PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015; **24**: 701–708
Published online 27 May 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3792

ORIGINAL REPORT

Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? The example of haloperidol

Miriam Jacoba Warnier[1,2], Frans Hendrik Rutten[2], Patrick Cyriel Souverein[1], Anthonius de Boer[1], Arno Wilhelmus Hoes[2] and Marie Louise De Bruin[1]*

[1] *Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
[2] *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*

ABSTRACT

Purpose Monitoring of the QT duration by electrocardiography (ECG) prior to treatment is frequently recommended in the label of QT-prolonging drugs. It is, however, unknown how often general practitioners in daily clinical practice are adhering to these risk-minimization measures. We assessed the frequency of ECG measurements in patients where haloperidol was initiated in primary care.
Methods Patients (≥18 years) with a first prescription of haloperidol in the UK Clinical Practice Research Datalink (2009–2013) were included. The proportion of ECGs made was determined in two blocks of 4 weeks: during the exposure period when haloperidol was initiated, and during the control period, 1 year before. Conditional logistic regression analysis was applied to calculate the relative risk of having an ECG in the exposure period compared with the control period. Subgroup analyses were performed to assess the proportion of ECG measurements in patients with one or more additional risk factors for QT prolongation.
Results In total, 3420 patients were prescribed haloperidol during the exposure period, and 1.8% of them had an ECG at treatment initiation, compared with 0.8% during the control period (relative risk [RR] 2.4 [1.5–3.8]). Of the patients with additional risk factors for QT prolongation, 1.9% of the patients had an ECG at initiation of the prescription, compared with 1.0% during the control period (RR 2.1 [1.2–3.5]).
Conclusions Compliance with recommendations to perform an electrocardiogram when starting a new QT-prolonging drug is extremely low, when haloperidol is taken as an example. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—communication; regulatory; risk minimization; cardiac arrhythmia; antipsychotic agent; epidemiology; pharmacoepidemiology

Received 20 September 2014; Revised 4 March 2015; Accepted 1 April 2015

INTRODUCTION

Drugs are a frequent cause of QT interval prolongation on the electrocardiogram (ECG), a sign of increased cardiac repolarization time that may facilitate the development of torsade de pointes.[1] Torsade de pointes is a transient polymorphic ventricular tachycardia that, when sustained, may evolve into ventricular fibrillation and potentially cause sudden cardiac arrest, but it may also resolve, leaving no trace. The risk of developing torsade de pointes and cardiac arrest is higher in patients with additional risk factors for QT prolongation, such as prior myocardial infarction, heart failure, hypokalaemia, concomitant use of other arrhythmogenic drugs and a (family) history of congenital long QT syndrome.[2] The estimated incidence of torsade de pointes in the population at large is 0.5 per 10 000 person-years,[3] while the estimated incidence of out-of-hospital cardiac arrest is approximately 10 per 10 000 person-years.[4–6] The study of Straus *et al.* shows that QT-prolonging drugs increase the risk of sudden cardiac death to about three times compared with no use (adjusted odds ratio 2.7 [1.6–4.7]).[6] Although this relative risk of sudden cardiac death is substantial, the absolute risk is low, and therefore, sudden cardiac death remains rare also in patients taking QT-prolonging drugs.

Nevertheless, QT prolongation is one of the most common adverse drug reactions leading to regulatory

*Correspondence to: M. L. De Bruin, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, PO Box 80082, Utrecht 3508 TB, The Netherlands. Email: m.l.debruin@uu.nl

Presentation of manuscript: This manuscript has not been presented at a meeting.

action, including withdrawal of a drug from the market.[7,8] Several drugs have been reported to increase the risk of QT prolongation and ventricular arrhythmia; for example, the relative risk for sudden cardiac death with ciprofloxacin was 2.4 (0.5–11.7) and with the use of risperidone 3.9 (1.1–13.5).[9] Still, prolongation of the QT interval is anything but an ideal marker for the risk of torsade de pointes or sudden cardiac death. Not all drugs that prolong the QT interval increase the risk of torsade de pointes or sudden cardiac death to an equivalent degree, and importantly, on the other hand, not all drugs that increase the risk of torsade de pointes or sudden cardiac death prolong the QT interval.[10,11]

Irrespective of the low absolute risk related to QT interval prolongation,[1,12] the regulatory authorities have adopted stringent requirements for pre-marketing testing of pro-arrhythmic effects of new drugs over the last decade, with a focus on QT interval duration.[13,14] Apart from the recommendations on how and when to perform thorough QT studies, the ICH E14 guideline provides guidance on how information on QT prolongation should be addressed in the drug labelling. One of the risk-minimization measures suggested in the ICH E14 is to include 'Recommendations for patient monitoring (ECG and electrolytes) and management of patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia' in the labelling of QT-prolonging drugs.

