



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Sudden cardiac and sudden unexpected death related to antipsychotics: A meta-analysis of observational studies

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Salvo, F., Pariente, A., Shakir, S., Robinson, P., Arnaud, M., Thomas, S.H.L., et al. (2016). Sudden cardiac and sudden unexpected death related to antipsychotics: A meta-analysis of observational studies. *CLINICAL PHARMACOLOGY & THERAPEUTICS*, 99(3), 306-314 [10.1002/cpt.250].

Availability:

This version is available at: <https://hdl.handle.net/11585/568145> since: 2016-11-17

Published:

DOI: <http://doi.org/10.1002/cpt.250>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the peer reviewed accepted manuscript of the following article:

Salvo F, Pariente A, Shakir S, Robinson P, Arnaud M, Thomas SHL, Raschi E, Fourrier-Reglat A, Moore N, Sturkenboom M, Hazell L, Investigators Aritmo Consortium. *Sudden Cardiac and Sudden Unexpected Death Related to Antipsychotics: A Meta-analysis of Observational Studies*.

Clinical Pharmacology & Therapeutics 2016, 99(3), 306-314

Final peer reviewed version available at: <http://dx.doi.org/10.1002/cpt.250>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Sudden cardiac and sudden unexpected death related to antipsychotics: a meta-analysis of observational studies.

Francesco Salvo^{1,2} PhD, Antoine Pariente^{1,2,3} PhD, Saad Shakir⁴ FRCP, Philip Robinson^{3,5} PhD, Mickael Arnaud¹ MsC, Simon HL Thomas⁶ MD, Emanuel Raschi⁷ PhD, Annie Fourier-Réglat^{1,2} PharmD, Nicholas Moore^{1,2,3} PhD, Miriam Sturkenboom⁸ PhD, Lorna Hazell⁴ MSc. *On behalf of Investigators of the ARITMO consortium.*

- 1 Univ. Bordeaux, INSERM U657, F33000 Bordeaux, France
- 2 CHU Bordeaux, F33000 Bordeaux, France
- 3 CIC Bordeaux CIC1401, F33000 Bordeaux, France;
- 4 Drug Safety Research Unit, Southampton, Hampshire UKSO311AA, United Kingdom
- 5 ADERA, F33600 Pessac, France;
- 6 Medical Toxicology Centre, Institute of Cellular Medicine, Newcastle University, Newcastle UKNE24HH, United Kingdom;
- 7 Department of Medical and Surgical Sciences, University of Bologna, IT40126 Bologna, Italy;
- 8 Department of Medical Informatics, Erasmus University Medical Centre, NL3000 DR Rotterdam, Netherlands.

Corresponding author:

Francesco Salvo

146 Rue Léo Saignat, BP 36, Université de Bordeaux, INSERM U657

F-33000 Bordeaux

Phone: +33 5 57 57 15 60

Fax: +33 5 57 57 46 71

e-mail: francesco.salvo@u-bordeaux.fr

ABSTRACT

To estimate the risk of sudden cardiac death (SCD) or sudden unexpected death (SUD) related to the individual antipsychotics, a meta-analysis of observational studies was performed.

Adjusted Odds Ratio (OR) of SCD/SUD with 95% confidence intervals (CI) were extracted and pooled; heterogeneity was studied using Q statistic and I^2 index, and its potential causes (e.g. hERG blockade potency) explored using meta-regression. Two cohort (740,306 person-years) and four case-control (2,557 cases; 17,670 controls) studies, investigating nine antipsychotics, were included. Compared with non-users, the risk was increased for quetiapine (OR=1.72, 95%CI 1.33-2.23), olanzapine (OR=2.04, 1.52-2.74), risperidone (OR=3.04, 2.39-3.86), haloperidol (OR=2.97, 1.59-5.54), clozapine (OR=3.67, 1.94-6.94), and thioridazine (OR=4.58, 2.09-10.05). Heterogeneity was found (Q=20.0, p=0.01; I^2 =60.0%), and the increasing mean hERG blockade potency (p=0.01) accounted for 43% of this. The SCD/SUD risk differed between individual antipsychotics, and mean hERG blockade potency could be an explanatory factor. This should be considered when initiating antipsychotic treatment.

INTRODUCTION

Some antipsychotic drugs have been shown to increase the risk of sudden cardiac death (SCD) and/or sudden unexpected death (SUD) (1, 2). One potential mechanism is via blockade of the cardiac potassium channel coded by *hERG*, the human Ether-à-go-go-Related Gene, usually referred to as the hERG channel (3), which is responsible for the rapid delayed rectifier potassium current (I_{Kr}). This blockade can result in delayed cardiac repolarization, prolongation of the QT interval on the ECG (4), and an increased risk of the polymorphic ventricular tachycardia termed *torsade de pointe*, a cardiac rhythm disorder that may result in cardiac arrest.

Pharmacoepidemiological studies have previously been performed to investigate the risk of SCD/SUD associated with the use of antipsychotic drugs. Some of these compared typical and atypical antipsychotics and found no inter-class difference (1, 5, 6), but all had limited power to compare risks associated with the use of individual antipsychotics (1, 6). Thus, a meta-analysis of observational studies was conducted to evaluate the risk of SCD/SUD associated with the use of individual antipsychotic drugs and to explore sources of potential heterogeneity among drugs.

