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Domperidone and the Risks of Sudden Cardiac Death and Ventricular Arrhythmia: A Systematic Review and Meta-Analysis of Observational Studies

Running Title: Domperidone and Ventricular Arrhythmia

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ABSTRACT

Aims: Concerns exist regarding the cardiovascular safety of domperidone. However, many of the previous studies addressing this issue had important limitations. We aimed to examine domperidone and the risks of sudden cardiac death and ventricular arrhythmia through a systematic review and meta-analysis of observational studies, including an in-depth methodological assessment.

Methods: We systematically searched MEDLINE, PubMed, EMBASE, Scopus, and CINAHL Plus to identify observational studies examining the association of domperidone and sudden cardiac death and/or ventricular arrhythmia. We assessed study quality in duplicate using the ROBINS-I tool supplemented by an assessment of specific biases and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. Data were pooled across studies using DerSimonian and Laird random-effects models.

Results: Six case-control studies, one case-crossover study, and one retrospective cohort study were included (n: 480,395). Based on ROBINS-I, three studies had moderate risk of bias, four had serious risk, and one had critical risk. The overall GRADE rating is moderate. When data were pooled across non-overlapping studies, domperidone was associated with an increased risk of composite endpoint of sudden cardiac death or ventricular arrhythmia compared to non-use (adjusted odds ratio [OR]: 1.69; 95% confidence interval [CI]: 1.46, 1.95; I^2: 0%; τ^2: 0). This association persisted when restricted to higher-quality studies (OR: 1.60; 95% CI: 1.30, 1.97; I^2: 0%; τ^2: 0).

Conclusions: Domperidone is associated with an increased risk of sudden cardiac death and ventricular arrhythmia compared to non-use. Further investigation comparing domperidone to an active comparator and in younger populations are warranted.

INTRODUCTION

Domperidone, a peripheral dopamine antagonist, is approved for a variety of pharmacologic uses, including gastrointestinal motility disorders associated with gastritis and diabetic gastroparesis, as well as nausea and vomiting from the use of anti-Parkinson agents.[1, 2] It is also frequently used off-label for postpartum prolactin stimulation.[3, 4] Despite its frequent use in many jurisdictions, concerns exist regarding its safety. Since 2012, there have been warnings by multiple regulatory agencies (Health Canada, European Medicines Agency, Medicines and Healthcare products Regulatory Agency in United Kingdom, and Health Sciences Authority in Singapore) against the use of domperidone in daily doses greater than 30 mg and in patients aged more than 60 years due to concerns of sudden cardiac death and ventricular arrhythmia.[5-8] These recommendations were based on increased risks observed in two observational studies.[9, 10] The findings may be explained by domperidone's propensity to prolong QT-interval and cardiac repolarization, which can trigger severe forms of ventricular arrhythmia (Torsades de Pointes) that can result in sudden cardiac death.[11, 12] Despite these warnings, drug utilization studies show that there has not been substantial changes in its prescribing in several European countries.[13, 14]

In recent years, several additional observational studies have investigated the possible association between domperidone and the risk of sudden cardiac death and ventricular arrhythmia.[15-18] These studies have provided widely divergent results, ranging from a small increase that did not reach statistical significance to a 4-fold increased risk of sudden cardiac death. Two systematic reviews on this potential adverse drug effect have been published.[19, 20] However, they have not been updated with recently published studies[21, 22], and these previous reviews had important methodological limitations, including the use of the Newcastle-Ottawa Scale for quality assessment. This scale has been shown to have several important limitations[23],

including high inter-user variability[24] and includes some concepts related to external validity as part of its quality assessment[25]. In addition, an assessment of the overall body of evidence would be optimal to determine the need for future studies in this area. Given the heterogeneity of the existing literature, lack of reliable assessment on the risk of bias, the severity of purported adverse events, and unchanged prescribing patterns, there remains an urgent need to examine this potential association. This systematic review with meta-analysis aims to provide a comprehensive and rigorous assessment of the existing literature of observational studies regarding the association between domperidone and the risks of sudden cardiac death and ventricular arrhythmia. We also aim to explicitly explore the quality of studies in this area and potential heterogeneity in the literature through subgroup analyses.