It has been reported that 63% of the QT-prolonging drugs and 29% of the potentially QT-prolonging drugs, ECG monitoring prior to treatment is recommended in the drug label.[15]

Haloperidol is a widely prescribed antipsychotic agent in both hospital and primary care settings to manage agitation, delirium and psychosis. Haloperidol has been linked to QT prolongation and torsade de pointes in case reports[16–20] and post-marketing studies.[21] The UK product label of the innovator of haloperidol (i.e. Haldol) currently states: 'Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination' (Box 1).[22] The product information of generic haloperidol products are in line with this labeling. It is, however, unknown how adequate these risk-minimization measures, as called by the regulatory authorities, are being adhered to in daily clinical practice. Therefore, the objective of this study was to assess whether the advice of the drug label to perform an ECG in patients before prescribing a QT-prolonging drug is followed in daily practice, and we took haloperidol as the example.

Box 1. Recommendation in the summary of product characteristics to perform an ECG prior to starting haloperidol.[22]

4.4 Special warnings and precautions for use

'Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms.'

QTc: QT interval corrected for heart rate

METHODS

Setting and study design

Data were obtained from the Clinical Practice Research Datalink, which comprises the computerized longitudinal medical records of patients derived from primary care practices throughout the United Kingdom (UK).[23] The records include the patient's demographic information and data on routine care such as prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major clinical outcomes. General practitioners play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals.[23,24]

Study population and measures

All patients aged 18 years and older with a new prescription of haloperidol between January 1, 2009 and May 1, 2013, were identified. We started with the data collection in 2009 to allow enough time for adherence to the ECG monitoring recommendation, which was reported in the label for the first time in 2006. The date of the start of the first prescription of haloperidol was defined as the index date. A new prescription of haloperidol (exposure of interest) was defined as not having had a prescription of the drug in the 365 days before the index date. For each patient, we assessed whether an ECG was performed or a referral for an ECG (outcome of interest) was provided during two measurement periods of 4 weeks (Figure 1). The first measurement period was the exposure period, that is, the period 2 weeks before until 2 weeks after the index date. We used a matched pairs exposure assessment. The control period when the patient did not use haloperidol was taken as the period from 2 weeks before till 2 weeks

DOI: 10.1002/pds

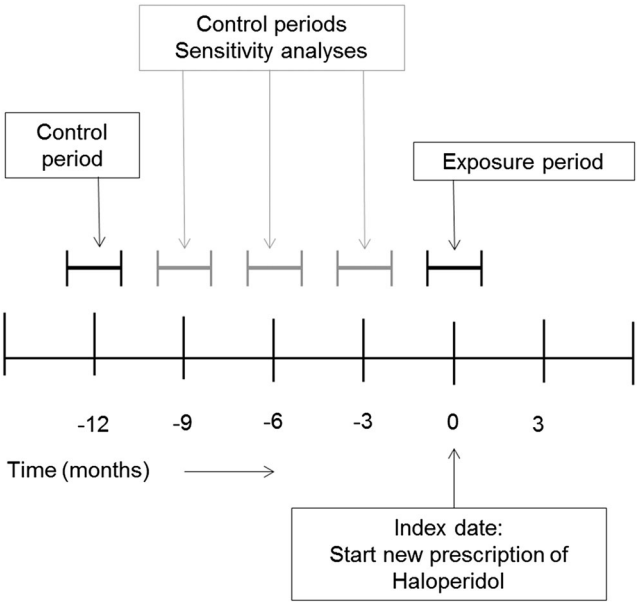

Figure 1. Study design

after the date that fell 12 months before the index date (Figure 1). Patients were included when at least 379 days of valid data collection before the index date was available, as the control period started 1 year and 2 weeks before the index date. Patients that had less than 365 days of valid follow-up after the index date were excluded, as we intended to exclude prescriptions in terminally ill patients or those with a shorter life expectancy.