RESULTS

Study selection

A systematic literature search identified 4,000 articles, 782 of which were duplicates and were thus removed. Of the 3,218 individual remaining articles, 3,178 were found to be irrelevant and excluded after review of title and abstract. The remaining 40 references underwent full-text examination (see supplementary information file for selection process details), which generated the final selection of six observational studies eligible for the meta-analysis (see Figure S1 in the supplementary information file) (1, 2, 6-9).

Characteristics of included studies

Of the selected six studies, two were cohort studies (1, 6) and four were case-control studies (2, 7-9). Four studies used medical record databases [four used primary care records (2, 6, 9), one used hospital records (8)], one used claims database records (1), and one was a field study (7). Four studies provided risk estimates for SCD (1, 6, 8, 9), and two for SUD (2, 7). Relative effect estimates were reported as odds ratio (OR), relative risk (or risk ratio, RR), or IRR (incidence rate ratio; Table 2).

Concerning quality (10), the two cohort studies obtained the highest possible score on the Newcastle-Ottawa Scale (nine stars, see supplementary file, Table S1). For the case-control studies, this score ranged from seven to nine stars (see supplemental file, Table S2); weaknesses concerned the selection of controls from hospital rather than community settings (7, 8), and lack of information on response rate (8).

Risk estimates were available for nine individual antipsychotics. Haloperidol was investigated in five studies; chlorpromazine, quetiapine, risperidone, and thioridazine were studied in three studies each; clozapine, flupentixol, fluphenazine, and olanzapine in one study each (Table 2). In the cohort studies, 435 cases of SCD/SUD were found in current users of antipsychotics (cumulated follow-up: 115,921 person-years), and 993 in the non-user group (648,414 person-years); in case-control studies, 132 exposed cases (2,425 non-exposed cases) and 169 exposed controls (17,501 non-exposed controls) were found.

Meta-analysis

Risk estimates of SUD/SCD for individual drugs ranged from OR 0.06 (95%CI 0.00 to 6.00) for fluphenazine, to OR 9.40 (95%CI 0.21 to 420.75) for flupentixol, for which only one estimate was available from the selected studies (Figure 1). The risk was non-significantly

increased for chlorpromazine use compared to non-use (OR 1.66, 95%CI 0.83 to 3.29; three studies). It was found to be significantly increased for quetiapine (OR 1.72, 95%CI 1.33 to 2.23; three studies) and olanzapine (OR 2.04, 95%CI 1.52 to 2.74; one study); higher estimates were observed for clozapine (OR 3.67, 95%CI 1.94 to 6.94; one study), haloperidol (OR 2.97; 95%CI 1.59 to 5.54; six studies), risperidone (OR 3.04, 95%CI 2.39 to 3.86; three studies), and thioridazine (OR 4.58, 95%CI 2.09 to 10.05; three studies).

The incidence rate in the study reported by Ray *et al.* was 1.4 per 1,000 person-years (95%CI 1.3 to 1.5) in the non-use group (1); the attributable number of cases was then calculated for the studied antipsychotics, and it varied from 1.0 per 1,000 person-years (95%CI 1.3 to 1.5) for quetiapine, to 5.1 per 1,000 person-years (95%CI 1.5 to 13.8) for thioridazine (Table 3). A significant heterogeneity between the individual risk estimates (intra-drug heterogeneity) was found only for haloperidol ($Q = 16.7$, $p = 0.002$; $I^2 = 76\%$, Figure 1). Conversely, a significant heterogeneity between the pooled estimates of each drug (inter-drug heterogeneity) was found ($Q = 20.0$, $p = 0.01$; $I^2 = 60\%$; Figure 1).

Meta-regression

The overall OR of SUD/SCD for antipsychotics was 2.65 (95%CI 2.13 to 3.29). Univariate meta-regression analyses (11, 12) found that heterogeneity was explained by mean hERG blockade potency ($p = 0.01$; Figure 2), but not by individual study ($p = 0.61$), study design (cohort *versus* case-control; $p = 0.21$), mean age ($p = 0.32$), proportion of males ($p = 0.41$), or antipsychotic type (typical *versus* atypical; $p = 0.44$). The multivariate meta-regression model (13), built using manual backward elimination, found that heterogeneity was explained only by mean hERG blockade potency (i.e. this was the only variable that remained).

The R^2 index, used to quantify the proportion of the variability in the risk with each potential source of heterogeneity (14, 15), for mean hERG blockade potency was 43%, while for other covariates was nil or very low (2% for study design).

DISCUSSION

The present meta-analysis included data for nine antipsychotics, the use of six of which being associated with an increased risk of SCD/SUD. Heterogeneity was found between drugs; the highest risk was associated with clozapine, haloperidol, risperidone, and thioridazine, and the data indicate that there were a considerable number of attributable fatal cases related to these drugs. Meta-regression indicated that the risk of SCD/SUD increased with increasing of mean hERG blockade potency.

hERG channel blockade is recognized as one of the mechanisms for QT prolongation which is an intermediate finding for *torsade de pointe* and ventricular arrhythmia (3). Although this association is evident, up to today the hERG affinity has not been related to SCD/SUD risk in clinical practice. The present study support the hypothesis that hERG affinity of antipsychotics is an independent risk factor for SCD/SUD. In the present analysis, R^2 index indicates that hERG blockade potency explains more than 40% of the heterogeneity found among drug estimates. However, the performance of the R^2 index in meta-regressions are limited when less than 40 estimates are included in the analysis (15). Moreover, published data concerning hERG blockade potency of antipsychotics is limited, and other mechanisms may also be involved (*e.g.* drug effects on other myocardial ion channels). Despite these considerations, it is of note that among the variables we tested as potential cause of heterogeneity, mean hERG blockade potency was the only one that was significantly associated both in univariate and multivariate analyses; forcing all variables in the model, did not alter this result (data not shown).

