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Journal of Clinical Epidemiology 140 (2021) 93-100

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Domperidone increases harmful cardiac events in Parkinson's disease: A Bayesian re-analysis of an observational study

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Accepted 5 September 2021; Available online 8 September 2021

Abstract

Objectives: To assess the risks of ventricular tachyarrhythmia/sudden cardiac death (VT/SCD) with domperidone use in Parkinson's disease (PD).

Study designs and Settings: Using Bayesian methods, results from an observational study were combined with prior beliefs to calculate posterior probabilities of increased relative risk (RR)) of VT/SCD with use of domperidone compared to non-use and of harm, defined as risk exceeding 15%. The analyses were carried with normally distributed priors (log (RR)): uninformative (N(0,10)) or informative (N(0.53,179)), derived from a meta-analysis (OR (95%CI):1.70 (1.47-1.97)). Sensitivity analyses used: different priors' strengths, different priors, and Bayesian meta-analysis

Results: The uninformative prior yielded a RR: 1.23 (95% credible interval (CrI):0.94- 1.62), like the published frequentist RR: 1.22 (95% CI:0.99-1.50), with 69% probability of harm. With an informative prior weighted at 100%, 50% and 10%, the RR were 1.63 (1.41-1.88), 1.57 (1.31-1.91) and 1.39 (1.10-1.93), respectively. The corresponding probabilities of harm were 100%, 99%, and 94%, respectively.

Conclusion: While both the frequentist and Bayesian approaches with an uninformative prior were unable to reach a definitive conclusion concerning the arrhythmic risk of domperidone in PD patients, the Bayesian analysis with informative priors showed a high probability of increased risk that was robust to multiple prior sensitivity analyses. © 2021 Elsevier Inc. All rights reserved.

Keywords: Bayesian analysis; Observational study; Domperidone safety; Parkinson disease

Conflicts of interest: None.This work was supported by The Canadian Network for Observational Drug Effect Studies (CNODES), (Grant 1 DSE-111845).CNODES, a collaborating center of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research.

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What is new?

- Bayesian methods are rarely used in observational studies.
- Bayesian models combine newly observed data with prior beliefs.
- A weighted prior allows to account for different beliefs in its strength.
- This Bayesian analysis shows domperidone to increase harm in Parkinson's disease.
- Reporting inferences in a probabilistic manner is intuitive and easy to interpret.

1. Introduction

Over the last two decades, Bayesian methods have gained popularity and their implementations have widened in statistical sciences and applied fields. From a healthcare perspective, regulatory agencies are now accepting Bayesian approaches for earlier phases of drug development [1,2] and comparative effectiveness research [3,4]. At the drug development level, Bayesian adaptive analytical approaches have been particularly attractive for achieving greater efficiency in reducing sample size, time and cost of trials [5]. In comparative effectiveness research, Bayesian methods have been used to increase observational studies' (OS) scientific validity and efficiency at the design and analysis levels [3,6].

Bayesian statistics' most valuable and defining feature is their ability to combine prior belief with observed data through Bayes theorem to generate a posterior distribution. This posterior distribution can then be used as a prior belief for future research. This process of sequential learning and measurement allows statistical inferences to be drawn based on past and new data. The validity of those inferences depends on the validity of the prior, the current data and the statistical model [7]. Prior beliefs have often been criticized as a source of subjectivity. However, the analyst's choice of the model's parameters and justification of the prior distribution must be transparently stated. Moreover, the robustness of the posterior distribution to the prior can be assessed by comparing the impact of a weakly, moderately, or strongly skeptical choice when incorporated with current data according to the objective rules of probability. Another important advantage of Bayesian statistics is the generation of probability-based inferences that are intuitive, flexible and provide direct answers to questions that are relevant to policy decision-makers.

The Canadian Network for Observational Drug Effect Studies (CNODES) [8] is a pan-Canadian collaboration of researchers created by the Drug Safety and Effectiveness Network (DSEN), whose mandate is to answer DSEN questions about drug safety and effectiveness. CNODES [8] researchers have access to Canadian

health-administrative databases in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia and a non-Canadian database, the Clinical Practice Research Datalink (CPRD), from the UK. Like most research, CNODES studies are typically conducted using frequentists statistical methods.

