ORIGINAL ARTICLE

Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies

Ashleigh Hooimeyer[1] [iD] | Alice Bhasale[1] [iD] | Lucy Perry[1] [iD] | Alice Fabbri[1,2] [iD] | Annim Mohammad[1] [iD] | Eliza McEwin[1] | Barbara Mintzes[1] [iD]

[1]Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia

[2]Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital and University of Southern Denmark, Odense, Denmark

Correspondence
Barbara Mintzes, Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia.
Email: barbara.mintzes@sydney.edu.au

Abstract

Information on rare adverse effects is often limited when a medication is initially approved for marketing. Medicines regulators use safety advisories to warn health professionals and consumers about emerging harms. This study aimed to identify characteristics and advice provided in cardiac safety advisories released by regulators in Australia, Canada, the United Kingdom, and the United States. This was a retrospective study of safety advisories about cardiac-related adverse events issued by these four international medicines regulators between 2010 and 2016. A descriptive overview was followed by a more detailed content analysis, focusing on recommended actions for health professionals, including monitoring advice. For the latter, we applied the systematic information for monitoring (SIM) scale to assess adequacy. Over this period, 164 safety advisories about cardiac harms were issued by the four regulators. There were 61 drugs with advisories of cardiac risk, only 9 (14.7%) of which had advisories from all regulators in countries where the drug was approved. The most common adverse events were cardiac arrhythmias (n = 97, 59.1%) and coronary artery disorders (n = 39, 23.8%). The most frequent advice to prescribers was to monitor patients (n = 74, 45.1%), although only 41.2% of these advisories provided detailed advice on how monitoring should occur. We found many differences in the decision to warn and the advice provided. Patient monitoring was most often recommended, but key information such as frequency or thresholds for action was often lacking. Healthcare professionals and consumers need consistent information about rare serious harms so that they can make informed decisions.

KEYWORDS
cardiac harm, drug-related side effects and adverse reactions, pharmaceutical policy, pharmaceutical regulators, risk communication

1 | INTRODUCTION

Decisions to approve new drugs by medicines regulators are often made based on limited information about safety collected during clinical trials. Longer-term or rare adverse events are often detected only once a drug is on the market.[1] Post-market safety advisories are issued by national medicines regulators when new information about a drug's effects become known after regulatory approval, for a drug already on the market. They are one key means with which safety messages can be communicated to healthcare professionals and consumers. Regulators use various forms of safety advisories to communicate about emerging risks, including letters (direct health professional communications or DHPCs), website alert notices, and drug safety bulletins. Advisories may be accompanied by other regulatory actions such as updates to product information or prescribing guidelines and inclusion of black box warnings.

Our team previously compiled all the post-market safety advisories issued by the US United States (US) Food and Drug Administration (FDA), Health Canada (HC), the Australian Therapeutic Goods Administration (TGA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA), between 1 January 2007 and 31 December 2016. A previous publication from our group identified a low level of concordance between these four regulators in their decisions to warn healthcare professionals and the public, with all regulators issuing warnings about an approved medicine in only 10% of cases.[2]

A number of commonly prescribed drugs are associated with increased risks of cardiac adverse events.[3] These include non-steroidal anti-inflammatories (NSAIDs), antihyperglycaemics, and antiemetics.[3] For example, in observational studies domperidone has been found to increase the risk of ventricular arrhythmia and sudden cardiac death.[4-7] NSAIDs have also been extensively studied for their increased risk of ischemic heart disease,[8-14] and those which are more selective for cyclooxygenase type 2 receptors (COX-2) have been shown to be associated with an increased risk.[15]

This study aims to provide an overview of safety advisories about cardiac-related adverse events (referred to from here on as cardiac advisories) issued by four international regulators between 2010 and 2016, investigating:

- Which regulators issued advisories about which drugs?
- How often did all countries where a drug was marketed issue warnings?
- Which types of cardiac adverse effects featured most often?

We further aimed to investigate the content of these advisories and where these regulators concurred or differed in the information provided, specifically detailing:

- The advice provided to health professionals.
- Whether patient monitoring advice was provided, and whether it included key information elements needed for effective implementation.
- Evidence cited in the advisories.

What is already known about this subject

- Medicines safety advisories are one way in which new information about adverse drug reactions are communicated to healthcare professionals and the public.
- Efficacy of these warnings has previously been shown to be variable.
- Many drugs are associated with cardiac adverse effects which may have a high mortality and morbidity burden.

What this study adds

- Between 2010 and 2016, there were few cases where regulators from Australia, the United Kingdom, Canada, and the United States all issued advisories about the same drug.
- The most frequent advice for health professionals was to monitor for adverse effects although often this advice was too limited to provide useful clinical guidance

2 | MATERIALS AND METHODS

2.1 | Sample selection

All advisories issued by the TGA, FDA, HC, or MHRA between 2007 and 2016 had been previously compiled into a database, as described by Perry et al[2,16] Safety advisories were defined as communications to prescribers and/or the public about potential or confirmed drug safety risks due to the medicine itself, not problems with manufacturing or improper use. These were categorized into four types: Alerts, Investigations, DHPCs, and Bulletins. Advisories were downloaded from regulators' websites and were coded by drug (using Anatomical Therapeutic Chemical classifications)[17] and type of harm (using the Medical Dictionary for Regulatory Activities [MedDRA version 19.1]).

