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Domperidone for insufficient lactation in England 2002-2015: a drug utilization study with interrupted time series analysis

Running head: Postpartum use of Domperidone

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Abstract

Purpose: Our aim was to describe trends in the prescription of domperidone for insufficient lactation in England, the characteristics of women prescribed it post-partum, and the impact of a 2014 European Medicines Agency recommendation (EMA) to restrict its use due to a potential increased risk of sudden cardiac death associated with its use.

Methods: We conducted a population-based cohort study with interrupted time series analysis using data from the Clinical Practice Research Datalink linked to Hospital Episode Statistics. We identified women with live births from 2002 to 2015, excluding those with non-lactation indications for domperidone (n=247,349). We evaluated trends in the prescription rate of domperidone in the 6 months postpartum and differences in this rate before and after the EMA recommendation.

Results: Domperidone was prescribed among 1,438 deliveries at a rate of 1.24 per 100 person-years. This rate increased from 0.56 to 2.1 per 100 person-years between 2002-04 and 2011-13 (rate ratio: 3.8; 95% CI 3.2-4.6). Prescribing decreased in level by 0.35 (95% CI -0.86, 0.16) per 100 person-years immediately following the recommendation with little change in trend (0.003, 95% CI -0.059, 0.065 per 100 person-years). Following the recommendation, prescription of doses >30mg and co-prescription of drugs with a risk of torsade de pointes decreased. No arrhythmic events were observed among domperidone users.

Conclusions: Although we observed an important increase in prescribing during the study period, domperidone remains infrequently prescribed postpartum in England. While overall prescribing changed little, some prescribing practices became more restricted following the EMA's recommendation.

Key Points

- There was a 3.8-fold increase in postpartum domperidone prescribing from 2002-04 to 2011-13 in England, from 0.56 to 2.1 per 100 person-years. Prescriptions were given earlier after delivery and at higher doses. However, overall post-partum prescribing remained in England.

- Following European Medicines Agency recommendations, postpartum prescribing of domperidone decreased in level, while the upward trend continued. There was a decrease in prescribing of doses >30mg and of co-prescribing of drugs with a torsade de pointes risk following the recommendation.

Introduction

Domperidone is a dopamine antagonist used for nausea, vomiting, and dyspepsia related to motility disorders.[1] Although not licensed for lactation induction in any country, domperidone is the only medication currently listed by the United Kingdom's National Institute for Health and Care Excellence (NICE) to address breastfeeding problems[2] and is increasingly being used internationally to induce lactation among women experiencing low milk supply.[3,4] However, a growing number of studies have implicated domperidone in cardiac deaths.[1,5-8] In addition, a recent Canadian study reported a potentially increased risk of ventricular arrhythmia associated with postpartum domperidone use (hazard ratio [HR] = 2.25, 95% confidence interval [CI] 0.84-6.01), with the increased risk driven by use among women with a history of ventricular arrhythmias.[9] To reduce cardiac risks, regulatory agencies in Canada and the European Union have advised that domperidone doses not exceed 30 mg per day, that domperidone not be used in conjunction with medications that intensify its cardiac effects, and to avoid use among patients with risk factors such as existing heart problems or severe hepatic impairment.[10,11]

The primary objective of this study was to describe the characteristics of women prescribed domperidone for insufficient lactation in England in terms of their demographic, obstetric, and medical profile, and to describe trends over time as well as the dosage, timing of prescriptions, and co-prescription of medications with arrhythmogenic properties. Our secondary objectives were to determine whether prescribing of domperidone for insufficient lactation decreased following a European Medicines Agency (EMA) recommendation to restrict its use and to describe cardiac outcomes and all-cause mortality among women prescribed domperidone postpartum.

Methods

Data source

We constructed a population-based cohort study using data from the Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES). The CPRD contains detailed clinical information on persons in the United Kingdom seen at over 700 general practitioner practices and includes routinely collected demographic, behavioural (e.g. smoking), and diagnostic information using the Read coding system as well as prescriptions written.[12] Approximately 75% of English CPRD patients are linkable to HES, which contains hospitalization records for National Health Service hospitals in England, including a maternity file with specific information about the birth. HES contains diagnoses recorded using the International Classification of Diseases tenth revision (ICD-10) coding system and procedures recorded using the OPCS Classification of Interventions and Procedures version 4. Both the CPRD and HES undergo ongoing quality checks and have been validated extensively.[13-17] We also linked to the Index of Multiple Deprivation to obtain deprivation scores (a proxy of socioeconomic status) and to the Office for National Statistics vital statistics data.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 16_178) and the research ethics board of the Jewish General Hospital (protocol number 16_255), Montreal, Canada.

Study population

Our cohort consisted of all women aged 15 to 45 years with a delivery between May 1, 2002 and March 31, 2015 who were linkable to HES and had a minimum of one year of observation time in the CPRD prior to delivery, in order to ensure accurate assessment of medical and obstetric history. Cohort entry was defined in HES by end of a delivery episode, and

in the CPRD by Read codes indicating a delivery. As our study was assessing domperidone use for insufficient lactation, we restricted inclusion to women with livebirths and excluded those with non-lactation indications for domperidone use. Non-lactation indications included a diagnosis of Parkinson's disease or use of antiparkinsonian agents,[18] a recorded diagnosis of gastroparesis**,** two or more pre-pregnancy proton pump inhibitor prescriptions in the year prior to conception (indicative of pre-existing gastrointestinal conditions, except where a woman was pregnant in the year prior to conception), or pre-pregnancy domperidone use other than use in the year following a previous birth. The study included repeat live births by the same woman. Cohort exit was defined by end of follow-up (six months after the delivery), death, onset of Parkinson's disease or gastroparesis, another birth, end of the study period, or end of registration at the CPRD practice, whichever occurred first.

