control study from the Netherlands with 83,212 patients reported a 44% increased risk for serious VA and SCD with domperidone at 40 mg/day compared with proton pump inhibitors only, and a 59% increased risk of VA or SCD with domperidone use compared with non-users.[31] However, the validity of these results is biased as participants had other comorbid factors that could cause VA or SCD, specifically cardiomyopathy in 3.3%, heart failure in 35%, history of VA in 0.2%, ischemic heart disease in 37.4%, liver failure in 1.4%, other arrhythmias in 13.4%, QT-prolonging medications in 22.2%, and current or past use of CYP3A4 inhibitors in 11.3%.[31]) Other studies based in Europe that have associated domperidone with SCD or VA have concerning limitations.[32–34] Those studies are mostly retrospective case–control studies that mainly relied on hospital and community-based records and databases. Additionally, the studies by Straus *et al*, De Bruin *et al*, and van Noord *et al* did not use serial ECGs to assess or monitor at-risk patients. Also, 2 of these studies were performed in the Netherlands, where domperidone is available over the counter, which introduces a potential bias in these studies as this might well lead to inaccuracies reported by patients in their usage data.[32 33 35]

The FDA-IND protocol for domperidone emphasizes and recommends careful QTc monitoring in all patients. Their mandate is to obtain an ECG before, within 1 week, and 1 month after starting therapy and subsequently at 2-month intervals. The FDA also recommends scrutinizing concomitant use of all medications known to prolong the QT interval and being aware of the medications that inhibit the CYP3A4 pathway as coadministration of these drugs can potentiate QTc prolongation even more. In addition, serial laboratory analysis every 2 months to detect clinically significant hypokalemia or hypomagnesemia and periodic office visits to assess the patient's clinical status continuously were incorporated. Clinical acumen and vigilance are

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Table 5 Prolactin-related events as well as other side effects associated with chronic therapy with high-dose domperidone

Most recent dose (mg)	Highest dose (mg)	Nipple discharge	Breast enlargement	Breast tenderness	Menstrual irregularity	Restlessness	Muscle spasms	Heart palpitations	Chest pain
120	120					X			
70	80					X	X	X	X
60	60				X				
40	80			X	X				
80	120						X		
40	80		X						
60	60						X	X	
120	120					X		X	
40	40				X				
60	80	X							
100	100			X					
80	80					X			
40	80				X				
80	80						X	X	

required by the clinician when domperidone is prescribed, and we (the authors) highlight the following guidelines: (1) discuss and document potential side effects with your patient; (2) obtain a baseline ECG and serum electrolytes prior to starting domperidone, as well as at 3-month intervals during treatment, with a QTc of >450 ms in males and >470 ms in females and/or significant, sustained hypokalemia or hypomagnesemia serving as contraindications to either starting or continuing therapy[5]; (3) begin with a dose of 10 mg four times a day—30 minutes prior to meals and at bedtime, and gradually uptitrate the dose (maximum 120 mg/day) until a satisfactory therapeutic effect is achieved[36]; (4) dosing should be reassessed if symptoms of shortness of breath, chest pain, palpitations, syncope or prolactin-mediated complaints arise.

Our study had some limitations. The main limitation is that it is a retrospective study with a small sample size. Another possible limitation was that ECG follow-up relied on patients' adherence to office appointments, and thus missed appointments could have led to the loss of some follow-up data. Telephone calls were periodically made to patients and their primary care physicians to obtain additional clinical information as well as ECG results, including tracings that were faxed. Lastly, we were not able to assess serial prolactin levels in our patients.

In summary, our study is unique in that we used higher doses than the standard 30 mg/day, specifically doses in excess of 60 mg/day and up to 120 mg/day in patients with GP, and for long periods of time ranging up to 96 months with a mean of 52 months in patients with GP who had exhausted other therapeutic options, the majority failing metoclopramide or unable to tolerate its side effects. This is a real challenge that is frequently faced by practicing gastroenterologists, and hence our data provide evidence-based guidance for clinicians in the further management of patients with GP. We conclude that high-dose domperidone has a satisfactory cardiovascular risk profile while effectively reducing symptoms of GP, particularly nausea and vomiting.

Contributors KW drafted the article, compiled the data and interpreted the data under the guidance of RM. MG did formal data analysis, substantial revision of the manuscript, and literature search. ZG drafted and edited the article. MB-B drafted the article. IS reinforced the IRB protocol compliance and contributed to the manuscript input. KE participated in acquisition of data. NW assisted in data compilation and analysis. TS individually reviewed and interpreted all patient EKGs. RM conceptualized and designed the study, drafted the article, and revised it critically for intellectual content and final approval of the version to be submitted. All authors discussed the results and contributed to the final manuscript. RM is responsible for the overall content as the guarantor.

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