From this database, a subset of advisories was selected for inclusion. Only advisories released between 1 January 2010 and 31 December 2016 were included. Cardiac advisories were selected by filtering listed adverse events using MedDRA higher-level group terms (HLGTs) within the system order class grouping of "cardiac disorders". Early warning advisories and notices about investigations of possible adverse events were excluded as these described unconfirmed risks.

2.2 | Data collection and coding

A data extraction tool was created using REDCap (Research Electronic Data Capture).[18] Key areas of interest included:

- Nature of the safety concern and outcomes (adverse events, risk of death)

- Source of evidence of harms (eg, randomized controlled trials, case reports, etc)
- Advice to health professionals (eg, dosage advice, patients who should not receive the medication, monitoring, etc)

Five rounds of pilot testing the data extraction tool preceded data collection. In order to test reliability of data coding, 49 advisories were double coded. Reliability was calculated using the intraclass correlation coefficient (ICC).[19] A threshold of ≥0.75[19] was pre-specified as indicating sufficient reliability to support single coding of advisory content.

2.3 | Analysis

Descriptive statistics were calculated for advisory frequencies by country, year, communication method(s), drug, and safety concern, with differences between regulators compared using the χ^2 statistic. Data analysis was performed using SPSS (Version 24).

As warnings about cardiac risks often mention monitoring, we used the systematic information for monitoring (SIM) score to assess the usefulness of the monitoring advice (Table 1).[20-23] The SIM score has previously been used to assess advice in Summaries of Product Characteristics. The scoring system focuses on the quality of monitoring advice provided for six criteria: what to monitor, when to start monitoring, when to stop monitoring, how frequently to monitor, a "critical value," and how to respond. Each of these components were scored 0 or 1, depending on whether the advice was specified and sufficient. (Table 1).

2.4 | Case study

An illustrative case study of citalopram and escitalopram was used in order to compare the content of advisories between regulators. This example was chosen because all regulators had issued warnings about cardiac arrhythmia risks with citalopram and/or escitalopram,

and these closely related antidepressants are commonly used in primary care.[24]

3 | RESULTS

3.1 | Reliability testing

Based on the 49 double-coded advisories, the calculated ICC was 0.878 (95% CI 0.784-0.931). This was well above the threshold of 0.75 for reliability and was considered adequate for single coding of the remaining advisories.[19]

3.2 | Overview of cardiac advisories

A total of 164 advisories were identified about cardiac risks (Figures 1 and 2). Of these, 57 (34.8%) were issued by the MHRA, 40 (24.4%) by the FDA, 35 (21.3%) by the TGA, and 32 (19.5%) by HC (Table 2). There was a significant difference between the number of advisories issued by each country over this timeframe ($\chi^2 = 9.12$, $P = .028$).

The regulators varied in the types of communication used ($\chi^2 = 91.22$, $P < .001$), with the FDA using mostly alerts, HC using DHPCs, and the TGA using bulletin articles (Table 2). For Canada, the US, and the UK, we were able to access DHPCs from the regulators. In Australia, however, DHPCs are not made publicly available and our team was unable to obtain a comprehensive set via requests to companies or a freedom of information request to the TGA.[25] Therefore, DHPCs from Australia have not been included in this study.

The most commonly reported adverse events based on MedDRA HLGT classification were cardiac arrhythmias (n = 97, 59.1%), coronary artery disorders (n = 39, 23.8%), and cardiac disorders, signs, and symptoms (n = 21, 12.8%; Table 2). Cardiac arrhythmias included adverse events such as increased heart rate, QT prolongation, and

TABLE 1 SIM criteria and examples

SIM Criteria	Examples of adequate advice (scored 1)	Examples of inadequate advice (scored 0)
What to monitor	ECG, heart rate, blood pressure, electrolytes	Cardiac monitoring (no additional detail)
When to start monitoring	At the beginning of treatment, before treatment	Not stated
When to stop monitoring	After 12 hours, when ceasing medication, 6 weeks after ceasing	Not stated
How frequently to monitor	Every 2 weeks, every month	Frequent monitoring
Critical Value	QT interval >470 milliseconds, heart rate <45 bpm	QT prolongation, bradycardia
How to respond	Cease medication, reduce dose, extended/increased monitoring	Not stated

cardiac arrest. Coronary artery disorders primarily consisted of myocardial infarction, while cardiac disorders, signs, and symptoms included a large range of cardiac symptoms.

There were 61 drugs in total with advisories on cardiac risks, only nine (14.7%) of which had advisories from all regulators in countries where the drug was approved.