Exposure assessment

Domperidone use was defined as having been prescribed domperidone orally in the six months following childbirth. Patients were stratified based on a first prescription dose of domperidone of ≤ 30 mg/day and >30 mg/day.[1,5,10,11] A small number of women received more than one prescription for domperidone at the time of their first prescription (i.e., on the same day); to provide conservative estimates, we assumed that they started on the lowest dose among prescriptions received. We further assessed the average dose and postpartum day of first prescription, and the average number of domperidone prescriptions given in the six months postpartum. Information on duration of prescription was not available.

EMA recommendations

On March 6, 2014, the EMA's Pharmacovigilance Risk Assessment Committee made recommendations restricting the use of domperidone that were then endorsed by a regulatory

body representing European Union member states.[10] These recommendations included restricting the indication of domperidone to relieving symptoms of nausea and vomiting as evidence was not deemed sufficient to support its use for other indications. They also recommended a maximum oral dose in adults of 10 mg up to three times a day, because of evidence of an increase in cardiac risk with oral doses more than 30 mg/day, and a maximum treatment duration of one week. In addition, they recommended avoiding domperidone use among persons with risk factors such as existing heart problems or severe hepatic impairment or those taking other medications that enhance domperidone's effects or reduce its breakdown. Table 1 describes the sequence of key restrictions and recommendations issued on domperidone in Europe, the U.K, and internationally.

Covariates

Maternal characteristics of interest were age, body mass index (BMI, <18.5 kg/m,^{2} 18.5-24.9 kg/m,^{2} 25-30 kg/m,^{2} ≥30 kg/m,^{2} and missing), smoking status, alcohol-related disorders, and socioeconomic status as measured by the Index of Multiple Deprivation. We further assessed obstetric characteristics such as parity, preterm birth (defined as <37 weeks of gestation), caesarean delivery, multifetal gestation (i.e., twin or higher order pregnancies), diabetes or gestational diabetes mellitus, and gestational or pre-existing hypertension. We assessed pre-existing (prior to childbirth) cerebrovascular and cardiac conditions such as circulatory disorders complicating pregnancy, cardiomyopathy, cerebrovascular disease, ventricular tachycardia/fibrillation, ischaemic heart disease, heart failure, pulmonary heart disease, valvular heart disease, history of pacemaker/defibrillator use, or use of anti-arrhythmic agents. We assessed whether women experienced renal impairment, asthma, schizophrenia, liver disease, proton pump inhibitor use, and cancer diagnosis prior to childbirth.

Co-prescribing of medications with arrhythmogenic properties was based on a list of medications that prolong the QT interval of the electrocardiogram maintained by the Arizona Centre for Education and Research on Therapeutics under a contract with the Federal Drug Administration (Appendix table 1).[19,20] Co-prescribing was defined as receiving a prescription of a potentially arrhythmogenic drug in the 30 days before or after receiving a domperidone prescription. We assessed cardiac outcomes based on recorded diagnoses in CPRD, HES, or Office for National Statistics data.

Statistical analysis

Standardized differences were used to compare patient characteristics among women prescribed and not prescribed domperidone in the six months following childbirth, with a standardized difference of 0.1 considered important.[21] Temporal trends in domperidone prescribing were assessed before and after the EMA recommendation. Analyses of trends in domperidone use in the six months postpartum were assessed in 3-year intervals. The grouped years 2011-13, referred to as pre-recommendation years, included January and February 2014 as they were the months prior to the EMA recommendation; the grouped years referred to as 2014-15 started March 2014 until the study end. Follow-up time was censored at the time of a woman's first domperidone prescription when estimating prescription rates per 100 person-years. For analyses of prescribing details (average dose at first prescription, average postpartum day at first prescription, and average number of domperidone prescriptions) and trends in co-prescribing, births that occurred in the final six months of the study period were excluded to allow adequate follow-up time. For analyses of cardiac outcomes, event-specific follow-up was censored at the time of event, and exposure was defined by ever-use in a time-dependent manner.

Calculation of the upper limit of the 95% CIs for outcomes with zero events incorporated the rate characteristics of the population.[22]

We used an interrupted time series analysis to estimate changes in domperidone prescribing after the EMA recommendations, assessing monthly changes in the trend and level of prescribing in the six months postpartum.[23] The interrupted time series used trends before the recommendation (May 2002 to March 2014) to predict the trends had the recommendations not occurred and controlled for baseline trends.[24] Generalized least-squares models that allowed for a first order autoregressive structure were used to account for correlation between consecutive months. Alternative models with variations in the autocorrelation structure (or no autocorrelation structure) were compared using likelihood ratio tests.

In sensitivity analyses, we modeled the interrupted time series assuming the effect would occur one year prior to the recommendation, when the notification of the domperidone safety assessment was published by the EMA. We further modeled the pre-recommendation period as starting March 2011 to account for a steeper increase prior to the recommendation. We further tested for seasonality in prescribing based on the hypothesis that insufficient lactation may be more common in the winter months. An additional sensitivity analysis restricted the cohort to first pregnancies to determine whether the analysis would be affected by women who had previously delivered. Analyses were performed using SAS version 9.4, the R statistical package, and OpenEpi (Version 3.01, www.OpenEpi.com).