Subgroups with risk factors for QT prolongation

We assessed whether patients with an increased risk of QT prolongation were more likely to have an ECG prior to starting haloperidol. Increased risk was defined as the presence of one or more of the following risk factors on the index date: age 65 years or older, history of heart failure, ischaemic heart disease, QT prolongation or congenital long QT syndrome, or the concurrent use of anti-arrhythmic (Vaughan-Williams class I or III[25]) or class 1 QT-prolonging drugs (according to the Arizona Center for Education & Research on Therapeutics eTable 1[26]). Information on these factors was extracted from the clinical and prescription records in the database. Patients were defined as having a history of QT prolongation, congenital long QT syndrome, ischaemic heart disease or heart failure when they had a diagnosis coded in the database ever before the index date. Drug use was defined as concurrent if the prescription date fell in a period of 90 days before the index date or the reference date, 1 year earlier.

Data analysis

Absolute numbers and proportions of ECGs performed during the index period and the control period were evaluated. Conditional logistic regression analysis was used to calculate the relative risk of having an ECG in the exposure period compared with the control period. To show the prevalence over time, the proportion of ECGs performed per month before and after index date (start haloperidol prescription) was calculated from 12 months before the index date to 6 months after the index date. In addition, we calculated the proportion of ECGs performed each calendar year to assess time trends.

Three sensitivity analyses were conducted. First, we performed the aforementioned analyses without excluding patients with less than 1 year of follow-up. Next, sensitivity analyses were performed with three other 4-week control periods (3, 6 and 9 months before the index date, instead of 12 months, Figure 1). Finally, a sensitivity analysis was conducted defining concurrent drug use as having a prescription in a period of 30 days before the index date instead of 90 days. All data were analysed using the statistical software package of SPSS (SPSS for Windows, version 20.0, SPSS Inc.).

RESULTS

During the study period, 3420 patients aged 18 years or older with a new prescription of haloperidol were included (Figure 2). The mean age was 65.3 (standard deviation 20.4, range: 18–106) years, and 58% was female (Table 1).

Of those receiving a new prescription of haloperidol, 1.8% had an ECG recorded ($n = 63$) as compared with 0.8% during the control period 1 year earlier ($n = 27$, relative risk [RR] 2.4 [1.5–3.8], Table 2). Figure 3 indicates the proportion of ECGs per month and shows that the proportion of ECGs was highest at the index date (1.8%) and 1 month before the index date (1.8%). The proportion of ECGs in the remaining months ranged from 0.5% to 1.3%.

Of the patients with at least one additional risk factor for QT prolongation, 1.9% had an ECG at the start of haloperidol as compared with 1.0% during the control period (RR 2.1 [1.2–3.5]). Of the patients without additional risk factors for QT prolongation, 1.6% received an ECG prior to the start of haloperidol as compared with 0.4% during the control period (RR 2.8 [1.0–7.8]).

Patients aged 45–64 or 65–84 years more often had an ECG performed prior to starting with haloperidol (exposure period 2.3% and 2.6%, control period 0.4% and 1.2%, RR 5.3 [1.6–18.3] and 2.3 [1.2–4.3], respectively) than younger patients (18–44 years, exposure

