Clin Drug Investig (2016) 36:97–107
DOI 10.1007/s40261-015-0360-0

SYSTEMATIC REVIEW

Domperidone and Risk of Ventricular Arrhythmia and Cardiac Death: A Systematic Review and Meta-analysis

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Published online: 9 December 2015

Abstract

Background and Objective Domperidone is a drug used globally for relieving nausea and vomiting and stimulating breast milk production. Several case reports and studies linked domperidone usage with major cardiovascular adverse events (cardiac arrhythmia and sudden cardiac death). However, multiple randomized controlled efficacy studies failed to detect such adverse events. Our objectives were to systematically review and meta-analyze the association between current domperidone exposure and cardiovascular adverse events.

Methods The first author performed EMBASE, PubMed and Scopus searches to identify human studies assessing the association between current domperidone exposure and cardiac arrhythmia or sudden death. Thirteen related articles were identified and the first and second authors independently reviewed the articles. Six studies were included in the final analysis. Meta-analysis was performed with a random effect model using the inverse variance approach. Heterogeneity was evaluated using the Q statistic and I^2 test.

Results Five case-control studies and one case-crossover study were included in this meta-analysis. Pooled risk estimates demonstrated that the current use of domperidone increased the risk of ventricular arrhythmia and sudden cardiac death (pooled adjusted odds ratio = 1.70; 95 % confidence interval 1.47–1.97; $I^2 = 0$ %). The I^2 test showed that the underlying population was homogeneous.

Conclusions Evidence from this meta-analysis suggests that current domperidone use increases the risk of cardiac arrhythmia and sudden cardiac death by 70 %. Domperidone usage in older populations should be discouraged. Larger observational studies or randomized controlled trials are needed to confirm the findings of this analysis.

Key Points

Use of domperidone increased the risk of cardiac arrhythmia and sudden cardiac death.

Domperidone usage in older populations should be discouraged.

More research should be done on the association between domperidone use and risk of cardiac arrhythmia and sudden cardiac death in women of child-bearing potential.

Electronic supplementary material The online version of this article (doi:10.1007/s40261-015-0360-0) contains supplementary material, which is available to authorized users.

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1 Introduction

Domperidone is a specific dopamine receptor blocker that is used for motility disorders and breast milk stimulation. It has some superiority compared with the two other common clinically useful prokinetic agents, cisapride and metoclopramide. Domperidone is associated with fewer central nervous system side effects (e.g. somnolence and mental activity reduction) than metoclopramide because domperidone does not readily cross the blood-brain barrier [1]. In addition, domperidone is more effective than metoclopramide [2, 3] and cisapride [4] for the treatment of gastroparesis. Domperidone can also directly act at the chemoreceptor trigger zone which is involved in vomiting initiation while cisapride lacks this activity [1]. The efficacy of domperidone as an antiemetic and prokinetic agent has been supported by several human studies [5–7]. The drug has been used for the treatment of gastrointestinal symptoms in several diseases including diabetic gastroparesis [5] and gastroesophageal reflux [6]. Domperidone is approved as a prokinetic drug in several countries, including Australia, Canada, and Thailand [8]. Although domperidone is not approved in the USA for this indication, it is legally available under the investigational new drug approved protocol for symptomatic treatment in patients with motility disorders [9] and is accessible from other countries [10]. Domperidone also has a non-approved off-label indication as a galactagogue which helps stimulate breast milk production [11]. The efficacy of domperidone as a galactagogue has been supported by several studies [12–15].

Despite the effectiveness of domperidone as a prokinetic agent and a galactagogue, its safety in human use has been questioned. In vitro studies suggest that domperidone binds to cardiac hERG (human ether-a-go-go-related gene) proteins, the subunit of native cardiac rapid delayed rectifier potassium (I_{Kr}) channels, delaying ventricular repolarization and prolonging action potential duration [8]. The inhibition of hERG channels leads to long QT-interval syndrome which increases the risk of ventricular arrhythmias and sudden cardiac death [16]. Human studies and case reports in neonate and adult populations showed that domperidone was significantly associated with prolonged QT intervals [17–20]. A systematic review about domperidone and QT-interval prolongation is provided elsewhere [20]. Also, several case reports [21–23] linked domperidone usage to the risk of cardiac arrest or sudden cardiac death. In addition, domperidone also has potential drug interactions with drugs metabolized by cytochrome P450 (CYP) 3A4, as well as CYP1A2, CYP2B6, CYP2C8 and CYP2D6 [8], which creates further complications in patients receiving polypharmacy. A randomized controlled trial showed an interaction between domperidone and ketoconazole via CYP 3A4 that led to QT prolongation in healthy volunteers [18]. This cumulative evidence of domperidone adverse events supports the Health Canada advisory [24] and the warning from the US Food and Drug Administration (FDA) against the use of domperidone because of the increase in risk of cardiac arrest [25].