Results

Patient characteristics

Our cohort included 247,349 livebirths (Figure 1), with 1,438 postpartum domperidone prescriptions in the six months postpartum among 116,247.7 person-years of follow up for an

overall prescription rate of 1.24 per 100 person-years. Compared to women who were not prescribed domperidone postpartum, women who were prescribed domperidone were less likely to be aged <25 years, to have BMI ≥30 kg/m^2 or a missing BMI, to have had a preterm births, multiple births, or to have had a caesarean section (Table 2). They were also more likely to have diabetes or gestational diabetes and to have used proton pump inhibitors prior to childbirth. Having a history of circulatory or cardiac disorders was very rare among women prescribed domperidone (<5 among women prescribed domperidone, exact number suppressed due to CPRD privacy policy), as was having a history of liver disease (0.35% of domperidone users).

Prescription rates and prescribing characteristics

The prescription of domperidone increased from 0.56 to 2.1 per 100 person-years between 2002-04 and 2011-13 prior to the EMA recommendation, representing a 3.8-fold increase (95% CI 3.2-4.6) (Table 3). First prescriptions were given earlier (average 31.6 days earlier, 95% CI 22.1-41.2) and at higher doses (average 20.1 mg higher, 95% CI 12.9-27.2) in 2011-3 vs. 2002-04, while the average number of domperidone prescription in the six months postpartum increased from 1.3 to 1.9 per 100 person-years (mean increase of 0.60, 95% CI 0.42-0.77). Domperidone use increased among women with cesarean, preterm, and multiple deliveries between 2002-04 and 2011-13. The proportion of preterm birth among women prescribed domperidone increased from 29.3% in 2002-04 to 36.5% in 2011-13, and 44.4% in 2014-15 following the EMA recommendation.

Impact of EMA recommendations

Following the EMA recommendations, postpartum prescribing of domperidone reduced in level (-0.35, 95% CI -0.86, 0.16, per 100 person-years), which represents a 15% decrease in level immediately following the recommendation, with little change in the trend (0.003, 95% CI

-0.059, 0.065 per 100 person-years) (Figure 2). The overall rate of domperidone prescriptions per 100 person-years was 2.1 in 2011-13 and 2.0 per 100 person-years in 2014-15 after the EMA recommendation (Table 3). Prior to the EMA recommendation, prescribing of domperidone increased similarly among women with preterm, cesarean, or multiple deliveries. There was a substantial drop in the rate of women whose first domperidone prescription was greater than 30 mg per day after the EMA recommendation as compared to the three years prior (rate ratio = 0.59, 95% CI 0.42, 0.80). Co-prescribing of drugs with known, conditional, or possible torsade de pointes risk increased from 0.12 to 0.34 per 100 person years between 2002-04 and 2011-13 and decreased substantially following the EMA recommendation (rate ratio = 0.42, 95% CI 0.22, 0.72).

Cardiac events

Among women prescribed domperidone in the six months postpartum, no ventricular arrhythmias, cardiac arrests, or sudden cardiac deaths were observed (Table 4). The rate of all cause death was 0.20 per 100 person-years (95% CI 0.03, 1.41) among women prescribed domperidone and 0.03 per 100 person-years (95% CI 0.03, 0.05) among women not prescribed domperidone.

Sensitivity analyses

Alternative models with variations in the autocorrelation structure (or no autocorrelation structure) led to similar estimates and interpretations. Sensitivity analyses found no decrease in prescribing following the notification one year prior to the recommendation (Appendix figure 1). Sensitivity analyses only modeling the three years prior to the recommendation (which assumes the sharp increase just prior to the recommendation would have continued) found that the recommendation would have had an even stronger decrease in level of prescribing (-0.66, 95%

CI -1.22, -0.09 per 100 person-years), with little change in trend (-0.003, 95% CI -0.07, 0.06 per 100 person-years; Appendix figure 2). Analyses restricting the cohort to each woman's first delivery resulted in a stronger decrease in prescribing (Appendix figure 3). No seasonal patterns in prescribing were observed.

Discussion

In this population-based cohort study, we found a 3.8-fold increase in postpartum domperidone prescribing from 2002-04 to 2011-13 in England, from 0.56 to 2.1 per 100 person-years. Prescriptions were given earlier following delivery and at higher doses, while co-prescribing with QT-prolonging medications and prescriptions of domperidone doses > 30 mg per day increased during this period. The most common indications that drove co-prescribing of QT-prolonging medications with domperidone were bacterial infections (e.g. metronidazole, erythromycin), depression (e.g. citalopram, sertraline, fluoxetine), fungal infections (e.g. fluconazole), and asthma (e.g. salmeterol).

Following the EMA recommendations to restrict domperidone use, there was a non-significant 0.34 per 100 person-years decrease (95% CI -0.86 to 0.16) in the monthly level of prescribing and no important change in trend. After the recommendation, some prescribing practices became more restricted, with a 41% reduction (95% CI 20% to 58%) in first prescription doses of >30 mg and a decrease in co-prescribing of drugs with a torsade de pointes risk (58% reduction, 95% CI 28% to 78%) between 2011-13 and 2014-15. These findings suggest that physicians may have responded to the recommendation by restricting some prescribing patterns of domperidone among postpartum women.

