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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 ±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.[1–4] 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.[1] Studies of drug safety in Canada and Europe indicate that close to one in five drugs was associated with a serious postmarket safety issue.[3 4] Similarly, a cohort study of drugs approved by the US Food and Drug Administration (FDA) found that 32% had a postmarket safety issue.[2]

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).[5]

Systematic reviews suggest advisories issued by regulators may influence clinical practice.[6–9] 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.[9] 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,[7 8 10 11] the literature's focus on a limited number of drug classes[7–10] and publication bias.[9 10]

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[12 13] (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.[14] 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,[5] and a similar database of DHPCs issued during 2007–2018 in Denmark.[15] 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 ≥24 months preceding an index advisory and ≥12 months following an advisory in at least one country, and the drug was on the market for ≥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 ≥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 ±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 Utilization 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.[16–18] 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).[19] Aggregate data by month on prescription drugs dispensed through the Pharmaceutical Benefits Scheme in Australia were publicly available online[20] (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)[21] 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).[21]

Statistical analysis

We used interrupted time series analysis[12 13] 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[22] and autocorrelation[23] 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.[24 25] 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.[26]

We conducted random-effects meta-analyses with inverse-variance weighting to estimate the average association of advisories with percentage change in drug utilisation,[14] 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.[14] 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.[14] 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,[27–50] 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),[21] and included 2 drugs (febuxostat and fingolimod) that entered the market within 6 years prior to the advisories studied.