Although studies have shown the link between cardiovascular adverse events and domperidone usage, several efficacy studies in breastfeeding populations failed to detect any significant cardiotoxicity associated with domperidone [12–15]. In addition, studies using retrospective chart review [9, 26] demonstrated that domperidone was not associated with cardiac complaints or electrocardiogram changes and had a low risk of cardiac adverse events even when it was used at high doses (80–120 mg). Because of the conflicting results on the safety of domperidone, a meta-analysis of studies on the cardiotoxicity of domperidone is needed. We hypothesized that current domperidone usage increases the risk of major cardiovascular adverse events (ventricular arrhythmia and sudden cardiac arrest). The secondary objective was to investigate the effect of domperidone on cardiac adverse events in a vulnerable population, especially in newborns and women of childbearing age. These age groups were selected because domperidone has been used off-label as a galactagogue and also used for the treatment of gastrointestinal diseases in neonates [27].

2 Methods

2.1 Search Strategy

A systematic literature search was performed using Medline, EMBASE and Scopus, from 1980 to October 2015 using the terms "domperidone" AND "cardiac arrhythmia" AND "cardiac arrest" without applying language restrictions. The Medline database was searched through PubMed by using Medical Subject Headings (MESH) and Text Words (TW). EMBASE was searched using Emtree terms and synonyms. The full search strategies are provided in the Electronic Supplementary Material 1–3. References of review articles and letters were searched for potential pertinent studies.

2.2 Inclusion and Exclusion Criteria

Studies were included in this meta-analysis if they were (i) human studies, (ii) studies that explicitly indicate exposure to domperidone, and (iii) studies that explicitly indicate cardiac arrhythmia or cardiac arrest or cardiac

death as exposures. Studies were excluded if they were (i) review articles, (ii) case reports or case series, or (iii) studies with data that could not be used to calculate a risk ratio. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram of the systematic literature review process.

2.3 Data Extraction

After the literature search by the first author, articles were retrieved and stored in a citation manager (EndNote X7, Thomson Reuters, New York, NY, USA). Redundant articles were removed and the titles of the rest of the articles were reviewed by searching for specific words for exclusion (e.g., to exclude nonhuman studies, words such as in vitro, in vivo, animal, rat, mice, pig, and fish were searched). After the titles were reviewed, the abstracts of the rest of the articles were reviewed. For non-English articles, English abstracts were used to determine if the articles relate to our current meta-analysis. When non-English full texts were provided, the articles were searched for risk ratios (with confidential intervals) to determine if further translation would be required. Information on study design, location, demographic data of the studied population, matching variables, and confounders were independently extracted from included studies by the first and second authors. In case of disagreement, the third author was consulted and the disagreement was resolved by consensus.

2.4 Assessment of Study Quality

Study quality was independently evaluated using the Newcastle-Ottawa Quality Assessment scale for case-control studies [28] by the first and second authors. Disagreement was also resolved by consultation and consensus.

2.5 Statistical Methods

Random effects models with inverse variance weighting were created using Review Manager (RevMan 5.3, The Nordic Cochrane Center, Copenhagen, Denmark). The heterogeneity of the underlying population was assessed using the Q-statistic and I^2 test [29]. For the interpretation, I^2 of less than 30 % was considered to be negligible heterogeneity while I^2 values greater than 60 % were considered to be heterogeneous [30]. Stratification by age and gender was planned prior to the analysis. Post hoc analyses on the study population and outcomes were also performed. Publication bias was assessed by visually evaluating a funnel plot.