This study aimed to conduct a Bayesian analysis of a published CNODES [8] OS of the safety of domperidone in Parkinson's disease (PD) (Renoux et al. [9]). This work was intended to demonstrate how Bayesian methods allow the sequential incorporation of prior evidence, leading to transparent probabilities and therefore, to more informed decision-making.

2. Methods

2.1. Renoux study's characteristics

Renoux et al. [9] conducted a retrospective, nested casecontrol study involving evidence synthesis of seven Canadian administrative databases and one from the UK. The primary objective was to assess the risk of the combined endpoints of ventricular tachyarrhythmia (VT) and sudden cardiac death (SCD) in current users of domperidone (exposed) compared to non-users of domperidone (unexposed). Table 1 provides the study's key characteristics.

2.2. Renoux study's results: Frequentist analysis

Conditional logistic regression was used to estimate the rate ratio (RR) of VT/SCD in propensity score-matched cohorts (N = 214,962). The data from each of the eight databases were analyzed independently and their results combined in a meta-analysis. The results showed a higher risk of VT/SCD with current use of domperidone vs. non-use (RR:1.22; 95% CI: 0.9-1.50). As this borderline increased risk of VT/SCD was not considered definitive, the investigators concluded that "domperidone may increase the risk of VT/SCD in patients with PD" [9].

2.3. Bayesian analysis

We reanalyzed Renoux's study [9] data using a Bayesian random-effects model which comprised the following components:

- Prior probability distribution: an "a priori" belief regarding the possible drug effect.
- Likelihood function: observed data from Renoux's study [9].
- Posterior probability distribution: the distribution of possible drug effects based on the combination of prior beliefs with the likelihood.

2.3.1. Uninformative or skeptical priors

The model considered a neutral clinical opinion, i.e., "clinical equipoise," regarding the association of domperidone use with VT/SCD. We used a normal distribution on

Population	Patients newly diagnosed with Parkinson's disease or with a first prescription for an antiparkinsonian drug between January 1, 1990 (or 1 year after site-specific data was available, whichever was later) and June 3, 2012: aged 50 years or older (or 66 or older in Alberta, Ontario and Nova Scotia)
Cases	Patients with a first diagnosis of ventricular tachyarrhythmia (VT) or sudden cardiac death (SCD) recorded at any time after cohort entry
Control	Up to 30 patients/one case, matched on age, sex, date of cohort entry and duration of follow-up
Outcomes	Composite endpoint of VT and SCD in current users of domperidone vs nonusers
Design	Retrospective cohort with nested case-control analysis
Sources	Canadian provincial health administrative databases in Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Québec and Saskatchewan, as well as the Clinical Practice Research Datalink (CPRD) in the UK

Table 1. Renoux's study characteristics

 Table 2. Relative risk (95% Crl) and probabilities of harm using uninformative or skeptical priors

	RR	CI		
Renoux's frequentist results	1.22	0.99 - 1.50		
Prior's strength	RR	95% Crl	Posterior probability of harm with threshold of harm set at:	
			> 1.0	> 1.15
Uninformative ($\sigma = 10$)	1.23	0.94 - 1.62	0.94	0.69
Moderately skeptical ($\sigma = 0.355$)	1.28	0.96 - 1.87	0.95	0.78
Strongly skeptical ($\sigma = 0.07$)	1.29	0.96 - 1.90	0.95	0.79

a logarithmic scale (log RR) with a mean centered at 0. It was assumed that a normal distribution would adequately approximate the prior and the likelihood due to the considerably large sample size.