The high risk of cardiac arrhythmias associated with thioridazine use is widely accepted, resulting in the drug being withdrawn in 2005 in several countries; this study confirmed its strong association with SCD/SUD. The increased risk found of SCD/SUD for clozapine should be considered with caution: the risk estimate was not precise (only one study for this drug), and the reported hERG blockade potency is highly variable between assays (IC50 from 0.32 to 2.63 mmol) (16-18). More importantly, as a second-line treatment for resistant psychoses often used at high-dose (1, 19), which could lead to concentrations that far exceed its hERG IC50. Additionally, clozapine is the only antipsychotic related to myocarditis and cardiomyopathy (20) which, if unrecognized in fatal cases, could be classified as a sudden death.

The risk associated with haloperidol was also high. This is consistent with its extremely high potency for hERG channel blockade, and its myocardial cell concentration being higher than other antipsychotics (21). Nevertheless, the interpretation of this result requires caution owing to the heterogeneity found between its estimates, with consequently wide 95% CIs. This could be related to multiple indications of haloperidol (including delirium or non-psychiatric conditions), and different routes of administration. Further investigations are required to clarify this issue and to make more definitive conclusions about its risk.

For risperidone, the magnitude of risk was consistent between individual study estimates. Risperidone has one of the highest mean hERG channel blockade potency, and a high intra-myocardial concentration (21). A potential alternative explanation is that risperidone is preferentially prescribed to at-risk patients, such as the elderly with dementia for which it is indicated. However, there was a lack of data regarding the population using risperidone that limited investigation of such aspects, as was the case for other drugs considered herein.

Quetiapine, a drug with low mean hERG blockade potency, showed a lower increase in the risk of SCD/SUD, and estimates among the three included studies were consistent. This study

indicates that quetiapine is the atypical antipsychotic related to the lower increased risk of SCD/SUD.

Olanzapine, which also has low mean hERG channel blockade potency, was also associated with more limited increase in risk; although only one study was retrieved, this was large.

Other epidemiological evidence indicate that olanzapine has a lower risk of SCD when compared with haloperidol, but that this risk is higher than that for quetiapine (22). For chlorpromazine and flupentixol the increase in risk was not significant; there was no evidence of heterogeneity among estimates for chlorpromazine, and for flupentixol only one study was included, and not many patients were exposed, limiting the conclusions that can be drawn.

According to our hypothesis concerning hERG channel blockade, the high potency of flupentixol does however suggest the need for further investigations. Fluphenazine was associated with a point estimate less than 1.0 yet, as for flupentixol, the estimate was derived from a single case-control study and the 95%CI are too wide to allow any meaningful conclusion.

This meta-analysis has certain limitations. For instance, studies evaluating SCD with those evaluating SUD, which could also be related to other diagnoses, such as tonic-clonic epilepsy, were pooled. Nevertheless, the included studies that did investigate SUD, alone or in relation with SCD, used strict criteria to avoid the inclusion of unexpected death from causes other than arrhythmias (2, 7, 23). Despite this wide definition, the present analysis was only able to pool data for nine of the more than fifty antipsychotics available worldwide, but these do represent the most commonly used typical and atypical antipsychotics. Also, the analysis according to dose was performed in only two of the included studies (1, 7), and no information was found concerning different formulations of included drugs (*e.g.* prolonged release) or different routes of administration. This advocates for the conduct of additional

observational studies focusing on the risk of SCD/SUD associated with the use of individual antipsychotics, such as those envisioned in the ARITMO project.

Another important aspect is that patients with psychiatric bipolar disorders, schizophrenia, and dementia have an increased risk of all-cause mortality in comparison with the general population, thus an indication bias cannot be excluded. It is likely that this would not be differential across the drugs used as first-line treatments, while it is likely to have been greater for clozapine, a second-line treatment reserved for more severe psychoses, and for atypical antipsychotics, which are more commonly used in the elderly. Studies did address this issue by matching or adjusting for psychiatric disorders, cardiovascular diseases, or through propensity scores; in addition one study also adjusted for hypokalemia and alcohol abuse (2), and a second for use of drugs that could induce hypokalemia (9). The results provided by the latter studies did not differ to those provided by others. Residual confounding could also be present in all included studies that, even matched or adjusted, remain observational and thus cannot control for all potential risk factors of SCD/SUD. One of these potential residual confounders is obesity, which was considered in none of the included studies. Obesity was recently related to SCD in patients in middle-aged, non-smoking individuals (24); nevertheless, this increased risk seems mediated by traditional cardiovascular risk factors (such as arteriosclerosis), which were taken into account in all of the included studies.