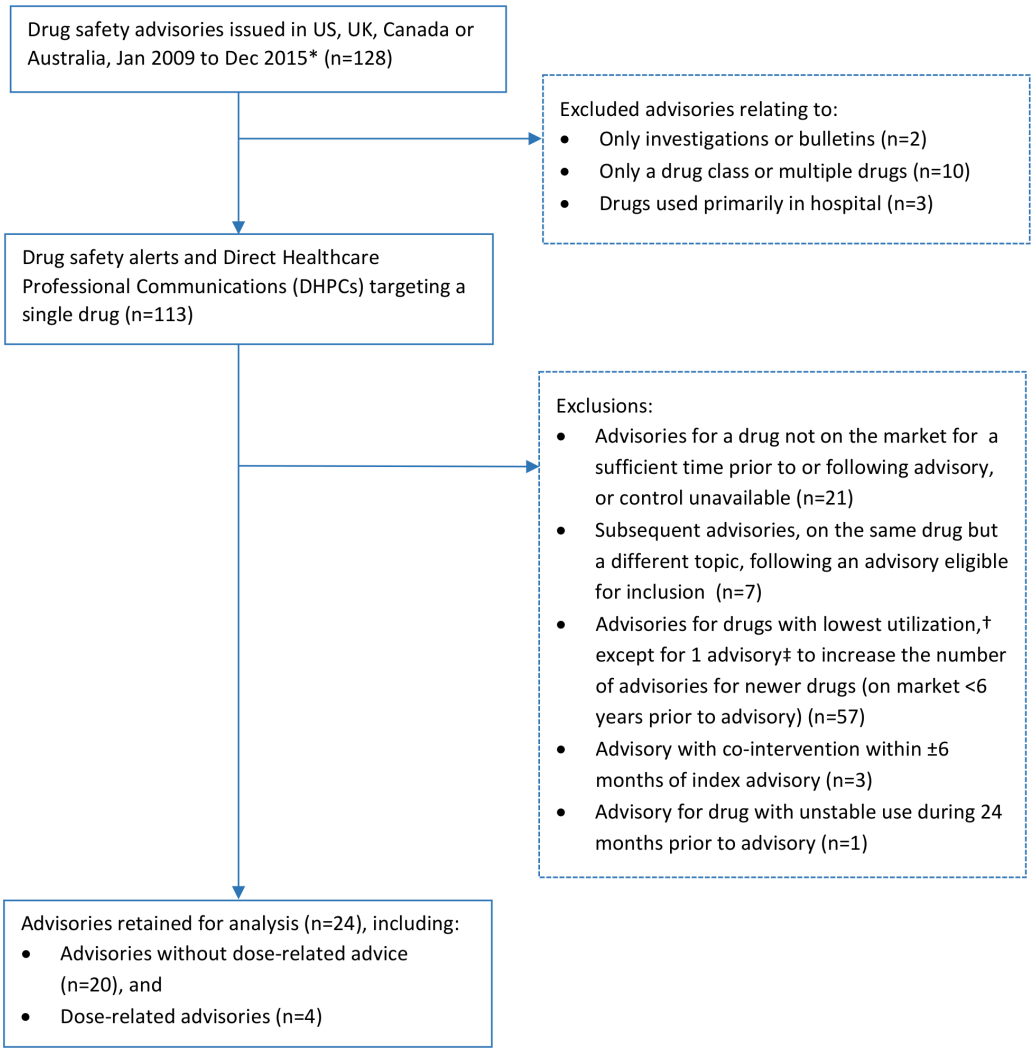

Figure 1 Selection of drug safety advisories for inclusion. *Excluding advisories relating to all-clear statements, drugs available over-the-counter in ≥1 country, drug-drug interactions, drugs marketed in only one of the countries and vaccines. Multiple advisories on the same topic were counted only 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
(a) Advisories without dose-related advice*				
Aripiprazole-impulse control disorders[30]	CA	DK	2 November 2015	Alert
Azithromycin-cardiac arrhythmias[43]	USA	USA†	12 March 2013	Alert
Clopidogrel-acquired haemophilia[38]	DK	AU	28 August 2013	DHPC
Febuxostat-epidermal and dermal conditions[27]	UK	USA†	6 May 2012	DHPC
Finasteride-breast cancer male[34]	UK	CA	1 December 2009	Alert
Fingolimod-PML[40]	USA	CA	29 August 2013	Alert
Insulin-glargine-neoplasm malignant[50]	USA	DK	1 July 2009	Alert
Isotretinoin-epidermal and dermal conditions[32]	CA	DK	11 February 2010	DHPC
Ketoconazole-adrenal gland disorders‡[41]	USA	USA†	26 July 2013	Alert
Leflunomide methotrexate-hepatotoxicity[49]	USA	AU	13 July 2010	Alert
Methylphenidate-sexual dysfunction[39]	USA	USA†	17 December 2013	Alert
Mycophenolate-aplasia pure red cell[33]	UK	USA†§	2 June 2009	DHPC
Nitrofurantoin-lack of effect[36]	UK	AU¶	1 August 2013	Alert
Olmesartan-malabsorption[42]	USA	AU¶	3 July 2013	Alert
Ondansetron-cardiac arrhythmias[45]	USA	AU¶	15 September 2011	Alert
Pioglitazone-bladder cancer[48]	USA	USA†	15 June 2011	Alert
Quetiapine-metabolic syndrome[29]	UK	UK†	23 December 2011	DHPC
Tacrolimus-neoplasm malignant‡[28]	DK	CA	1 May 2012	DHPC
Testosterone-cardiovascular disorder[31]	CA	UK	15 July 2014	Alert
Topiramate-congenital anomaly[37]	DK	CA	1 March 2011	DHPC
(b) Advisories with dose-related advice*				
Citalopram escitalopram-cardiac arrhythmias[46]	USA	USA†	24 August 2011	Alert
Fluconazole-congenital anomaly[47]	USA	USA†	3 August 2011	Alert
Hydroxyzine-cardiac arrhythmias[35]	UK	CA	29 April 2015	Alert
Zolpidem-cognitive impairment[44]	USA	USA†	10 January 2013	Alert

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*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)

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*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