For the uninformative prior, representing a belief that "there is not much information available regarding the effect size," a large SD (σ) was used to reflect a distribution that is essentially flat over a wide range of plausible log (RR) values (N [0, 10]). A second scenario considered a moderately skeptical prior representing a belief that "there is conflicting or unreliable evidence regarding the effect size, but a very large effect is impossible." This was summarized by a 0.95 probability that the OR is between 2 and 0.5 (N [0, 0.354]). A third scenario considered a strongly skeptical prior representing a belief that "the drug has no effect or, if any, a very small effect." This was summarized by a 0.95 probability that the OR is between 1.15 and 1/1.15 (N [0, 0.07]).

2.3.2. Informative priors

In this analysis, the model considered a prior derived from a meta-analysis of OS. The MA [10] identified 9 OS [11-19] that measured the association between domperidone use and VT/SCD. Three studies [13,17,18] were excluded from the analysis since they overlapped with a larger study and six [11,12,14-16,19] were retained for the analysis. The MA [10] used a random-effects model to calculate the pooled OR. Heterogeneity between the selected studies was addressed by using adjusted ORs to calculate the pooled adjusted estimate (1.70; 95 % CI: 1.47–1.97; $I^2 = 0\%$). The authors also conducted sensitivity analyses by excluding studies that differed on the patients' age, type of database, and outcome measured. All exclusions did not change the associations between domperidone exposure and the risk of VT/SCD. The pooled estimate from the MA [10] (OR:1.70; 95 % CI: 1.47–1.97) formed the prior distribution for our model.

Again, three scenarios were considered. The first, a weak belief in the evidence such as "current evidence points to a harmful effect, but the available data are not robust." This was summarized by a prior's mean centered at the MA [10] estimated log (OR) with 10% of its precision (N [0.53, 17.9]). The second, a belief that "current evidence shows the drug to be harmful, but there is not enough data to rule out a beneficial effect." This was summarized by the same mean with 50% of the precision (N [0.53, 89]). The third, a belief that "the evidence from the MA [10] and from available pharmacodynamic studies [20-24] are robust and strongly links the drug to a harmful effect." This was summarized by the same mean with 100% of the precision (N [0.53, 179]).

Additional sensitivity analyses evaluated the OS [11,12,14-16,19] identified in the MA [10] and Renoux's [9] results sequentially by their publication date. The first study (De Bruin et al. (2006)) [12] was analyzed using an uninformative prior ($\sigma = 10$), assuming nothing is known about the risk of harm with use of domperidone. Subsequent trials were analyzed using the preceding trials' posterior log (RR) and σ as a prior.

A final analysis included the effect estimate of each OS, along with Renoux's [9] results, in a Bayesian randomeffects meta-analysis. Two priors were considered: 1) uninformative prior (N [0, 10]) allowing the observed data (likelihood) to dominate the posterior distribution and 2)

	RR	CI			
Renoux's Frequentist Results	1.22	0.99 - 1.50			
Prior's strength	RR	95% CrI	Posterior prob harm set at:	Posterior probability of harm with threshold of harm set at:	
			> 1.0	> 1.15	
Weak (10% weight)	1.39	1.09 - 1.93	1.0	0.94	
Moderate (50% weight)	1.57	1.31 - 1.91	1.0	1.0	
Strong (100% weight)	1.63	1.41 - 1.88	1.0	1.0	

Table 3. Relative risk (95% CrI) and probabilities of harm using informative priors based on a published meta-analysis

moderately skeptical prior (N [0, 0.355]) based on the belief that evidence points to a harmful effect, but a large effect is unlikely, allowing a 0.95 probability that the risk is between 0.5 and 2.

All point estimates (RR) are presented with 95% credible intervals (CrI) and were computed using "Win-BUGS" version 1.4.3. [25] and Markov Chain Monte-Carlo (MCMC) simulations [26,27]. MCMC is a sampling method used to approximate the posterior distribution of the effect estimate by random sampling of probabilities where each sampled value is correlated with the previous value. The posterior distributions were based on 40,000 draws of the Gibbs-chain and a burn-in of 10,000. Convergence was verified visually by simultaneously running three chains with different initial values until all chains overlapped.