The results may also be affected by the quality of the included studies. According to the Newcastle-Ottawa scale, the quality of five studies reached the highest value; for others it was one to two points below this. The quality of the studies reported by Kenbubpha *et al.* (7) and by Reilly *et al.* (8) was adversely affected by the selection of controls in hospital as opposed to community settings, but, as in these case-control studies cases were selected from the same population, this may not be too great a concern. The study reported by Reilly *et al.* (8) was

also affected by non-response rate as for certain variables there was missing data, but it was not made clear in the published article whether there was any imbalance across groups.

Heterogeneity is also a concern in meta-analyses, yet it is common when meta-analyses of observational studies are performed (25), and it may reach very high values (26, 27). When heterogeneity is found intra-drug this could be considered a limitation, but when this is inter-drug, this could be considered as an interesting aspect to investigate the risk profiles of drugs in a real-life setting. In this study we investigated heterogeneity using meta-regression, which could also be affected by certain limitations, such as aggregation or ecological bias (28, 29). However, among tested variables, aggregation bias could affect only age and gender, while the multilevel meta-regression performed excluded ecological bias. The estimations for each antipsychotic are affected by a certain degree of imprecision. This affects in particular drugs rarely used in clinical practice, such as flupentixol or fluphenazine. From a general point of view, imprecision leads to an underestimation of heterogeneity among estimates; thus in the present article, it could have reduced the chance to find a difference in risk among studied drugs.

More generally, a publication bias could have affected results. Nevertheless, in observational studies this is difficult to detect and to evaluate as registers are not systematically used as they are for clinical trials. In addition, owing to the differential risk among the investigated drugs, a funnel plot could be appropriate and informative when at least ten estimates for the same drug is available (30), which was not the case in the present meta-analysis. The existence of a publication bias could be considered unlikely for different reasons: the first studies were published in 2002 (7, 8); only two of the six studies were privately funded (2, 6); the included articles studied antipsychotics as a class, without any specific analysis for a single drug; this meta-analysis evaluated more than 700,000 person-year for cohort studies, and more than 3,000 cases for case control ones; the results are coherent with pharmacological profile of the

studied drugs. If a selective publication for positive results could be expected for observational studies, the large effect size found in this meta-analysis strongly reduce the possibility that new evidences changes substantially the results of the present meta-analysis. In conclusion, this study strongly suggests that the risk of SCD/SUD differs between individual antipsychotics, and that this difference in absolute terms is clinically important. It also suggests that mean hERG blockade potency is an explanatory factor for this difference in real-life situations. This should be considered when initiating antipsychotic treatment, in particular as indications for these have been widened to non-schizophrenic patients in whom arrhythmogenic risk is less extensively studied.

METHODS

Data sources and data extraction

As part of the ARITMO project, an extensive systematic review was conducted to identify observational studies that evaluated the risk of ECG disorders and ventricular arrhythmias related to antipsychotics, anti-infectives, and antihistamines. The results concerning use of individual antipsychotics and risk of SCD/SUD in comparison with non-use are presented herein. The studies evaluating SCD, defined as sudden natural death attributable to cardiac causes or non-attributable to a non-cardiac cause, and SUD, defined as sudden death both of cardiac origin or other natural origin, were considered eligible to be included in the present meta-analysis.

Studies eligible for inclusion in this meta-analysis were cohort studies (prospective or retrospective), case-control studies, or case-based studies including case-crossover and self-controlled case series, providing adjusted risk estimates of SCD/SUD. For this study, a protocol specifying the meta-analysis objective and context, the principles and modalities of the literature search, and the data analysis was developed during the ARITMO project period.

This study followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (see supplement file) (31, 32).

References meeting the inclusion criteria were searched in Medline, EMBASE, and ISI web of Knowledge. The search strategy with detailed literature keywords used in Medline database is reported in the data supplement. EndNote X4 for Macintosh (Thomson Reuters) was used to compile the bibliography. This search was last updated on February 13, 2014. The process used for the identification and selection of the retrieved studies is detailed in the data supplement.

Data were extracted from the selected studies using a standardized form. These included the definition of the events of interest, the number of cases in the exposed and non-exposed group for cohort studies, the number of exposed cases and exposed controls for case-control studies, and the adjusted risk measure of SCD/SUD for each individual antipsychotic.

The Newcastle-Ottawa Scale was used for assessing the quality of the included studies. Each study was scored from zero to nine stars for the selection and the comparability of the groups, and for the ascertainment of either the exposure for case-control or outcome of interest for cohort studies (10).

Meta-analysis

The overall risk of SCD/SUD associated with the use of each individual antipsychotic was estimated. Adjusted estimates of risk were extracted from each selected study, and included in a forest plot as OR, which is a good risk measure when the diseases are rare, and when different study designs are pooled in a single meta-analysis. For each antipsychotic, the pooled OR with 95% confidence interval (CI) for use *versus* non-use was computed using inverse variance method and random-effect models (11). Statistical heterogeneity was

evaluated using the Q statistic (with $p < 0.10$ considered significant) and the I^2 index (33) between the individual risk estimates for a given drug (intra-drug heterogeneity), and between the pooled estimates of each drug (inter-drug heterogeneity). The meta-analysis was conducted using Review Manager software (RevMan version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration); all p values were two sided.

