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# Influence of drug safety advisories on drug utilisation: an international interrupted time series and meta-analysis

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## ABSTRACT

**Objective** To evaluate the association between regulatory drug safety advisories and changes in drug utilisation.

**Design** We conducted controlled, interrupted times series analyses with administrative prescription claims data to estimate changes in drug utilisation following advisories. We used random-effects meta-analysis with inverse-variance weighting to estimate the average postadvisory change in drug utilisation across advisories.

**Study population** We included advisories issued in Canada, Denmark, the UK and the USA during 2009–2015, mainly concerning drugs in common use in primary care. We excluded advisories related to over-the-counter drugs, drug-drug interactions, vaccines, drugs used primarily in hospital and advisories with co-interventions within  $\pm 6$  months.

**Main outcome measures** Change in drug utilisation, defined as actual versus predicted percentage change in the number of prescriptions (for advisories without dose-related advice), or in the number of defined daily doses (for dose-related advisories), per 100 000 population.

**Results** Among advisories without dose-related advice ( $n=20$ ), the average change in drug utilisation was  $-5.83\%$  (95% CI  $-10.93$  to  $-0.73$ ;  $p=0.03$ ). Advisories with dose-related advice ( $n=4$ ) were not associated with a statistically significant change in drug utilisation ( $-1.93\%$ ; 95% CI  $-17.10$  to  $13.23$ ;  $p=0.80$ ). In a post hoc subgroup analysis of advisories without dose-related advice, we observed no statistically significant difference between the change in drug utilisation following advisories with explicit prescribing advice, such as a recommendation to consider the risk of a drug when prescribing, and the change in drug utilisation following advisories without such advice.

**Conclusions** Among safety advisories issued on a wide range of drugs during 2009–2015 in 4 countries (Canada, Denmark, the UK and the USA), the association of advisories with changes in drug utilisation was variable, and the average association was modest.

## INTRODUCTION

Medicines are essential in providing effective healthcare and are also associated with risk of harm.<sup>1–4</sup> Among epidemiological studies quantifying adverse drug reactions (ADRs) in a European setting, a median of 3.6% of hospital admissions were due to an ADR, and a median of 10.1% of patients experienced an ADR during a hospital admission.<sup>1</sup> Studies of drug safety in Canada and Europe indicate that close to one in five drugs was associated with a serious postmarket safety issue.<sup>3,4</sup> Similarly, a cohort study of drugs approved by the US Food and Drug Administration (FDA) found that 32% had a postmarket safety issue.<sup>2</sup>

When new evidence of harm emerges during the postmarket period, regulators may issue drug safety advisories to warn health professionals and the public of harm and to promote safer use. Advisories may take the form of Direct Healthcare Professional Communications (DHPCs, which are letters or emails sent to individual health professionals), alerts (safety information posted to a regulator's website and addressed to a broad audience rather than individual clinicians), investigations (statements on ongoing reviews or analyses, early monitoring reviews or detailed investigation reports) or bulletins (articles in a regulator's newsletter or drug safety bulletin).<sup>5</sup>

Systematic reviews suggest advisories issued by regulators may influence clinical practice.<sup>6–9</sup> Weatherburn *et al* found that regulatory risk communications in the UK

with a recommendation to change practice based on a change or restriction in indication were associated with a 34% change in the rate of prescribing in the intended direction, while risk communications to 'be aware' of new information about a drug's risk were associated with an 11% change in prescribing.<sup>9</sup> These findings suggest prescribing changes may differ in relation to how information about drug risk is communicated in an advisory. However, it is difficult to know the average impact of drug safety advisories on drug prescribing from existing systematic reviews, due to the inconsistent methodological quality of studies of advisories,<sup>7 8 10 11</sup> the literature's focus on a limited number of drug classes<sup>7–10</sup> and publication bias.<sup>9 10</sup>

This study aimed to estimate the average impact of drug safety advisories on drug utilisation with data from Australia, Canada, Denmark, the UK and the USA. A secondary aim was to evaluate whether the inclusion of prescribing advice in an advisory was associated with a greater postadvisory change in drug utilisation. Prescribing advice was defined as explicit advice regarding a prescribing decision, such as a change in indication or a recommendation to take the risk of a drug into account when considering treatment options.

## METHODS

### Study design

We selected drug safety advisories for inclusion from among those issued in Australia, Canada, Denmark, the UK and the USA during 2009–2015 inclusive. We used interrupted time series analysis to estimate the change in drug utilisation following each advisory, adjusted by the change in drug utilisation in a concurrent or historical control<sup>12 13</sup> (see [box 1](#) for the criteria used in selection of advisories and controls, and the 'Statistical analysis' section for details on the interrupted time analysis). After performing time series analyses to estimate the change in drug utilisation following each advisory, we used random-effects meta-analysis to estimate the average postadvisory change in drug utilisation across advisories.<sup>14</sup> We stratified our analyses based on whether an advisory contained dose-related advice, which was defined as advice that revised the recommended or maximum dose of a drug or warned about risk associated with higher doses.

