Article details: 2020-0084	
Title	**Off-label use of Domperidone among postpartum women: a multi-database study**
Authors	Carolina Moriello MSc, J. Michael Paterson MSc, Pauline Reynier MSc, Matthew Dahl BSc; Wusiman Aibibula MD, PhD, Anat Fisher, MD, PhD, John-Michael Gamble, BSc (Pharm) PhD, I fan Kuo PharmD, MSc, Paul E. Ronksley, PhD; Brandace Winquist PhD, Kristian B. Filion PhD for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators
Reviewer 1	Trine Munk-Olsen
Institution	Aarhus University
Reviewer comments	This is a multi-database cohort study on use of domperidone use in postpartum women using Canadian register data from 5 provinces. The authors measured domperidone use in the six months postpartum and assessed the impact of two changes in advisories on prescribing practices. This was done via interrupted time series analysis. Further, the authors also estimated crude VT/SCD rates. I found the manuscript well-written, although as a non-Canadian I missed more explanation about the provinces and what differences there might be between them. Further thoughts/comments (some reflecting minor comments and some major comments): Page 4 (in PDF): How does your study stand out compared to the study mentioned (lines 44-51)? For the available data, I struggled to understand details about what data is available, for which period it is available etc. How detailed is information on dose? Number of prescriptions? Duration of treatment? Also, I missed a clear overview of any differences across provinces. A woman can be in the study twice if she has two births during the study period? How is this handled in the analyses? For the study design, I completely miss to understand when women are at risk of VT/SCD? The study period for domperidone is 0-6 months. But when are VT's measured? I miss knowing if the risk of e.g. VT is observed right after taking the drug or months/years after the drug was taken. How detailed is the information on e.g. comorbidities? The word safety analyses is used. Does this relate to analyses on risk of VT and SCD? Exposure status: does 1 prescription with domperidone = exposed regardless of dose/duration? Duration of first prescription is used as indicator for treatment, but how are second prescriptions handled. I understand that a 7-day grace period is applied, but again,

	more detailed information would be useful. Maybe a figure to illustrate different scenarios? Page 12 (in PDF file): “A total of 137.401 observations were exposed…” I don't understand this sentence. Domperidone users have higher prevalence of medication use and comorbidities. Is this not considered in the crude analyses of risk of VT/SCD? For me crude = unadjusted. Is this also the case here? If so, I am very uncomfortable with the presented results, as they are most likely confounded by e.g. differences in comorbidities. I will find it unethical to present results on such an important outcome as death, if the analyses are not sufficiently done and confounders are not sufficiently considered. Limitations: The authors have stated limitations, which I always appreciate. They emphasize (1) that prescription drug claims data do not hold information on indication and that (2) assessment of VT/SCD is challenged. I appreciate very much the honesty of presenting these limitations, but the two limitation are crucial to any interpretation of the study and its results. If no indication is available, I don’t find it appropriate to study off-label use and particularly focus on indication for breastfeeding, when this information is not available. I realize the authors have attempted to exclude users of the drug based on previous diagnoses, but this does not convince me that misclassification isn't present. Also, if VT/SCD is misclassified/registration is challenged (whatever that means), I find it almost unethical to present any estimates for risk of VT/SCD (especially considering that they are unadjusted for important confounders if I understand the analyses correctly). I would need to see some very strong arguments from the authors to convince me of the usefulness of the presented results considering these limitations. I am sorry about being so critical and I acknowledge the hard work the authors have put into this manuscript.
Reviewer 2	Surasak Jantarasaengaram
Institution	Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand, Department of Obstetrics and Gynecology
Reviewer comments	This study has very good rationale. It is interesting to know 1) How many postpartum women use Domperidone as galactogogue in a population? and 2) Does postpartum Domperidone usage increase serious cardiac risks such as ventricular arrhythmia (VT) and sudden cardiac death (SCD) in population level? Major comment: Methods 1. As for international readers who are not recognize the included health system databases and health system in Canada, it would be nice if the authors can give a brief explicit about those databases (Do the databases cover every single individual or include only a number of individual who are members of the relevant medicate systems?, How many percentage of the population that all 5 databases included?, etc.) 2. Do they have any different data registration/recording/coding among the included databases and how the authors deal with the differences? 3. As VT/SCD is one of the main outcomes measured. How to document the events should be clearly elaborated in the Methods not in the Supplement