METHODS

A pre-specified protocol was followed in conducting this systematic review, and reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26]

Search Strategy

We systematically searched MEDLINE, PubMed, EMBASE, Scopus, and CINAHL Plus from inception to December 2019 to identify observational studies examining the association of domperidone with sudden cardiac death and/or ventricular arrhythmia. Search terms included Medical Subject Heading (MeSH) terms for PubMed, MEDLINE, and CINAHL Plus, as well as Emtree terms for Embase. Keywords for domperidone and all types of ventricular arrhythmia and sudden cardiac death were added to the search strategy and used in all five databases (**Supplementary Table S1**). No restrictions were applied on the type of study or the language of publication. References of previous systematic reviews and relevant articles were manually screened.

Inclusion and Exclusion Criteria

Observational studies (cohort, case-control, case-cohort, and case-crossover studies) were included. Inclusion was further restricted to studies of adults aged 18 years or older and studies with sample sizes greater than 1000 subjects to ensure adequate power to provide meaningful estimates of the risks of sudden cardiac death and ventricular arrhythmias due to their rare occurrence. Statistical adjustment or matching for age was considered a necessary inclusion criterion as it is a strong, independent risk factor for cardiovascular diseases. Cross-sectional studies, randomized controlled trials, case reports, case series, letters to the editor, commentaries and editorials, previous reviews and meta-analyses, animal studies, and basic science studies were

excluded. Finally, unpublished data and conference abstracts were excluded as they usually contain insufficient information for quality assessment and their results can be preliminary.

Titles and abstracts were screened by two independent reviewers (L.B.O. and C.M.) and any publication deemed potentially relevant by either reviewer was carried forward to full-text review. Following full-text review, the final list of included studies was determined by the two reviewers, with any discrepancies to be resolved by consensus or, if necessary, by a third reviewer (K.B.F.).

The primary outcome of this systematic review was a composite endpoint of sudden cardiac death and ventricular arrhythmia. For studies that only investigated sudden cardiac death, the estimates for sudden cardiac death were included in the primary analysis as they are specific and often occur due to ventricular arrhythmia.[27, 28]

Data Extraction

Information extracted independently by two reviewers included: 1) study characteristics (study design, sample size, patient population, intervention versus comparator, study outcomes, country of study, data source, and study period); 2) baseline patient characteristics (age, sex, smoking, history of cardiovascular diseases: cardiomyopathy, heart failure, valvular heart disease, hypertension, dyslipidemia, myocardial infarction, ischemic heart disease, cerebrovascular disease, and arrhythmia); 3) concomitant medication use (QT-prolonging medications and cytochrome P450 3A4 inhibitors); 4) point estimates and corresponding 95% confidence intervals [CI] for measure of association (hazard ratio [HR], odds ratio [OR], or rate/risk ratio) with event counts. When the outcome measures were adjusted for or matched on covariates, these variables were recorded. Specific concomitant medications were assessed. Due to domperidone's effect on the QT-interval, other QT-interval prolonging medications could cause additive effects.[12] As a CYP

3A4 substrate, inhibition of CYP 3A4 could increase the concentration of domperidone and lead to higher risk of adverse events.[1]

Quality Assessment

The included studies underwent quality assessment by two independent reviewers using the ROBINS-I (Risk of Bias in Non-Randomized Studies – of Interventions) tool.[25] In this tool, studies were compared to a perfect "target study" resembling a randomized controlled trial. The seven domains of bias assessed include bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in the selection of reported results. Signaling questions helped guide assessment for each domain where the risk of bias was assessed as "low", "moderate", "serious", "critical" or "no information" for each study.

Our ROBINS-I assessment was supplemented by the detailed assessment of specific biases, including prevalent user bias, persistent user bias (case-crossover studies only), time-window bias, misclassification of exposure, and residual confounding. Prevalent user bias is a selection bias in which chronic users were included in the study.[29] This results in the depletion of susceptible subjects as patients who had the event during the initial exposure period will not survive to be included in the study. In case-crossover studies, persistent user bias occurs when non-transient exposures are assessed and usually biases the estimates upwards due to long-term medication use and right truncation.[30] Time-window bias occurs due to differential duration of follow-up for cases and controls resulting in differential opportunity for exposure (i.e., the longer the follow-up time, the higher the probability of exposure).[31] Misclassification of exposures can be either differential or non-differential, depending on whether the probability of misclassification is different or comparable in the different groups. Lastly, residual confounding arises due to

unmeasured or unknown confounding, inappropriate or lack of adjustment of certain confounding variables, or the absence of adjustment for time-varying confounding.