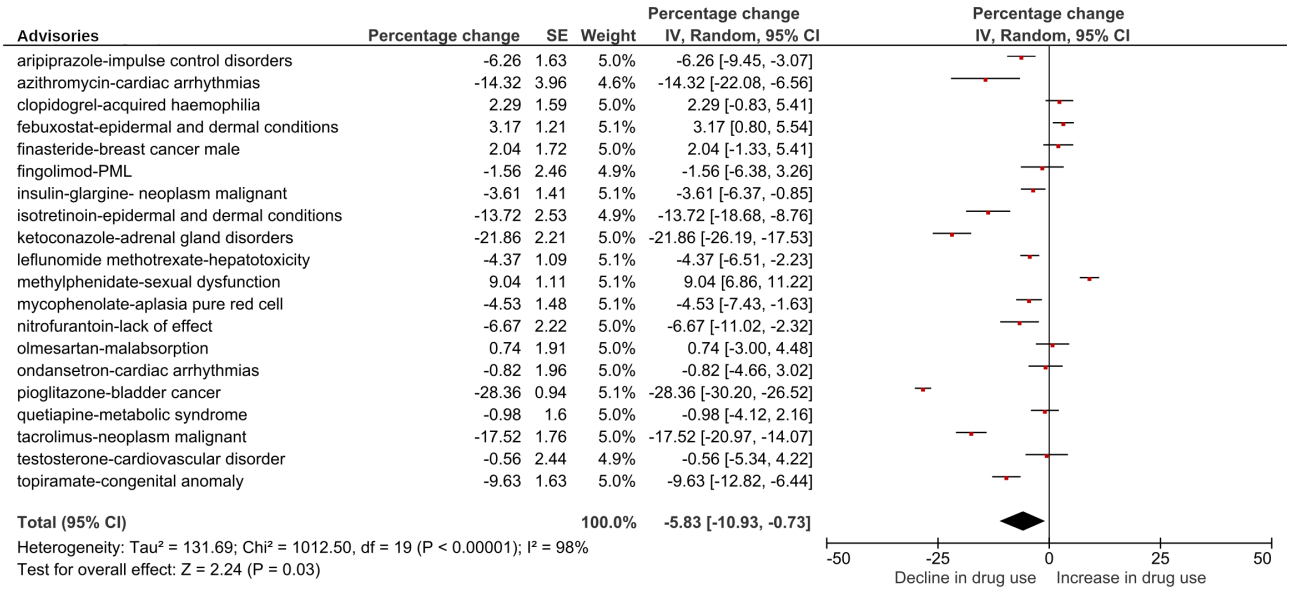

Figure 2 Actual versus predicted percentage change in the rate of prescriptions following drug safety advisories without dose-related advice,* adjusted by change in controls without an advisory. *Actual versus predicted percentage change in the number of prescriptions written or dispensed per 100 000 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.[6 7 9] 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%.[9] 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,[9] 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

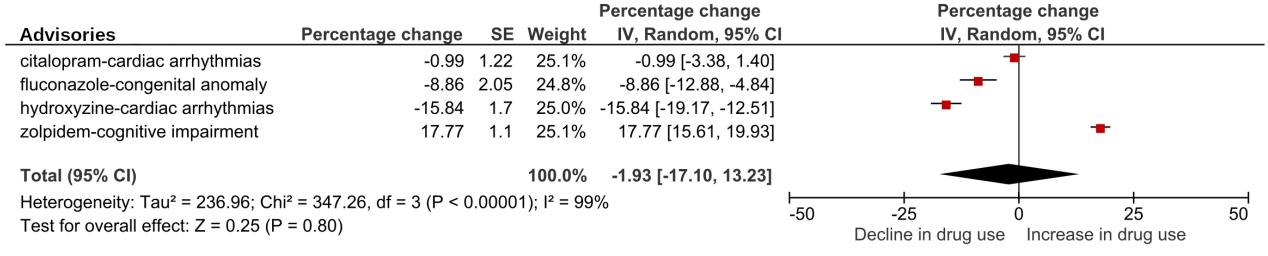

Figure 3 Actual versus predicted percentage change in the rate of defined daily doses following dose-related drug safety advisories,* adjusted by change in controls without an advisory. *Actual versus predicted percentage change in the number of defined daily doses prescribed or dispensed per 100 000 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.[51] In contrast, our sample did not contain advisories relating to major changes in indication with the exception of an advisory limiting use of ketoconazole.[41]

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.[6 9]

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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SUPPLEMENTARY APPENDIX

Contents:

Table S1. Sources of prescription drug data by country

Country	Data sources	Population	Drug data
Australia	Pharmaceutical Benefits Scheme (PBS) from the Australian Government Department of Health	All residents of Australia (~22.5 million residents in 2011-2012, the mid-point of the study).	Prescription drugs dispensed, including the majority supplied by community pharmacies and some supplied by public and private hospital pharmacies and other facilities.
Canada	National Prescription Drug Utilization Information System (NPDUIS) from the Canadian Institute for Health Information (CIHI)	Most residents of the provinces of British Columbia (~4.5 million residents on January 1, 2012) and Saskatchewan (~1.1 million residents on January 1, 2012). Data excluded individuals enrolled in federally insured drug plans (for eligible Indigenous people, members of the Royal Canadian Mounted Police, members of the military, veterans, refugee claimants, and federal inmates). Data from these sources included approximately 15% of the Canadian population.	Prescription drugs dispensed at community pharmacies.
Denmark	Danish National Prescription Registry (NPR)	All residents of Denmark (~5.6 million in December 2011).	Prescription drugs dispensed at community pharmacies.
United Kingdom	Clinical Practice Research Datalink (CPRD) Gold database	Patients of UK general practitioners (GPs) who contributed data to the database at any time during 2007-2016 (5,618,454 patients in December 2011, comprising 9% of UK population).	Prescriptions written by GPs from practices participating in CPRD.
United States	MarketScan Commercial Claims and Encounters Database (CCAE) and the MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)	Patients <65 years enrolled in private drug plans contributing data to US IBM MarketScan Research Databases. Patients ≥65 years with Medicare and enrolment in supplemental private drug plans contributing data to US IBM MarketScan Research Databases. These linked databases included 36,534,851 patients in December 2011, comprising 12% of US population.	Outpatient prescription drugs dispensed.

Created by the authors.