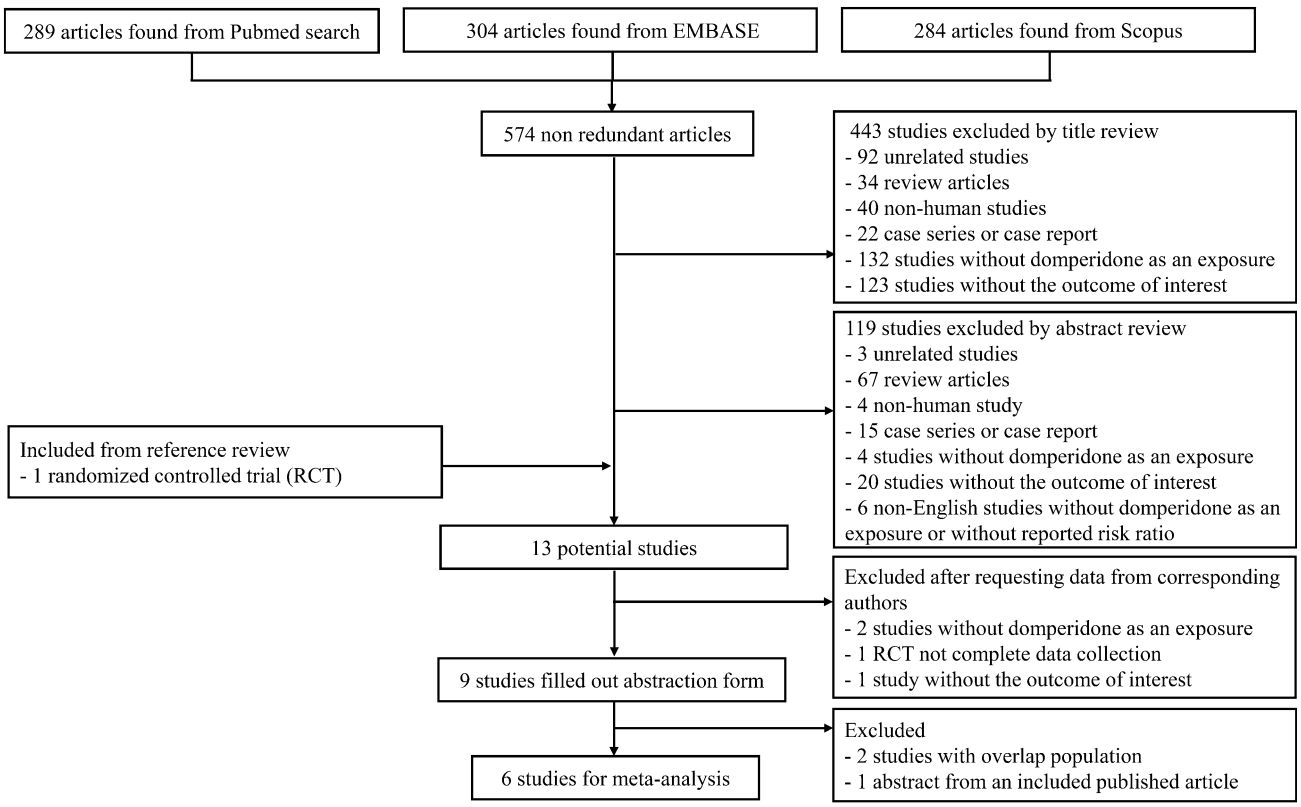

Fig. 1 PRISMA diagram

3 Results

3.1 Characteristics of Included Studies

The systematic literature search, performed using the three databases, retrieved 574 non-redundant manuscripts. Nine observational studies that measured the association between domperidone exposure and the risk of cardiovascular adverse events [31–39] were identified. Three studies [31, 34, 37] were excluded because the study population and study period overlapped with a larger study [35, 38]. Six case-control studies were included in this meta-analysis [32, 33, 35, 36, 38, 39] (Table 1). Two of the six had a nested case-control design [36, 37]. One of the six had a case-crossover study design [39]. Five studies identified patients from administrative databases and one study used death records [33]. Three studies reported sudden cardiac arrest as a sole outcome [32, 33, 38]. One study reported ventricular arrhythmia and sudden cardiac arrest as a pooled outcome [36] and two studies reported both sudden cardiac arrest and the pooled events (ventricular arrhythmia and sudden cardiac arrest) as outcomes [35, 39].

According to the Newcastle-Ottawa Quality Assessment Scale for case-control studies, four studies were evaluated as high quality [35, 36, 38, 39] (Table 2).Two of them [35, 36] were cited by the Health Canada advisory on domperidone [24]. The other two studies with lower quality had less adequate case definitions and case representativeness. Five of the six selected studies were conducted in North America or Europe so the majority of participants were assumed to be Caucasian. Most of the studies included patients aged 60 years or older (the mean age ranged from 59.6 to 72.5 years). Only one study included a younger population with an age of 44 ± 23 (mean ± standard deviation) years [38]. Most of the studies where data were provided showed that the gender distribution was not equal and there were more male participants than female (percentage male ranging from 57.9 to 66.1). Only one study included more female participants (30.1 % males) [38]. No study reported a stratified odds ratio (OR) based on gender or age. Cases in every study had concomitant drug use including the use of drugs that may prolong the QT interval (e.g., amitriptyline, clarithromycin, and haloperidol). A summary of the demographics and other important information is shown in Table 1.

Publication bias was evaluated by creating a funnel plot of the adjusted association between domperidone use and the major cardiovascular adverse events (ventricular arrhythmia and cardiac death). The funnel plot shows an asymmetric distribution of log OR values which could be interpreted as potential publication bias (Fig. 2). Small studies that did not find a significant association between domperidone use and cardiac death may not have been published. However, the small number of studies included in this analysis discouraged further analysis (e.g., Egger test of Funnel Plot Asymmetry) [40].

3.2 Domperidone and Risk of Ventricular Arrhythmia or Sudden Cardiac Death

In the unadjusted analysis, crude ORs for the studies by Arana et al. [38], Johannes et al. [36], and van Noord et al. [35] were calculated based on the number of participants they provided, while crude ORs for the studies by De Bruin et al. [32], Chen et al. [39], and Jolly et al. [33] used for the calculation were the ORs provided in the studies. We found that domperidone use significantly increased the risk of ventricular arrhythmia and sudden cardiac death (OR = 2.02; 95 % CI 1.53–2.67) (Fig. 3). However, the underlying heterogeneity in these populations was high (I^2 = 63 %). In the pooled adjusted analysis, the association between domperidone use and the two major cardiovascular events was lower than in the unadjusted analysis but still statistically significant (OR = 1.70; 95 % CI 1.47–1.97) (Fig. 4). The adjusted odds ratios used to calculate the pooled adjusted estimate were homogeneous (I^2 = 0 %), indicating that all variability in the effect estimate is due to sampling error, not heterogeneity [30].