### Data sources

Data sources for selection of advisories

We previously created a database of advisories issued during 2007–2016 by the Australian Therapeutic Goods Administration, Health Canada, the UK Medicines and Healthcare products Regulatory Agency and the US FDA,<sup>5</sup> and a similar database of DHPCs issued during 2007–2018 in Denmark.<sup>15</sup> We used these databases and dates of drug approval and withdrawal collected from regulators' websites to select advisories and controls to include in the study. We included

## Box 1 Criteria for selection of drug safety advisories and controls for analysis

Inclusion criteria for advisories:

- ▶ Safety alerts posted on a regulator's website or Direct Healthcare Professional Communications.
- ▶ Advisory related to a drug on the market for  $\geq 24$  months preceding an index advisory and  $\geq 12$  months following an advisory in at least one country, and the drug was on the market for  $\geq 36$  months in at least one country without the advisory (to serve as a control).
- ▶ If advisories for different topics were issued for the same drug during 2009–2015, we only included an advisory on the first topic meeting other inclusion criteria to limit analysis to one advisory per drug.

Exclusion criteria for advisories:

- ▶ Advisory related to an 'all-clear' statement (ie, no problem was ultimately identified), drugs available over-the-counter in  $\geq 1$  country, drug-drug interactions, drugs marketed in only one of the countries or vaccines.
- ▶ Advisory was only an announcement that a safety concern was under investigation or an article in the regulatory agency's drug safety bulletin.
- ▶ Advisory was for a drug class or multiple drugs, or drugs used primarily in hospitals.
- ▶ Advisories for drugs with lowest utilisation (based on data from US IBM MarketScan Research Databases) were excluded, but additional drugs not meeting this criterion were considered for inclusion to ensure a sufficient number of newer drugs were included (ie, drugs on the market for  $< 6$  years prior to the advisory).
- ▶ Advisory had co-intervention(s) within  $\pm 6$  months of an advisory (such as an additional advisory for the same drug coinciding with a marked change in drug utilisation).
- ▶ Advisory was for a drug that had unstable use in the 24 months prior to the advisory (eg, a new drug might have an initial low rate of use followed a steep rise in use, rather than a consistent trend), based on visual inspection of preadvisory data.

For each advisory, we selected one control from among possible controls as follows:

- ▶ We required use of the advisory drug to be stable during the 24-month preadvisory period in the control country (or historical control period), based on visual inspection, and we required the ratio of the preadvisory median monthly drug utilisation rates to be minimally comparable in the control and index country (ie, not exceeding a ratio of 10:1).
- ▶ We preferred a control country in which we expected drug use was less likely to be affected by the advisory in the index country (to avoid controls with a spillover effect) (online supplemental table S3), based on

Continued

## Box 1 Continued

a priori expectations (due to the population size, geographic proximity and interaction of medical cultures of countries) and an empirical analysis of changes in drug utilisation following a small subset of advisories.

- ▶ We preferred a concurrent control over a historical control. If no suitable concurrent controls were available, we used data from the 36 months prior to an advisory as a historical control period.
- ▶ If the above criteria were met by multiple possible controls, we preferred the control in which preadvisory drug utilisation rate was most similar to that in the index country.

advisories from Canada, Denmark, the UK and the USA in the study, but no Australian advisories met our inclusion criteria. We still used Australian drug utilisation data in the study, because Australia served as a control in several cases for studying the impact of advisories from other countries.

#### Data sources for measuring drug utilisation

To assess changes in drug utilisation, we used administrative health data from the National Prescription Drug Utilisation Information System accessed through the Canadian Institute for Health Information, the Clinical Practice Research Datalink (CPRD) Gold database with approval granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol 20\_000191) and US IBM MarketScan Research Databases accessed through IBM Watson Health.<sup>16–18</sup> In Denmark, the Danish National Prescription Registry was accessed through the Research Service Unit of Statistics Denmark (FSEID-00004357/DST-project no. 707524), and approval for processing of personal health data was obtained through the UCHP (ref. no.: 514-0301/19-3000).<sup>19</sup> Aggregate data by month on prescription drugs dispensed through the Pharmaceutical Benefits Scheme in Australia were publicly available online<sup>20</sup> (for further detail on these databases, see online supplemental table S1). These data sources primarily captured drugs prescribed (CPRD) or dispensed (other databases) in a community setting rather than in hospital. Prescribing and dispensing are collectively referred to in this paper as ‘utilisation’.

#### Study population

The study included data from residents with public or private drug coverage in Australia, Canada, Denmark, the UK and the USA (online supplemental table S1). In Australia and Denmark, the study population included all residents. In Canada, the study population included residents of the provinces of British Columbia and Saskatchewan (which had better

capture of prescription drug dispensations than other provinces), excluding the small proportion of residents with federal drug coverage. (Data from these provinces comprised approximately 15% of the Canadian population.) In the UK, the study population included patients whose general practitioners participated in the CPRD (comprising 9% of the UK population). The US study population included persons <65 years with private drug plans, and persons ≥65 years with Medicare coverage and supplemental private plans, collected by the US IBM MarketScan Research Databases (comprising 12% of the US population). If an advisory only applied to a specific demographic group, we restricted the analysis by age or sex. Similarly, if an advisory applied only to a specific drug form or route of administration (eg, oral), we restricted analysis to the relevant form of the drug.