Table S2. Rationale for criteria used to select advisories and controls

Criteria	Rationale for criteria
a) Inclusion criteria for advisories:	
Safety alerts posted on a regulator's website or Dear Healthcare Professional Communications (DHPCs).	• We anticipated these types of advisories might lead to changes in drug utilization.
Advisory related to a drug on the market for ≥24 months preceding an index advisory and ≥12 months following an advisory in at least 1 country, and the drug was on the market for ≥36 months in at least one country without the advisory (to serve as a control).	• This allowed for sufficient data to conduct an interrupted time series analysis to assess the association of advisories with changes in drug utilization and for analyzing a concurrent control (if appropriate). • We felt this was necessary for conducting a robust analysis of changes in drug utilization, although a trade-off was that advisories for drugs on the market for <24 months prior to an advisory could not be included.
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 1 advisory per drug.	• We limited the analysis to 1 advisory per drug so that our analyses would include advisories on a diverse range of drugs.
b) Exclusion criteria for advisories:	
Advisory related to an "all-clear" statement (i.e., no problem was ultimately identified), drugs available over-the-counter in ≥1 country, drug-drug interactions, drugs marketed in only 1 of the countries, or vaccines.	• Advisories with all-clear statements were not expected to reduce drug utilization. • We lacked reliable data on the use of over-the-counter drugs and vaccines. • Excluding advisories on drug-drug interactions was a cost-saving measure; assessing concomitant drug use would require acquiring data on a greater number of drugs.
Advisory was only an announcement that a safety concern was under investigation or an article in the regulatory agency's drug safety bulletin.	• Investigations and bulletins were anticipated to have little impact on drug utilization.
Advisory was for a drug class or multiple drugs, or drugs used primarily in hospitals.	• Excluding advisories on drug classes and multiple drugs was a cost-saving measure; assessing impacts on drug utilization would require acquiring data on a greater number of drugs. • We lacked reliable access to data on in-hospital drug use.

Advisories for drugs with lowest utilization (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 (i.e., drugs on the market for <6 years prior to the advisory).	• We included advisories for drugs with higher utilization to allow for more precise estimation of changes in drug utilization during the post-advisory period. • We aimed to include 20-30 advisories so that we would have adequate statistical power for meta-analysis. We made an initial selection of advisories based on a preliminary assessment of pre-advisory drug utilization with available data from the US. This preliminary assessment was required to determine data to request for all countries in the study. • Some of the advisories selected initially were later excluded after we acquired data from all included countries and applied all exclusion criteria.
Advisory had co-intervention(s) within ±6 months of an advisory (such as an additional advisory for the same drug coinciding with a marked change in drug utilization).	• We excluded advisories with co-interventions within ±6 months, because co-interventions occurring close in time to advisories would make it impossible to reliably distinguish between the effect of advisories and the effect of co-interventions.
Advisory was for a drug that had unstable use in the 24 months prior to the advisory (for example, 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 pre-advisory data.	• We excluded advisories for drugs with unstable use prior to the advisory to allow for reliable estimation of changes to drug utilization in the post-advisory period compared to the pre-advisory trend. • Unstable use was based on visual inspection of drug utilization rates in the 24 months prior to an advisory.
c) For each advisory, we selected 1 control from among possible controls as follows:	
We required use of the advisory drug to be stable during the 24-month pre-advisory period in the control country (or historical control period), based on visual inspection, and we required the ratio of the pre-advisory median monthly drug utilization rates to be minimally comparable in the control and index country (i.e., not exceeding a ratio of 10:1).	• We required stable pre-advisory use of a drug to allow for reliable estimation of changes in postadvisory drug utilization. • We expected controls with more comparable drug utilization rates would more reliably represent changes in drug utilization that might have occurred in the index country in the absence of an advisory.

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) (Table S2), based on 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 utilization following a small subset of advisories.	• If an advisory in the index country affected drug utilization in a control country, this would bias the adjusted estimate of the change in drug utilization toward the null.
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.	• We expected concurrent controls would more reliably represent changes in drug utilization that might have occurred in the index country in the absence of an advisory, although a suitable concurrent control was not always available based on all of the selection criteria.
If the above criteria were met by multiple possible controls, we preferred the control in which pre-advisory drug utilization rate was most similar to that in the index country.	• We expected controls with more comparable drug utilization rates would more reliably represent changes in drug utilization that might have occurred in the index country in the absence of an advisory.

Table S3. Expected influence* of index advisory on drug utilization in possible control

Control	Index advisory				
	US	Canada	UK	Denmark	Australia†
US	x	weak/medium	medium	weak	x
Canada	strong	x	weak/medium	weak	x
UK	medium	weak/medium	x	strong	x
Denmark	medium	weak	strong	x	x
Australia	weak	weak	weak	weak	x

*based on 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 utilization following a small subset of advisories. †No Australian advisories were selected as index advisories. Created by the authors.