The secondary objective could not be accomplished because no study provided data stratified by age or gender. However, we did a subset analysis that included only patients aged greater than 60 years (Fig. 5) by excluding only one study that included a younger patient population [38]. Our analysis found that the adjusted OR for patients aged 60 years old was 1.70 (95 % CI 1.47–1.98, I^2 = 0 %), which is equal to the insignificant risk of cardiac arrest in patients at aged younger than 60 years as reported by Arana et al. [38] (adjusted OR = 1.71; 95 % CI 0.92–3.18).

Three subset analyses were performed based on post hoc analysis criteria. The first subset analysis excluded the article by Jolly et al. [33] because this study used a death database while the other studies used hospital or community databases. The exclusion of this study did not change the association between domperidone exposure and the risk of ventricular arrhythmia or cardiac arrest (pooled adjusted OR: 1.71; 95 % CI 1.47–1.97; I^2 = 0 %, Fig. 6). The second subset analysis was performed on the articles that provided cardiac arrest as a sole outcome. The exclusion of the study by Johannes et al. [36] slightly increased the association between domperidone exposure and the risk of cardiac arrest (pooled adjusted OR: 1.80; 95 % CI 1.48–2.19; I^2 = 0 %; Fig. 7).The last subset analysis was performed on the articles that provided average daily dose [35, 38, 39] to see the effect of dose on the risk of sudden cardiac arrest. The risk of sudden cardiac arrest increased

Table 1 Description of included studies

Author and year of study	Location	Case population	Control population	Outcomes	Matching	Confounder adjusted
Arana [38]	UK Clinical Practice Research Datalink (CPRD) GOLD (2005–2011), England	Population: 3239 Definition: patients with sudden cardiac death [46] Age: no data available Gender: no data available Note: Age of exposure cohort: 44 ± 23 years Gender of exposure cohort: male 30.1 %	Population: 12,572 Definition: matched patients Age: no data available Gender: no data available	Sudden cardiac death	Index date, year of birth, gender and practice	Gender, age, medical conditions, medication, and lifestyle variables
De Bruin [32]	Academic Medical Center (1995–2003), The Netherlands	Population: 150 Definition: patients experiencing circulatory arrest and advanced life support resuscitation team was requested Age: 59.6 ± 21.7 years Gender: male 65.7 %	Population: 560 Definition: matched patients Age: 47.5 ± 26.8 years Gender: male 48.9 %	Cardiac arrest	Index date	Age, gender, cardiac arrhythmia, other cardiac diseases, diabetes mellitus, pulmonary disease, total number of current drugs, serum chemistry
Chen [39]	Taiwan's Longitudinal Health Insurance Database (2000–2011), Taiwan	Case-crossover design Population: 25,356 Case period: 1- to 30-day period before the ventricular arrhythmia Control period: 91- to 120-day period before the ventricular arrhythmia Age: 61 ± 19 years Gender: no data available		Ventricular arrhythmia Sudden cardiac death	No matching. Patients served as their own control	Co-morbidities (e.g., coronary heart disease, heart failure, diabetes mellitus, depression, epilepsy, organ transplantation), current medication exposure (e.g., metoclopramide, CYP3A4 inhibitors)
Johannes [36]	Universal health care database (1990–2005), Canada	Population: 1608 Definition: patients with serious ventricular arrhythmia or sudden cardiac deaths Age: not stated Gender: not stated	Population: 6428 Definition: matched patients Age: not stated Gender: not stated	Ventricular arrhythmia and sudden cardiac death	Index date, age, gender, and diabetes status	Medical conditions (e.g., history of ventricular tachycardia and ventricular fibrillation), current medication exposure, medication use during 1 year before the index date, health-care utilization indicator
Jolly [33]	Community (2003–2007), England	Population: 1010 Definition: arrhythmic deaths Age: 67.6 ± 12.4 years Gender: male 67.4 %	Population: 3030 Definition: deaths with any causes Age: 67.6 ± 12.3 years Gender: male 67.4 %	Sudden cardiac death	Age, gender, and cardiovascular diseases	Heart failure, myocardial infarction, atrial fibrillation, revascularization, hypokalemia, bradycardia, syncope, epilepsy, renal dysfunction, history of alcohol abuse