DOI: 10.1002/pds

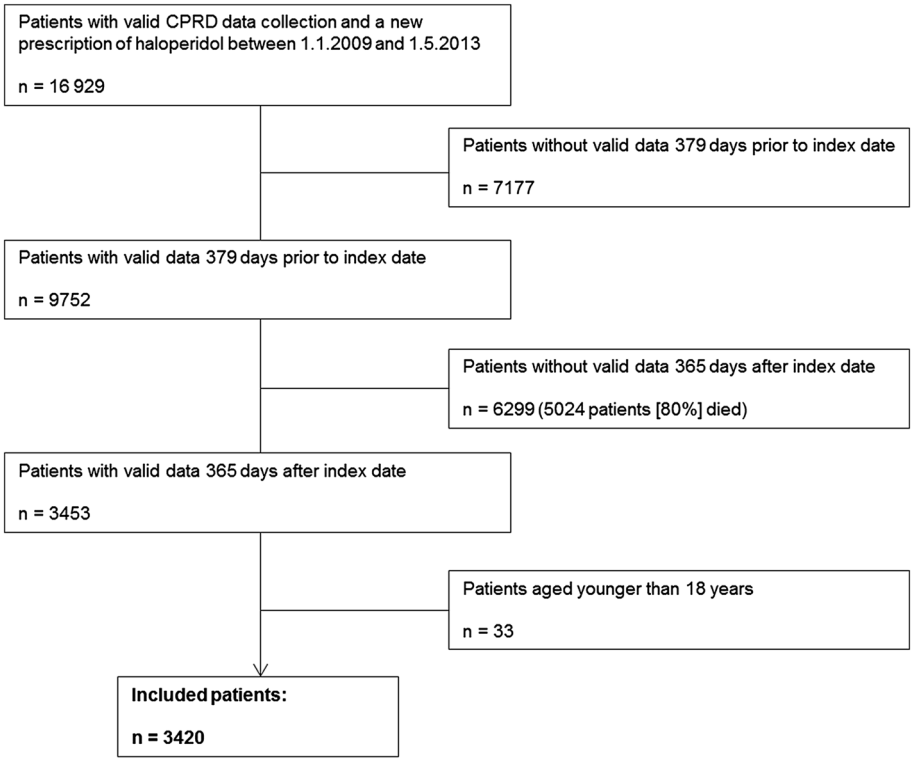

Figure 2. Flowchart of included and excluded patients. CPRD, Clinical Practice Research Datalink

Table 1. Baseline characteristics of the study population: all incident haloperidol users between 1.1.2009 and 1.5.2013 ($n = 3420$)

Baseline characteristics	Study population
Mean age (years, SD)	65.3 (20.4)
Age category (years)	
18–44	693 (20.3%)
45–64	750 (21.9%)
65–84	1312 (38.4%)
>84	665 (19.4%)
Female sex	1984 (58.0%)
Smoking	
Current	751 (22.0%)
Former	1129 (33.0%)
Never	862 (15.2%)
Unknown	678 (19.8%)
History of	
Ischaemic heart disease	585 (17.1%)
Heart failure	168 (4.9%)
Diabetes mellitus	627 (18.3%)
Chronic obstructive pulmonary disease	243 (7.1%)
QT prolongation/ long QT syndrome	1 (0.03%)
Current use of concomitant QT-prolonging drugs	
Class 1 QT-prolonging drugs[a]	903 (26.4%)
Class 2 QT-prolonging drugs[a]	739 (21.6%)
Class I/III anti-arrhythmic drugs[b]	47 (1.4%)

Data are number (%) unless otherwise indicated.
SD, standard deviation.
[a]Drugs with (possible) risk of QT prolongation according to the Arizona Center for Education & Research on Therapeutics.[26]
[b]Classes I and III anti-arrhythmic drugs, according to the classification of Vaughan-Williams.[25]

period 1.2%, control period 0.5, RR 4.0 [0.8–18.8]) or the very old (>84 years, exposure period 0.6%, control period 0.7%, RR 1.0 [0.3–4.0]). In women, ECGs were performed less often during both the exposure and control period (1.4% and 0.5%, respectively, RR 2.7 [1.3–5.6]) than men (2.5% and 1.2%, RR 2.2 [1.2–4.0], respectively). No clear increase or decrease of the proportions of ECGs performed during initiation of haloperidol was shown over time (Figure 3).

As expected, sensitivity analyses performed in the full cohort of 9719 new haloperidol users (including patients with less than 1 year of follow-up) resulted in lower proportions of ECGs (exposure period: 1.4%, control period: 1.1%, RR 1.3 [1.0–1.6]). Sensitivity analyses performed with three other control periods (3, 6 and 9 months before the index date, instead of 12 months) and with another definition of concurrent drug use (i.e. a prescription during a 30-day period instead of a 90-day period, before the index date) yielded comparable results.

