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Introduction: Metoclopramide and domperidone are medications that block dopamine receptors on the lactotrophs, allowing prolactin levels to rise. Both medications are prescribed to boost milk production in mothers with low milk production due to hypoprolactinemia. The Food and Drug Administration has not approved the use of domperidone in the U.S. because of concerns about increased risk of cardiac arrhythmias. Metoclopramide is often recommended instead. Unfortunately, metoclopramide affects the central nervous system (CNS) and increases the risk of both depression and tardive dyskinesia (TD).

Method: The present study is an online survey of self-reported side effects of 1,990 mothers, representing 25 countries, who took metoclopramide, domperidone, or both medications to enhance milk production. Data were collected in 2010.

Results: The results indicated that side effects, in general, affected only a small percentage of women who took either medication. Women were 3.6 times more likely to report no side effects when taking domperidone vs. metoclopramide. There were no significant differences in cardiac arrhythmias for women who took metoclopramide versus domperidone. Racing heart was more common with metoclopramide. Less than 1% reported these symptoms in both groups. However, CNS effects were significantly more common in women who took metoclopramide. Risk of depression increased by seven times, and symptoms of TD (tremors, involuntary grimaces, and jerking) increased by 4 to 19 times when women took metoclopramide.

Discussion: The results of the present study are preliminary, but suggest that cardiac arrhythmias are a rare side effect with both medications. The CNS side effects with metoclopramide are more concerning, particularly depression and TD. It is hoped that the recommendations regarding the relative safety of these medications will be re-examined in light of these findings.

Keywords: domperidone; metoclopramide; milk production; breastfeeding; hypoprolactinemia; depression; cardiac arrhythmias

Frequent and effective removal of milk is required to maintain milk production and continued release of prolactin from the pituitary. Unfortunately, there are times, despite frequent draining of the breasts, low milk production persists. In some of these cases, hypoprolactinemia, or low prolactin levels, may be involved (Buckley, 2015).

Prolactin (PRL) is an essential hormone required for the continued synthesis of human milk, and is the driving force because it maintains the lactocyte in a milk-producing state (Buckley, 2015; Czank, Henderson, Kent, Lai, & Hartmann, 2007; Stuebe, Meltzer-Brody, Pearson, Pedersen, & Grewen, 2015). Its function is to maintain the physiology and tight junctions of the

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lactocytes in the alveoli of the breast, thus facilitating the synthesis of human milk. (Nguyen & Neville, 1998). One study found that if the mother maintained PRL levels ranging from as low as 79 ng/ml up to 300 ng/ml, they were able to produce up to 755 ml of milk daily (Cox, Owens, & Hartmann, 1996). Average intake for a breastfeeding baby ranges from 570 ml to 900 ml/day (Bonyata, 2017).

While extraordinarily high levels of prolactin are not actually required for milk synthesis, modest plasma levels will produce all the milk an infant needs. Minimum levels of prolactin probably range less than 79 ng/ml up, although the actual range required for the maintenance of milk synthesis is unknown (Cox, Owens, & Hartmann, 1996). The normal non-lactating range for women is 10–20 ng/ml. While prolactin levels at birth range as high as 400 ng/ml, levels drop rapidly the first week to approximately 200 ng/ml. Regardless,

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prolactin levels must be higher in lactating women for milk synthesis to continue.

Lactotrophs are cells in the anterior pituitary that produce and store prolactin in response to hormonal signals (Czank et al., 2007). Dopamine levels rise between feedings thus leading to synthesis and storage of prolactin in the storage granule in the lactotroph. When breastfeeding, the hypothalamus inhibits the release of dopamine and prolactin is rapidly released into the mother's plasma compartment. This is called the "prolactin surge" which peaks at about 45 minutes after breastfeeding. However, it is well known that some mothers simply have insufficient levels of prolactin to maintain milk synthesis, which we presume is somewhere < 50 ng/ml.