3. Results

3.1. Bayesian analysis with uninformative or skeptical priors

As expected, the analysis with an uninformative prior resulted in a posterior RR of 1.23 (0.94-1.62), identical to the reported frequentist's estimate, as the likelihood (data information) dominated the posterior distribution. With a moderately or strongly skeptical prior, the posterior RR increased but remained stable with values indicating 28% to 29 % higher risk of VT/SCD with current use of domperidone (Table 2).

The relative influence of the prior and the data on the posterior distribution was estimated by their respective weight, i.e., their precision (1/variance). In this analysis, the prior information was 1/100 = 0.01, whereas the data information was 1/0.0114 = 87, explaining the data dominance over the posterior distribution. In the moderately skeptical scenario ($\sigma = 0.355$), the prior information was 1/0.126 = 8, almost ten times less than the data information and in the strongly skeptical scenario ($\sigma = 0.07$) the prior was 1/0.005 = 200, more than twice the data information. The smaller the value of σ , the greater the influence of the prior relative to the observed data (likelihood).

In contrast to standard frequentist analyses, Bayesian analyses provides the flexibility of drawing inferences based on marginal probabilities, thereby permitting an examination of various thresholds of clinical meaningfulness. Graphically, these probabilities are based on the calculation of the area under the curve (AUC) to the left and right of vertically assigned thresholds. Fig. 1 illustrates the results derived with a strongly skeptical prior ($\sigma = 0.07$) and shows the 3 chains are quite superimposable indicating that the Markov chains have converged. The area under the curve (AUC) to the right of 1.0 shows a 95% probability of increased risk. However, one could argue that any risk less than 15% is probably not clinically significant and represents a region of practical equivalency (ROPE). In this case, the probability of >15% additional risk is the AUC to the right of an imaginary vertical line drawn at 1.15 and is equal to 79 %.

3.2. Bayesian analysis with informative priors

Including the adjusted odds ratio (1.70; 95 % CI: 1.47– 1.97) from the MA [10] as a prior in the analysis resulted in a RR of 1.63 (95% CrI: 1.41–1.88) (Table 3). Fig. 2 displays the updated posterior distribution for the risk associated with current use of domperidone using informative prior beliefs. As expected, this additional information has resulted in a narrowing of the distribution and a shift to an increased mode RR, as this posterior distribution is a weighted average of the prior and likelihood functions.

Considering heterogeneities resulting from the MA [10] underlying biases and differences in the populations studied, some additional uncertainty was included in the model. The sensitivity analysis results, where the prior was used at 10%, 50% and 100% to reflect various readers' belief in its validity, are shown in Table 3. Although the down-weighting increased the posterior variance, in all cases there was virtually 100% probability of an increased risk with domperidone and 94% to 100% probability of >15% increased risk. Looking at the influence of the prior on the calculations, a 100% of the prior equaled twice that of the data information (precision: 179 vs. 87) and consequently, dominated the posterior distribution. With 50% of the prior, the prior information and the data information



Fig. 1. Histogram of posterior distribution for the risk of VT/SCD with current use of domperidone using a strongly skeptical prior (N (0, 0.07)). The areas under the curve (AUC) represent the probabilities of risk obtained from running three chains of initial values.



Fig. 2. Histogram of posterior distribution for the risk of VT/SCD with current use of domperidone using 100% of an informative prior. The areas under the curve (AUC) represent the probabilities of risk obtained from running three chains of initial values.

tion had equal weights (precision: 89 vs. 87) and exercised equal influence on the posterior estimates.

In the sequential analysis based on the publication date of the OS [9,11,12,14-16,19], as data cumulated, the increased risk with domperidone use went up from 16% to 59% and at least 50% to 98% probability of this risk exceeding 15%. The final analysis encompassing Renoux's [9] results produced an RR (CrI) of 1.40 (1.05–2.31), equivalent to the estimates with a 10% weight of the MA [10] (Table 4).