#### Selection of advisories and controls

We applied several criteria to select advisories for inclusion from among those issued in Australia, Canada, the UK and the USA from January 2009 to December 2015 (box 1 shows selection criteria for advisories and controls, and online supplemental table S2 describes the rationale for the selection criteria). Subsequently, we identified Danish advisories that covered the same topics, in order to expand the number of jurisdictions available for analyses (eg, there was a UK advisory on clopidogrel and acquired haemophilia, and an advisory issued on this topic in Denmark). For each advisory topic (eg, all advisories on clopidogrel and acquired haemophilia), we designated the advisory from the country that issued the first advisory as the index advisory. We also identified a suitable control specific to that index advisory. A control was selected from among the five countries in the study, which was either a concurrent control (a country that did not issue a similar advisory within 12 months of the index advisory) or a historical control (data from the 36 months prior to an advisory from the same country, or a different country if necessary). When selecting concurrent controls, we preferred a control country in which we expected drug use was less likely to be affected by the advisory in the index country (to avoid controls with a spillover effect) (online supplemental table S3).

#### Outcomes

While all advisories included in the study highlighted drug risks and might influence whether a drug is prescribed, advisories with dose-related advice might also influence the dose prescribed. For advisories without dose-related advice, we used the monthly number of prescriptions written or dispensed per 100 000 population as the drug utilisation outcome measure. For advisories with dose-related advice, we used the monthly number of defined daily doses (DDDs)<sup>21</sup> prescribed or dispensed per 100 000 population as the drug utilisation outcome measure, to

capture changes in the dosage level as well as changes in the number of prescriptions. The number of DDDs was calculated as product of medication strength and quantity, divided by WHO DDD (an assumed average maintenance dose per day).<sup>21</sup>

### Statistical analysis

We used interrupted time series analysis<sup>12 13</sup> to estimate the change in drug utilisation for each index advisory and control during a postadvisory period. For each advisory, the crude change in drug utilisation was calculated as the difference between the actual and predicted postadvisory change in drug utilisation. We estimated the adjusted change in drug utilisation by adjusting the crude estimate by the change in drug utilisation in a concurrent control (a country in our study that did not issue an advisory during the same time period) or a historical control (if no suitable concurrent control was available). Each time series analysis used 24 months of data prior to an advisory, a transition period of 1 month during which an advisory was issued and an 11-month postadvisory period (or analogous periods during the 36 months prior to an advisory for historical controls). We estimated models with a linear time trend to adjust for secular trends, adjusted for seasonality<sup>22</sup> and autocorrelation<sup>23</sup> as necessary, using SAS V.9.4.

We calculated both the absolute difference and the percentage difference between the monthly actual and predicted drug utilisation rates during the postadvisory period for each index advisory and control. We used bootstrapping resampling methods with 5000 iterations to estimate percentile-based 95% CIs for the absolute and percentage differences.<sup>24 25</sup> We estimated the adjusted percentage change in drug utilisation by taking the difference between the percentage change following the index advisory and the percentage change in the control, and calculating a 95% CI.<sup>26</sup>

We conducted random-effects meta-analyses with inverse-variance weighting to estimate the average association of advisories with percentage change in drug utilisation,<sup>14</sup> stratified by advisories with and without dose-related advice. We used random-effects rather than fixed-effects models, because we anticipated the effects of advisories would be heterogeneous due to differences in the drugs targeted, content of advisories and populations studied.<sup>14</sup> The random-effects estimates in our models represent the average intervention effect for the advisories included in each analysis, calculated as a weighted average where the weight was the inverse of the variance of the estimated effect of each advisory.<sup>14</sup> Meta-analyses were performed with RevMan V.5.4.

### Post hoc subgroup analysis of advisories with versus without prescribing advice

We conducted a post hoc subgroup analysis to investigate whether postadvisory changes in drug utilisation varied according to whether the advisory contained advice to change prescribing. This analysis compared