3.3 | Common drugs featuring in cardiac advisories

Table 3 describes the top 11 drugs featuring in cardiac advisories. The aim was to describe the top 10 drugs; 11 are included
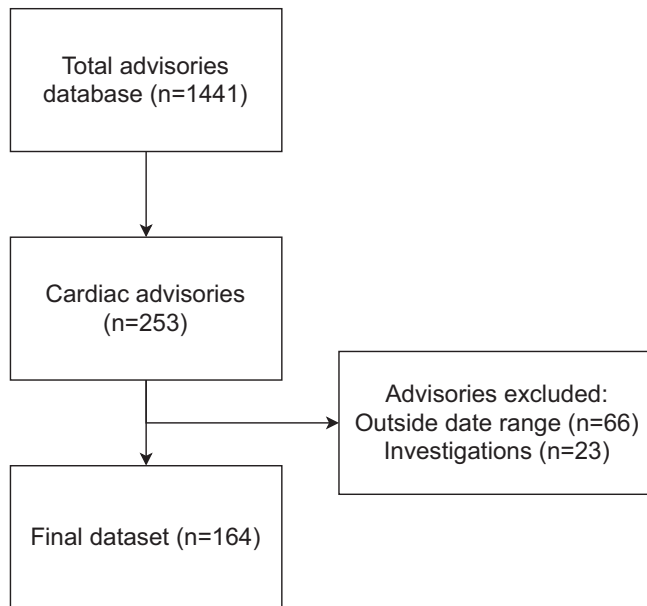

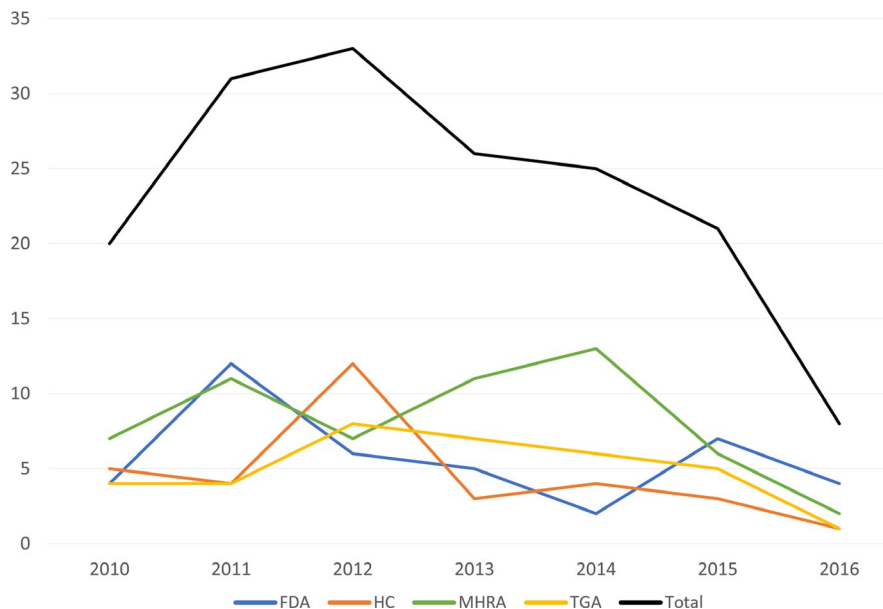**FIGURE 1** Flow chart of study sample selection from the full advisories database

as four drugs had equal numbers of advisories. In total, 87/149 (58.4%) cardiac advisories were about these drugs. Four have been removed from the market in some countries, rosiglitazone in the UK, dextropropoxyphene in all countries, ondansetron (in certain formulations) in the US, and strontium ranelate in the UK and Australia. Dextropropoxyphene had already been removed from the market in all of the countries except Australia by the time of the first advisory.[26] Domperidone was never approved in the US, while strontium ranelate was never approved in the US or Canada.

It is important to note that these numbers do not necessarily reflect the risk of the medication but can also reflect how much regulatory activity occurred during the timeframe. Dextropropoxyphene is a good example of this, as the TGA attempted to remove it from the market several times but the manufacturer appealed these attempts.[26] This led to a series of advisories that provided updates on the regulatory status, rather than new safety information about the drug.

3.4 | Advice provided to health professionals

Most advisories (n = 149, 90.9%) provided information for health professionals (Table 4). Of these advisories, 109 (73.2%) advised prescribers to take specific actions, while 39 (26.2%) provided awareness information only (ie, provided information about the adverse event without any actions for health professionals).

The FDA provided the most advice to educate, counsel, or advise patients (FDA = 18 (54.5%), HC = 7 (24.1%), MHRA = 14 (25.9%), TGA = 9 (27.3%), $\chi^2 = 9.749$, $P = .021$).

Australian advisories were most likely to inform prescribers to follow the product information (FDA = 8 (24.2%), HC = 8 (27.6%), MHRA = 10 (18.5%), TGA = 19 (57.6%), $\chi^2 = 15.877$, $P = .001$).