Table S4. Drug classes of medications featured in index advisories, by WHO Anatomical Therapeutic Chemical, level 3

Medication	ATC3 code 1*†	ATC3 description 1	ATC3 code 2*	ATC3 description 2
aripiprazole	N05A	antipsychotics		
azithromycin	J01F	macrolides, lincosamides and streptogramins	S01A	antiinfectives
citalopram	N06A	antidepressants		
clopidogrel	B01A	antithrombotic agents		
febuxostat	M04A	antigout preparations		
finasteride	D11A	other dermatological preparations	G04C	drugs used in benign prostatic hypertrophy
fingolimod	L04A	immunosuppressants		
fluconazole	J02A	antimycotics for systemic use	D01A	antifungals for topical use
hydroxyzine	N05B	anxiolytics		
insulin	A10A	insulins and analogues		
isotretinoin	D10B	anti-acne preparations for systemic use	D10A	anti-acne preparations for topical use
ketoconazole*	J02A	antimycotics for systemic use		
leflunomide	L04A	immunosuppressants		
methylphenidate	N06B	psychostimulants, agents used for adhd and nootropics		
mycophenolate	L04A	immunosuppressants		
nitrofurantoin	J01X	other antibacterials		
olmesartan	C09C	angiotensin II receptor blockers (arbs), plain		
ondansetron	A04A	antiemetics and antinauseants		
pioglitazone	A10B	blood glucose lowering drugs, excl. insulins		
quetiapine	N05A	antipsychotics		
tacrolimus*	D11A	other dermatological preparations		
testosterone	G03B	androgens		
topiramate	N03A	antiepileptics		
zolpidem	N05C	hypnotics and sedatives		

*All ATC3 codes of each drug have been included, except those for combination drugs and those relating to formulations that were not relevant to specific advisories (i.e., only ATC3 codes relating to oral ketoconazole and topical tacrolimus were included). †We have labelled these columns as ACT3 codes 1 and 2, although this is not intended to reflect the relative importance of each code. The "ATC3 code 1" column contains 19 distinct ATC3 codes. This represents a conservative estimate of the number of drug classes in the study, as any drug classes applicable to more than 1 medication are listed in this column. Created by the authors. WHO=World Health Organization ATC3= Anatomical Therapeutic Chemical, level 3

Table S5. Crude actual versus predicted change in drug utilization* in controls

Advisory category	Advisory (drug-risk group)	Control	Absolute change, prescription or DDD rate (95% CI)†	Percentage change, % (95% CI)
a) Advisories without dose-related advice‡	aripiprazole-impulse control disorders	DK	2.73 (-0.13,5.72)	2.6 (-0.1,5.4)
	azithromycin-cardiac arrhythmias	US§	-34.5 (-121.5,53.8)	-2.2 (-7.6,3.4)
	clopidogrel-acquired haemophilia	AU	-1.3 (-26.0,25.1)	-0.1 (-2.4,2.3)
	febuxostat-epidermal and dermal conditions	US§	-2.37 (-2.74,-2.00)	-8.9 (-10.2,-7.5)
	finasteride-breast cancer male	CA	-24.48 (-45.51,-3.38)	-1.9 (-3.5,-0.3)
	fingolimod-PML	CA	-0.10 (-0.42,0.23)	-1.3 (-5.5,3.1)
	insulin-glargine-neoplasm malignant	DK	0.68 (-1.33,2.62)	0.8 (-1.6,3.1)
	isotretinoin-epidermal and dermal conditions	DK	2.60 (0.53,4.61)	5.9 (1.2,10.4)
	ketoconazole-adrenal gland disorders	US§	-0.78 (-1.18,-0.36)	-4.3 (-6.6,-2.0)
	leflunomide-hepatotoxicity	AU	-2.32 (-3.13,-1.53)	-3.3 (-4.5,-2.2)
	methylphenidate-sexual dysfunction	US§	-19.23 (-27.54,-10.95)	-3.5 (-5.1,-2.0)
	mycophenolate-aplasia pure red cell	US§	0.30 (-0.06,0.66)	0.8 (-0.2,1.8)
	nitrofurantoin-lack of effect	AU¶	44.90 (5.13,85.02)	3.8 (0.4,7.3)
	olmesartan-malabsorption	AU¶	45.58 (6.99,85.40)	3.9 (0.6,7.3)
	ondansetron-cardiac arrhythmias	AU¶	-0.87 (-5.10,3.21)	-0.7 (-3.9,2.4)
	pioglitazone-bladder cancer	US§	-3.11 (-8.22,1.68)	-0.8 (-2.1,0.4)
	quetiapine-metabolic syndrome	UK§	-3.33 (-10.91,4.47)	-0.9 (-2.8,1.2)
	tacrolimus-neoplasm malignant	CA	-1.21 (-3.94,1.41)	-1.4 (-4.5,1.6)
	testosterone-cardiovascular disorder	UK	-1.85 (-5.03,1.30)	-1.7 (-4.6,1.2)
	topiramate-congenital anomaly	CA	73.84 (52.45,95.91)	7.0 (5.0,9.1)
b) Advisories with dose-related advice‡	citalopram-cardiac arrhythmias	US§	230 (-685,1173)	0.5 (-1.4,2.4)
	fluconazole-congenital anomaly	US§	35 (-27,98)	1.5 (-1.1,4.1)
	hydroxyzine-cardiac arrhythmias	CA	41 (-88,169)	0.6 (-1.4,2.6)
	zolpidem-cognitive impairment	US§	706 (189,1245)	1.8 (0.5,3.1)