DISCUSSION

Our study shows that less than 2% of the patients who had a new prescription of haloperidol received an ECG at initiation (exposure period: 1.8%, control period:

DOI: 10.1002/pds

Table 2. The proportion of electrocardiographs performed in the exposure period (from 2 weeks prior to 2 weeks after start of index date [new prescription of haloperidol]) compared with control period (from 2 weeks prior to 2 weeks after 1 year before the index date), stratified according to risk factors for QT prolongation

	Exposure period $n = 3420$	Control period $n = 3420$	Relative risk (95% CI)
All patients	63 (1.8%)	27 (0.8%)	2.4 (1.5–3.8)
Any additional risk factor for QT prolongation[a]			
Yes ($n = 2438$)	47 (1.9%)	22 (1.0%)	2.1 (1.2–3.5)
No ($n = 982$)	16 (1.6%)	5 (0.4%)	2.8 (1.0–7.8)
Age category in years			
18–44 ($n = 693$)	8 (1.2%)	4 (0.5%)	4.0 (0.9–18.8)
45–64 ($n = 750$)	17 (2.3%)	4 (0.4%)	5.3 (1.6–18.3)
65–84 ($n = 1312$)	34 (2.6%)	16 (1.2%)	2.3 (1.2–4.3)
>84 ($n = 665$)	4 (0.6%)	4 (0.7%)	1.0 (0.3–4.0)
Sex			
Male ($n = 1436$)	36 (2.5%)	17 (1.2%)	2.2 (1.2–4.0)
Female ($n = 1984$)	27 (1.4%)	10 (0.5%)	2.7 (1.3–5.6)
History of ischaemic cardiac disease or heart failure			
Yes ($n = 654$)	14 (2.1%)	9 (1.5%)	1.4 (0.6–3.4)
No ($n = 2766$)	49 (1.8%)	18 (0.6%)	2.9 (1.7–5.0)
Concurrent use of class 1 QT-prolonging drugs and/or anti-arrhythmic drugs[b]			
Yes ($n = 905$)	17 (1.9%)	8 (1.3%)	1.2 (0.4–3.9)
No ($n = 2515$)	46 (1.8%)	19 (0.7%)	2.4 (1.4–4.1)

CI, confidence interval.
[a]At least one of the following risk factors: age > 65 years, history of heart failure, ischaemic heart disease or concurrent use of class 1 QT-prolonging drugs or anti-arrhythmic drugs.
[b]Drugs with risk of QT prolongation according to the Arizona Center for Education & Research on Therapeutics,[26] and classes I and III anti-arrhythmic drugs, according to the classification of Vaughan-Williams.[25]

0.8%, RR 2.4 [1.5–3.8]). This was also the case in patients with at least one additional risk factor for QT prolongation (exposure period: 1.9%, control period 1.0%, RR 2.1 [1.2–3.5]). To the best of our knowledge, our study is the first to report on compliance with recommendations on ECG monitoring upon starting with a QT-prolonging drug in the population at large. Recently, Muzyk *et al*. examined in a hospital setting the effects of implementation of a computerized physician order entry on adherence to monitoring, of among others, the QT interval after intravenous haloperidol prescription. During the study period (2007–2010), 40% of the patients who received intravenous haloperidol had an ECG, which increased to 61% after the implementation of the intervention.[27]

Our study has several limitations. First, haloperidol is often prescribed for the very old and terminally ill patients to manage agitation and delirium, especially in primary care, and for understandable reasons, these patients are less likely to have an ECG. We therefore only included patients with a follow-up time of at least 1 year after the start of haloperidol in our main analysis. Sensitivity analyses performed in the full cohort (including patients with less than 1 year of follow-up) resulted in lower proportions of ECGs (1.4%). Second, as in some cases a medical specialist may have initiated haloperidol and ordered an ECG, this may not have been recorded in the medical files of the general practitioner. When the continued supply subsequently was managed by the general practitioner, as is common practice, this may have incorrectly been recorded as a first prescription of haloperidol in our study. This may have resulted in an underestimation of ECG recordings in the Clinical Practice Research Datalink database. Any underestimation is likely to be very small, however, as the vast proportion of haloperidol prescriptions included in our study were initiated in the primary care setting.

In view of the extremely low compliance with the drug label recommendation to record an ECG before initiation of a QT-prolonging drug such as haloperidol, a critical reappraisal of this recommendation seems warranted.