FIGURE 2 Number of advisories on cardiac harms issued per year by each regulator

TABLE 2 Characteristics of cardiac advisories

	FDA	HC	MHRA	TGA	Total
Total	40 (24.4%)	32 (19.5%)	57 (34.8%)	35 (21.3%)	164 (100%)
Adverse event type (percentages are of country total)					
Cardiac arrhythmias	18 (45%)	23 (71.9%)	34 (59.6%)	22 (62.9%)	97 (59.1%)
Coronary artery disorders	16 (40%)	6 (18.8%)	6 (10.5%)	11 (31.4%)	39 (23.8%)
Cardiac disorders, signs, and symptoms	5 (12.5%)	2 (6.3%)	11 (19.3%)	3 (8.6%)	21 (12.8%)
Heart failures	6 (15%)	3 (9.4%)	6 (10.5%)	2 (5.7%)	17 (10.4%)
Cardiac valve disorders	1 (2.5%)	2 (6.3%)	3 (5.3%)	1 (2.9%)	7 (4.3%)
Myocardial disorders	1 (2.5%)	0	1 (1.8%)	1 (2.9%)	3 (1.8%)
Congenital cardiac disorders	0	0	1 (1.8%)	0	1 (0.6%)
Communication type					
Alert	30 (75%)	10 (31.3%)	29 (50.9%)	19 (54.3%)	88 (53.7%)
DHPC	10 (25%)	22 (68.8%)	28 (49.1%)	0[a] (0%)	60 (36.6%)
Bulletin	0 (0%)	0 (0%)	0 (0%)	16 (45.7%)	16 (9.8%)

[a]We were unable to access Australian DHPCs.

The MHRA was most likely to recommend that a medication be stopped in patients on therapy (FDA = 5 (15.2%), HC = 4 (13.7%), MHRA = 16 (29.6%), TGA = 2 (6.1%), $\chi^2 = 8.618$, $P = .035$).

3.5 | Monitoring advice

Of the 109 (73.2%) advisories that advised prescribers to take action, 74 (67.9%) provided advice about testing or monitoring, but six were only about assessing suitability for treatment. Monitoring advice was assessed for the remaining 68 advisories using the SIM score (n = 68, 45.6%; Table 5).[20-23] The type of monitoring varied depending on the adverse event, but included clinical investigations such as electrocardiographs (ECGs) (60.8%), signs and symptoms (43.2%), and blood tests (17.6%).

The average total SIM score for advisories which provided monitoring advice was 2.57/6 (95% CI 2.17-2.95). In total, 28 (41.2%) of the advisories had a score ≥3, which has been considered by other studies to represent a minimum threshold for actionable advice.[20,21,23] Only two of the information items were provided in over half of advisories; what to monitor (75.0%) and when to start monitoring (55.9%).

Four advisories (5.9%) recommended monitoring without providing any details of what to monitor. There was no statistically significant difference between countries. However, there may not have been adequate power to detect a difference.

3.6 | Information about sources of evidence

Regulators reported a range of types of evidence for the harm, from systematic reviews to case studies (Table 6). While there was no statistically significant difference between the regulators on the types of cited evidence, the FDA was the only regulator that always reported the evidence used in decision-making.

3.7 | Case study: citalopram/escitalopram

Advisories for racemic citalopram and its S-enantiomer escitalopram, which belong to the selective serotonin reuptake inhibitor class of antidepressants and are widely used, were examined as an illustrative case study.[24] They present the highest risk for QT-prolongation and Torsades de Pointes among the drugs of this class.[27]

Between the four regulators, seven advisories were issued for citalopram and escitalopram between 2011 and 2012 (File S2). The FDA was the first regulator to issue a safety warning. The four regulators provided very similar information on risks of QT prolongation and on a change in recommended dose.

Despite all four regulators warning of the risk of Torsades de Pointes, only the FDA and HC mentioned the risk of death in their advisories. In all four countries, regulatory warnings were accompanied by a change to the product information advising prescribers to use lower doses. In their second advisory, the FDA mentioned more

TABLE 3 Top 11 drugs[a] by number of advisories

	Indication	FDA (n = 40)	HC (n = 32)	HC (n = 32)	TGA (n = 35)	Total (n = 164)
Rosiglitazone	Type 2 Diabetes	5 (12.5%)	4 (12.5%)	2 (3.5%)	1 (2.8%)	12 (7.3%)
Withdrawal		No	No	2010	No[c]	
Dextropropoxyphene	Mild-to-moderate pain	0	0	1 (1.8%)[d]	9 (25.7%)	10 (6.1%)
Withdrawal[b]		2010	2010		2012[e]	
Fingolimod	Multiple sclerosis	3 (7.5%)	3 (9.4%)	3 (5.3%)	1 (2.8%)	10 (6.1%)
Domperidone	Nausea	N/A	2 (6.3%)	6 (10.5%)	1 (2.8%)	9 (5.5%)
Denosumab	Osteoporosis	2 (5.0%)	1 (3.1%)	3 (5.3%)	2 (5.7%)	8 (4.8%)
Dronedarone	Cardiac arrhythmias	3 (7.5%)	2 (6.3%)	2 (3.5%)	0	7 (4.3%)
Ondansetron	Nausea	2 (5.0%)	2 (6.3%)	2 (3.5%)	1 (2.8%)	7 (4.3%)
Withdrawal[b]		2012[f]	No	No	No	
Citalopram	Depression	2 (5.0%)	1 (3.1%)	2 (3.5%)	1 (2.8%)	6 (3.7%)
Dabigatran	Venous thromboembolism	1 (2.5%)	2 (6.3%)	2 (3.5%)	1 (2.8%)	6 (3.7%)
Saquinavir	HIV infection	1 (2.5%)	2 (6.3%)	3 (5.3%)	0	6 (3.7%)
Strontium ranelate	Osteoporosis	N/A	N/A	3[g] (5.3%)	3[g] (8.6%)	6 (3.7%)

Note: N/A—not applicable as the drug was never marketed in that country or was not on the market between 2010 and 2016.