Table 1 continued

Author and year of study	Location	Case population	Control population	Outcomes	Matching	Confounder adjusted
van Noord [35]	Integrated Primary Care Information database (1995–2007), The Netherlands	Population: 1304 Definition: patients with serious idiopathic ventricular fibrillation or Torsade de Pointes or sudden cardiac deaths [47] Age: 72.5 ± 14.1 years[a], 64.9 ± 15.2 years[b] Gender: male 57.9 %[a], 66.1 %[b]	Population: 13,480 Definition: persons randomly drawn from source population Age: 66.3 ± 13.9 years[a], 61.6 ± 14.1 years[b] Gender: male 60.9 %[a], 69.2 %[b]	Ventricular arrhythmia and sudden cardiac death Ventricular arrhythmia. Sudden cardiac death	Age, gender and practice	Heart failure, insurance type, use of CYP 3A4 inhibitors, hERG inhibitors, laxatives, digoxin, diuretics, corticosteroids, β-blockers

CYP cytochrome P-450, *hERG* human ether-a-go-go-related gene

[a] Sudden cardiac death

[b] Serious ventricular arrhythmia

Table 2 Risk of bias assessment by Newcastle-Ottawa Assessment scale for case-control study

Author and year	Selection				Comparability of cases and controls (out of possible 2*)	Exposure			Total (*/10)
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure (out of possible 2*)	Ascertainment method	Non-response rate	
Arana [38]	–	*	*	*	**	–	*	*	7
De Bruin [32]	–	–	*	–	**	*	*	*	6
Chen [39]	–	*	*	*	**	–	*	*	7
Johannes [36]	*	*	*	*	**	–	*	*	8
Jolly [33]	–	–	*	*	**	–	*	*	6
van Noord [35]	*	*	*	*	**	–	*	*	8

* is a score for each criteria

when the dose was increased, as can be seen by the risk when using domperidone at a dose higher than 30 mg/day (pooled adjusted OR: 3.32; 95 % CI 1.38–7.96; $I^2 = 32$ %; Fig. 8) which was higher than when using a dose of 30 mg/day or ≤30 mg/day (pooled adjusted OR: 1.63; 95 % CI 1.35–1.96; $I^2 = 0$ %; Fig. 9).

4 Discussion

Domperidone is a drug that is effective as an antiemetic and a breast milk-stimulating agent, although it is not approved in several countries including the USA. Despite its efficacy, conflicting safety data of domperidone have been reported. We performed meta-analyses to investigate the effect of domperidone exposure on the risk of two major cardiovascular adverse events, ventricular arrhythmia and sudden cardiac death. The findings of this meta-analysis supported previous case reports, studies, and a systematic literature review that also found that domperidone use is associated with cardiotoxicity.

In this analysis, studies that did not provide data in a format that could be extracted for a meta-analysis, for example efficacy studies (e.g., in lactation [11]) and prevalence studies, were excluded. After the data abstraction, six selected studies were included in the analysis. This meta-analysis found a significant increase in the risk of ventricular arrhythmia or cardiac death in domperidone

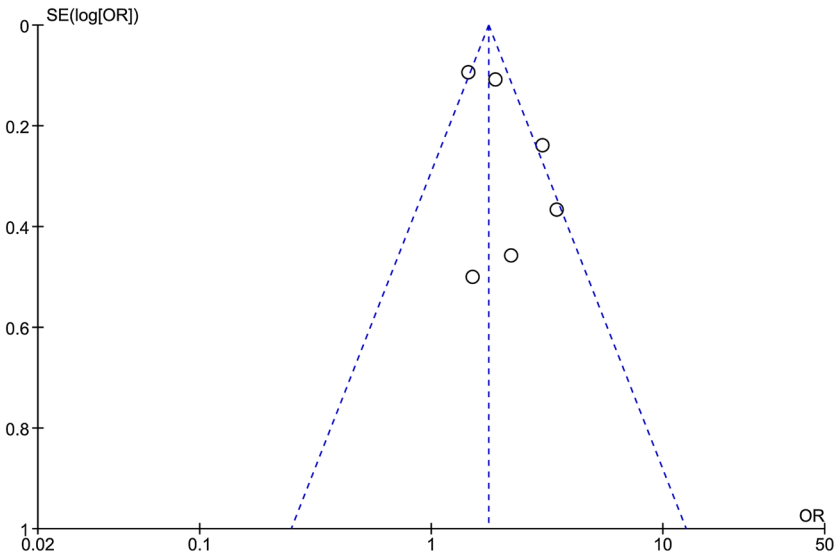

Fig. 2 Funnel plot of unadjusted association between domperidone use and ventricular arrhythmia and cardiac arrest. *OR* odds ratio, *SE* standard error