Exposure to domperidone postpartum was low throughout the study period in the United Kingdom, and we observed no cardiac morbidity among women exposed to domperidone postpartum and low use among women with cardiac risk factors. This finding is reassuring, given that in the previous Canadian study, the increased risk of ventricular arrhythmia among domperidone users postpartum was driven by use among women with a prior history of ventricular arrhythmia.[9] Similar to others, we found that domperidone use was associated with a high BMI, having a chronic condition (hypertensive disorder or diabetes in our study), and having had a preterm birth, multiple birth, or caesarean delivery.[3] Although all-cause death was higher among women prescribed domperidone, the confidence intervals overlapped, and the outcome was too rare to conclude that the crude risk was truly higher among domperidone users.

Although advisories and recommendations by regulatory agencies seldom affect prescribing, breastfeeding women are a special population where we would expect particular caution about prescribing. Our results are consistent with those of another study which reported rapid reductions in prescribing following regulatory advisories regarding postpartum codeine use.[25] Restricting to first deliveries resulted in an increase in the apparent effect of the recommendation, suggesting that physicians may be more likely to change prescribing practices for first time mothers. While the increasing trends of domperidone prescribing in our study were consistent with those found in Australia and Canada, [4,26] prescribing rates were substantially lower in England than in Canada. In Canada, between 2002 and 2011 rates of domperidone use in the six months postpartum increased from 8 to 19% for term births and 17 to 32% for preterm births.[3] The comparable rates in England (in the six months postpartum per live birth) were much lower, from approximately 0.28 to 1.05% among all deliveries and 1.2 to 5.2% among preterm deliveries between 2002-04 and 2011-13. It is unclear why postpartum domperidone use is

extremely high in Canada as compared with England. Canadian prescribing practices may have been influenced by Canadians leading clinical trials on domperidone use, and many Canadian expert leaders and organizations that have been proponents of domperidone use.[27-31] It is further unclear whether higher domperidone use in Canada has led to increased uptake and duration of breastfeeding, particularly among women with preterm infants, who can benefit most from breastmilk. Rates of ever breastfeeding were 89% in Canada in 2013 versus 83% in the United Kingdom in 2010, while any breastfeeding at 12 months was much higher in Canada than the United Kingdom (9% versus 0.5%).[32-34] The proportion of preterm births among women prescribed domperidone increased in the study, which supports the possibility that physicians may have been less likely to change practices for women with preterm infants, due to the advantages of breastmilk for these infants.

Our study also has several potential limitations. We only captured prescriptions written by general practitioners and thus may have some exposure misclassification. It is possible that some women may have obtained a domperidone prescription while in hospital or from a specialist, which could have resulted in the underestimation of use. Another limitation was that we had insufficient information to assess duration of use, which prevented the estimation of average dose of domperidone used over time. Consequently, the observed increase in the average number of prescriptions written per woman may merely reflect a trend towards shorter duration prescriptions. Although we cannot be certain that domperidone was used for insufficient lactation for all women, the postpartum timing of use and the exclusion of women with other indications for domperidone use make this assumption likely. The duration of follow-up time following the EMA recommendation was short (13 months), which may not have been enough time to detect the full effect of the recommendations. In addition, it is difficult to rule out

potential effects of other regulatory actions on prescribing practices. Finally, domperidone was available without a prescription in the United Kingdom prior to September 2014, and it is unclear to what extent we underestimated actual domperidone use. However, women have an incentive to seek domperidone by prescription as the medication is free with the maternity exemption. Regardless, the differences between Canada and England cannot be explained by over-the-counter use in England alone, particularly when over-the-counter domperidone was not available in the last six months of our study. Removal of the over-the-counter availability in September 2014 would have likely increased prescriptions written by general practitioners, making our estimates of the impact of the EMA recommendations conservative.

In conclusion, in this population-based study, we found an important increase in postpartum domperidone prescribing for insufficient lactation in England between 2002 and 2013, including an increase in dosage and an earlier initiation of the medication. While overall prescribing only decreased by 15% and the increasing trend remained unchanged, physicians appeared to have reacted to the 2014 EMA recommendation restricting co-prescribing and dosage >30 mg/day of domperidone.

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Dr. Adrian Root of the London School of Hygiene and Tropical Medicine contributed to drafting the study protocol, interpreting the results and revising the manuscript for important intellectual content but passed away before reviewing and approving the final copy of this manuscript, as required to meet the criteria for authorship. We are extremely grateful for all of his contributions to this work.

Conflicts of Interest

RWP reports personal consultant fees from Amgen, Abbvie, Eli Lilly, Pfizer, Novartis, and Searchlight Pharma and receives a salary as the Albert Boehringer chair in pharmacoepidemiology. No other authors have financial relationships with any organisations that might have an interest in the submitted and no other relationships or activities that could appear to have influenced the submitted work.

Contributions of Authors

AM conceived of the study, and AM, PR, RWP, and KBF developed the study design. PR and AM conducted the statistical analyses. AM wrote the first draft of the manuscript, and PR, RWP, and KBF made important contributions to the interpretation of the data and revised the article for important intellectual content. All authors read and approved the final manuscript. AM, RWP, and KBF are the guarantors of the study. See acknowledgements for contributions of Dr. Adrian Root, who passed away before reviewing the final version of the manuscript.

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Table 1. Sequence of regulatory actions issued on domperidone use.