[a]The aim was to describe the top 10; 11 are included as 4 had equal numbers of advisories.

[b]Year of market withdrawal if withdrawn during the study period (2010-2016); the UK issued an advisory on dextropropoxyphene, despite its 2005 withdrawal.

[c]Rosiglitazone was later withdrawn in 2019 post-study period.

[d]Withdrawn in 2005 prestudy period.

[e]Dextropropoxyphene was withdrawn in 2012 in Australia but reintroduced in 2013 and later withdrawn again.

[f]32 mg single-IV dose withdrawn.

[g]Withdrawn in 2017 post-study period.

types of patients who should not receive the drug, in addition to patients who had congenital QT prolongation.[28]

Of the seven advisories, six mentioned the results of Thorough QT (TQT) studies as evidence to support the cardiac risks of citalopram and escitalopram.[29-33] One advisory by HC cites only 'clinical trial data' without further detail.[34] In 2004, the FDA published a guidance including standard language to describe cardiac risks identified in TQT studies, which is reflected within the FDA advisories, such as incorporation of a precautionary statement about the risk and recommendations for patient dosage and monitoring.[35] Other regulators differed in the amount of detail provided. For example, although the TGA advisory did not mention a TQT study, the cited results were the same as those in a MHRA advisory citing TQT study results.[29,31]

Four of the six advisories about citalopram and escitalopram advised health professionals to monitor patients, although they varied in their recommendations. All regulators advised ECG monitoring, but while the TGA, MHRA, and FDA advised health professionals to monitor electrolytes, HC only mentioned that "Hypokalemia and hypomagnesemia should be corrected before administering Celexa". The regulators also differed in their advice on when ECGs should be done. The MHRA recommended only performing ECGs in patients with cardiac disease before initiation of treatment, and in patients who experience cardiovascular symptoms, while other regulators advised "more frequent" ECG monitoring in patients at risk of QT prolongation, without further specifying the frequency. SIM scores for the four advisories ranged from 1/6 to 5/6, with two regulators only telling health professionals what to monitor (ie, ECG monitoring) but providing no further advice.

4 | DISCUSSION

In this analysis of regulatory advisories on cardiac risks by the TGA, FDA, HC, and MHRA from 2007 to 2016, we found inconsistencies between regulators in which safety issues they provided warnings about and how many advisories each regulator published. This supports the findings of other studies.[2,36] Of the 61 different drugs for which advisories were issued on cardiac risks, only nine had warnings issued in all of the countries in which they were approved.

While some safety issues lead to the drug being removed from the market, as with dextropropoxyphene, for others, the regulators decided that updating health professionals on the risk, and providing mitigation strategies, was sufficient to ensure that the benefits of the drug continued to outweigh these risks. An example is domperidone, where use at low doses for short periods of time in low-risk patients was decided to be reasonably safe.[37] Instead of removing this drug from the market, each of the regulators changed dosing recommendations and contraindicated it in patients with underlying cardiac conditions.

TABLE 4 Advice provided to health professionals

	FDA (n = 33)	HC (n = 29)	MHRA (n = 54)	TGA (n = 33)	Total (n = 149)
General advice					
Recommended actions	24 (72.7%)	22 (75.9%)	45 (83.3%)	18 (54.5%)	109 (73.2%)
Awareness raising	9 (27.3%)	7 (24.1%)	9 (16.7%)	14 (42.4%)	39 (26.2%)
No recommendations	0	0	0	1 (3.0%)	1 (0.7%)
Focus of advice					
Avoid use in certain patients	15 (45.5%)	15 (51.7%)	31 (57.4%)	13 (39.4%)	74 (49.7%)
Test/monitor patients	16 (48.5%)	16 (55.2%)	30 (55.6%)	12 (36.4%)	74 (49.7%)
Educate/counsel/ advise patients	18 (54.5%)	7 (24.1%)	14 (25.9%)	9 (27.3%)	48 (32.2%)
Follow the product information/label	8 (24.2%)	8 (27.6%)	10 (18.5%)	19 (57.6%)	45 (30.2%)
Changes in dose	5 (15.2%)	8 (27.6%)	19 (35.2%)	5 (15.2%)	37 (24.8%)
Drug interactions	5 (15.2%)	10 (34.5%)	13 (24.1%)	5 (15.2%)	33 (22.1%)
Stop use in certain patients	5 (15.2%)	4 (13.7%)	16 (29.6%)	2 (6.1%)	27 (18.1%)
Change duration of use	2 (6.1%)	2 (6.9%)	9 (16.7%)	2 (6.1%)	15 (10.1%)
Switch to another medicine	2 (6.1%)	0	2 (3.7%)	2 (6.1%)	6 (4.0%)
Formulation change	1 (3.0%)	1 (3.4%)	2 (37.0%)	0	4 (2.7%)
Discontinue and restart as required	1 (3.0%)	0	0	1 (3.0%)	2 (1.3%)
Do not start new patients on therapy	1 (3.0%)	0	1 (1.9%)	0	2 (1.3%)