The body of evidence was then assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework. GRADE rates the quality of evidence as "high", "moderate", "low", or "very low" for any particular outcome. It can be influenced by a number of factors such as bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response relationship, and confounding.[32]

Statistical Analysis

Meta-analysis of adjusted point estimates of studies with non-overlapping databases was conducted using the DerSimonian-Laird random-effects models with inverse variance weighting. In subsequent analyses, studies were stratified by the overall risk of bias, dose, duration of use, and age. Heterogeneity of studies was assessed using I^2 statistic to estimate the variation between studies that was due to heterogeneity as opposed to chance and the τ^2, the between-study variance in the random-effects model. Publication bias was not assessed due to the limited number of included studies. An influence analysis was conducted using leave-one-out method where estimates were pooled omitting one study at a time. All statistical analyses were conducted using R version 3.4.3.

RESULTS

Search Results

Our search yielded 914 potentially relevant articles after duplicates were removed (**Figure 1**). Following title/abstract screening, 16 full-text articles were retrieved and assessed for eligibility. Finally, eight articles were included in the systematic review (six case-control studies[9, 10, 15-17, 21], one case-crossover study[18], and one retrospective cohort study[22]).

Study and Patient Characteristics

A total of 480,395 subjects (case-control studies, 10,900 cases and 123,788 controls; case-crossover study, 25,356 subjects; cohort study, 320,351 subjects) were included in this systematic review (**Table 1**). Two studies[15, 16] investigated the risk of sudden cardiac death with a number of QT-prolonging medications including domperidone, while the other six studies[9, 10, 17, 18, 21, 22] focused solely on domperidone. Study populations consisted of mostly older subjects with multiple comorbidities. Two studies[21, 22] restricted inclusion to Parkinson's patients and postpartum women, respectively. In the included case-control studies, exposures were assessed based on the index date (date of event) for current and past exposure, although the duration of days used to assess exposure varied between studies. Study periods ranged from 1990 to 2012, and outcomes included sudden cardiac death or the composite outcome of sudden cardiac death/ventricular arrhythmia.

Risk of Sudden Cardiac Death/Ventricular Arrhythmia

Domperidone was either compared to non-use or to an active comparator (proton pump inhibitors and/or metoclopramide). Five studies[9, 16, 17, 21, 22] reported treatment effects that suggested an increased risk that did not reach statistical significance (**Supplementary Table S3**). The reported harm ranged from an adjusted OR of 1.22 (95% CI: 0.99, 1.50) to 3.80 (95% CI: 1.50,

9.70). Straus[15] and Renoux et al.[21] were excluded from the meta-analyses as their data overlapped with those of other included studies. Following meta-analysis (**Figure 2**), domperidone was associated with an increased risk of sudden cardiac death and ventricular arrhythmia (adjusted OR: 1.69; 95% CI 1.46, 1.95; I^2: 0%; τ^2: 0). Two studies[10, 18] provided 87.9% of the weight of the overall analysis. **Figure 3** shows that this association persisted when analyses were restricted to higher quality studies (adjusted OR: 1.60; 95% CI: 1.30, 1.97; I^2: 0%; τ^2: 0). Among the three studies[10, 17, 18] that compared domperidone to proton pump inhibitors, two studies[10, 18] found an increased risk while the other[17] showed no difference (**Supplementary Table S4**); the adjusted OR ranged from 1.26 to 1.83. When domperidone was compared to metoclopramide for the outcome of sudden cardiac death, domperidone was associated with a decreased risk (OR: 0.40; 95% CI: 0.17, 0.94).[17]

Subgroup Analyses

Dose and Duration of Use

Due to differences in the cutoffs for dose and duration of use of domperidone in the studies, pooled analysis was only conducted for domperidone dose >30mg (**Supplementary Table S5**). The risk appears to be higher with >30mg compared to non-use (adjusted OR: 3.32; 95% CI: 1.38, 7.96; I^2: 32%; τ^2: 0.22). Only two studies explored a duration-response association. One study[17] showed that there were higher odds of sudden cardiac death in patients exposed to domperidone for <16 days compared to 16 or more days. In contrast, another study[21] showed no difference in harm based on the duration of exposure **(Supplementary Table S6**).