Date	Regulatory action
January 31, 1985	The injectable form of domperidone was voluntarily withdrawn by manufacturer due to cardiotoxicity.[35]
June 4, 2004	U.S. Food and Drug Administration issued a warning for women not to use domperidone to increase milk production (domperidone is not approved in the U.S. for any indication), and an alert to prevent the importing of domperidone into the U.S. due to concerns that lactating women were purchasing the medication from other countries.[36]
March 6, 2014	European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommends that domperidone use be restricted to those with nausea and vomiting (no longer for heartburn or bloating or other indications).[35]
April 23, 2014	European Medicines Agency Coordinating Group for Mutual Recognition and Decentralized Procedures endorsed the recommendations restricting the use of domperidone.
May 30, 2014	Medicines and Healthcare Products Regulatory Agency advises restrictions on the use of domperidone, including recommending a maximum duration of treatment of one week.[37]
September 4, 2014	Medicines and Healthcare Products Regulatory issues a pharmacy-level recall so that domperidone only be supplied by prescription.[38]

Table 2. Characteristics of deliveries where women were prescribed domperidone postpartum and those who were not, England, 2002 to 2015.

Characteristics	Prescribed domperidone n=1,438	Not prescribed domperidone n=245,911	All pregnancy n=247,349	Standardized difference
Age				
<25 years	229 (15.9)	51,371 (20.9)	51,600 (20.9)	0.13
25-29 years	345 (24.0)	61,694 (25.1)	62,039 (25.1)	0.03
30-34 years	485 (33.7)	76,710 (31.2)	77,195 (31.2)	0.05
35-39 years	290 (20.2)	45,881 (18.7)	46,171 (18.7)	0.04
≥40 years	89 (6.2)	10,255 (4.2)	10,344 (4.2)	0.09
BMI (in)				
<18.5 kg/m^2	50 (3.5)	9,469 (3.9)	9,519 (3.9)	0.02
18.5-24.9 kg/m^2	642 (44.7)	115,175 (46.8)	115,817 (46.8)	0.04
25-30 kg/m^2	307 (21.4)	50,384 (20.5)	50,691 (20.5)	0.02
≥30 kg/m^2	273 (19.0)	32,552 (13.2)	32,825 (13.3)	0.16
Missing	166 (11.5)	38,331 (15.6)	38,497 (15.6)	0.12
Smoker Yes				
Yes	810 (56.3)	139,092 (56.6)	139,902 (56.6)	0.00
Missing	22 (1.53)	8,675 (3.5)	8,697 (3.5)	0.13
Alcohol-related disorders	110 (7.7)	15,891 (6.5)	16,001 (6.5)	0.05
Index of Multiple Deprivation Decile	138 (9.6)	28,454 (11.6)	28,592 (11.6)	0.06
1 (least deprived)				
2-3	312 (21.7)	53,991 (22.0)	54,303 (22.0)	0.01
4-5	261 (18.2)	46,787 (19.0)	47,048 (19.0)	0.02
6-8	448 (31.2)	71,880 (29.2)	72,328 (29.2)	0.04
9-10 (most deprived)	273 (19.0)	44,051 (17.9)	44,324 (17.9)	0.03
Missing	6 (0.42)	748 (0.30)	754 (0.30)	0.02
Parity ≥1	525 (36.5)	95,474 (38.8)	95,999 (38.8)	0.05
Preterm	542 (37.7)	17,743 (7.2)	18,285 (7.4)	0.78
Caesarean delivery	535 (37.2)	56,709 (23.1)	57,244 (23.1)	0.31
Multifetal gestation	105 (7.3)	4,161 (1.69)	4,266 (1.72)	0.27
Diabetes or gestational diabetes	129 (9.0)	9,953 (4.1)	10,082 (4.1)	0.20
Gestational or pre-existing hypertension	203 (14.1)	22,243 (9.1)	22,446 (9.1)	0.16
Circulatory disorders complicating pregnancy	-*	543 (0.22)	-*	0.02
Cardiomyopathy	-*	43 (0.02)	-*	0.02
Cerebrovascular disease	-*	364 (0.15)	-*	0.03
Ventricular tachycardia/fibrillation	-*	75 (0.03)	-*	0.02
Heart failure	-*	49 (0.02)	-*	0.02
Ischaemic heart disease	-*	1,467 (0.60)	-*	0.05
Pulmonary heart disease	-*	243 (0.10)	-*	0.01

Valvular heart disease	-*	313 (0.13)	-*	0.00
Pacemaker/defibrillator	-*	49 (0.02)	-*	0.02
Antiarrhythmic agent	-*	167 (0.07)	-*	0.04
Renal impairment	-*	776 (0.32)	-*	0.01
Asthma	305 (21.2)	44,252 (18.0)	44,557 (18.0)	0.08
Schizophrenia	-*	151 (0.06)	-*	0.00
Liver disease	5 (0.35)	664 (0.27)	669 (0.27)	0.01
PPI use (prior to index birth)	217 (15.1)	18,690 (7.6)	18,907 (7.6)	0.24
Cancer	26 (1.81)	2,707 (1.10)	2,733 (1.10)	0.06

Data are presented as n (proportion). BMI refers to body mass index; PPI refers to proton pump inhibitor.
*Numbers <5 are suppressed, as per the confidentiality policies of the Clinical Practice Research Datalink.