In such mothers, giving them a medication that blocks the dopamine receptor site on the lactotrophs in the pituitary facilitates the release of prolactin into the plasma. Both domperidone and metoclopramide block dopamine receptors on the lactotrophs, thus facilitating rapid release of prolactin. This is the basis for the offlabel use of these medications for breastfeeding mothers with low milk production (Sewell, Chang, Chehab, & Nguyen, 2017).

Numerous studies have shown that domperidone and metoclopramide increase milk production in mothers with hypoprolactinemia (Campbell-Yeo et al., 2010; Knoppert et al., 2013; Wan et al., 2008). Tens of thousands of women worldwide use domperidone and metoclopramide annually to stimulate their prolactin levels and thus the production of breast milk. In countries, such as Canada and Australia, where it is legal, a growing number of providers are prescribing domperidone to mothers with low milk production (Grzeskowiak, Lim, Thomas, Ritchie, & Gordon, 2013)

Domperidone

Domperidone is a peripheral dopamine antagonist that blocks dopamine receptors in the gastrointestinal (GI) wall, in the chemoreceptive trigger zone (nausea center) in the brain stem, and in the pituitary. In both men and women, domperidone blocks the positive feedback inhibition of prolactin in the pituitary lactotroph, which allows the release of prolactin from the pituitary (Brown, Fernandes, Grant, Hutsul, & McCoshen, 2000; Wan et al., 2008).

A Canadian study of 15 women compared treating women with low milk production with 10 or 20 mg of domperidone three times a day for 4 weeks (Knoppert

et al., 2013). Both groups experienced a significant increase in their milk production. But, there was a clinically significant (but not statistically significant) difference between the two groups. Women who received 20 mg three times daily of domperidone had the largest increase in milk production.

Metoclopramide

Metoclopramide increases muscle contractions in the upper digestive tract, which speeds up the rate in which the stomach empties into the intestine. Metoclopramide blocks dopamine peripherally and centrally (Wikipedia, 2017). Depression and extrapyramidal symptoms are common side effects of metoclopramide. The most serious side-effect is tardive dyskinesia (TD), which can occur with prolonged use, causing the Food and Drug Administration (FDA) to issue a black-box warning (Rao & Camilleri, 2010). Interestingly, gastroenterologists were more likely to prescribe domperidone after the FDA black-box warning for patients with diabetic gastroparesis (Ehrenpreis et al., 2013).

Side Effects of Domperidone and Metoclopramide

Due to its structure, domperidone does not pass the blood-brain barrier, hence it does not have central nervous system (CNS) effects. It is poorly absorbed orally because it is instantly absorbed and metabolized in the gut wall, long before it even reaches the liver. Total oral bioavailability of domperidone in humans is low: 13%–17% (Chaudhuri & Fink, 1991; Heykants et al., 1981). The elimination half-life of domperidone following the use of oral tablets is reported to range from 4 to 9 hours (Apotex, 2012; Janssen, 2015).

Domperidone is currently not approved for human use in the U.S., with one exception, and that is a compassionate use exemption from the FDA for use in GI syndromes only (Sewell, Chang, Chehab, & Nguyen, 2017). Domperidone, however, has orphan drug status, which qualifies it for certain considerations during clinical testing. There is concern about cardiac arrhythmias as a side-effect of this medication. The FDA cites QT prolongation, torsades de pointes, and sudden cardiac death among lactating women in a recent advisory against domperidone (Sewell, Chang, Chehab, & Nguyen, 2017). This report cited three case studies of nonfatal cardiac symptoms in women taking domperidone for lactation enhancement. One patient was taking 20 mg of domperidone, 3 to 4 times per day.

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Case studies do raise some concerns. However, the total number of these case studies is small in comparison to the millions who have used domperidone. They provide no information about how common these side effects might be, or how the incidence of side effects compares to those of metoclopramide, which is often presented as the "safer" alternative. This study was designed to examine self-reported side effects reported in women taking metoclopramide or domperidone to increase milk production.

Pharmacologically, domperidone and metoclopramide differ considerably in their distribution, pharmacokinetics, and metabolism. Once understood, the inability of domperidone to enter the CNS, and its poor oral bioavailability likely account for the wide variance of side effects found between these two drugs. This study is the first large survey of self-reported symptoms found in breastfeeding mothers using these two drugs to stimulate milk production.