Age

Two studies[10, 17] conducted subgroup analyses stratified by age, and one study[22] only included postpartum women. When the study population was stratified by age, subjects >60 years

old had adjusted ORs of 1.64 (95% CI: 1.31, 2.05) in one study and 1.65 (95% CI: 0.89, 3.07) in another when domperidone was compared to non-use. The evidence was less clear in patients ≤60 years due to limited number of exposed events **(Supplementary Table S7**).

Sensitivity analysis

In our influence analysis, there was no evidence that any one study had a substantial impact on the overall results (**Supplementary Figure S1**).

Overall Quality Assessment

The overall quality assessment for each study was determined by the domain with the highest bias rating in ROBINS-I. Three studies had a "moderate" risk of bias, four had "serious" risk, and one had "critical" risk (**Table 2**). Four studies had the rating of "serious" in the confounding domain due to lack of adjustment of one or more important covariates, most often cardiomyopathy, valvular heart disease, or concomitant medications (**Supplementary table S8**). Four studies had the rating of "serious" in the selection of participants domain due to presence of prevalent user bias. One study (the case-crossover study) had the rating of "critical" due to the presence of persistent user bias and substantial differences in baseline characteristics. The body of evidence was rated to be "moderate" by the GRADE framework.

Prevalent User Bias

The inclusion of prevalent users was observed in multiple studies[9, 15, 16, 18, 22] where inclusion was not restricted to new users (**Table 2**). Only three studies[10, 17, 21] restricted their study population to new users with cohort entry as first exposure to any study drug to avoid depletion of susceptibles.[33] This bias may underestimate the risk of outcome as the subjects potentially at the greatest risk may have been excluded.

Persistent-user bias

Domperidone can be taken as needed for symptomatic relief of gastrointestinal disorders, but in most cases, patients use it on a regular basis. Therefore, its use is often not transient, and it may not be suitable for study using the cross-over design, where only discordant exposure pairs are included for the analysis. When medications are taken persistently, the most likely scenario involving discordant pairs is where case periods are exposed and control periods are unexposed due to underlying patterns of drug utilization. The opposite scenario of case period as unexposed and control period as exposed is unlikely.[30] This would bias the estimates upwards, which is consistent with the findings of Chen et al.[18], in which there was a consistent harmful effect when domperidone was compared to non-use.

Time-Window Bias

Time-window bias could be present in three population-based case-control studies.[9, 15, 16] Since these case-control studies did not match on follow-up time when selecting controls, it is possible that follow-up time was not equal among cases and controls. Matching on duration of follow-up is necessary to ensure that cases and controls have the same opportunity for exposure.

Misclassification of exposure

Non-differential misclassification of exposure likely occurred in the studies that used European databases as domperidone is available over-the-counter in many parts of Europe. In 2014, domperidone was switched to prescription only in the United Kingdom.[34] Due to the nature of the databases used, information on over-the-counter medication use was likely not available. This would potentially bias the estimates towards the null, resulting in an underestimated risk. Misclassification also occurred in Smolina et al.[22] when subjects were considered exposed until

30 days after the end of the prescription. The grace period may be too long given the purported mechanism.