Table 3. Trends in domperidone prescribing in England, before (2002-2013) and after (2014-15) an EMA recommendation restricting its use

	Rate per 100 postpartum person-years				Rate ratio	Rate and rate ratio after EMA recommendation	
Received domperidone Rx (in 6 months postpartum)	*2002-04*	*2005-07*	*2008-10*	2011-13*	2011-13* vs 2002-04	2014-15†	2014-15† vs 2011-13*
Any Rx / total deliveries	143/52,538	246/60,538	374/62,410	567/57,169	-	108/14,694	-
Overall	0.56	0.84	1.26	2.1	3.80 (3.17, 4.58)	2.0	0.96 (0.78, 1.17)
First prescription dose >30mg‡	0.23	0.42	0.73	1.41	6.21 (4.74, 8.25)	0.83‡	0.59 (0.42, 0.80)
Among caesarean deliveries	0.76	1.29	2.1	3.5	4.57 (3.04, 5.89)	3.2	0.93 (0.66, 1.28)
Among preterm deliveries	2.4	4.7	6.6	10.4	4.29 (3.10, 6.04)	11.6	1.11 (0.81, 1.51)
Among multiple deliveries	1.75	3.6	5.7	9.2	5.26 (2.53, 12.1)	15.3	1.66 (0.85, 3.09)
Prescribing details‡					Mean difference 2011-13 vs 2002-04	2014†	Mean difference 2014 vs 2011-13
Average dose at 1st prescription in mg/day (SD)	48.1 (37.4)	57.6 (46.8)	63.5 (44.7)	68.2 (44.0)	20 (12.9, 27.3)	60.9 (33.8)	-7.3 (-0.15.9, 1.3)
Average postpartum day at 1st prescription (SD)	73.3 (54.2)	62.6 (54.4)	51.4 (47.9)	41.6 (40.6)	-31.6 (-41.2, -22.1)	50.7 (47.6)	9.1 (-2.41, 20.6)
Average number of domperidone prescriptions (SD)	1.3 (0.9)	1.6 (1.4)	1.6 (1.3)	1.9 (1.4)	0.60 (0.42, 0.77)	1.7 (1.3)	-0.2 (-0.52, 0.12)
Trends in co-prescribing‡					Rate ratio 2011-13 vs 2002-04	2014†	Rate ratio 2014 vs 2011-13
Drugs with known TdP risk	0.04	0.05	0.07	0.10	2.71 (1.65, 4.60)	0.05	0.46 (0.14, 1.15)
Drugs with conditional or possible TdP risk	0.10	0.12	0.18	0.28	2.76 (2.03, 3.79)	0.13	0.46 (0.24, 0.83)
Any risk category	0.12	0.14	0.21	0.34	2.92 (2.20, 3.92)	0.14	0.42 (0.22, 0.72)

Top TdP risk drugs co-prescribed (frequency over 2002-2014): metronidazole (67), citalopram (52), sertraline (49), fluoxetine (44), fluconazole (31), erythromycin (30), salmeterol (25), metoclopramide (24), amitriptyline (19), loperamide (19), escitalopram (13), paroxetine (13), clarithromycin (12), ciprofloxacin (10), formoterol (9)

TdP denotes torsade de pointes, an abnormal heart rhythm that can lead to sudden cardiac death; EMA denotes European Medicines Agency; Rx denotes prescription; SD denotes standard deviation.

*Includes January and February 2014 (months before the recommendation).

†Starts March 2014 and ends March 2015 (or ends September 2014 when analyses exclude final six months).

‡Analyses exclude births that occurred in the final six months of the study period to allow adequate follow-up time.

Table 4. Cardiac events among women prescribed domperidone postpartum and those who were not, 2002 to 2015, England.

Outcome	Domperidone Rate per 100 person-years (95% confidence interval)	No domperidone Rate per 100 person-years (95% confidence interval)
Ventricular arrhythmia	0.0 (0.000-0.002)	0.007 (0.003-0.014)
Cardiac arrest	0.0 (0.000-0.002)	0.008 (0.004-0.015)
Sudden cardiac death	0.0 (0.000-0.002)	0.003 (0.001-0.009)
All cause death	0.20 (0.03-1.41)	0.03 (0.03-0.05)
Any outcome	0.20 (0.03-1.41)	0.04 (0.03-0.06)

Figure Legends

Figure 1. Construction of study cohort from deliveries in Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES).

Figure 2. Domperidone prescriptions per 100 person-years following an EMA recommendation to restrict domperidone use (dashed line). Following the recommendation, there was a non-significant decrease in level (-0.34, 95% CI -0.86, 0.16 per 100 person-years) and no important change in trend (0.003, 95% CI -0.05, 0.07).