Importantly, the QT prolongation is a poor marker of the risk of torsade de pointes, ventricular arrhythmia and sudden cardiac death. According to the ICH E14

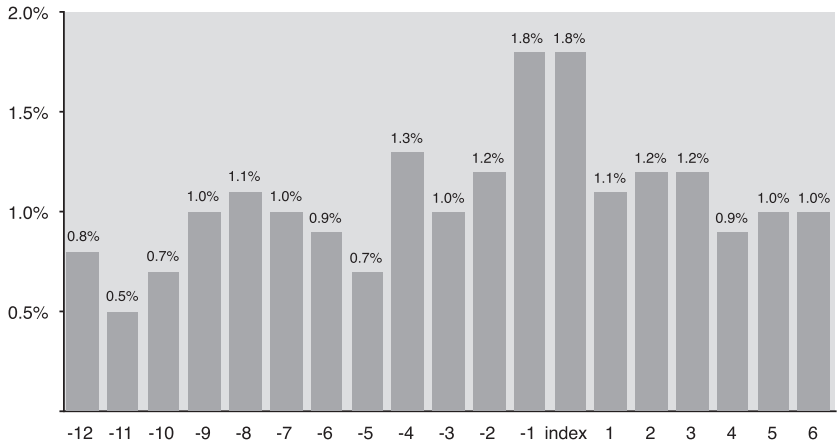

Figure 3. Proportion of ECGs performed per month before and after index date (start haloperidol prescription)

DOI: 10.1002/pds

guideline, a thorough QT study is negative when a drug increases the mean QT interval less than 10 ms. In clinical studies, a QT interval of 500 ms or more is accepted as a threshold of an increased risk of torsade de pointes.[13,14] However, the association between the risk of torsade de pointes and the length of the QT interval seems not to be linear.[13,14] A prolonged QT by no means will imply that a drug *per se* causes torsade de pointes, while some drugs have been removed from the market because of a high risk of torsade de pointes, although the mean QT interval was only moderately increased (5–10 ms).[28]

Furthermore, the absolute risk of torsade de pointes is very low. The use of 15 mg haloperidol (orally) causes an average increase in QT of 7 ms, which is below the accepted cut-off value of 10 ms.[21] However, this drug has clearly been linked to torsade de pointes in post-marketing adverse event reports, especially when used intravenously or when patients have additional risk factors.[21,29,30] In a study of Hennessy *et al*., incidence rate of 42 (35–50) per 10 000 person-years for the composite endpoint of cardiac arrest and ventricular arrhythmia in haloperidol users with schizophrenia was reported. The two control groups, patients with psoriasis or glaucoma, showed an incident rate of 18 (11–28) and 34 (28–41) per 10 000 person-years (adjusted rate ratios 2.4 [1.5–3.9] and 2.2 [1.7–3.0]).[31] Other studies reported incidence rates of composite endpoints combining sudden arrest and ventricular arrhythmia of 18 to 83 per 10 000 person-years for users of haloperidol.[32,33]

In users of antipsychotics, the proportion of patients that develop QT prolongation (>500 ms) is estimated between 0% and 2%, and the reported frequency of torsade de pointes was approximately 1 in 10 000 users.[34] About one-fifth of the cases of torsade de pointes convert into ventricular fibrillation (1 in 50 000 users), which in 85% of the cases was fatal.[34,35] On the basis of these findings, Bouvy *et al*. showed that for the current QT-prolonging antipsychotics on the market, routine ECG monitoring of all new users in clinical practice is not cost-effective.[34]

As the results of our study show, physicians do not comply with the ECG monitoring recommendations stated in the drug labels of QT-prolonging drugs. This may be due to two important barriers: first, lack of awareness among physicians, about the recommendation, and about the association between QT-prolonging drugs and sudden cardiac arrest. The knowledge on QT-prolongation risks among physicians has been shown to be suboptimal.[36] Although, haloperidol has been on the market since 1958[37] and has been prescribed since, physicians may never have observed a QT-related side effect in their practice. Moreover, the ultimate negative effect of QT prolongation, namely ventricular arrhythmia and sudden cardiac death, will not always be linked to the prescription of a QT-prolonging drug.

A second barrier may be the lack of feasibility. It could be argued that physicians, in contrast to regulatory authorities, find it not feasible to perform ECGs in every patient who starts a QT-prolonging drug. Several QT-prolonging drugs are widely prescribed by general practitioners, such as domperidone, (es)citalopram and haloperidol. It may very well be that clinicians consider the risk of QT prolongation acceptable, or they are willing to take the risk that this potentially fatal but very rare side effect occurs. Besides, in the case of haloperidol, alternative therapies carry the same risks as most antipsychotic medications have been shown to cause some degree of QT prolongation.[21]