The cohort study reporting the lowest incidence rate of SCD/SUD in the non-user group was used to calculate the number of attributable cases (and the corresponding 95% CI) per 1000 person-years. This incidence rate in this non-user group was multiplied by the pooled OR minus 1.0 for each antipsychotic associated with an increased risk of SCD/SUD.

Meta-regression analysis

Random-effect meta-regression analyses were performed to explore sources of heterogeneity between the individual estimates of SCD/SUD risk (11, 12). Potential sources of heterogeneity considered included: individual study (each included study was considered as a unique value of this variable), study design (cohort *versus* case-control), antipsychotic type (typical *versus* atypical), mean age (continuous variable), gender (proportion of males, continuous variable), and blockade potency of hERG channels (continuous variable). For the latter, for each studied drug, the mean published values for the concentrations inhibiting 50% of hERG channels (IC₅₀) in transfected mammalian cells was used (Table 1) (16-18, 34-46). The ARITMO consortium researchers retrieved the references used for this calculation via a systematic review of preclinical data of hERG channel blockade potency (47). Each potential source of heterogeneity was investigated using univariate meta-regression models. A multivariate meta-regression model was then built using manual backward elimination including only sources associated with $p < 0.05$ (13). The R^2 index was used to quantify the proportion of the variability in the SCD/SUD risk associated with each potential source of

heterogeneity (14, 15). The R^2 index informs on the practical significance, or the degree of influence, of a variable in the heterogeneity of the effect sizes in a meta-analysis (e.g. if a variable with $R^2 = 20\%$, then this variable explains 20% of the heterogeneity). The meta-regression analyses were performed using R software (version 3.0.3) via the “metafor” package (48).

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Taken alone, all published observational studies have limited power to compare risks of SCD/SUD associated with the use of individual antipsychotics.

What question did this study address?

Is there a difference in risk of SCD/SUD among individual antipsychotics?

What this study adds to our knowledge?

This study found that the risk of SCD/SUD varies among individual antipsychotics. This variation is not related to a class effect (typical vs. atypical antipsychotics), but it seems related to potency of antipsychotics to block hERG channels, which is particularly high for risperidone, haloperidol and thioridazine.

How this might change clinical pharmacology and therapeutics?

Indications of antipsychotics have been recently widened to non-schizophrenic patients. The number of exposed patients and the number of attributable cases of SCD/SUD is thus increasing. In order to prevent as possible their occurrence, the findings of the present studies should thus be considered when risks and benefits are balanced before the antipsychotic treatment initiation.

ACKNOWLEDGEMENTS

This study is a part of a research project that has received funding from the European Community's Seventh Framework Program under grant agreement number 241679 - the

ARITMO project. The corresponding author confirms the full access to all data in the study and the final responsibility.

CONFLICT OF INTEREST/DISCLOSURE

In the previous 3 years, FS, PR, MA, and ER have no relationships with companies that might have an interest in the submitted work; AP has had specified relationships on other matters with the following companies that might have an interest in the submitted work: Sanofi, Novartis, Lundbeck, Neptune; SS and LH has worked for the Drug Safety Research Unit. The DSRU has received unconditional research grants from companies that manufacture drugs used in the treatment of diabetes, though none of these is related to this study; SHLT has had specified relationships on other matters with the following drug companies that might have an interest in the submitted work: Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Baxter, EUSAPharm, Roche, PTC Therapeutics, Sanofi Aventis, Bristol Myers Squibb, PPD, Pfizer; AF has had specified relationships on other matters with the following drug companies that might have an interest in the submitted work: Pfizer, Merck Serono, Roche, Lundbeck, GSK; NM has had specified relationships on other matters with the following drug companies that might have an interest in the submitted work: Pfizer, Novartis, Axcan, Bristol-Myers Squibb, Celgene, Cephalon, Vivatec, Lundbeck, GlaxoSmithKline, Leo Pharma, Helsinn Healthcare, Orion, Genevrier, Takeda, Sanofi, and Johnson & Johnson; MS has had specified relationships on other matters with the following drug companies that might have an interest in the submitted work: Pfizer, Eli Lilly, Astrazeneca, Boehringer, Novartis. All authors declare that their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and that have no non-financial interests that may be relevant to the submitted work.

AUTHOR CONTRIBUTIONS

FS: wrote manuscript, designed research, performed research, and analyzed data.

AP: designed research, performed research, analyzed data, revised the article critically for important intellectual content.

SS: designed research, analyzed data, revised the article critically for important intellectual content.

PR: performed research, analyzed data, revised the article critically for important intellectual content.

MA: designed research, performed research, analyzed data, revised the article critically for important intellectual content.

SHLT: designed research, analyzed data, revised the article critically for important intellectual content.

ER: designed research, analyzed data, revised the article critically for important intellectual content.

AF: designed research, analyzed data, revised the article critically for important intellectual content.

NM: designed research, analyzed data, revised the article critically for important intellectual content.

MS: designed research, analyzed data, revised the article critically for important intellectual content.

LH: designed research, performed research, analyzed data, investigated accuracy and integrity of any part of the work.