	materials section. The authors seem to give suboptimal information involving the validation of VT/SCD events. Results 1. Too many information in the results text has referred to supplemental tables and figures. The relevant results that need to be described should be shown in appropriately designed main texts, tables or figures instead of the supplemental materials. 2. Regard to cardiac events (VT and SCD), gross numbers of the events should be described in the main articles. The presented results failed to clearly show how many affected cases in Domperidone usage group and how many cases in non-usage group. Does the data shown in Table 2 indicate that there was no SCD event in Domperidone usage group? 3. Supplemental Table 6 indicates that there was only 13 VT and 10 SCD cases (among total postpartum women?). The low number of affected cases enables describing detailed characteristics of each case (age, underlying cardiac disease or other systemic disease, history of arrhythmia, dosage/duration of Domperidone usage). This information is very interesting and may convey substantial clinical application. 4. In addition, the VT/SCD incidence variations among geography (provinces) and among health databases should be studied and compared. So, any confounding factors (if any) may be revealed. Interpretation 1. The prevalence of off-labeled postpartum Domperidone usage in this study should be compared with more other studies/reports (The authors mentioned only 1 study). 2. The presented trends of Domperidone usage should be compared with similar studies/reports in different countries/populations. 3. The presented VT, SCD incidences among Domperidone users should be compared with other studies/reports in both postpartum population and non-postpartum population (GI or Neurologic disease indicated). 4. The statistical non-significant odds of the cardiac events should be more noticeably addressed. 5. In Table 1 Co-morbidities row: 3%, 1.4%, 0.2% and 0.1%, of postpartum women who use Domperidone (a total of 4.7%) had previous history of arrhythmias or conductive disorders, ischemic heart disease, heart failure and cardiomyopathy, respectively. The data is striking. It would be nice if the authors can make further data analysis and discussion concerning 1) cardiac events incidence in this subgroup and 2) why Domperidone prescribing in such high risk groups happened. 6. Low mortality in postpartum Domperidone usage group may be from prescription bias that postpartum women who suffered severe underlying or concomitant diseases would have been barred from Doperidone and they were more susceptible for mortality. Minor comment: 1. The title may add -in Canada-. Off-label use of Domperidone among postpartum women in Canada: a multi-database study 2. All Tables and Figures may need revision to show relevant information in a more concise, precise and informative format. 3. Some of information in the supplemental materials may not necessary. The information can be provided to interested readers upon request.
Author's response	Major comment:

	Methods 1. As for international readers who are not recognize the included health system databases and health system in Canada, it would be nice if the authors can give a brief explicit about those databases (Do the databases cover every single individual or include only a number of individual who are members of the relevant medicate systems?, How many percentage of the population that all 5 databases included?, etc.) **Please refer to our response to comment #5 from the editors. We have also referenced the 2012 paper by Suissa and colleagues, which describes CNODES and its data sources. In addition, we now specify that "Canada has a socialized healthcare system that is administered provincially, with government drug insurance plans varying by province" for the international reader. We also have added an additional supplemental table that describes the included databases in greater detail.** 2. Do they have any different data registration/recording/coding among the included databases and how the authors deal with the differences? **Please refer to our response to the previous comment. Although some differences exist, we have used a common protocol to ensure a consistent approach across provinces. In addition, meta-analyses were conducted using random-effects models to account for heterogeneity across provinces. In response to this comment, we now explicitly state that a common protocol was used on page 6 of the revised manuscript. Differences in data availability are also acknowledged as a potential study limitation.** 3. As VT/SCD is one of the main outcomes measured. How to document the events should be clearly elaborated in the Methods not in the Supplement materials section. The authors seem to give suboptimal information involving the validation of VT/SCD events. **We agree that it is important to provide key information regarding the definition of how the main outcomes were measured. For this reason, in response to this comment, we have expanded our discussion of how VT/SCD was measured. On pages 9, we now state:** **Briefly, women with a first recorded VT or SCD were identified as possible events. The administrative data of these women were then manually reviewed by blinded reviewers to confirm that the events met the definition of VT or SCD.** **We would be happy to provide additional details in the manuscript regarding our approach if the editors would like us to do so. Additional material is available in the supplemental material for the interested reader.** Results 4. Too many information in the results text has referred to supplemental tables and figures. The relevant results that need to be described should be shown in appropriately designed main texts, tables or figures instead of the supplemental materials. **We appreciate the importance of including the main text, tables, and figures in the main body of the manuscript rather than the supplemental material and have done our best to do so. Unfortunately, given the journal's**