*During an 11-month postadvisory period (for concurrent controls) or analogous historical control period. †In part (a), the units are monthly prescriptions prescribed or dispensed per 100,000 population, and in part (b) the units are monthly defined daily doses (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. §historical control ¶concessional beneficiaries (e.g., seniors and individuals with a low household income) Created by the authors. AU=Australia CA=Canada DK=Denmark PML=progressive multifocal leukoencephalopathy

Table S6. Overview of assessment of whether advisories contain prescribing advice relevant to immediate prescribing decisions and not restricted to a small subgroup of patients

Advisory	Index advisory	Contains prescribing advice relevant to immediate prescribing decisions (Y/N)*	Prescribing advice restricted to a small subgroup of patients (Y/N/NA)*	Contains prescribing advice that is relevant to immediate prescribing decisions and not restricted to a small subgroup of patients (Y/N)*
aripiprazole-impulse control disorders	Canada	N	NA	N
azithromycin-cardiac arrhythmias	United States	Y	N	Y
clopidogrel-acquired haemophilia	Denmark	N	NA	N
febuxostat-epidermal and dermal conditions	United Kingdom	N	NA	N
finasteride-breast cancer male	United Kingdom	N	NA	N
fingolimod-progressive multifocal leukoencephalopathy	United States	N	NA	N
insulin-glargine- neoplasm malignant	United States	N	NA	N
isotretinoin-epidermal and dermal conditions	Canada	N	NA	N
ketoconazole-adrenal gland disorders	United States	Y	N	Y
leflunomide -hepatotoxicity	United States	Y	N	Y
methylphenidate-sexual dysfunction	United States	N	NA	N
mycophenolate-aplasia pure red cell	United Kingdom	N	NA	N
nitrofurantoin-lack of effect	United Kingdom	Y	N	Y
olmesartan-malabsorption	United States	N	NA	N

ondansetron-cardiac arrhythmias	United States	Y	Y	N
pioglitazone-bladder cancer	United States	Y	Y	N
quetiapine--metabolic syndrome	United Kingdom	N	NA	N
tacrolimus-neoplasm malignant	Denmark	N	NA	N
testosterone-replacement-products-cardiovascular disorder	Canada	N	NA	N
topiramate-congenital anomaly	Denmark	Y	N	Y

Created by the authors. Y=yes N=no NA=not applicable

Table S7. Assessment of whether advisories contain prescribing advice relevant to an immediate prescribing decision

Advisory	Index advisory	Contains prescribing advice relevant to immediate prescribing decision (Y/N)*	Quotation from the advisory to support this answer, if needed	Note to support answer, if needed
aripiprazole-impulse control disorders	Canada	N		
azithromycin-cardiac arrhythmias	United States	Y	"Health care professionals should consider the risk of torsades de pointes and fatal arrhythmia when considering treatment options with azithromycin or alternative antibacterial drugs. "	Recommends considering risk when prescribing.
clopidogrel-acquired haemophilia	Denmark	N	If patients receive confirmed diagnosis of acquired haemophilia, "clopidogrel should be discontinued".	Only advises discontinuing after adverse effect experienced.
febuxostat-epidermal and dermal conditions	United Kingdom	N	"Treatment should be stopped immediately if signs or symptoms of serious hypersensitivity reactions occur."	Only advises discontinuing after adverse effect experienced.
finasteride-breast cancer male	United Kingdom	N		
fingolimod-progressive multifocal leukoencephalopathy	United States	N		
insulin-glargine-neoplasm malignant	United States	N		
isotretinoin-epidermal and dermal conditions	Canada	N	"Patients should be monitored closely for severe skin reactions and discontinuation of ACCUTANE should be considered if warranted. "	Advises considering discontinuation only based on monitoring for adverse effect.