REFERENCES

1. Ray, W.A. Chung, C.P. Murray, K.T. Hall, K. Stein, C.M. Atypical antipsychotic drugs and the risk of sudden cardiac death. *New. Eng. J. Med.* **360**, 225-35 (2009).
2. Jolly, K. Gammage, M.D. Cheng, K.K. Bradburn, P. Banting, M.V. Langman, M.J.S. Sudden death in patients receiving drugs tending to prolong the QT interval. *Br. J. Clin. Pharmacol.* **68**, 743-51 (2009).
3. Trudeau, M.C. Warmke, J.W. Ganetzky, B. Robertson, G.A. HERG, a human inward rectifier in the voltage-gated potassium channel family. *Science.* **269**, 92-5 (1995).
4. Reilly, J.G. Ayis, S.A. Ferrier, I.N. Jones, S.J. Thomas, S.H. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet.* **355**, 1048-52 (2000).
5. Mehta, S. Chen, H. Johnson, M. Aparasu, R.R. Risk of serious cardiac events in older adults using antipsychotic agents. *Am. J. Geriatr. Pharmacother.* **9**, 120-32 (2011).
6. Jones, M.E. *et al.* Risk of Mortality (including Sudden Cardiac Death) and Major Cardiovascular Events in Users of Olanzapine and Other Antipsychotics: A Study with the General Practice Research Database. *Cardiovasc. Psychiatry. Neurol.* **2013**, 647476 (2013).
7. Kenbubpha, K. Silpakit, C. Association between antipsychotics and sudden death in psychotic in-patients. *Int. Med. J.* **9**, 27-31 (2002).
8. Reilly, J.G. Ayis, S.A. Ferrier, I.N. Jones, S.J. Thomas, S.H. Thioridazine and sudden unexplained death in psychiatric in-patients. *Br. J. Psychiatry.* **180**, 515-22 (2002).
9. Van Noord, C. Sturkenboom, M.C.J.M. Straus, S.M.J.M. Witteman, J.C.M. Stricker, B.H.C. Non-cardiovascular drugs that inhibit hERG-encoded potassium channels and risk of sudden cardiac death. *Heart.* **97**, 215-20 (2011).

10. Wells, G.A. *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2010 10 January 2014. Available from: http://www.ohri.ca/Programs/clinical_epidemiology/oxford.asp.
11. DerSimonian, R. Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials.* **7**, 177-88 (1986).
12. Jackson, D. White, I.R. Thompson, S.G. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat. Med.* **29**, 1282-97 (2010).
13. van Houwelingen, H.C. Arends, L.R. Stijnen, T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat. Med.* **21**, 589-624 (2002).
14. Raudenbush, S.W. Random effects models. In *The handbook of research synthesis* (eds. Foundation RS) 301-21 (New York, H. Cooper, & L. V. Hedges, 1994).
15. Lopez-Lopez, J.A. Marin-Martinez, F. Sanchez-Meca, J. Van den Noortgate, W. Viechtbauer, W. Estimation of the predictive power of the model in mixed-effects meta-regression: A simulation study. *Br. J. Math. Stat. Psychol.* (2013).
16. Crumb, W.J.J. *et al.* Effects of antipsychotic drugs on I(to), I (Na), I (sus), I (K1), and hERG: QT prolongation, structure activity relationship, and network analysis. *Pharm. Res.* **23**, 1133-43 (2006).
17. Lee, S.Y. Kim, Y.J. Kim, K.T. Choe, H. Jo, S.H. Blockade of HERG human K⁺ channels and IKr of guinea-pig cardiomyocytes by the antipsychotic drug clozapine. *Br. J. Pharmacol.* **148**, 499-509 (2006).
18. Tie, H. *et al.* Clozapine and sudden death. *J. Clin. Psychopharmacol.* **21**, 630-2 (2001).
19. Hennessy, S. *et al.* Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ.* **325**, 1070 (2002).

20. Fitzsimons, J. Berk, M. Lambert, T. Bourin, M. Dodd, S. A review of clozapine safety. *Expert. Opin. Drug. Saf.* **4**, 731-44 (2005).
21. Titier, K. *et al.* Determination of myocardium to plasma concentration ratios of five antipsychotic drugs: comparison with their ability to induce arrhythmia and sudden death in clinical practice. *Toxicol. Appl. Pharmacol.* **199**, 52-60 (2004).
22. Leonard, C.E. *et al.* Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States. *J. Clin. Exp. Cardiol.* **Suppl 10**, 1-9 (2013).
23. Modai, I. *et al.* Sudden death in patients receiving clozapine treatment: a preliminary investigation. *J. Clin. Psychopharmacol.* **20**, 325-7 (2000).
24. Adabag, S. *et al.* Obesity related risk of sudden cardiac death in the atherosclerosis risk in communities study. *Heart.* **101**, 215-21 (2015).
25. Sutton, A.J. *Methods for meta-analysis in medical research.* (Wiley, New York, 2000)
26. McGettigan, P. Henry, D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS. Med.* **8**, e1001098 (2011).
27. Varas-Lorenzo, C. *et al.* Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. *Pharmacoepidemiol. Drug. Saf.* **22**, 559-70 (2013).
28. Greenland, S. Quantitative methods in the review of epidemiologic literature. *Epidemiol. Rev.* **9**, 1-30 (1987).
29. Morgenstern, H. Uses of ecologic analysis in epidemiologic research. *Am. J. Public. Health.* **72**, 1336-44 (1982).