Residual Confounding

Residual confounding is present in all observational studies due to their non-randomized treatment allocation. With non-use as the comparison group for most included studies[9, 15, 16, 21, 22], confounding by indication is likely as those prescribed domperidone may be intrinsically different from non-users. Although studies adjusted for some covariates to address this issue, unmeasured or unknown confounding remains a potential limitation. The use of active comparator could attenuate this type of confounding.[35] However, confounding by indication or contraindication remains possible; for example, the protective association observed when comparing domperidone versus metoclopramide in the study by Arana et al.[17] may be the result of patients with risk factors for ventricular arrhythmias being preferentially prescribed metoclopramide given the safety concerns associated with domperidone. Important confounding variables requiring adjustment to warrant a bias assessment of "moderate" were age, sex, cardiomyopathy, heart failure, history of myocardial infarction, history of arrhythmia, diabetes mellitus, valvular heart disease, and concomitant medications.[36, 37] There were also concerns when variables were measured until the index date in case-control studies (date of event) as oppose to at baseline as this could result in adjustment for the consequence of exposure. Time-varying confounding was also not considered in any of the included studies.

DISCUSSION

Our systematic review was designed to synthesize the available evidence regarding the real-world effect of domperidone on the risks of sudden cardiac death and ventricular arrhythmia. We identified eight observational studies of varying quality that suggest domperidone is associated with a 60% increased risk of sudden cardiac death and ventricular arrhythmia compared to non-use. This risk was especially evident with higher doses and in elderly individuals. There is, however, a lack of evidence in patients younger than 60 years due to the small number of exposed events in the studies. The results were conflicting when domperidone was compared to active comparators. Our detailed analysis of specific biases showed that five studies included prevalent users, three studies did not consider equal follow-up time for cases and controls, five studies could be affected by exposure misclassification, and four studies could have important residual confounding.

Two previous systematic reviews[19, 20] published on this topic had important limitations as study quality was assessed using the outdated Newcastle-Ottawa Quality assessment scale for evaluation of nonrandomized studies. Reliability between reviewers assessing the quality of the studies has shown to be a limitation of the Newcastle-Ottawa Quality assessment scale due to lack of clear instructions and ambiguity of undefined factors.[23, 24] In our review, we used the more contemporary ROBINS-I quality assessment tool for each individual study and thorough assessment of specific biases in addition to the GRADE framework to assess the overall body of evidence. ROBINS-I offers a more comprehensive assessment of different biases and includes extensive instructions with signaling questions to minimize inter-user variability. Furthermore, we included two recently published observational studies. Our updated review and utilization of ROBINS-I allowed us to conduct a pooled analyses stratified by study quality, which showed that

some studies with higher risk of bias may overestimate the risk of sudden cardiac death and ventricular arrhythmia compared to those studies rated "moderate". These results demonstrated that there is a consistent increased risk of sudden cardiac death and ventricular arrhythmia associated with domperidone compared to non-use, but the effect may not be as large as some studies suggest. Moreover, we conducted multiple subgroup analyses not present in previous reviews, including analyses stratifying by active comparators, domperidone dose, duration of use, and age.

In some jurisdictions, alternatives to domperidone such as proton pump inhibitors or metoclopramide for diabetic gastroparesis are available.[38] However, prescriptions for domperidone in special populations remain prominent given the lack of therapeutic alternatives. In Parkinson's patients, domperidone remains the first choice for nausea and vomiting as an antiemetic and prokinetic agent.[39] The use of metoclopramide is not recommended as it could lead to drug-induced parkinsonism and increased severity of disease.[40] As part of the Canadian Network for Observational Drug Effect Studies (CNODES), Renoux et al.[21] demonstrated that a clinically significant increased risk remains possible in this patient population, although the results did not reach statistical significance. Similarly, domperidone was prescribed to one in five Canadian postpartum women for breastfeeding in 2011, often in doses greater than 30 mg.[41] A systematic review of randomized controlled trials on domperidone for breast milk production concluded that there were no reported cases of prolonged QT syndrome or sudden cardiac death with short-term benefit in breast milk volume.[4] However, the sample sizes of included trials are often too small to detect rare adverse events. The only observational study we identified in postpartum women[22] did not identify a definitive association and had important limitations, including a small number of events, exposure and outcome misclassification, and important

residual confounding. Risks in this population remain uncertain as patients are usually young with minimal comorbidities and comedication use. Through our subgroup analyses, we identified that risks may be increased with doses >30 mg. Nonetheless, the effect from duration of exposure is less clear.