	maximum number of tables and figures that can be included in the main body of the manuscript, it is not feasible to include all results in the main body. This is particularly challenging for multi-jurisdictional research such as the present study, where it is important to balance the reporting of the overall, pooled results with the results of the contributing provinces. We are happy to discuss further with the editors regarding transferring any of the supplemental material to the main text. 5. Regard to cardiac events (VT and SCD), gross numbers of the events should be described in the main articles. The presented results failed to clearly show how many affected cases in Domperidone usage group and how many cases in non-usage group. Does the data shown in Table 2 indicate that there was no SCD event in Domperidone usage group? **We thank the reviewer for the opportunity to clarify this issue. We agree that it would be ideal to report the number of events by treatment group. However, we are unable to do so because of the small number of events included in this study. To protect patient privacy, data custodial requirements prevent the reporting of any cell with a count less than 6. In response to this comment, we have added a footnote to Table 2 to explain why event totals are not reported. This footnote reads:** **Event totals by treatment group are not reported due to the presence of small cells (counts <6).** **In addition, we now mention the total number of events (across treatment groups) on page 11 of the revised manuscript:** **Events were rare (22 composite events, 13 VTs, 10 SCDs, 168 all-cause deaths), with rates ranging from 0.18 (95% CI: 0.09, 0.33) per 10,000 person-years for SCD to 2.95 (95% CI: 2.54, 3.44) per 10,000 person-years for all-cause mortality.** **The reviewer is correct that there were no SCD events in the domperidone group.** 6. Supplemental Table 6 indicates that there was only 13 VT and 10 SCD cases (among total postpartum women?). The low number of affected cases enables describing detailed characteristics of each case (age, underlying cardiac disease or other systemic disease, history of arrhythmia, dosage/duration of Domperidone usage). This information is very interesting and may convey substantial clinical application. **We agree that it would be very interesting to describe the detailed characteristics of each case. Unfortunately, do the privacy restrictions imposed by data custodians described above, we are not permitted to do so.** 7. In addition, the VT/SCD incidence variations among geography (provinces) and among health databases should be studied and compared. So, any confounding factors (if any) may be revealed. **We agree that variation in the incidence rate of VT/SCD across provinces could be interesting. However, we did not estimate province-specific rates given the sparse data. Given the very limited number of events identified in**

	each province and the corresponding wide 95% confidence intervals that would accompany province-specific rates, it is not feasible to compare rates across provinces in a meaningful manner. In addition, it is important to emphasize that all rates presented in this study are crude as there were too few events to construct regression models. Consequently, it is not feasible to assess potential confounding factors. Interpretation 8. The prevalence of off-labeled postpartum Domperidone usage in this study should be compared with more other studies/reports (The authors mentioned only 1 study). **Please refer to our response to comment #14 from the editors.** 9. The presented trends of Domperidone usage should be compared with similar studies/reports in different countries/populations. **We agree that it may be of interest to the reader for the presented trends in domperidone use to be compared with those reported by similar studies. For this reason, we have increased our discussion of previous utilization studies among postpartum women (please refer to our responses to comment #14 from the editors). We have focused our comparisons within this population as we believe that this represents the most relevant literature to the current study. Unfortunately, due to space constraints, we have been unable to add comparisons between our trends and those reported in other populations, although we would be happy to do so if the editors believed that the inclusion of this information was important and were open to a longer word count.** 10. The presented VT, SCD incidences among Domperidone users should be compared with other studies/reports in both postpartum population and non-postpartum population (GI or Neurologic disease indicated). **We thank the reviewer for the opportunity to clarify this important point. We agree that it would be helpful to compare the incidence rates from the present study with those previous reported in the literature. For this reason, we have expanded our discussion of the study by Smolina and colleagues and now contrast our crude event rates with those reported by Mehrabadi and colleagues using data from the United Kingdom. This section now reads:** **Smolina and colleagues found that domperidone may increase the risk of ventricular arrhythmias or cardiac arrest (HR: 2.25, 95% CI: 0.84, 6.01) using British Columbia data (11). Our utilization analyses described similar trends but included four additional provinces and up to six years of more contemporary data. Although we identified fewer events, it is likely the result of differences in event definitions, with Smolina also including atrial arrhythmia codes and the present study restricting events to those considered sudden and unexpected, and exposure grace periods. Despite these differences, the estimates reported by Smolina and colleagues are compatible with our estimates (crude HR: 2.01, 95% CI: 0.47, 8.60). The rates of VT and SCD among domperidone users reported in the present study are higher than those reported by Mehrabadi and colleagues (22), who reported**