Finally, the results of a Bayesian random-effects metaanalysis of all OS [9,11,12,14-16,19] (including Renoux [9]), with either an uninformative or moderately skeptical prior, produced risk estimates (RR) >1.50 and $\geq 97\%$

Table 4. Sensitivity analyses

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Analysis by date of publication					
Prior (each study's estimate serves as a prior for subsequent one, except De Bruin (N(0, 10))	RR	95% Crl	Posterior probability harm set at:	Posterior probability of harm with threshold of harm set at:	
			> 1.0	> 1.15	
De Bruin (2006)	1.04	0.56 - 1.94	0.55	0.38	
Jolly (2009)	1.08	0.58 - 1.95	0.59	0.41	
Johannes (2010)	1.16	0.62 - 1.98	0.68	0.51	
Van Noord (2010)	1.20	0.68 - 2.11	0.74	0.56	
Arana (2015)	1.26	0.72 – 2.14	0.79	0.63	
Chen (2015)	1.34	0.77 – 2.18	0.85	0.70	
Renoux (2016)	1.40	1.05 – 2.31	0.99	0.90	
Bayesian random-effects meta-analyses					
Prior's strength	RR	95% Crl	Posterior probability harm set at:	Posterior probability of harm with threshold of harm set at:	
			> 1.0	> 1.15	
Uninformative ($\sigma = 10$)	1.51	1.15 – 1.89	0.99	0.97	
Skeptical moderate ($\sigma = 0.355$)	1.59	1.24 – 2.26	1.0	0.99	

probability of harm being above the defined ROPE of 1.15 (Table 4).

4. Discussion

In this Bayesian reanalysis of Renoux et al. [9] data we have demonstrated that current use of domperidone is associated with an increased risk of VT/SCD in patients with Parkinson's disease.

The use of uninformative prior allowed the observed data to dominate the posterior distribution, which resulted in an essentially identical RR as the frequentist (1.23; 95% CrI: 0.94-1.62 vs. 1.22; 95% CI: 0.99-1.50). Reducing the value of σ to levels representing moderately to skeptical prior beliefs produced higher RRs (1.28; 95% CrI: 0.96-1.87 and 1.29; 95% CrI: 0.96-1.90) due to an increased influence of the prior relative to the observed data (likelihood). The Bayesian analyses also led to wider credible intervals than the confidence intervals as the uncertainty about the random effects' variance is acknowledged in the pooled effect. At the opposite, in the frequentist analyses the pooled estimate uses a fixed-point estimate of the variance thereby suppressing some uncertainty. In all three analyses (with uninformative, moderately, or strongly skeptical prior), the probability of domperidone being harmful (RR > 1) was $\geq 94\%$ and there was a 69% to 79% probability of harm being >1.15.

With an informative prior, derived from a published MA [10] and weighted according to a weak, moderate or strong prior belief, the results showed a 39%, 57%, and 63% increased risk with domperidone, respectively. The probability of any harm was 100% and there was a \geq 94% probability of harm being >1.15. Other sensitivity analy-

ses, whether based on the analysis of OS by publication date or on a Bayesian meta-analysis of OS, confirmed earlier results as the final RR ranged from 1.40 to 1.59. The probability of domperidone being harmful (RR >1) was \geq 99% and there was a 90% to 99% probability of harm being >1.15.

While the main inference (RR:1.22; 95% CI: 0.99–1.50) from the frequentist analysis regarding the increased risk of VT/SCD with current use of domperidone was inconclusive, Bayesian statistics allowed the calculation of various effect estimates according to the nature and strength of prior beliefs and direct estimation of clinically relevant probabilities, that is, the harm that is associated with use of domperidone. The flexibility of Bayesian methods means we are not restricted to uninformative priors but can update our belief with informative priors when appropriate data exists. We have demonstrated that incorporating prior beliefs, in this case a meta-analysis [10] of similar OS, with current data resulted in a higher RR point estimate with increased certainty (≥90% probability of >15% risk increase). This increased risk was relatively robust to a discounting of the prior evidence due to uncertainties regarding its comparability with Renoux's [9] data.