30. Higgins, J.P.T. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration; 2011. Available from: <http://www.cochrane-handbook.org>.
31. Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* **6**, e1000100 (2009).
32. Stroup, D.F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* **283**, 2008-12 (2000).
33. Higgins, J.P. Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **21**, 1539-58 (2002).
34. Drolet, B. Yang, T. Daleau, P. Roden, D.M. Turgeon, J. Risperidone prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. *J. Cardiovasc. Pharmacol.* **41**, 934-7 (2003).
35. Fossa, A.A. *et al.* Differential effect of HERG blocking agents on cardiac electrical alternans in the guinea pig. *Eur. J. Pharmacol.* **486**, 209-21 (2004).
36. Guo, L. Guthrie, H. Automated electrophysiology in the preclinical evaluation of drugs for potential QT prolongation. *J. Pharmacol. Toxicol. Methods.* **52**, 123-35 (2005).
37. Hanson, L.A. Bass, A.S. Gintant, G. Mittelstadt, S. Rampe, D. Thomas, K. ILSI-HESI cardiovascular safety subcommittee initiative: evaluation of three non-clinical models of QT prolongation. *J. Pharmacol. Toxicol. Methods.* **54**, 116-29 (2006).
38. Katchman, A.N. Koerner, J. Tosaka, T. Woosley, R.L. Ebert, S.N. Comparative evaluation of HERG currents and QT intervals following challenge with suspected torsadogenic and nontorsadogenic drugs. *J. Pharmacol. Exp. Ther.* **316**, 1098-106 (2006).
39. Kim, K.S. Kim, E.J. The phenothiazine drugs inhibit hERG potassium channels. *Drug. Chem. Toxicol.* **28**, 303-13 (2005).

40. Kirsch, G.E. *et al.* Variability in the measurement of hERG potassium channel inhibition: effects of temperature and stimulus pattern. *J. Pharmacol. Toxicol. Methods.* **50**, 93-101 (2004).
41. Kongsamut, S. Kang, J. Chen, X.L. Roehr, J. Rampe, D. A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs. *Eur. J. Pharmacol.* **450**, 37-41 (2002).
42. Martin, R.L. McDermott, J.S. Salmen, H.J. Palmatier, J. Cox, B.F. Gintant, G.A. The utility of hERG and repolarization assays in evaluating delayed cardiac repolarization: influence of multi-channel block. *J. Cardiovasc. Pharmacol.* **43**, 369-79 (2004).
43. Milnes, J.T. Witchel, H.J. Leaney, J.L. Leishman, D.J. Hancox, J.C. hERG K⁺ channel blockade by the antipsychotic drug thioridazine: An obligatory role for the S6 helix residue F656. *Biochem. Biophys. Res. Commun.* **351**, 273-80 (2006).
44. Morissette, P. Hreiche, R. Mallet, L. Vo, D. Knaus, E.E. Turgeon, J. Olanzapine prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. *J. Psychopharmacol.* **21**, 735-41 (2007).
45. Silvestre, J.S. Prous, J.R. Comparative evaluation of hERG potassium channel blockade by antipsychotics. *Methods. Find. Exp. Clin. Pharmacol.* **29**, 457-65 (2007).
46. Yao, X. *et al.* Predicting QT prolongation in humans during early drug development using hERG inhibition and an anaesthetized guinea-pig model. *Br. J. Pharmacol.* **154**, 1446-56 (2008).
47. Sturkenboom, M. ARITMO: Arrhythmogenic potential of drugs. Project Final Report. 2013. Available from: <http://cordis.europa.eu/docs/results/241679/final1-aritmo-final-report-v2-0final.pdf>.
48. Viechtbauer, W. Conducting meta-analyses in R with the metafor. *J. Stat. Soft.* **36**, 1-48 (2010).

FIGURES LEGENDS

Figure 1. Forest plot of the risk of SCD/SUD related to individual antipsychotics. Odds ratio for individual antipsychotics obtained from included studies is presented with 95% confidence interval (CI); arrowheads indicate the CI exceeding the limits of the graph. Overall odds ratio (OR) for individual drugs is also presented (black diamonds). Weight of each estimate in the pooled OR for each drug was calculated using the inverse variance method.

Figure 2. Log Odds Ratio of Sudden Cardiac Death/Sudden Unexpected death according to the 50% inhibitory concentration (IC50) of hERG channel for individual antipsychotics. Each estimate of risk is represented by a circle, the area of which is proportional to the estimation weight in the meta-analysis (larger studies correspond to larger circles). The black line represents the predictive values obtained by the random-effects meta-regression model ($p = 0.01$).

TABLES (SEPARATE FILES AFTER BIBLIO)

Table 1. Fifty percent of inhibitory concentration (IC50) of hERG channel, expressed as mmol, of antipsychotics included in this meta-analysis.