TABLE 5 Monitoring advice for prescribers: Systematic information for monitoring (SIM) scores[a]

Items of information	FDA (n = 15)	HC (n = 15)	MHRA (n = 30)	TGA (n = 8)	Total (n = 68)
What to monitor	12 (80%)	13 (86.7%)	18 (60%)	8 (100%)	51 (75.0%)
When to start monitoring	8 (53.3%)	8 (53.3%)	18 (60%)	4 (50.0%)	38 (55.9%)
When to stop monitoring	5 (33.3%)	6 (40%)	7 (23.3%)	0	18 (26.5%)
How frequently to monitor	8 (53.3%)	5 (33.3%)	9 (30%)	4 (50.0%)	26 (38.2%)
Critical value	5 (33.3%)	4 (26.7%)	8 (26.7%)	1 (12.5%)	18 (26.5%)
How to respond	5 (33.3%)	5 (33.3%)	13 (43.3%)	1 (12.5%)	24 (35.3%)
Average total score	2.87	2.73	2.43	2.25	2.57

[a]SIM score calculated based on papers by Ferner et al (2005), Geerts et al (2012), Nederlof et al (2015), and Højer et al (2020).

Monitoring advice, where provided, was fairly limited. Information about the critical value (the threshold representing a potential risk to the patient) and when to stop monitoring was usually absent (only provided in 26.5% of advisories each). This may create ambiguity for prescribers in clinical decision making as to when therapy should be changed or ceased. A 2020 study of Danish DHPCs also found that key needed detail was often lacking in these communications: only 16% of DHPCs stated the critical value and only 20% provided information about how often monitoring should occur.[23]

	FDA (n = 40)	HC (n = 32)	MHRA (n = 57)	TGA (n = 35)	Total (n = 164)
Any evidence cited	40 (100%)	26 (81.3%)	47 (82.5%)	30 (85.7%)	143 (87.2%)
Systematic review	3 (7.5%)	1 (3.1%)	4 (7.0%)	1 (2.9%)	9 (5.5%)
Clinical trials	20 (50%)	11 (34.4%)	25 (43.9%)	11 (31.4%)	68 (41.5%)
Observational studies	3 (7.5%)	5 (15.6%)	5 (8.8%)	3 (8.6%)	16 (9.8)
Case reports	8 (20%)	11 (34.4%)	18 (31.6%)	12 (34.4%)	49 (29.9%)
Literature (unspecified)	1 (2.5%)	2 (6.3%)	1 (1.8%)	2 (5.7%)	6 (3.7%)
Post-market data (unspecified)	1 (2.5%)	1 (3.1%)	4 (7.0%)	1 (2.9%)	7 (4.3%)

TABLE 6 Information on supporting evidence

The FDA generally provided more information in their advisories than other regulators. This is reflected in the format of the advisories. Advisories from the FDA contained four sections: nature of the concern, advice for patients, advice for health professionals, and a data summary. In this sample, a more structured approach tended to result in more details being provided.

The case study of citalopram and escitalopram showed that all four regulators provided fairly similar advice, although there were differences in the amount of detail provided, especially on monitoring. Advisories from all four countries referred to clinical trial evidence but did not cite a specific reference to a published or unpublished trial report. However, all of the regulators provided broadly similar recommendations. One important difference was the mention of risk of death in the advisories. The FDA and HC both mentioned that there was a risk of death, while the TGA and MHRA did not.

The extent to which differences in content of advisories may affect their impact in clinical practice is not certain. Current research on the effectiveness of advisories is mixed and has mostly focused on individual advisories and regulators. There have been a small number of systematic reviews which have investigated the effects of these advisories on rates of prescribing.[38-42] These have generally found that the current evidence is mixed, as advisories may have intended or unintended effects, to varying degrees, emphasizing that more research is required to understand why these effects are seen. One review which looked into papers on FDA advisories found that there was a mixed impact depending on the type of advisory.[38] Advisories which recommended patient monitoring had a minimal impact on prescribing and some advisories may have had unintended effects such as deceased use in patients not targeted by the advisory. Another review looking at papers on MHRA advisories found that the communication type made a difference, as DHPCs had more of an impact on prescribing than other types of advisories.[39]

Several studies have investigated the effectiveness of rosiglitazone advisories in a number of countries.[43-49] All of these studies found that there was a decrease in use following an advisory. Interestingly, an Australian study found that a decrease in use occurred after the initial European Medicines Agency and FDA warnings, but that there was no significant decline after a later TGA advisory or subsequent warnings.[46]

While it may appear beneficial to issue more advisories, there has been some research into the effects of public health communications and the risk of "alert fatigue". A 2013 study found an inverse relationship between number of communications and the ability to recall specific information.[50] Regulators need to balance the need to provide enough information to health professionals against oversaturating them with too much information.