Our systematic review has several important strengths. To our knowledge, this is the first review to thoroughly assess study quality and its impact on overall results. Second, our search strategy was broad with no restrictions on the type and language of publication. Third, we defined our inclusion criteria to only include quality studies with adequate power to detect the outcome. Fourth, we followed a pre-specified protocol.

Our study also has some potential limitations. We did not conduct a search of the gray literature or include any unpublished results in our review as we felt the results would be incomplete. Due to the scarcity of high-quality evidence, inclusion was restricted to observational studies; while these studies provide key information regarding real-world effects, confounding by indication and by other variables remains possible. Although ventricular arrhythmia and sudden cardiac death often occur with no prodromal symptoms, protopathic bias cannot be ruled out. As is true with all knowledge syntheses, our study may have been affected by publication bias. ROBINS-I is designed for target trials and may not perform optimally in detecting the extent of bias in case-control studies; however, it is still the most comprehensive and rigorous risk assessment tool for non-randomized studies. We also did not include any studies conducted in the pediatric populations as the focus was on the adult population. Lastly, we treated estimates of OR and HR interchangeably and pooled them together. In nested case-control studies with risk-set sampling, the OR provides an unbiased estimator of the hazard ratio.[42] In addition, in traditional case-control studies, the OR estimates relative risk under the rare disease assumption. With HRs

estimating relative risks under the assumption of constant hazards, we are confident this assumption did not considerably affect our results.

CONCLUSIONS

Domperidone is associated with an increased risk of sudden cardiac death and ventricular arrhythmia compared to non-use. The strength of evidence was stronger in older patients using daily doses above 30 mg. While many of the included studies had important methodological limitations, similar results were observed when restricting to higher quality studies. Most of the included studies were conducted in older individuals with large comorbidity burden. While one recent study was identified in post-partum women, the amount of evidence that is available for this population remains limited.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY

The data are available in the article and in its online supplementary material. No additional data is available.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b). [43-45]

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Table 1. Characteristics of observational studies examining association of domperidone with sudden cardiac death and/or ventricular arrhythmia.

Study	Study Design	Study Sample Size	Patient Population	Exposure vs. Reference Group	Study Outcome(s)	Study Location	Data Source	Study Period
Straus[15] 2005	Population based Case-control	N=775 cases, 6297 controls	Subjects 18 years and older Age: 71 years (cases), 69 years (controls) Gender: 40% females	Domperidone vs. non-use	Sudden cardiac death	Netherlands	Integrated Primary Care Information (IPCI) database	1995 – 2003
Jolly[16] 2009	Population based Case-control	N=1010 cases, 3030 controls	Adults aged 20 – 85 years who had died in the community Age: 67.6 years Gender: 32.6% female	Domperidone vs. non-use	Sudden cardiac death	United Kingdom	Public Health Mortality Files	2003 – 2007
van Noord[9] 2010	Population based Case-control	N=1366 cases, 14 114 controls	Patients 18 years and older Age: SCD: 72.5±14.1 years (cases), 66.3±13.9 years (controls) Gender: 40% female	Domperidone vs. non-use	Sudden cardiac death, non-fatal ventricular arrhythmia	Netherlands	Integrated Primary Care Information (IPCI) database	1996 – 2007
Johannes[10] 2010	Nested case-control	N=1608 cases, 6428 controls	Eligible patients enrolled health database Age: 79.4 years Gender: 53% female	Domperidone vs. non-use, PPI	Serious ventricular arrhythmia/ sudden cardiac death	Canada	Saskatchewan Health Database	1990 – 2005
Arana[17] 2015	Nested case-control	N= 3239 cases, 12 572 controls	Subjects at least 2 years of age Age: 55 ± 19 years Gender: 56.9% female	Domperidone vs. non-use, metoclopramide, PPI	Sudden cardiac death	United Kingdom	Clinical Practice Research Datalink (CPRD)	2005 – 2011
Chen[18] 2015	Case-crossover[a]	N=25 356	Patients 18 years or older Age: 61 ± 19 years Gender: unknown	Domperidone vs. non-use, metoclopramide, PPIs	Ventricular arrhythmia, Sudden cardiac death	Taiwan	Taiwan's Longitudinal Health Insurance Database (LHID)	2000 – 2011
Renoux[21] 2016	Nested case-control	N=2902 cases, 81 347 controls	Patients aged 50 or older with first diagnosis of Parkinson's disease or first prescription for anti-Parkinson agent during study period Age: 74.4 years Gender: 52.6% female	Domperidone vs. non-use	Ventricular tachyarrhythmia/ sudden cardiac death	Canada, United Kingdom	Canadian Provincial Database, CPRD	1990 – 2012
Smolina[22] 2016	Retrospective cohort	N=320 351 (21 events)	All women with live birth Age: majority from 25 – 39 years Gender: 100% female	Domperidone vs. non-use	Hospitalization for ventricular arrhythmia or cardiac arrest	Canada	British Columbia Health Database	2002 – 2011