Finally, it can be questioned whether inclusion of such a recommendation in the drug labelling is effective, when not accompanied by more direct communication to prescribing physicians. Changing prescribing behaviour is extremely difficult. Even strong actions may have only a moderate impact on prescription patterns. For example, Piening *et al*. evaluated the effect of direct healthcare professional communications or 'dear doctor letters' and found that such a letter caused a long-term change of use of only one-third of the drugs in question and a mean decrease of 27% in the use of such drugs.[38] As another example, in September 2007, the Irish Medicines Board issued a warning regarding the use of, among others, haloperidol in patients with cardiovascular disease, additionally recommending that patients should undergo ECG prior to treatment. Musleh *et al*. determined prescribing rates 12 months before and after the warning, which showed that the warning had no significant effect on prescribing of the drug, although alternative therapies are available.[39]

CONCLUSIONS

Our study showed that the compliance with recommendations to perform ECGs when starting a new QT-prolonging drug, in our example haloperidol, is extremely poor. In view of this and the fact that the QT interval is a weak marker of future torsade des pointes and sudden cardiac death and these adverse events are very rare, the recommendation to record an ECG before prescribing QT-prolonging drugs such as haloperidol should be reconsidered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DOI: 10.1002/pds

KEY POINTS

- Prior to prescribing the QT-prolonging drug haloperidol, only 1.8% of all patients and 1.9% of the patients with at least one additional risk factor for QT prolongation had an ECG as compared with 0.8% and 1.0% of the patients during the control period 1 year before, when no haloperidol was used (RR 2.4 [1.5–3.8] and RR 2.1 [1.2–3.5], respectively).
- Taking into account this extremely low compliance to the recommendation, the low absolute risk of torsade de pointes, ventricular tachycardia and sudden cardiac death, as well as the fact that the QT interval prolongation is a weak marker of such future events, the recommendation to record an ECG before prescribing QT-prolonging drugs such as haloperidol should be reconsidered.

ETHICS STATEMENT

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the CPRD, protocol number 13_158R.

ACKNOWLEDGEMENTS

M. W. and M. D. B. designed the study and drafted the manuscript. M. W. and P. S. performed the statistical analyses and collected the data. P. S., F. R., M. D. B., A. H., A. B., and M. W. contributed to discussions and interpretation of the data, and to the writing of the report. All authors had full access to data, and reviewed and approved the drafts of the manuscript, including the final draft. No medical writer or other people participated in the study design, data analysis or writing of this report.

This work was supported by the Utrecht University. The funders had no role in design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