	no exposed ventricular arrhythmias, cardiac arrests, or SCDs. Importantly, although our analysis suggests that domperidone may increase VT/SCD risk, estimates are crude and imprecise. While this analysis suggests a potential doubling of the risk, the absolute risk in this population remains very small. Our analyses also suggest a potential decreased risk of all-cause mortality, but this observation may be explained by confounding. Ultimately, given the unadjusted nature of these analyses, they should be interpreted very cautiously. **We have not compared our rates with those reported in other populations due to space constraints. Given the age of our study population and its lower comorbidity burden relative to other studies of domperidone use (typically conducted in older adults), the rates observed in the present study are expected to be substantially lower than those reported in these previous studies. In addition, given the sparse data and corresponding wide 95% confidence intervals, such comparisons may be difficult to interpret.** 11. The statistical non-significant odds of the cardiac events should be more noticeably addressed. **We agree that the safety analysis needs to be interpret with great caution. Estimates are crude and thus likely confounded. In addition, they are accompanied by wide 95% confidence intervals that include both the null and clinically important increased risks. Thus, while the available evidence suggests a potential increased risk, this safety analysis is inconclusive. We have alerted the reader this issue in several places.** **Page 11-12:** **Crude incidence rates for our composite endpoint of VT/SCD were numerically higher with current use of domperidone than with no current use (crude rate ratio: 2.01, 95% CI: 0.47, 8.60; crude rate difference: 0.37, 95% CI: -0.67, 1.41 per 10,000 person-years).** **Page 14:** **Importantly, although our analysis suggests that domperidone may increase VT/SCD risk, estimates are crude and imprecise. While this analysis suggests a potential doubling of the risk, the absolute risk in this population remains very small. Our analyses also suggest a potential decreased risk of all-cause mortality, but this observation may be explained by confounding. Ultimately, given the unadjusted nature of these analyses, they should be interpreted very cautiously.** **Page 14:** **The limited number of events did not allow for formal safety analyses.** **Page 16:** **Our safety analysis revealed a crude VT/SCD rate that was relatively higher among domperidone users than non-users. However, due to sparse data and the lack of statistical adjustment, these results should be interpreted with caution. Nonetheless, the absolute VT/SCD rate is very low in this population, suggesting that any potential increased risk in VT/SCD is likely**

	minimal at the population level. 12. In Table 1 Co-morbidities row: 3%, 1.4%, 0.2% and 0.1%, of postpartum women who use Domperidone (a total of 4.7%) had previous history of arrhythmias or conductive disorders, ischemic heart disease, heart failure and cardiomyopathy, respectively. The data is striking. It would be nice if the authors can make further data analysis and discussion concerning 1) cardiac events incidence in this subgroup and 2) why Domperidone prescribing in such high risk groups happened. **We agree that it would be interesting to conduct subgroup analyses in this higher-risk group. Unfortunately, given the sparse data and very small number of events overall, it is not feasible to conduct safety analyses in this subgroup. Furthermore, the administrative databases used in the present study do not include indication for use or provide information regarding the rationale for prescribing a specific medication to specific patients. Consequently, we are unable to determine why domperidone was prescribed in these higher risk patients.** 13. Low mortality in postpartum Domperidone usage group may be from prescription bias that postpartum women who suffered severe underlying or concomitant diseases would have been barred from domperidone and they were more susceptible for mortality. **We agree that the safety analyses are likely confounded by indication, contraindication, and/or by other variables. This confounding is the most likely explanation for the suggested protective association between domperidone use and all-cause mortality. On page 14, we alert the reader to this possibility:** **Our analyses also suggest a potential decreased risk of all-cause mortality, but this observation may be explained by confounding. Ultimately, given the unadjusted nature of these analyses, they should be interpreted very cautiously.** 14. Minor comment: 15. The title may add -in Canada-. Off-label use of Domperidone among postpartum women in Canada: a multi-database study. **We thank the reviewer for this suggestion. We have revised the title, which now reads:** **Off-label Use of Domperidone Among Postpartum Women in Canada: A Multi-database Cohort Study** 16. All Tables and Figures may need revision to show relevant information in a more concise, precise and informative format. **We agree that it is important for tables and figures to show relevant information in a concise, precise, and informative format. Unfortunately, we are unsure of what specific changes the reviewer would like to the tables and figures. We would be happy to revise our tables and figures if the reviewer or editors have any suggestions.** 17. Some of information in the supplemental materials may not necessary. The information can be provided to interested readers upon request.

	We agree that our supplemental material contains a fair bit of information. Given the multi-jurisdictional nature of this study, results are generated at the level of the individual provinces and across the network. In addition, this study includes a descriptive component, interrupted time-series analyses, and an assessment of safety. We have included the information provided in the supplemental material to increase the transparency of our reporting and the reproducibility of our work. However, we would be happy to remove any supplemental table or figure that the editors believe is unnecessary.