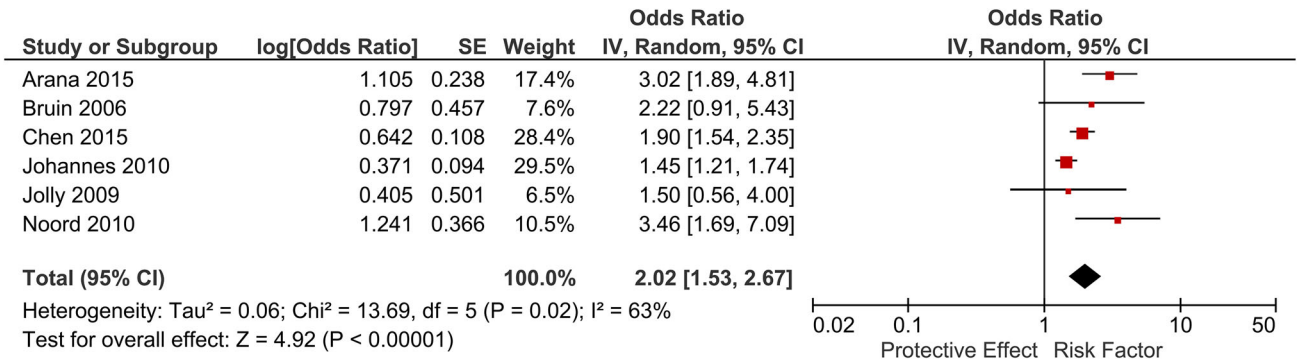

Fig. 3 Forest plot of unadjusted association between domperidone use and ventricular arrhythmia and cardiac arrest. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

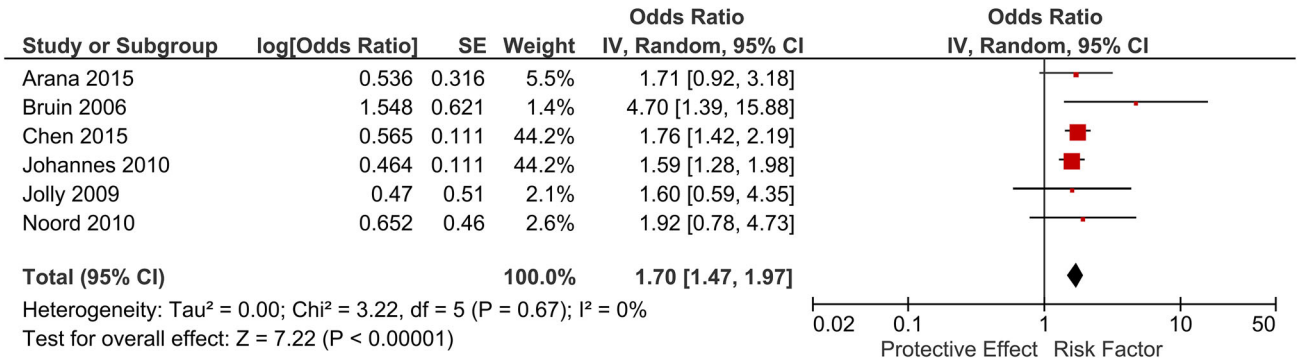

Fig. 4 Forest plot of adjusted association between domperidone use and ventricular arrhythmia and cardiac arrest. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

users. This finding is in agreement with findings from a recently published systematic review [41] which also reviewed articles included in this meta-analysis [32, 35, 36] and found that oral domperidone usage in adults was associated with an increased risk of adverse events. Moreover, one randomized placebo-controlled study found that domperidone increased the QT interval [18]. Our findings agreed with these previous studies because a long

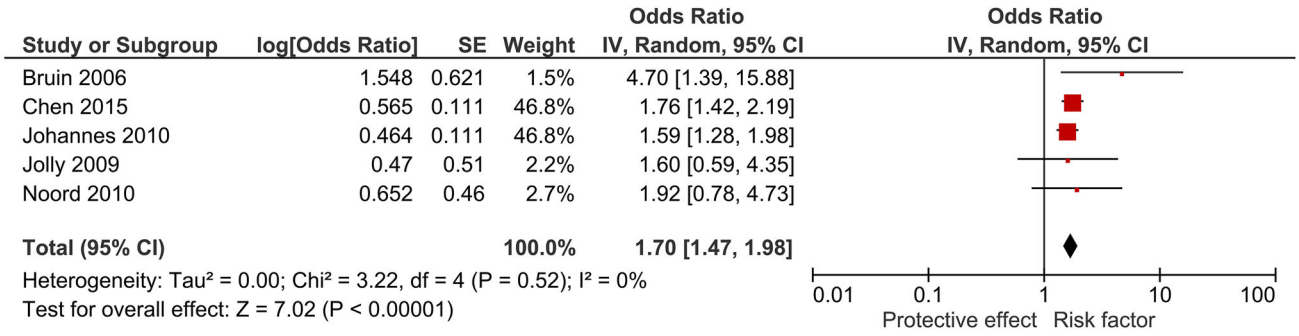

Fig. 5 Forest plot of adjusted association between domperidone use and cardiac arrest in older population. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