Method

Participants

The sample included 1,990 participants, representing 25 countries, who completed an online survey. Sixtyseven percent (n = 1,325) were from the U.S., 13% from Canada (n = 250), 3% from New Zealand (n = 63), 2% from Australia (n = 38), 2% from the Netherlands (n =48), and 2% from Great Britain (n = 37). The mean age of participants was 33.16 years (range = 14–50), and they averaged 28.49 years, when they had their first babies. They had an average of 2.01 babies. Seventy-seven percent were White. Eighty-four percent were married, the remaining 16% were single, separated, divorced, or cohabitating with a partner. Three mothers identified as having same-sex partners. The participants were well-educated: 62.7% had a bachelor's degree or higher, and 7.8% had a doctoral degree. Fifty-one percent were employed outside the home.

To be eligible for the study, participants had to indicate they that had taken either domperidone or metoclopramide to increase their milk production. In terms of use, 58% (n = 1,161) had used domperidone alone, 21% had used metoclopramide alone (n = 235), and 12% had used both domperidone and metoclopramide.

Sample Recruitment

The sample was recruited from notices on Facebook [blinded for review] and websites. Mothers were asked to complete a survey about their experiences with domperidone and metoclopramide used to increase milk production. Mothers were provided with a survey link on the Texas Tech University Health Sciences Center website. Data were collected between June 25, 2010 and December 15, 2010. The survey was approved by the Texas Tech University Health Sciences Center Institutional Review Board.

Questionnaire

The questionnaire contained 101 close-ended questions about basic demographic data, the health of both themselves and their infants, their milk production, and their experiences with domperidone and metoclopramide. Mothers were given an identical list of symptoms for both medications and asked if they had experienced any of these. The dosages that they reported taking of each and the length of time they took the medications are reported on Tables 1–4.

Data Analysis

Data were analyzed using χ^2 risk analysis, using SPSS, 20th edition.

Results

Cardiovascular Symptoms

There was no significant difference in cardiac arrhythmias, heart palpitations, or chest pain for women taking domperidone versus metoclopramide. However, women were almost seven times

Table 1.	Daily Dosage of Domperidone
(in mg)	

Total daily dosage	Number of women
0.00-19.99	63
20.00-39.99	322
40.00-59.99	131
60.00-79.99	112
80.00-99.99	396
100.00-119.99	8
120.00-139.99	84
140.00-159.99	6
160.00-179.99	42
180.00-199.99	1
260.00-279.99	2
300.00-319.99	1

Table 2. Length of Time on Domperidone				
Time on medication	Number of women	Percent (%)		
<1 week	15	1.2		
7–14 days	64	5.3		
15-30 days	104	8.7		
1-6 months	572	47.6		
6-12 months	301	25.0		
More than 1 year	146	12.1		

(1/0.148) more likely to report a racing heart with metoclopramide.

Central Nervous System Symptoms

CNS symptoms were significantly more likely when mothers took metoclopramide versus domperidone. Most concerning for metoclopramide, the risk of depression increased by seven times (1/0.149) for mothers taking this medication. In addition, insomnia was more than twice (1/0.426) as high with metoclopramide. Sedation was 11 times (1/0.90) higher, weakness was four times (1/0.24) higher, and fatigue was three times higher (1/0.326) for metoclopramide. Irritability was almost four times (1/0.267) more likely and dizziness was about twice (1/0.525) more likely.

A rare, but highly concerning symptom with metoclopramide is TD, or involuntary grimaces or tics. Since 1979, when metoclopramide was first marketed in the U.S., a significant number of cases of TD have been reported. In a summary of highly variable studies on metoclopramide-induced TD, in groups consuming more than 27 million prescriptions of metoclopramide, at least 1,206 possible cases of TD were reported. While not completely accurate, age at onset averaged around

Table 3. Daily Dosage of Metoclopramide (in mg)				
Total daily dosage	Number of women			
0.00-19.99	114			
20.00-39.99	313			
40.00-59.99	73			
60.00-79.99	10			
80.00-99.99	13			
100.00-119.99	1			

70 years of age, the average daily dose was approximately 31–33 mg/day and the estimated duration ranged from 4 to 37 months. Thus, the available data suggested that the risk of TD is probably less than 1% with the consumption of metoclopramide (Rao & Camilleri, 2010).