M. L. De Bruin, the corresponding author, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Kramer D, Zimetbaum P. Long-QT syndrome. *Cardiol Rev* 2011; **19**: 217–225.
2. Gupta A, Lawrence AT, Krishnan K, *et al.* Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 2007; **153**: 891–899.
3. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol* 1999; **47**: 307–313.
4. Berdowski J, Berg RA, Tijssen JG, *et al.* Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 2010; **81**: 1479–1487.
5. Nichol G, Thomas E, Callaway CW, *et al.* Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; **300**: 1423–1431.
6. Straus SM, Sturkenboom MC, Bleumink GS, *et al.* Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J* 2005; **26**: 2007–2012.
7. Stockbridge N, Morganroth J, Shah RR, *et al.* Dealing with global safety issues: was the response to QT-liability of non-cardiac drugs well coordinated? *Drug Saf* 2013; **36**: 167–182.
8. Mol PG, Straus SM, Piening S, *et al.* A decade of safety-related regulatory action in the Netherlands: a retrospective analysis of direct healthcare professional communications from 1999 to 2009. *Drug Saf* 2010; **33**: 463–474.
9. van Noord C, Sturkenboom MC, Straus SM, *et al.* Non-cardiovascular drugs that inhibit hERG-encoded potassium channels and risk of sudden cardiac death. *Heart* 2011; **97**: 215–220.
10. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; **350**: 1013–1022.
11. Yang T, Snyders D, Roden DM. Drug block of I(kr): model systems and relevance to human arrhythmias. *J Cardiovasc Pharmacol* 2001; **38**: 737–744.
12. Cubeddu L. QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. *Am J Ther* 2003; **10**: 452–457.
13. *Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs*. U.S. Department of Health and Human Services, Food and Drug Administration: Rockville, USA; 2005. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf [March 2013].
14. *Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonarrhythmic Drugs (CHMP/ICH/2/04)*. European Medicines Agency: London, 2005. Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf [March 2013].
15. Warnier MJ, Holtkamp FA, Rutten FH, *et al.* Quality of drug label information on QT interval prolongation. *Int J Risk Saf Med* 2014; **26**: 89–98.
16. Akers W, Flynn J, Davis G, *et al.* Prolonged cardiac repolarization after tacrolimus and haloperidol administration in the critically ill patient. *Pharmacotherapy* 2004; **24**: 404–408.
17. Jackson T, Ditmanson L, Phibbs B. Torsade de pointes and low-dose oral haloperidol. *Arch Intern Med* 1997; **157**: 2013–2015.
18. O'Brien JM, Rockwood RP, Suh KI. Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; **33**: 1046–1050.
19. Perrault LP, Denault AY, Carrier M, *et al.* Torsades de pointes secondary to intravenous haloperidol after coronary bypass grafting surgery. *Can J Anaesth* 2000; **47**: 251–254.
20. Tisdale JE, Rasty S, Padhi ID, *et al.* The effect of intravenous haloperidol on QT interval dispersion in critically ill patients: comparison with QT interval prolongation for assessment of risk of torsades de pointes. *J Clin Pharmacol* 2001; **41**: 1310–1318.
21. Beach SR, Celano CM, Noseworthy PA, *et al.* QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; **54**: 1–13.
22. SPC Haldol 5 mg tablets. Available at: http://www.medicines.org.uk/emc/medicine/17422 [September 2013].
23. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997; **350**: 1097–1099.
24. Parkinson J, Davis S, van Staa T. Pharmacovigilance. In *The General Practice Research (GPRD) Database: Now and the Future*, Mann R (ed.). John Wiley & Sons: Chichester, England, 2007; 341–348.
25. Vaughan Williams EM. Classification of antidysrhythmic drugs. *Pharmacol Ther B* 1975; **1**: 115–138.
26. Arizona Center for Education & Research on Therapeutics. QT drug lists. Available at: https://www.crediblemeds.org/index.php [18 July 2013].
27. Muzyk AJ, Rivelli SK, Jiang W, *et al.* A computerized physician order entry set designed to improve safety of intravenous haloperidol utilization: a retrospective study in agitated hospitalized patients. *Drug Saf* 2012; **35**: 725–731.
28. Killeen MJ. Drug-induced arrhythmias and sudden cardiac death: implications for the pharmaceutical industry. *Drug Discov Today* 2009; **14**: 589–597.
29. Meyer Massetti C, Vaerini S, Rätz Bravo A, *et al.* Comparative safety of antipsychotics in the WHO pharmacovigilance database: the haloperidol case. *Int J Clin Pharmacol* 2011; **33**: 806–814.
30. Meyer-Massetti C, Cheng CM, Sharpe BA, *et al.* The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *J Hosp Med* 2010; **5**: E8–E16.
31. Hennessy S, Bilker WB, Knauss JS, *et al.* Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ* 2002; **325**: 1070.
32. Leonard CE, Freeman CP, Newcomb CW, *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* 2013; **10**: 1–9.
33. Hennessy S, Bilker WB, Knauss JS, *et al.* Comparative cardiac safety of low-dose thioridazine and low-dose haloperidol. *Br J Clin Pharmacol* 2004; **58**: 81–87.
34. Bouvy JC, Koopmanschap MA, Shah RR, *et al.* The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. *Clin Pharmacol Ther* 2012; **91**: 281–288.
35. Nielsen J, Graff C, Kanters JK, *et al.* Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs* 2011; **25**: 473–490.
36. Al-Khatib SM, Allen LaPointe NM, Kramer JM, *et al.* A survey of health care practitioners' knowledge of the QT interval. *J Gen Intern Med* 2005; **20**: 392–396.
37. Lopez-Munoz F, Alamo C. The consolidation of neuroleptic therapy: Janssen, the discovery of haloperidol and its introduction into clinical practice. *Brain Res Bull* 2009; **79**: 130–141.
38. Piening S, Reber KC, Wieringa JE, *et al.* Impact of safety-related regulatory action on drug use in ambulatory care in the Netherlands. *Clin Pharmacol Ther* 2012; **91**: 838–845.
39. Musleh S, Kraus S, Bennett K, *et al.* Irish Medicines Board safety warnings: do they affect prescribing rates in primary care? *Pharmacoepidemiol Drug Saf* 2011; **20**: 979–986.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

DOI: 10.1002/pds