ketoconazole-adrenal gland disorders	United States	Y	-As a result of new information, "Nizoral oral tablets should not be a first-line treatment for any fungal infection". -"Limitation of the usage of Nizoral tablets by removing indications in which the risk outweighs the benefits." -"Nizoral tablets are not indicated for the treatment of fungal infections of the skin or nails."	Advisory warns to limit the drug's use by changing indications and limiting first-line use.
leflunomide - hepatotoxicity	United States	Y	"Only patients for whom the anticipated therapeutic benefit is expected to outweigh the risk of severe liver injury should be considered for leflunomide treatment."	Recommends considering risk when prescribing.
methylphenidate-sexual dysfunction	United States	N		
mycophenolate-aplasia pure red cell	United Kingdom	N	"Dose reduction or discontinuation of CellCept should be considered in patients who develop PRCA."	States only that dose reduction or discontinuation should be considered following an adverse effect.
nitrofurantoin-lack of effect	United Kingdom	Y	"Nitrofurantoin is … contraindicated in patients with <60 mL/min creatinine clearance."	Adds a contraindication.
olmesartan-malabsorption	United States	N	"If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued."	Only advises discontinuing after adverse effect experienced.
ondansetron-cardiac arrhythmias	United States	Y†	"The labels are being revised to include a warning to avoid use in patients with congenital long QT syndrome because these patients are at particular risk for Torsade."	Adds a contraindication.
pioglitazone-bladder cancer	United States	Y†	Recommends health professionals should "Not use pioglitazone in patients with active bladder cancer" and "Use pioglitazone with caution in patients with a prior history of bladder cancer."	Adds a contraindication and advises caution in some patients.

quetiapine--metabolic syndrome	United Kingdom	N		
tacrolimus-neoplasm malignant	Denmark	N	"Healthcare Professionals are reminded of the following risk minimisation measures . . . Protopic should be used in patients with moderate to severe atopic dermatitis who failed to respond adequately or were intolerant to conventional therapies such as topical corticosteroids"	Prescribing information is only a reminder rather than new information following from risks in the advisory.
testosterone-replacement-products-cardiovascular disorder	Canada	N		
topiramate-congenital anomaly	Denmark	Y	"Healthcare providers should consider the benefits and the risks of TOPAMAX when administering this drug in women of childbearing potential." Advisory notes prescribing information has been revised to say "Women of childbearing potential should be apprised of the potential fetal risks of TOPAMAX® exposure and should be counseled about alternative therapeutic options."	Recommends considering risk when prescribing.

Created by the authors. Y=yes N=no †Contain prescribing advice, but advice was restricted to a small subgroup of patients.

Table S8. Assessment of whether prescribing advice is restricted to a small subgroup

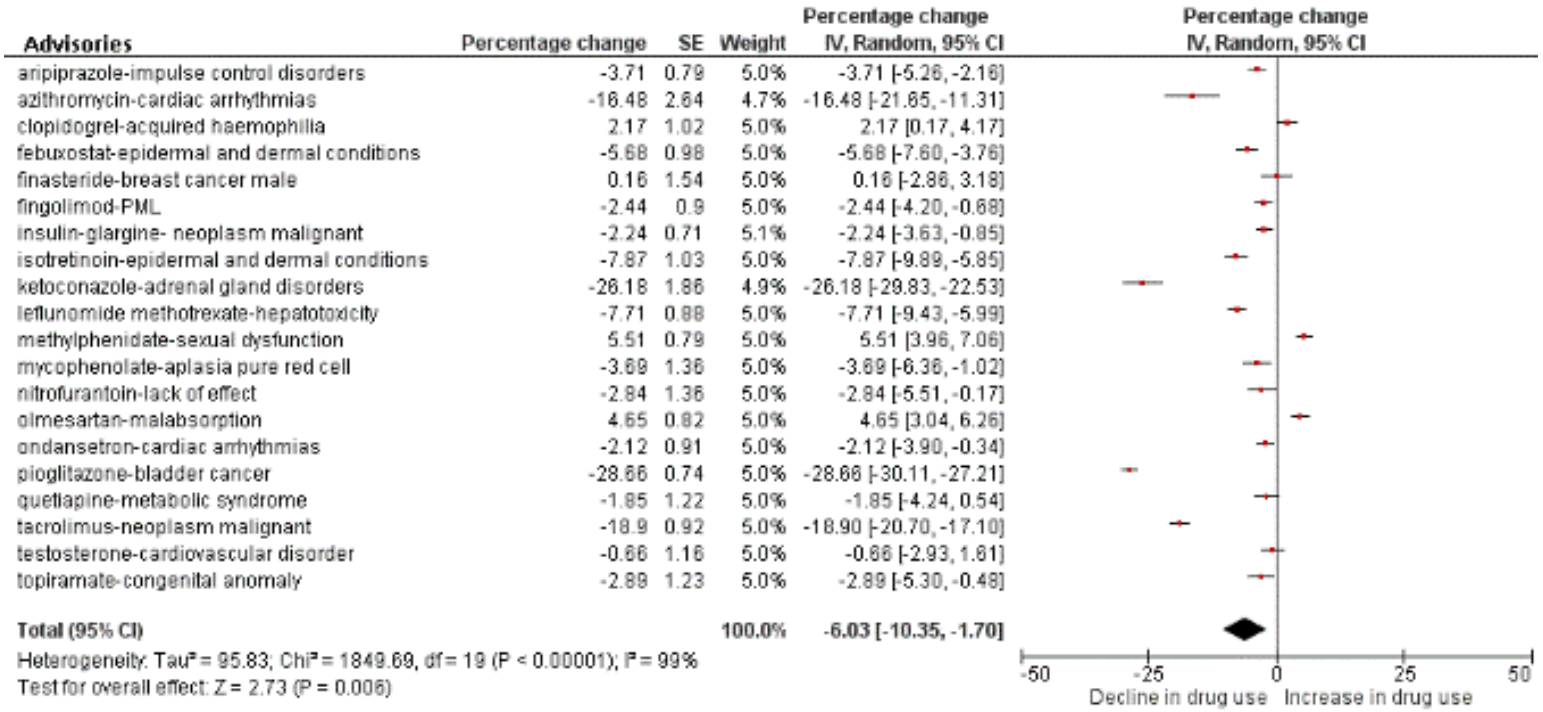
Advisory	Index advisory	Prescribing advice restricted to a small subgroup of patients (Y/N/NA)*	Quotation from the advisory to support this answer, if needed	Note to support this answer, if needed
aripiprazole-impulse control disorders	Canada	NA		
azithromycin-cardiac arrhythmias	United States	N		-While the advisory highlights higher risk for certain patients, it also contains prescribing advice not restricted to these patients. -In addition, higher risk patients were not a small subgroup. A review of our study data for azithromycin users in the month prior to the advisory estimated patients at higher risk represent >15% of azithromycin users (including patients with bradyarrhythmias or heart failure and patients taking drugs known to prolong the QT interval).
clopidogrel-acquired haemophilia	Denmark	NA		
febuxostat-epidermal and dermal conditions	United Kingdom	NA		
finasteride-breast cancer male	United Kingdom	NA		
fingolimod-progressive multifocal leukoencephalopathy	United States	NA		
insulin-glargine-neoplasm malignant	United States	NA		
isotretinoin-epidermal and dermal conditions	Canada	NA		