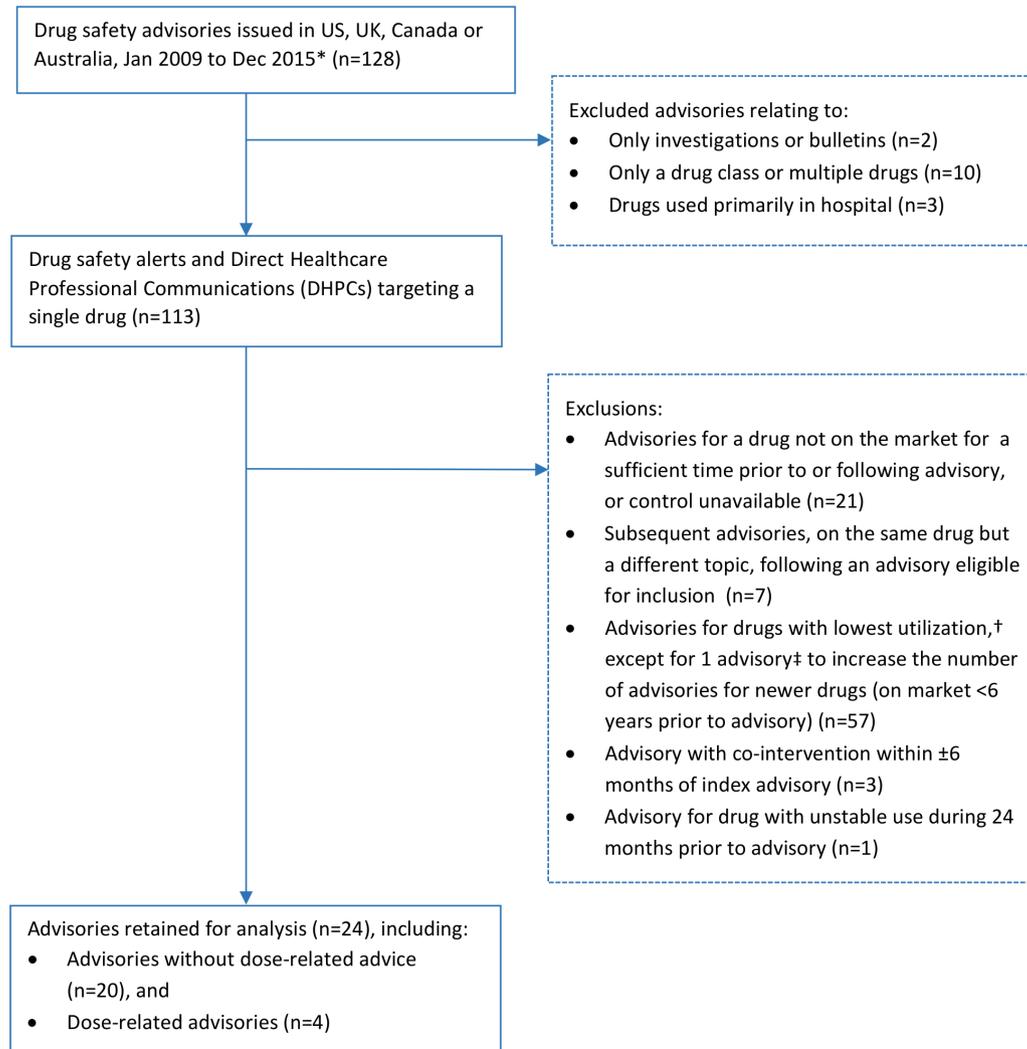
advisories with versus without prescribing advice relevant to an immediate prescribing decision and not restricted to a small subgroup of patients. A member of the study team (RLM) classified the advisories without dose-related advice into subgroups for this analysis. We did not apply the same analysis to dose-related advisories, as they all by definition contained prescribing advice (regarding dose). First, advisories were classified according to whether they contained explicit prescribing advice relevant to an immediate prescribing decision. For example, this could include a recommendation to consider the risk of a drug when prescribing or describe a change in indication, but advice to consider discontinuation after a patient experienced an adverse effect was not considered 'relevant to an immediate prescribing decision'. Second, advisories deemed to contain prescribing advice at the first step were assessed according to whether the advice was restricted to a small subgroup, which was defined as under 2% of patients receiving a medication. We excluded prescribing advice focused on changing practice after a patient experienced an adverse effect or targeting a small subgroup of patients, because we believed it was less likely to have a measurable impact on prescribing. A meta-analysis was conducted, and Cochran's Q test was used to test for subgroup difference. In addition, we conducted a descriptive analysis of physician perspectives on prescribing advice in drug safety advisories, based on assessments of the advisories by a general practitioner who agreed to assist the study for this purpose (JAL) and an emergency department physician from our research team (JL).

### Patient and public involvement

Neither patients nor member of the public were involved in the design, conduct, reporting or dissemination plans for this study.

### RESULTS

We screened 128 advisories from Australia, Canada, the USA and the UK to identify advisories for inclusion in the study (counting multiple advisories on the same topic only once) (figure 1). Following exclusions, we retained 24 advisories for analysis,<sup>27-30</sup> including 20 advisories without dose-related advice and 4 with dose-related advice. Half of the index advisories were issued in the USA (12), while the remainder were issued in Canada (3), Denmark (3) and the UK (6) (table 1). No Australian advisories qualified as an index advisory. Safety alerts (17) served more frequently as index advisories compared with DHPCs (7). The 24 drugs featured in the advisories represent 19 different drug classes (according to the WHO Anatomical Therapeutic Chemical, level 3) (online supplemental table S4),<sup>21</sup> and included 2 drugs (febuxostat and fingolimod) that entered the market within 6 years prior to the advisories studied.



**Figure 1** Selection of drug safety advisories for inclusion. \*Excluding advisories relating to all-clear statements, drugs available over-the-counter in  $\geq 1$  country, drug-drug interactions, drugs marketed in only one of the countries and vaccines. Multiple advisories on the same topic were counted only once. Danish advisories were included in analysis, but not in the process of selection of advisories to include. †Based on data from US IBM MarketScan Research Databases. ‡Advisory for fingolimod and progressive multifocal leucoencephalopathy. Created by the authors.

The majority of controls (14) were concurrent controls (another country that did not issue a concurrent advisory on the same topic) rather than historical controls (10) (table 1). Each of the five countries served as a control for some advisories: Australia (5), Canada (5), Denmark (3), the UK (2) and the USA (9).