In the present study, TD was significantly more likely for mothers taking metoclopramide versus domperidone. Involuntary grimaces were four times (1/0.250)more likely, involuntary jerking was almost 19 times (1/0.053) more likely, and tremors were more than 12 times (1/0.08) more likely.

Gastrointestinal Symptoms

Not surprisingly, given its action in the GI tract, GI symptoms were significantly more common in women taking domperidone. Abdominal cramping was 1.82 times more likely, and constipation was 2.5 times more likely. However, there was no significant difference in diarrhea between the two groups.

General Symptoms

There were a few other side effects that were more likely when mothers took domperidone. Weight gain was

Table 4. Length of Time on Metoclo- pramide				
Time on medication	Number of women	Percent (%)		
<1 week	94	16.0		
7–14 days	184	31.4		
15-30 days	131	22.4		
1-6 months	137	23.4		
6-12 months	31	5.3		
More than 1 year	9	1.5		

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five times more likely, but only affected about 12% of patients. Engorgement was about 3.5 times more likely. Skin rash was 2.5 times more likely, and flushing was about a half as likely. Headache was 1.38 times higher. There were no significant differences in hot flashes or leg cramps.

Mothers who took domperidone were 3.6 times more likely to report no symptoms at all compared with those who took metoclopramide (Table 5).

Discussion

Around the world, healthcare providers prescribe domperidone and metoclopramide to women with low milk production. The overall percentage of mothers reporting side effects from both medications are low, but some types of symptoms raise concerns. Asztalos et al. (2017) reported serious side effects in 90 mothers talking 10 mg of domperidone three times per day. Electrocardiograms in this study showed no Q-Tc

Table 5 Symptoms Reported for Domperidone and Metoclopramide					
Symptom	Domperidone # (%) reporting symptom	Metaclopramide # (%) reporting symptom	Risk estimate	95% confidence interval	Þ
Cardiac symptoms					
Cardiac arrhythmias	11 (0.8%)	16 (0.9%)	.688	.320, 1.478]	.343
Heart palpitations	21 (1.2%)	28 (1.6%)	.750	[.427, 1.316]	.319
Racing heart	9 (0.4%)	61 (3.2%)	.148	[.073, .296]	.000
Chest pains	8 (0.4%)	5 (0.3%)	1.600	[.524, 4.882]	.423
Central nervous system syr	nptoms				
Depression	34 (1.8%)	228 (12.1%)	.149	[.105, .213]	.000
Involuntary grimaces	5 (0.2%)	20 (1.1%)	.250	[.094, .665]	.003
Dizziness	52 (2.8%)	99 (5%)	.525	[.378, .732]	.000
Tremors	2 (0.1%)	25 (1.2%)	.080	[.019, .337]	.000
Headache	188 (9.8%)	136 (7%)	1.382	1.119	1.708
Insomnia	23 (1.1%)	54 (2.9%)	.426	[.262, .691]	.000
Sedation	6 (0.3%)	67 (3.4%)	.090	[.039, .206]	.000
Weakness	12 (0.6%)	50 (2.8%)	.240	[.128, .449]	.000
Jerking	1 (0.1%)	19 (1.1%)	.053	[.007, .393]	.000
Gastrointestinal symptoms					
Constipation	45 (2.1%)	18 (0.9%)	2.5	[1.452, 4.303]	.001
Diarrhea	78 (4.1%)	60 (3.1%)	1.3	[.934, 1.810]	.120
Abdominal cramping	89 (4%)	49 (2.4%)	1.816	[1.289, 2.560]	.001
Dry mouth	96 (4.7%)	53 (2.7%)	1.811	[1.303, 2.518]	.000
General symptoms					
Flushing	11 (0.6%)	24 (1.3%)	.458	[.225, .933]	.028
Irritability	47 (2.2%)	176 (9.1%)	.267	[.195, .366]	.000
Hot flashes	20 (1%)	25 (1.4%)	.800	[.446, 1.436]	.459
Leg cramps	13 (0.6%)	8 (0.5%)	1.625	[.675, 3.912]	.285
Fatigue	62 (3.2%)	190 (9.7%)	.326	[.247, .432]	.000
Skin rash	25 (1%)	10 (0.5%)	2.500	[1.204, 5.191]	.016