PPI=Proton Pump Inhibitors

[a]Case period: 1-30 days before ventricular arrhythmia, Control period: 91-120 days before ventricular arrhythmia

Table 2. Quality assessment using the ROBINS-I tool, supplemented by the assessment of specific biases present in studies of the association between domperidone and the risk of sudden cardiac death

Study	ROBINS-I rating	Prevalent user bias	Time-window bias	Persistent user bias[a]	Misclassification of exposure	Important residual confounding
Straus 2005	Serious	x	x		x	x
Jolly 2009	Serious	x	x		x	x
van Noord 2010	Serious	x	x		x	x
Johannes 2010	Moderate					
Arana 2015	Moderate				x	
Chen 2015	Critical	x		x		
Renoux 2016	Moderate					
Smolina 2016	Serious	x			x	x

[a]Present in case-crossover studies

FIGURE LEGENDS

Figure 1 PRISMA flow diagram of studies identified on domperidone and the risks of sudden cardiac death and ventricular arrhythmia.

Figure 2 Forest plot of the association of domperidone and the risks of sudden cardiac death and ventricular arrhythmia. NA: Non-applicable

Figure 3 Forest plot of the association of domperidone and the risks of sudden cardiac death and ventricular arrhythmia stratified by overall study quality based on the ROBINS-I tool. NA: Non-applicable

Figure 1.