### Interrupted time series analysis of changes in drug utilisation

Changes in drug utilisation following advisories without dose-related advice

Among advisories without dose-related advice (n=20), the crude actual versus predicted change in the number of prescriptions per 100 000 population following the index advisories (unadjusted by the change in controls) ranged from a decrease of 29.2% following the pioglitazone-bladder cancer advisory to an increase of 5.5% following the methylphenidate-sexual dysfunction advisory (table 2). (Actual vs predicted change in drug utilisation among controls is reported in online

supplemental table S5.) Adjusted analyses of actual versus predicted change in prescription rates following advisories without dose-related advice indicated that 8 of 20 advisories (40%) were followed by a decline in the prescription rate of  $>5\%$ , and 5 (25%) were followed by a decline of  $>10\%$  (figure 2).

Changes in drug utilisation following dose-related advisories

Among dose-related advisories (n=4), the crude actual versus predicted change in the number of DDDs per 100 000 population following the index advisories ranged from a decrease of 15.2% following the hydroxyzine-cardiac arrhythmias advisory to an increase of 19.5% following the zolpidem-cognitive impairment advisory.

Adjusted analyses of actual versus predicted change in the rates of DDDs following dose-related advisories indicated that two of four advisories were followed by a decrease in drug utilisation of  $>5\%$  (the fluconazole-congenital anomaly and hydroxyzine-cardiac

**Table 1** Advisory characteristics

Advisory (drug-risk group)	Index country	Control	Advisory date	Advisory type
<b>(a) Advisories without dose-related advice*</b>				
Aripiprazole-impulse control disorders <sup>30</sup>	CA	DK	2 November 2015	Alert
Azithromycin-cardiac arrhythmias <sup>43</sup>	USA	USA†	12 March 2013	Alert
Clopidogrel-acquired haemophilia <sup>38</sup>	DK	AU	28 August 2013	DHPC
Febuxostat-epidermal and dermal conditions <sup>27</sup>	UK	USA†	6 May 2012	DHPC
Finasteride-breast cancer male <sup>34</sup>	UK	CA	1 December 2009	Alert
Fingolimod-PML <sup>40</sup>	USA	CA	29 August 2013	Alert
Insulin-glargine-neoplasm malignant <sup>50</sup>	USA	DK	1 July 2009	Alert
Isotretinoin-epidermal and dermal conditions <sup>32</sup>	CA	DK	11 February 2010	DHPC
Ketoconazole-adrenal gland disorders <sup>41</sup>	USA	USA†	26 July 2013	Alert
Leflunomide methotrexate-hepatotoxicity <sup>49</sup>	USA	AU	13 July 2010	Alert
Methylphenidate-sexual dysfunction <sup>39</sup>	USA	USA†	17 December 2013	Alert
Mycophenolate-aplasia pure red cell <sup>33</sup>	UK	USA†§	2 June 2009	DHPC
Nitrofurantoin-lack of effect <sup>36</sup>	UK	AU¶	1 August 2013	Alert
Olmesartan-malabsorption <sup>42</sup>	USA	AU¶	3 July 2013	Alert
Ondansetron-cardiac arrhythmias <sup>45</sup>	USA	AU¶	15 September 2011	Alert
Pioglitazone-bladder cancer <sup>48</sup>	USA	USA†	15 June 2011	Alert
Quetiapine-metabolic syndrome <sup>29</sup>	UK	UK†	23 December 2011	DHPC
Tacrolimus-neoplasm malignant <sup>28</sup>	DK	CA	1 May 2012	DHPC
Testosterone-cardiovascular disorder <sup>31</sup>	CA	UK	15 July 2014	Alert
Topiramate-congenital anomaly <sup>37</sup>	DK	CA	1 March 2011	DHPC
<b>(b) Advisories with dose-related advice*</b>				
Citalopram escitalopram-cardiac arrhythmias <sup>46</sup>	USA	USA†	24 August 2011	Alert
Fluconazole-congenital anomaly <sup>47</sup>	USA	USA†	3 August 2011	Alert
Hydroxyzine-cardiac arrhythmias <sup>35</sup>	UK	CA	29 April 2015	Alert
Zolpidem-cognitive impairment <sup>44</sup>	USA	USA†	10 January 2013	Alert

Created by the authors.

\*Dose-related advice was defined as advice that revised the recommended or maximum dose of a drug or warned about risk associated with higher doses.

†Historical control.

‡Advisory applied to a specific route of administration (oral for ketoconazole and topical for tacrolimus), so analysis was restricted to relevant forms of the drug.

§A historical control from the UK was unavailable due to a lack of sufficient preadvisory data, so a US historical control was used.

¶Restricted to drug use of concessional beneficiaries (eg, seniors and individuals with a low household income), due to better data capture in this population for these drugs.

AU, Australia; CA, Canada; DHPC, Direct Healthcare Professional Communication; DK, Denmark; PML, progressive multifocal leucoencephalopathy.

arrhythmias advisories), and one of four advisories was followed by a decrease of >10% (the hydroxyzine-cardiac arrhythmias advisory) (figure 3). In contrast, the zolpidem-cognitive impairment advisory was associated, in the controlled analysis, with an increase in the rate of DDDs dispensed of 17.77% (95% CI 15.61 to 19.93). A post hoc descriptive sensitivity analysis indicated that the zolpidem advisory was followed by a shift towards prescribing lower strengths of the drug (consistent with advice in the advisory), but that the average quantity of medication dispensed rose, apparently explaining the increased rate of DDDs dispensed (online supplemental figure S4).