(continued)

Table 5 Symptoms Reported for Domperidone and Metoclopramide (continued)					
Symptom	Domperidone # (%) reporting symptom	Metaclopramide # (%) reporting symptom	Risk estimate	95% confidence interval	Þ
Engorgement	201 (9.7%)	58 (3%)	3.466	[2.605, 4.610]	.000
Weight gain	224 (11.7%)	42 (2.2%)	5.333	[3.859, 7.372	.000
Mothers reporting no symptoms	542	148	3.662	[3.087, 4.344]	.000

abnormalities. In the U.S., the FDA banned the use of domperidone, citing its purported risk of cardiac arrhythmias, leaving only metoclopramide as an approved option. Cardiac arrhythmias are a rare side-effect for both medications, and there was no significant difference in self-reported symptoms for either medication. The only significant difference for cardiovascular symptoms was for racing heart, which was higher for metoclopramide.

More concerning are the CNS symptoms. Metoclopramide increased risk of depression by seven times. This is not a benign side-effect. This medication would be particularly contraindicated for mothers with a history of depression, or who were at high risk. The increased risk of TD and related symptoms with metoclopramide is also concerning. Although this is also a rare side-effect, the effect may be permanent and is of concern, especially when metoclopramide is presented as the "safer" alternative.

Domperidone increased GI symptoms. Given its action on the GI wall, this is not surprising. Mothers reported that it also increased weight gain, which is a side-effect most mothers would object to. However, only 12% of mother on domperidone reported weight gain. No mothers reported myocardial arrhythmias.

The data on dosage suggests that recommended dosage by healthcare providers varies substantially, and raises an important question for future studies: what dosage is necessary to increase milk production. And how long should mothers continue to take these medications? The FDA has at least one case study where a mother took 60 mg to 80 mg/day, and had some cardiac side effects. What is the safe range? A substantial percentage of mothers were on much higher doses, yet the overall percentage of reported side effects was quite low. The majority of the literature reporting use of domperidone to increase milk production, use 10–20 mg three times daily. In one study, there was a significant increase in milk production at both 10 mg TID dosing and 20 mg TID dosing (Wan et al., 2008). The 20 mg dosing provided only a minor increase in milk production.

The results of our study are preliminary. It is a self-report measure. We hope our findings encourage further research. The symptoms the mothers reported were not confirmed by medical examinations. However, we believe our findings provide some reassurance about domperidone, and raise some important concerns about metoclopramide. Although our findings regarding domperidone are reassuring, caution is advised if a mother taking any other medications that can increase the Q-Tc interval or that inhibits domperidone's metabolism, such as oral "azole" antifungals, macrolides, monoamine oxidase inhibitors, histamine H2-blockers, or any other medication that allows high levels to accumulate.

Summary

This study was a preliminary examination of selfreported side effects for mothers taking domperidone or metoclopramide to increase their milk production. Our sample included a large group of mothers who had taken domperidone, metoclopramide, or both. The largest percentage of mothers were on these medications for 1 to 6 months. There was no significant difference in cardiac arrhythmias between the two groups. But there was significantly more depression and other CNS symptoms in the metoclopramide group. Data from the present study indicate fewer side effects with domperidone than metoclopramide. These data suggest that U.S. regulatory bodies need to reconsider the safety of both metoclopramide and domperidone for mothers who need these medications to increase their milk production.

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