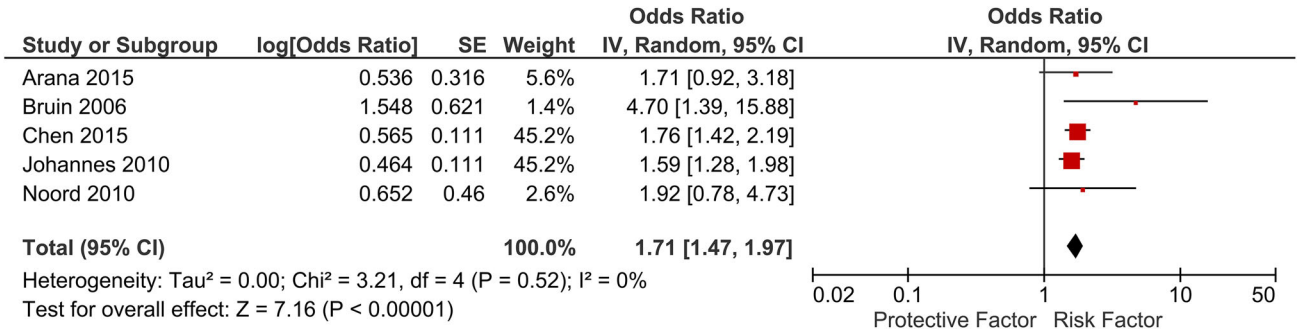

Fig. 6 Forest plot of adjusted association between domperidone use and ventricular arrhythmia and cardiac arrest from studies utilizing administrative database. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

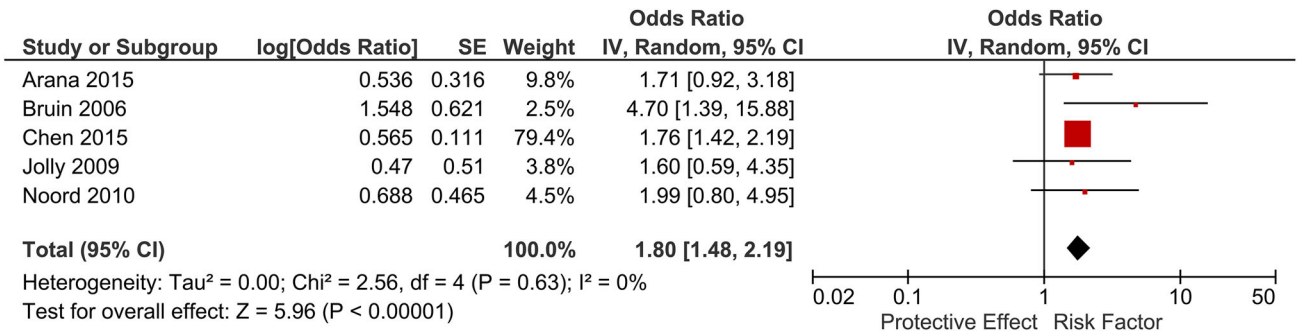

Fig. 7 Forest plot of adjusted association between domperidone use and cardiac arrest. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

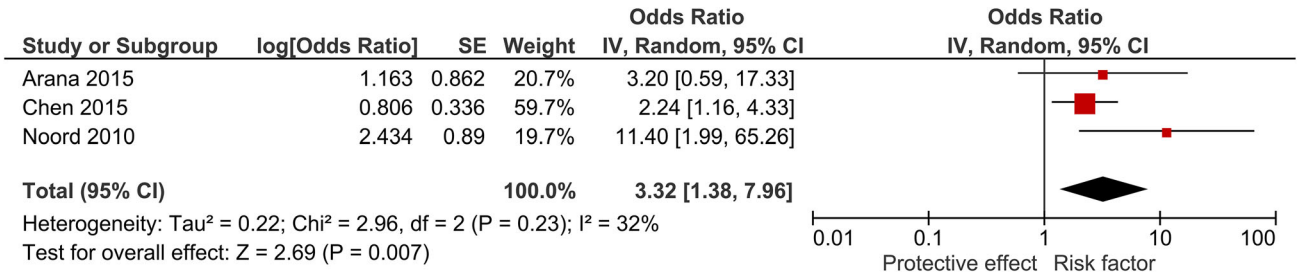

Fig. 8 Forest plot of adjusted association between domperidone use (higher than 30 mg per day) and cardiac arrest. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

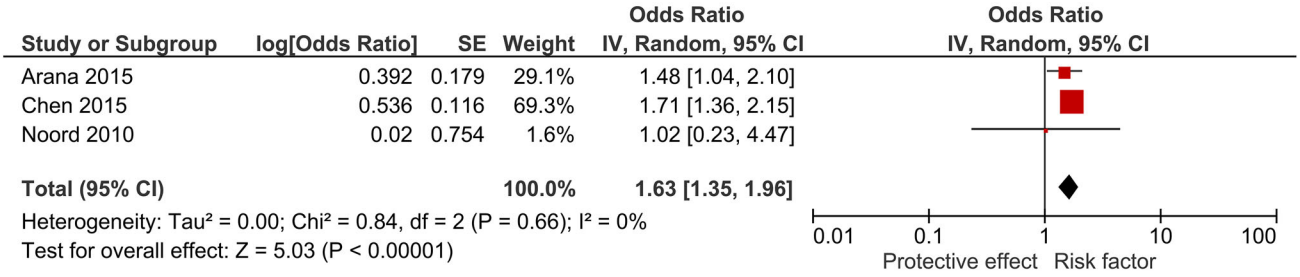

Fig. 9 Forest plot of adjusted association between domperidone use (30 mg per day or lower) and cardiac arrest. *CI* confidence interval, *df* degree of freedom, *IV* inverse variance, *SE* standard error