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Figure 1

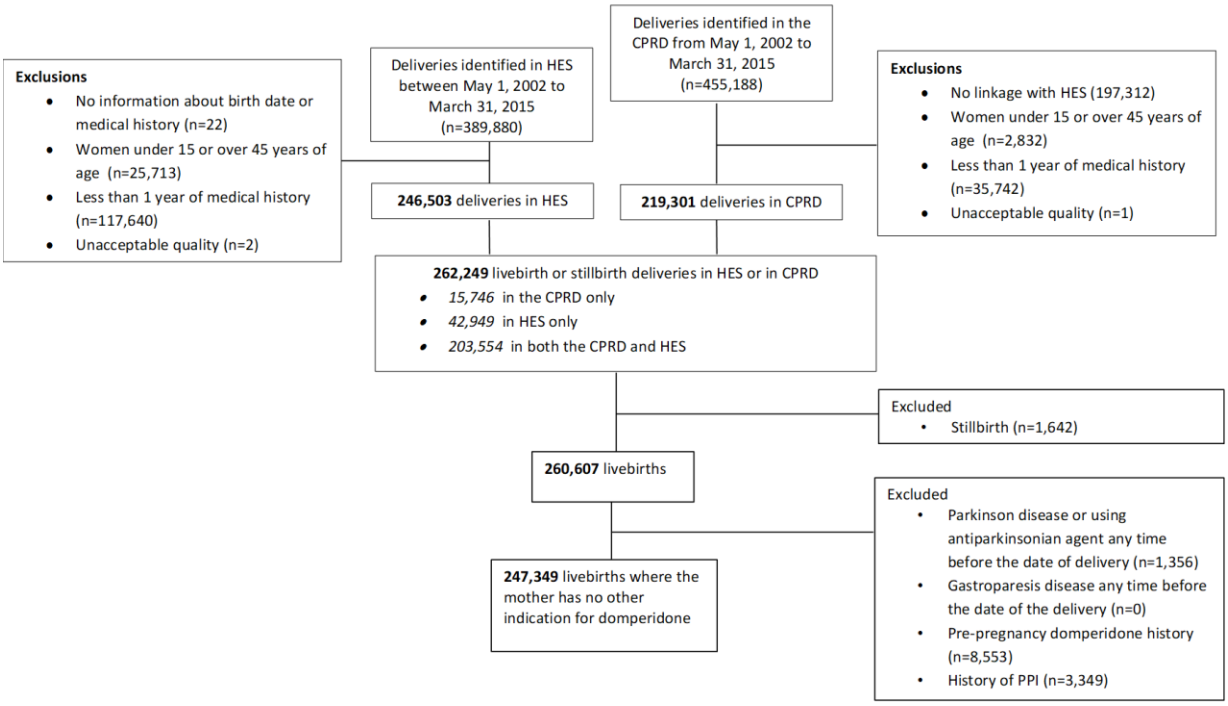

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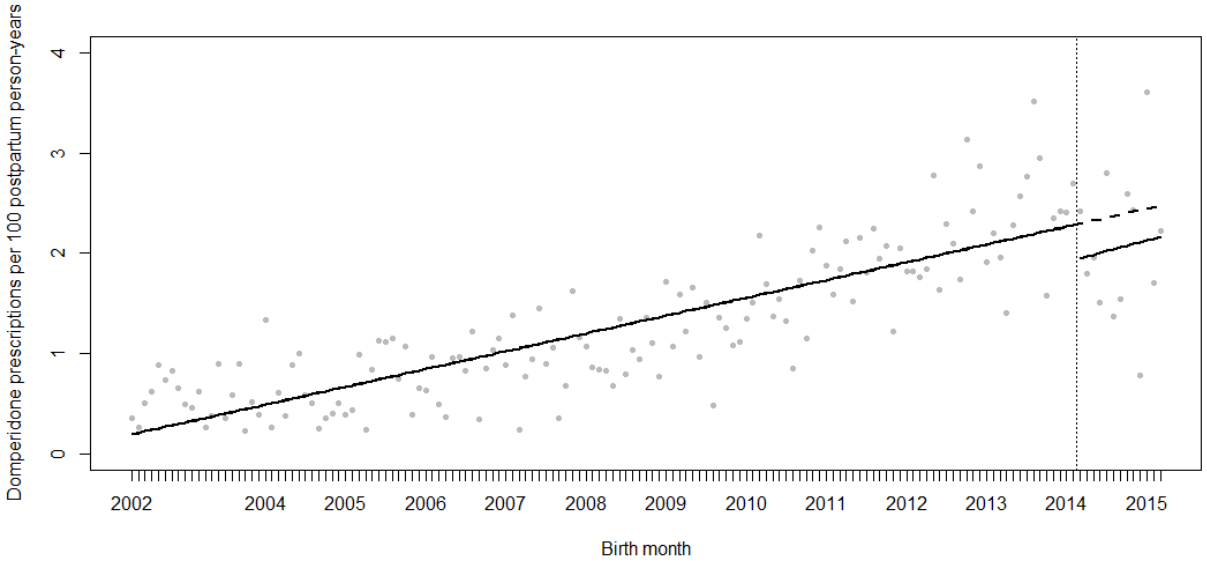
Figure 2



Appendix

Supplementary Table 1. Classification of medications with arrhythmogenic properties

Risk category	Description
1) Drugs with known risk of torsade de pointes	Drugs with substantial evidence supporting that they can cause potentially fatal ventricular arrhythmias in some people.
2) Drugs with conditional or possible risk of torsade de pointes	Drugs that can prolong the QT interval on the electrocardiogram but lack substantial evidence that they cause torsade de pointes, or that the drugs carry a risk of torsade de pointes or QT prolongation only in situations of overdose, drug interaction, or among patients with congenital long QT syndrome.
3) Any risk category	Either risk category 1 or 2