Further research is needed to compare the effects of these advisories on prescribing, as well as how they affect doctors' and consumers' awareness of cardiac risks. A comparison of changes in prescribing between these countries might show how differences in advisory content may or may not have an effect. It would also be helpful to understand how regulators decide when to issue safety warnings, as in this study, we observed that regulators did not always issue the same warnings.

4.1 | Limitations

Our study has several limitations. Firstly, we used an otherwise comprehensive dataset of all advisories issued by the four included countries within a specified period, but we were unable to access DHPCs from Australia. This might explain some of the differences between the TGA and other regulators. Secondly, we were limited to only four regulators. Thirdly, we did not consider advisories outside the chosen time frame, and warnings may have been issued shortly before or after this time frame.

5 | CONCLUSIONS

In this overview of cardiac safety advisories, there was a low level of concordance between regulators in the decision to warn clinicians, leading to potential differences in knowledge and care between patients in different countries. Monitoring information was also often inadequate. This is particularly concerning considering the potentially fatal nature of many cardiac adverse effects.

DISCLOSURE

Lucy Perry is employed by George Clinical Pty Ltd a contract research organization that provides services to pharmaceutical companies.

AUTHOR CONTRIBUTIONS

AH, BM, and AF contributed to the conception, design, and interpretation of data. AH, AB, LP, AM, and EM contributed to data collection and the development of the data extraction tool. All authors reviewed the manuscript, give final approval, and agree to be accountable for all aspects.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ashleigh Hooimeyer (iD) https://orcid.org/0000-0002-8526-1837
Alice Bhasale (iD) https://orcid.org/0000-0002-5387-8760
Lucy Perry (iD) https://orcid.org/0000-0002-3337-1321
Alice Fabbri (iD) https://orcid.org/0000-0001-8413-0440
Annim Mohammad (iD) https://orcid.org/0000-0003-3744-2219
Barbara Mintzes (iD) https://orcid.org/0000-0002-8671-915X

REFERENCES

1. Psaty BM, Meslin EM, Breckenridge A. A Lifecycle approach to the evaluation of FDA approval methods and regulatory actions: opportunities provided by a new IOM report. *JAMA*. 2012;307(23):2491-2492.
2. Perry LT, Bhasale A, Fabbri A, et al. Comparative analysis of medicines safety advisories released by Australia, Canada, the United States, and the United Kingdom. *JAMA Intern Med*. 2019;179(7):982-984.
3. Hopper I. Cardiac effects of non-cardiac drugs. *Aust Prescr*. 2011;34(2):52-54.
4. Arana A, Johannes CB, McQuay LJ, Varas-Lorenzo C, Fife D, Rothman KJ. Risk of out-of- hospital sudden cardiac death in users of domperidone, proton pump inhibitors, or metoclopramide: a population-based nested case-control study. *Drug Saf*. 2015;38(12):1187-1199.
5. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case- control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-888.
6. Smolina K, Mintzes B, Hanley GE, Oberlander TF, Morgan SG. The association between domperidone and ventricular arrhythmia in the postpartum period. *Pharmacoepidemiol Drug Saf*. 2016;25(10):1210-1214.
7. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-1014.
8. Fosbøl EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther*. 2009;85(2):190-197.
9. Gudbjornsson B, Thorsteinsson SB, Sigvaldason H, et al. Rofecoxib, but not celecoxib, increases the risk of thromboembolic cardiovascular events in young adults-a nationwide registry-based study. *Eur J Clin Pharmacol*. 2010;66(6):619-625.
10. de Abajo FJ, Gil MJ, García Poza P, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2014;23(11):1128-1138.
11. Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients–a nationwide study. *PLoS One*. 2013;8(1):e54309.
12. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2009;2(3):155-163.
13. Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation*. 2011;123(20):2226-2235.
14. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. *N Engl J Med*. 2000;343(21):1520-1528.
15. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633-1644.
16. Perry L, Bhasale A, Fabbri A, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Canada, Australia, the United Kingdom and the United States - 2007 to 2016. *Pharmacoepidemiol Drug Saf*. 2020.29 1054–1063.
17. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC. ATC classification index with DDDs. 2020. https://www.whocc.no/. Accessed September 15, 2020.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
19. Koo TK, Li MY. A Guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163.
20. Nederlof M, Stoker LJ, Egberts TC, Heerdink ER. Instructions for clinical and biomarker monitoring in the summary of product characteristics (SmPC) for psychotropic drugs: overview and applicability in clinical practice. *J Psychopharmacol*. 2015;29(12):1248-1254.
21. Geerts AF, De Koning FH, Van Solinge WW, De Smet PA, Egberts TC. Instructions on laboratory monitoring in 200 drug labels. *Clin Chem Lab Med*. 2012;50(8):1351-1358.
22. Ferner RE, Coleman J, Pirmohamed M, Constable SA, Rouse A. The quality of information on monitoring for haematological adverse drug reactions. *Br J Clin Pharmacol*. 2005;60(4):448-451.
23. Højer M-MG, De Bruin ML, Boskovic A, Hallgreen CE. Are monitoring instructions provided in direct healthcare professional communications (DHPCs) of sufficient quality? A retrospective analysis of DHPCs sent out between 2007 and 2018. *BMJ Open*. 2020;10(5):e036498.
24. PBS Information and Management Section, Pricing and PBS Policy Branch, Technology Assessment and Access Division. *Expenditure and Prescriptions Twelve Months to 30 June 2019*. Pharmaceutical Benefits Scheme; 2019.
25. Torka M, Mintzes B, Bhasale A, Fabbri A, Perry L, Lexchin J. Secret safety warnings on medicines: a case study of information access requests. *Pharmacoepidemiol Drug Saf*. 2019;28(4):551-555.