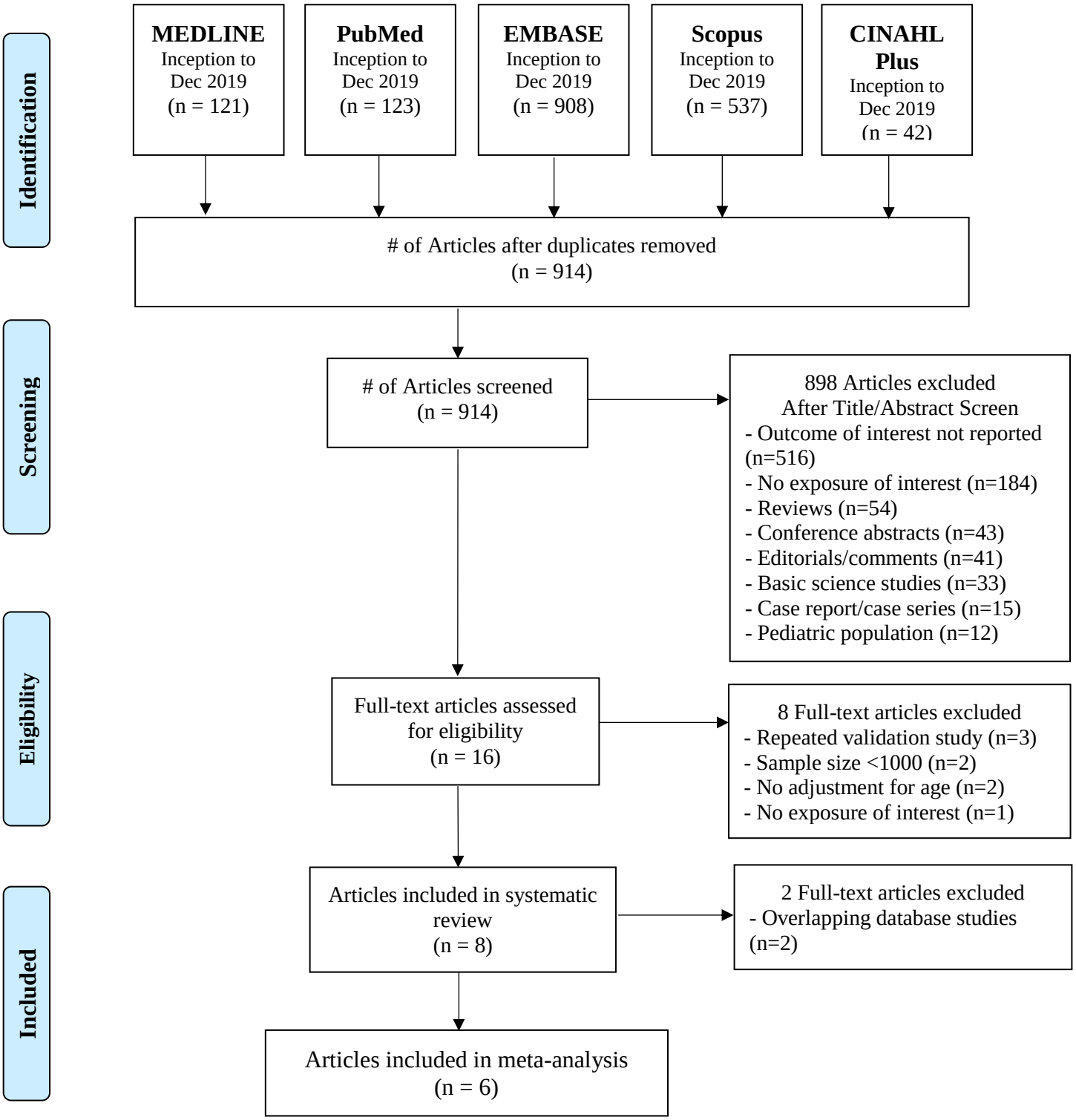

Figure 2.

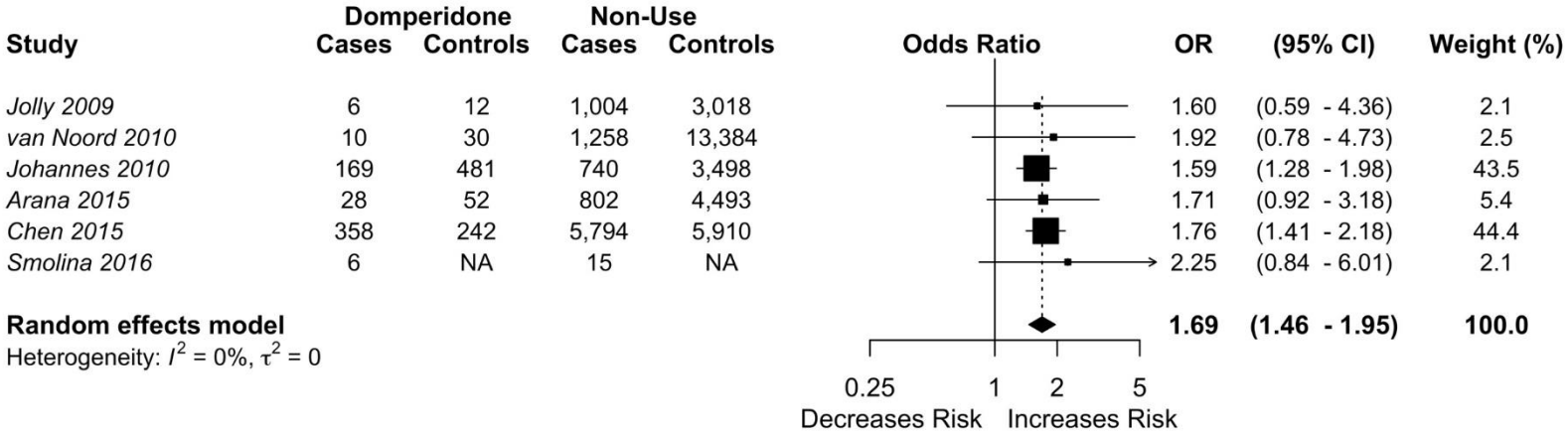

Figure 3.