	IC50		
	mean (SD)	min	max
<i>Typical Antipsychotics</i>			
Chlorpromazine (39)	1.56*	--	--
Flupentixol (45)	0.59*	--	--
Fluphenazine (45)	1.00*	--	--
Haloperidol (16, 37, 38, 40, 42, 46)	0.05 (0.05)	0.02	0.17
Thioridazine (16, 36-41, 43, 45)	0.18 (0.11)	0.03	0.39
<i>Atypical antipsychotics</i>			
Clozapine (16-18)	1.82 (1.30)	0.32	2.63
Olanzapine (16, 36, 41, 44)	3.01 (2.47)	0.23	6.01
Quetiapine (41)	5.77*	--	--
Risperidone (16, 34, 35, 41)	0.15 (0.10)	0.01	0.26

* Only one estimate; SD: Standard deviation.

Table 2. Characteristics of selected studies.

	Data source and setting	Study population	Comparison group, adjustment or matching variables of interest	Outcome and definition	Sample size	Drugs	NOS Score (Up to 9)
<i>Cohort Studies</i>							
					<i>P-Ys (n cases)</i>	<i>Studied drugs (n cases; n P-Ys)</i>	
Jones, <i>et al.</i> (6)	Primary care records database	Mean age (y): 60 Male (%): 42	Patients with psychiatric diagnoses, but non-users of antipsychotics. Adjusted for age, sex, psychiatric history, CV history, CV risk factors, drug use	SCD*	28,516 (191)	TA: haloperidol (47; 1,236); AA: quetiapine (46; 3,407)	9
Ray, <i>et al.</i> (1)	Claims database, outpatients	Mean age (y): 46 Male (%): 35	Non-users of antipsychotics matched for age, sex and first day of follow-up. Adjusted for psychiatric comorbidities, CV risk, drug dose	SCD: sudden pulseless condition that was fatal, and consistent with a ventricular tachyarrhythmia	735,889 (1,237)	TA: haloperidol (58; 21,728), thioridazine (65; 15,715); AA: clozapine (19; 4,654), olanzapine (75; 27,257), quetiapine (40; 17,355), risperidone (85; 24,589),	9
<i>Case-control studies</i>							
					<i>Cases / controls</i>	<i>Studied drugs (n exposed cases; n exposed controls)</i>	
Jolly, <i>et al.</i> (2)	Primary care records database	Mean age (y): 68 Male (%): 67	Controls matched for age, sex, existence of CV history. Adjusted for CV disease, epilepsy, renal dysfunction, alcohol abuse, hypokaliemia	SUD: post-mortem examination where a clear cause of death could not be identified	1,010 / 3,030	TA: chlorpromazine (4; 8), haloperidol (6; 3); AA: quetiapine (3; 4), risperidone (15; 10)	9
Kenbubpha, <i>et al.</i> (7)	Hospital based field study	Mean age (y): 41 Male (%): 63	Patients with CV history were excluded. Controls matched on sex. Adjusted for age, use of other antipsychotics, number of psychiatric admissions	SUD: a person observed to be alive and experiences onset of symptoms and is dead within one hour.	54 / 108	TA: chlorpromazine (23; 54), thioridazine (21; 18)	8
Reilly, <i>et al.</i> (8)	Hospital records	Mean age (y): 67 Male (%): 31	Controls matched for age, sex, in-patient stay duration. Adjusted for psychiatric disorder, CV diseases, COPD, mood stabilizer drugs	SCD: sudden death without evidence of non-cardiac cause	69 / 69	TA: chlorpromazine (5; 6), flupentixol (5; 3), fluphenazine (3; 6), haloperidol (7; 13), thioridazine (24; 19)	7
Van Noord, <i>et al.</i> (9)	Primary care records database	Mean age (y): 73 Male (%): 58	Controls matched for age, sex, calendar time. Adjusted for CV diseases, CV drugs, diabetes, hypercholesterolemia, use of QTc prolonging drugs, CYP3A4 affecting drugs, laxatives, diuretics, oral corticosteroids, beta-agonists	SCD: sudden and witnessed natural death attributable to cardiac causes, or unwitnessed, unexpected death of someone seen in a stable medical condition less than 24 h previously with no evidence of a non-cardiac cause	1,424 / 14,443	TA: haloperidol (11; 16); AA: risperidone (5; 9)	9

*Derived from death certificates with International Classification of Diseases 10th version using the following codes: I10, I11.9, I20, I21, I22, I23, I24, I25, I42.8, I42.9, I46, I47, I49.0, I49.8, I49.9, I51.6, I51.9, I70.9, R09.2, R96.1, R98, from Read codes in GPRD that correspond to these ICD10 codes, or from free text in the \pm 3 weeks before or after the death recording.
AA: Atypical antipsychotics; COPD: Chronic Obstructive Pulmonary Disease; CV, Cardiovascular; CYP3A4: cytochrome p450 isoform 3A4; IRR, Incidence Rate Ratio; OR, Odds Ratio, RR, relative ratio; P-Ys, Person-years; QTc: corrected QT tract of electrocardiogram; SCD, Sudden cardiac death; SUD, Sudden unexpected death; TA: typical antipsychotics. .

Table 3. Number of attributable cases per 1000 person-years

	Attributable cases per 1000 P-Y (95% CI)
Quetiapine	1.0 (0.4-1.9)
Olanzapine	1.5 (0.7-2.7)
Haloperidol	2.8 (0.8-6.9)
Risperidone	2.9 (1.9-4.4)
Clozapine	3.8 (1.3-9.1)
Thioridazine	5.1 (1.5-13.8)