26. Buckley NAF, Thomas A. Trials and tribulations in the removal of dextropropoxyphene from the Australian register of therapeutic goods. *Med J Aust*. 2013;199(4):257-260.

27. Funk KA, Bostwick JR. A Comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother*. 2013;47(10):1330-1341.

28. US Food and Drug Administration. FDA Drug Safety Communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. US Food and Drug Administration. 2012. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related. Accessed 15 September, 2020.

29. Therapeutic Goods Administration. Medicines Safety Update, Volume 3, Number 1, February 2012. Therapeutic Goods Administration (TGA). 2012. https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-1-february-2012. Accessed 15 September, 2020.

30. Gagné M. Celexa (citalopram) - Association with abnormal heart rhythms - For Health Professionals - Recalls and safety alerts. Health Canada. 2012. https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/14672a-eng.php. Accessed 15 September, 2020

31. Medicines and Healthcare products Regulatory Agency. Citalopram and escitalopram: QT interval prolongation. Medicines and Healthcare products Regulatory Agency. 2011. https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation. Accessed September 15, 2020.

32. Jones A. Association of Cipramil (citalopram hydrobromide) with dose-dependent QT interval prolongation. Lundbeck. 2011. https://webarchive.nationalarchives.gov.uk/20141206114903/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134754.pdf. Accessed September 15, 2020.

33. US Food and Drug Administration. FDA Drug Saftey Communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-abnormal-heart-rhythms-associated-high-doses-celexa-citalopram. Accessed 15 September, 2020.

34. Health Canada. Antidepressant Cipralex (escitalopram): updated information regarding dose-related heart risk - Recalls and safety alerts. Health Canada. https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/13674a-eng.php. Accessed 15 September, 2020.

35. US Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry - E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. 2005.

36. Zeitoun JD, Lefevre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European union pharmaceutical regulator safety communications: a cross-country comparison. *PLoS One*. 2014;9(10):e109100.

37. Pharmacovigilance Risk Assessment Committee. *Domperidone-Containing Medicinal Products Assessment Report*. European Medicines Agency; 2014.

38. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care*. 2012;50(6):466-478.

39. Weatherburn CJ, Guthrie B, Dreischulte T, Morales DR. Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: systematic review, time series analysis and meta-analysis. *Br J Clin Pharmacol*. 2020;86(4):698-710.

40. Georgi U, Lämmel J, Datzmann T, Schmitt J, Deckert S. Do drug-related safety warnings have the expected impact on drug therapy? A systematic review. *Pharmacoepidemiol Drug Saf*. 2020;29(3):229-251.

41. Piening S, Haaijer-Ruskamp FM, de Vries JTN, et al. Impact of safety-related regulatory action on clinical practice: a systematic review. *Drug Saf*. 2012;35(5):373-385.

42. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions - systematic review and methodological considerations. *Br J Clin Pharmacol*. 2018;84(3):419-433.

43. Herdeiro MT, Soares S, Silva T, Roque F, Figueiras A. Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a country-wide study in Portugal. *Fundam Clin Pharmacol*. 2016;30(5):440-449.

44. Hsu JC, Cheng C-L, Ross-Degnan D, et al. Effects of safety warnings and risk management plan for thiazolidinediones in Taiwan. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1026-1035.

45. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifirò G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. *Br J Clin Pharmacol*. 2013;75(3):861-868.

46. Niyomnaitham S, Page A, La Caze A, Whitfield K, Smith AJ. Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Serv Res*. 2014;14(1):151.

47. Noh Y, Kang DR, Kim DJ, Lee KJ, Lee S, Shin S. Impact of clinical evidence communications and drug regulation changes concerning rosiglitazone on prescribing patterns of antidiabetic therapies. *Pharmacoepidemiol Drug Saf*. 2017;26(11):1338-1346.

48. Qato DM, Trivedi AN, Mor V, Dore DD. Disparities in discontinuing rosiglitazone following the 2007 FDA safety alert. *Med Care*. 2016;54(4):406-413.

49. Ruiter R, Visser LE, van Herk-Sukel MPP, et al. Prescribing of rosiglitazone and pioglitazone following safety signals. *Drug Saf*. 2012;35(6):471-480.

50. Baseman JG, Revere D, Painter I, Toyoji M, Thiede H, Duchin J. Public health communications and alert fatigue. *BMC Health Serv Res*. 2013;13(1):295.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.