### Meta-analysis of changes in drug utilisation

Average change in drug utilisation following advisories without dose-related advice

Among advisories without dose-related advice, random-effects meta-analysis yielded a crude average change in the number of prescriptions per 100 000 population of -6.03% (95% CI -10.35 to -1.70) (online supplemental figure S1). The actual versus predicted percentage change in drug utilisation

following advisories without dose-related advice, adjusted by the change in controls, was heterogeneous ( $I^2=98%$ ) (figure 2). The adjusted average change in the number of prescriptions per 100 000 population following advisories without dose-related advice was -5.83% (95% CI -10.93 to -0.73) (figure 2). In a post hoc sensitivity analysis, the average change in the number of prescriptions per 100 000 population among controls was -0.43% (95% CI -2.11 to 1.26) (online supplemental figure S3).

### Average change in drug utilisation following dose-related advisories

Among dose-related advisories, the crude average change in the number of DDDs per 100 000 population was -0.85% (95% CI -15.43 to 13.74) (online supplemental figure S2). The actual versus predicted per cent change in drug utilisation following dose-related advisories, adjusted by the change in controls, varied widely ( $I^2=99%$ ) (figure 3). Analysis of the adjusted average change in drug utilisation following dose-related advisories indicated that dose-related advisories were not associated with a statistically

**Table 2** Crude actual versus predicted change in drug utilisation in the 11 months following the month of each index advisory

Advisory category	Advisory (drug-risk group)	Index country	Absolute change, prescription or DDD rate (95% CI)*†	Percentage change, % (95% CI)*
(a) Advisories without dose-related advice‡	Aripiprazole-impulse control disorders	CA	-43.9 (-62.0 to -25.4)	-3.7 (-5.2 to -2.1)
	Azithromycin-cardiac arrhythmias	USA	-246 (-323 to -164)	-16.5 (-21.7 to -11.0)
	Clopidogrel-acquired haemophilia	DK	11 (1 to 22)	2.2 (0.2 to 4.1)
	Febuxostat-epidermal and dermal conditions	UK	-0.5 (-0.6 to -0.3)	-5.7 (-7.6 to -3.7)
	Finasteride-breast cancer male	UK	0.8 (-13.5 to 14.7)	0.2 (-2.9 to 3.1)
	Fingolimod-PML	USA	-0.2 (-0.4 to -0.1)	-2.9 (-4.9 to -0.9)
	Insulin-glargine-neoplasm malignant	USA	-9.2 (-14.3 to -4.1)	-2.8 (-4.4 to -1.2)
	Isotretinoin-epidermal and dermal conditions	CA	-18.7 (-23.5 to -13.9)	-7.9 (-9.9 to -5.9)
	Ketoconazole-adrenal gland disorders	USA	-4.4 (-5.0 to -3.8)	-26.2 (-29.8 to -22.5)
	Leflunomide-hepatotoxicity	USA	-1.6 (-1.9 to -1.2)	-7.7 (-9.4 to -5.9)
	Methylphenidate-sexual dysfunction	USA	29.2 (21.0 to 37.4)	5.5 (4.0 to 7.1)
	Mycophenolate-aplasia pure red cell	UK	-1.1 (-1.9 to -0.3)	-3.7 (-6.3 to -1.0)
	Nitrofurantoin-lack of effect	UK	-10.7 (-20.7 to -0.5)	-2.8 (-5.5 to -0.1)
	Olmesartan-malabsorption	USA	14.8 (9.8 to 19.8)	4.6 (3.1 to 6.2)
	Ondansetron-cardiac arrhythmias	USA	-4.5 (-11.5 to 2.4)	-1.5 (-3.8 to 0.8)
	Pioglitazone-bladder cancer	USA	-107.7 (-112.7 to -102.6)	-29.2 (-30.5 to -27.8)
	Quetiapine-metabolic syndrome	UK	-7.6 (-17.5 to 2.2)	-1.8 (-4.2 to 0.5)
	Tacrolimus-neoplasm malignant	DK	-6.7 (-7.3 to -6.1)	-18.9 (-20.7 to -17.2)
	Testosterone-cardiovascular disorder	CA	-16.9 (-46.8 to 11.8)	-2.3 (-6.2 to 1.6)
	Topiramate-congenital anomaly	DK	-3.3 (-6.6, to -0.3)	-2.6 (-5.2 to -0.2)
(b) Advisories with dose-related advice‡	Citalopram-cardiac arrhythmias	USA	-286 (-1039 to 494)	-0.5 (-1.9 to 0.9)
	Fluconazole-congenital anomaly	USA	-197 (-276 to -116)	-7.4 (-10.3 to -4.4)
	Hydroxyzine-cardiac arrhythmias	UK	-193 (-227 to -159)	-15.2 (-17.9 to -12.5)
	Zolpidem-cognitive impairment	USA	8319 (7617 to 9029)	19.5 (17.9 to 21.2)

Created by the authors.

\*Unadjusted by change in controls.

†In part (a), the units are monthly prescriptions written or dispensed per 100 000 population, and in part (b) the units are monthly DDDs prescribed or dispensed per 100 000 population.

‡Dose-related advice was defined as advice that revised the recommended or maximum dose of a drug or warned about risk associated with higher doses.

CA, Canada; DDD, defined daily dose; DK, Denmark; PML, progressive multifocal leucoencephalopathy.

significant change in the number of DDDs per 100 000 population (-1.93%; 95% CI -17.10 to 13.23).