Our Bayesian reanalysis of Renoux et al. [9] data has some limitations. Since raw data (number of cases and controls) from the participating sites in Renoux's [9] study was not accessible, we used the published summary effect estimates. This may have contributed additional heterogeneity in our effect size estimate. Also, the prior used for the analysis was derived from a meta-analysis with potential biases. This situation reflects real life where, very often, the "perfect prior" based on a well-designed RCTs with no or minimal bias does not exist. If it did exist, further research would not have been needed; on the contrary its absence is commonly the instigator of new research. Such was the case of Renoux's [9] study. The relevance of the MA [10] of OS in generating a prior for the current analysis may be rightfully questioned given potential biases. We have used various approaches to conduct our reanalysis. First, by ignoring existing evidence and modeling a clinical "equipoise" regarding the harmful effects of domperidone in Parkinson's disease. In this approach, the effect size was centered at "0" and the values of σ were varied relative to different beliefs' strength to adjust the proportion of the distribution that falls within a given range of practical equivalence (ROPE). Second, by downweighting the precision of the MA [10] by 90%, 50%, and 0%. These various weights allowed to decrease the prior's influence on the likelihood and the calculated posterior estimates. This provided skeptical readers with probability estimates that correspond to a weak, moderate, or strong belief in the validity of the prior. Third, by analyzing the OS [9,11,12,14-16,19] by their publication date using the posterior estimates as a prior for the subsequent trial. This produced different priors allowing for a variation of the width of the distribution (σ) and the effect size (σ). Fourth, by conducting a Bayesian random-effects meta-analysis of the OS [9,11,12,14-16,19] while varying σ as to assess the variation in the posterior effect size relative to those produced by the other approaches. Finally, using a Bayesian random-effects model helped account for the variation in the trials' effect size while the different approaches used defined where most of the probability mass of the prior and the posterior were located and centered.

The current study demonstrates some of the advantages of Bayesian methods including: 1) building from prior beliefs and 2) drawing intuitive probability inferences and conclusions that are useful and easy to interpret and to communicate. While the frequentist analysis could only somewhat vaguely conclude that domperidone may increase VT/SCD risk, the present Bayesian analysis allows the incorporation of previous work, better quantifies the risk and leads to more informed decision-making.

These advantages are also sought-after in the field of Drug development [5,28]. In this area, adaptive trials use Bayesian statistics to offer the flexibility to incorporate prior information gathered before, during, or outside the trial, such as data from Phase I trial becoming the prior for Phase 2 trials, their posterior becoming the prior for Phase 3 trials, and their posterior becoming the prior for postmarketing trials and surveillance. Moreover, Bayesian methods have been considered ideal for enabling frequent monitoring of trials' results, adapting to information gathered during a trial and allowing mid-course adjustments to trials' design. These represent important advantages for drug development mainly: smaller sample size, efficient timelines, and reduced costs.

In conclusion, our study provides an example of how Bayesian statistics can provide relevant answers that are more intuitive than frequentist statistics to questions raised by clinicians and policy decision-makers. However, until researchers become more familiar with Bayesian methods, conducting both analyses (frequentist and Bayesian) could yield informative results.

CRediT authorship contribution statement

Gisèle Nakhlé: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing – original draft, Writing – review & editing. James M. Brophy: Validation, Methodology, Writing – review & editing. Christel Renoux: Writing – review & editing. Paul Khairy: Writing – review & editing. Patrick Bélisle: Software. Jacques LeLorier: Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition.

Acknowledgments

- This study was made possible through data sharing agreements between CNODES member research centres and the respective provincial governments of Alberta, British Columbia, Manitoba (HIPC #2013/2014-43), Nova Scotia, Ontario, Quebec, Saskatchewan, and the CPRD
- The opinions, results, and conclusions reported in this paper are those of the authors. No endorsement by the provinces or data stewards is intended or should be inferred.
 - Other Acknowledgments:
- We would like to thank Ms. Marie Bernard Brind'Amour for her diligent proof-reading of this paper.
- We would like to also thank the CNODES investigators, and collaborators for their contribution in the study referred to in this paper.

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