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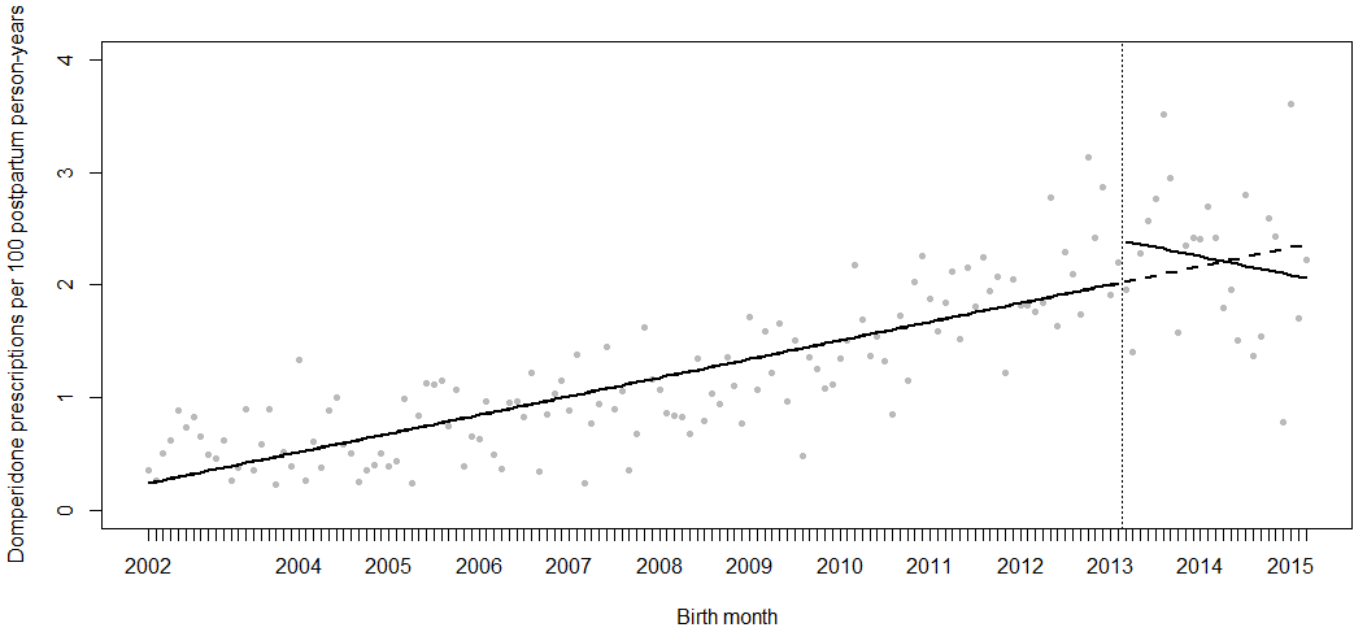
Supplementary figure 1. Domperidone prescriptions per 100 person-years assuming European Medicines Agency (EMA) notification had effect 1 year prior to EMA recommendation. Increase in level: 0.38, 95% CI 0.01, 0.75 per 100 person-years and small decrease in trend: -0.02, 95% CI -0.05, -0.004. Dashed line represents when EMA released their notification of the domperidone investigation.



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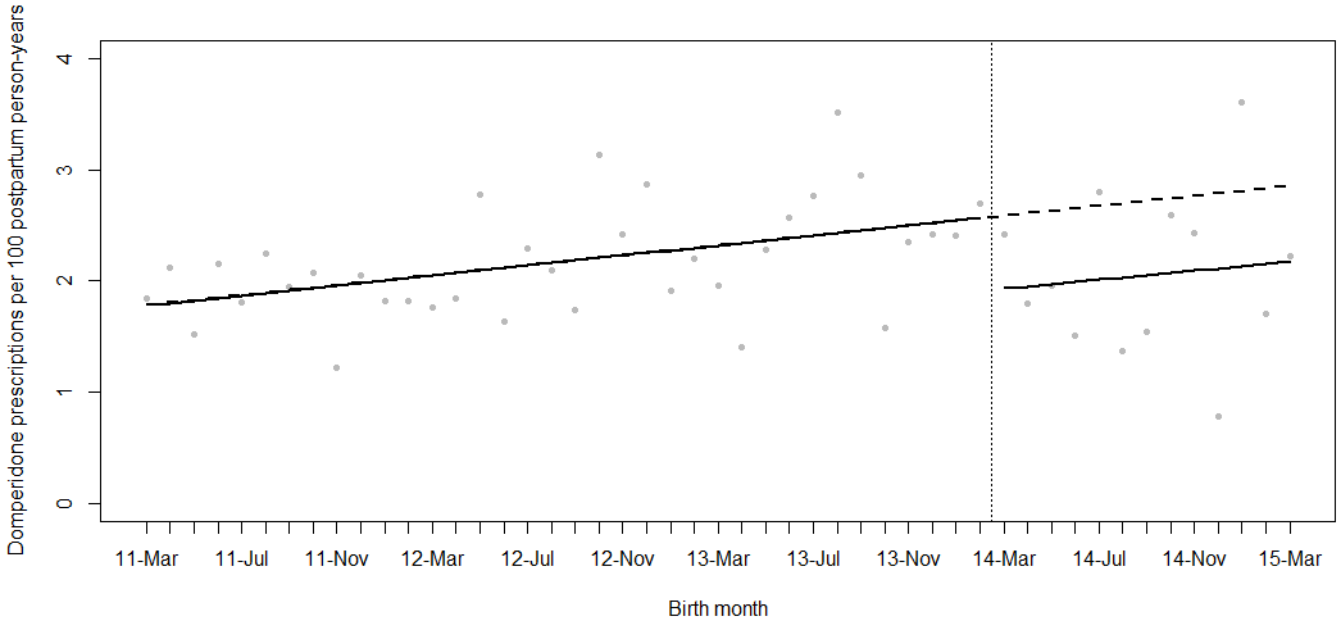
Supplementary figure 2. Domperidone prescriptions per 100 person-years only modeling 3 years prior to European Medicines Agency (EMA) recommendation. A decrease in level was found: -0.66, 95% CI -1.22, -0.09 per 100 person-years, with little change in trend: -0.003, 95% CI -0.07, 0.06. Dashed line represents time that the EMA recommendation was released.



Supplementary figure 3. Domperidone prescriptions per 100 person-years restricted to 1st deliveries in the database. A decrease in level -0.68, 95% CI -1.32, -0.05 per 100 person-years, and a small increase in trend 0.03, 95% CI -0.04, 0.11 Dashed line represents time that the EMA recommendation was released.