Post hoc subgroup analysis of advisories with versus without prescribing advice

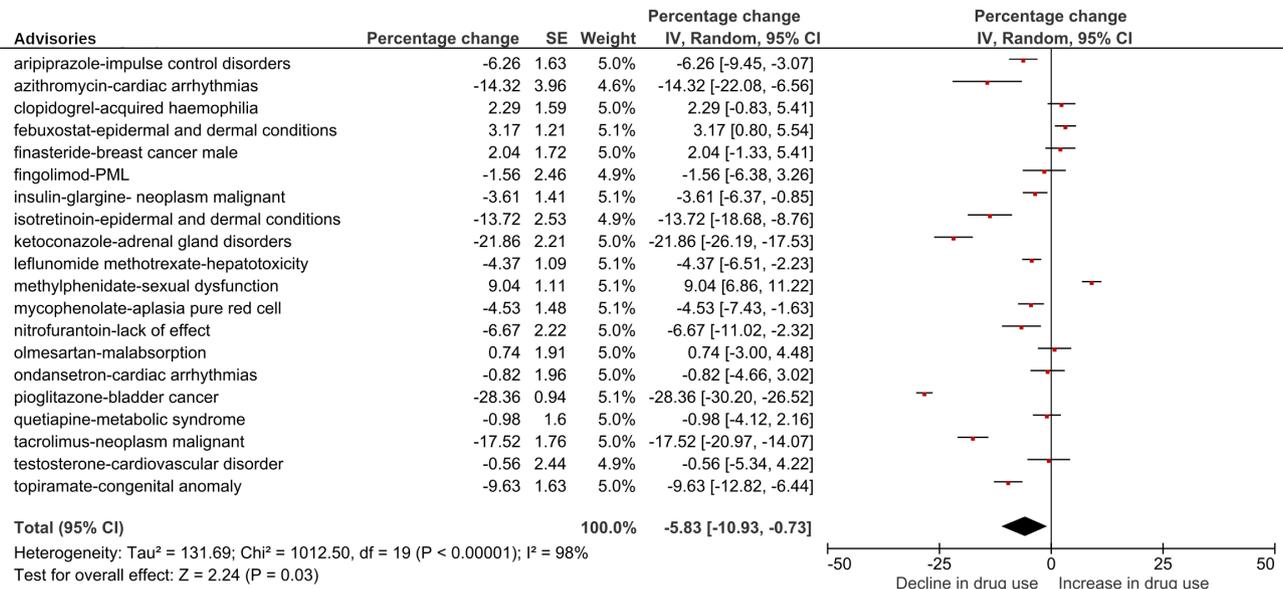
Among 20 advisories without dose-related advice, 5 contained explicit prescribing advice relevant to an immediate prescribing decision and not restricted to a small subgroup as defined above (online supplemental table S6). Several other advisories also contained prescribing advice, but this advice either only applied to patients who had experienced an adverse effect (five advisories) or it was restricted to a small subgroup (two advisories) (online supplemental tables S7 and S8). In our post hoc subgroup analysis, the actual versus predicted percentage change in drug utilisation was -11.13% (95% CI -17.31 to -4.96) following advisories with prescribing advice relevant to immediate prescribing decisions and not limited to a small subgroup and -4.04% (95% CI -10.50 to

2.41) following advisories without such advice (online supplemental figure S5). However, Cochran's Q test for difference between these subgroups was not statistically significant ( $p=0.12$ ). A descriptive analysis of assessments of these advisories by two physician reviewers is reported in online supplemental box S1.

## DISCUSSION

### Summary of findings

Overall, the association of drug safety advisories with changes in drug utilisation was modest but highly variable. Advisories without dose-related advice were associated with a modest, statistically significant decrease in the rate of utilisation. Among a small sample of dose-related advisories, the average association between advisories and DDDs used was not statistically significant. One of the dose-related advisories, concerning zolpidem and cognitive impairment, was associated with an increase in the rate of DDDs dispensed. The presence of explicit prescribing advice



**Figure 2** Actual versus predicted percentage change in the rate of prescriptions following drug safety advisories without dose-related advice,\* adjusted by change in controls without an advisory. \*Actual versus predicted percentage change in the number of prescriptions written or dispensed per 100 000 population during an 11-month period following the month a drug advisory was issued. Created by the authors. IV, inverse variance; PML, progressive multifocal leucoencephalopathy.

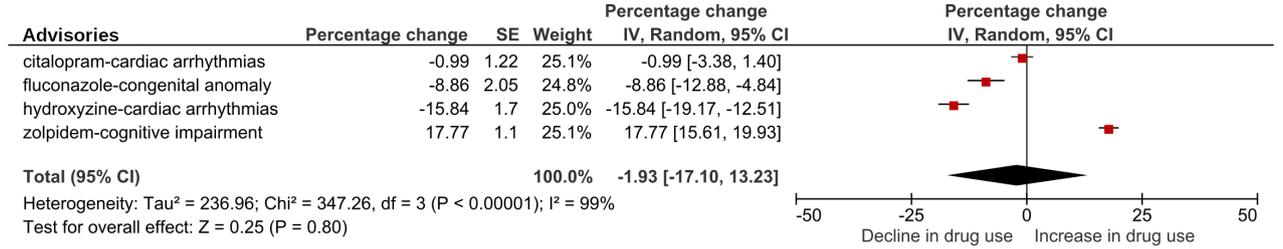
relevant to an immediate prescribing decision did not explain the heterogeneity in our meta-analysis of advisories without dose-related advice. Potential sources of the heterogeneity of effects in our analyses include other differences among advisories and populations in the study.