QT syndrome increases the risk of ventricular arrhythmias and sudden cardiac death [16]. However, there are other studies that found the opposite conclusion. There is one systematic review [42] and one meta-analysis of the efficacy of domperidone as a galactagogue [11] in which no adverse events occurred among the maternal or neonatal cohorts. These two reviews were based on randomized control trials that had an adverse events outcome as a secondary endpoint. In addition, the meta-analyses did not perform an analysis on the association between domperidone exposure and adverse events. Therefore, these two studies are not good comparators for our findings.

Overall, the results of this analysis were convincing because the studies involved in this analysis were of moderate to high quality. According to the Newcastle-Ottawa Quality Assessment Scale for case-control studies, four studies [35, 36, 38, 39] were of high quality and provided adequate case definitions and justification for selection bias. However, biases were possible and may affect the association between domperidone exposure and risk of cardiac adverse events. Exposure misclassification was very likely because none of the studies validated the domperidone exposure. Also, domperidone is a drug for symptomatic relief which can be discontinued by patients at any time, so the exposure could be overestimated. The number of patients exposed to domperidone could be higher than reported by the studies. The differences in domperidone status in study countries could be the reason that the exposure was underestimated. In The Netherlands, domperidone is an over-the-counter drug and the exposure of over-the-counter medications could be unreported, leading to a lower number of cases than might have occurred. However, the effect of these biases was toward the null and does not explain the finding of our meta-analysis. Finally, the selected studies failed to account for potential confounders. For example, cardiovascular symptoms can be caused by underlying gastrointestinal diseases (e.g., swallowing-induced tachyarrhythmia or arrhythmias-complete heart block induced by inflammatory bowel disease [43]) and vice versa (e.g., flatulence and gastrointestinal distress induced by paroxysmal tachycardia [44]). Only one study [37] controlled for the underlying gastrointestinal diseases which, in some cases, could be the cause of the outcome of interest (arrhythmia). Therefore, reverse causality could be possible if domperidone was used for the treatment of those gastrointestinal discomforts.

Other than the quality of the original studies which affects the quality of this meta-analysis, another limitation was in the small number of articles included in the analysis. Only 13 articles were found from the literature search. Some other studies used general terms to refer to drugs that can prolong the QT-interval which may include domperidone [45, 46], so extracting data from these studies was not possible. However, after contacting the corresponding authors, some confirmed that domperidone exposure was not included in their studies. Also, this meta-analysis is not applicable to some populations, especially breastfeeding women. Demographics of the cases and controls in included studies indicated that the majority of them were older males. Only one study [38] can be used to represent this population because it has higher female participants with a mean age in the child-bearing-potential age range. In addition, most of the studies included in this analysis had a small number of cases which can lead to false negative findings in some selected studies.

Therefore, larger studies, especially in the countries where domperidone is approved, should be conducted to answer this research question. However, the selective prescribing will be an issue for large observational studies because of the previous evidence that relate domperidone to an increased risk of ventricular arrhythmia and cardiac death. Large randomized controlled trials are better alternatives to address this research question. However, conducting the trials will raise ethical issues and should be performed with caution. Any studies that will be conducted should have a more representative population of domperidone users. This meta-analysis showed that most of the participants were male and elderly. However, domperidone

users are usually the general population and can include neonates and the breastfeeding population. In fact, there is an ongoing clinical trial [47] addressing the efficacy and safety of domperidone in breastfeeding women. That study will add more information to this topic and perhaps will warrant revisiting a meta-analysis on this topic. In addition, future studies should compare the adverse effects associated with domperidone with adverse effects associated with other prokinetic agents, especially metoclopramide, to evaluate the risk-benefit ratio of the use of domperidone.

5 Conclusion

In conclusion, this meta-analysis of six studies that evaluated the use of domperidone among mostly older males found that domperidone use is significantly associated with ventricular arrhythmia or cardiac arrest. This validates the warnings put out by Health Canada and the FDA. However, in the future, larger randomized trials should be performed among more diverse populations.

Acknowledgments Nattawut Leelakanok would like to acknowledge the support from The Royal Thai Government Scholarship. We thank Saket Girotra for his assistance. We also thank Xiaomei Gu for her help in developing search terms; Daniel Fife from Johnson & Johnson for his references list; Elizabeth Asztalos, Mathieu Pasquier, and Patrick Pun for providing useful information from their publications.

Compliance with Ethical Standards

Funding There was no external source of funding. MLS receives salary support from a VA Health Services and Research Career Development Award (CDA 11-215).

Conflict of interest NL, AH and MLS have no conflicts of interest to declare.

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