**Comparison with other studies**

Our finding that advisories have widely varied impacts was consistent with previous systematic reviews of studies of regulatory safety advisories.<sup>6 7 9</sup> However, the modest association of advisories with changes in drug utilisation in our study differed from a systematic review by Weatherburn *et al*, which reported that UK regulatory risk communications were associated with changes in targeted prescribing of 11%–34%.<sup>9</sup> This difference between the studies likely relates to differences in selection of risk communications. Many of the studies in systematic review by Weatherburn *et al* focused on only 4 classes of medication, suggesting

that they do not reflect the diversity of drugs which are the subject of regulatory advisories, compared with the 19 classes in our study. In addition, their systematic review focused on published studies and its authors raised the possibility that the published literature could be subject to publication bias. Consequently, the more modest association of advisories with changes in drug utilisation in our study may provide a more realistic assessment of the average effect of advisories.

Weatherburn *et al* found that risk communications with a recommendation to change practice based on a change or restriction in indication were associated with a larger change in prescribing than those without an explicit recommendation to change practice,<sup>9</sup> whereas we did not find a statistically significant difference between advisories with and without prescribing advice, although our exploratory analysis suggested a similar direction of effect. Again, the findings of our study may differ from those of Weatherburn *et al* due to differences in the risk communications included



**Figure 3** Actual versus predicted percentage change in the rate of defined daily doses following dose-related drug safety advisories,\* adjusted by change in controls without an advisory. \*Actual versus predicted percentage change in the number of defined daily doses prescribed or dispensed per 100 000 population during an 11-month period following the month a drug advisory was issued. Dose-related advisories are those with dose-related advice. Created by the authors. IV, inverse variance.

for analysis. The sample of risk communications by Weatherburn *et al* with a recommendation to change practice contained multiple risk communications related to major changes or restrictions in indication, such as regulatory communication to restrict the use of selective serotonin reuptake inhibitors among youth.<sup>51</sup> In contrast, our sample did not contain advisories relating to major changes in indication with the exception of an advisory limiting use of ketoconazole.<sup>41</sup>

#### Varied impact of advisories on drug utilisation

The varied impact of advisories on drug utilisation might relate to several factors. Advisories may differ in content in various ways, including the severity of risks reported, identification of patients at risk, changes to labelling and strength of evidence. Advisories may be sent directly to individual healthcare professionals or communicated as an alert on a regulator's website. Other factors may differ as well, such as the availability of alternative therapies, the extent of media coverage, repetition of messages in the healthcare community or changes to reimbursement of drugs. It is important to enhance our understanding of factors related to advisories that contribute to changes in drug utilisation, such as advisory content, mode of communication or other considerations.

#### Strengths and weaknesses of study

Strengths of this study included evaluating advisories related to a wide range of drug classes and applying rigorous methods to estimate the association of advisories with changes in drug utilisation. We selected advisories based on prespecified criteria and used data extracted from administrative health databases rather than from published studies, so our analyses were not subject to publication bias. This study also has limitations. Our data sources for analysing drug utilisation captured drugs prescribed in the UK and drugs dispensed in the other countries included in the study, so our analyses of UK advisories may more closely reflect prescribing behaviour while analyses of advisories in other countries may reflect both prescribing decisions and patient decisions regarding whether to fill a prescription. Neither measure precisely reflects drug use, because even filled prescriptions may not be used by the patient. Our analysis of dose-related advisories was inconclusive, due to a lack of statistical power. In addition, although we used a controlled interrupted time series design to adjust for time-varying confounders, we cannot conclude that our findings were unaffected by factors such as drug promotion, market entry of new drugs or changes to drug reimbursement. It is possible that the choice of controls influenced the estimated postadvisory changes in drug utilisation for some individual advisories. However, it is unlikely that the choice of controls biased our estimate of the average change in drug utilisation following advisories without dose-related advice, as a

sensitivity analysis did not find a statistically significant change in drug utilisation among controls.

Our study had certain limitations in scope and generalisability. We limited the scope of our study to drug utilisation outcomes, which omitted important outcomes such as impacts on health monitoring and health outcomes. Our findings may not generalise to all types of drug safety advisories, such as those pertaining to vaccines (which were excluded because we lacked access to reliable data on vaccine use). In addition, this study focused on drugs prescribed or dispensed in a community setting in selected countries, and it is uncertain whether the findings apply in other care settings or countries. Further research is required to investigate direct and contextual factors that contribute to the effectiveness of drug safety advisories. It would also be valuable for future research to investigate the impact of drug safety advisories on patient health outcomes.<sup>6,9</sup>

#### Conclusions

Among drug safety advisories issued during 2009–2015 by regulators in Canada, Denmark, the UK and the USA, the association of advisories with changes in drug utilisation was variable and the average association was modest. Future research should investigate factors related to drug safety advisories that contribute to changes in prescribing.

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