ketoconazole-adrenal gland disorders	United States	N		While the FDA has "added a strong recommendation against its use (contraindication) in patients with liver disease", which may be a small subgroup, the advisory also contains prescribing advice not limited to a small subgroup.
leflunomide - hepatotoxicity	United States	N		Although the advisory warns to avoid using the drug in patients with pre-existing liver disease, which may be a small subgroup, the advisory also contains prescribing advice not limited to a small subgroup.
methylphenidate-sexual dysfunction	United States	NA		
mycophenolate-aplasia pure red cell	United Kingdom	NA		
nitrofurantoin-lack of effect	United Kingdom	N	"Nitrofurantoin is … contraindicated in patients with <60 mL/min creatinine clearance."	-Patients with renal impairment likely do not represent a small subgroup of nitrofurantoin users. -In the month prior to the advisory, 85% of nitrofurantoin users in our data were women and 53% were >65 years. -Nitsch et al 2006 suggest 12.9% of men and 35.9% of women over 65 years have renal impairment.[1] -Similarly, Cumming et al 2004 found 19% of men and 35% of women had estimated creatinine clearances of <50mL/min in a population with mean age 65 years.[2] -Based on the age and sex breakdown of nitrofurantoin users in our data and Nitsch et al's estimates of renal impairment, it is estimated >17% of nitrofurantoin users in our sample had renal impairment.

olmesartan-malabsorption	United States	NA		
ondansetron-cardiac arrhythmias	United States	Y	"The labels are being revised to include a warning to avoid use in patients with congenital long QT syndrome because these patients are at particular risk for Torsade."	Patients with congenital long QT syndrome likely represent a very small subgroup. Schwartz et al 2009 estimated a prevalence of congenital long QT syndrome of 1 in 2534 apparently healthy live births.[3]
pioglitazone-bladder cancer	United States	Y	Recommends health professionals should "Not use pioglitazone in patients with active bladder cancer" and "Use pioglitazone with caution in patients with a prior history of bladder cancer."	-Patients with active or past bladder cancer likely represent a small subgroup of <1.5% of pioglitazone users. -This estimate is based on the age and sex breakdown of pioglitazone users in the month prior to the advisory in our data, in relation to the median age of bladder cancer diagnosis of 73 years[4] and lifetime prevalence of bladder cancer for men (3.7%) and women (1.1%).[5]
quetiapine--metabolic syndrome	United Kingdom	NA		
tacrolimus-neoplasm malignant	Denmark	NA		
testosterone-replacement-products-cardiovascular disorder	Canada	NA		
topiramate-congenital anomaly	Denmark	N		Women of childbearing age are not a small subgroup, particularly because our analysis of topiramate utilization focused on women 15-54 years of age.

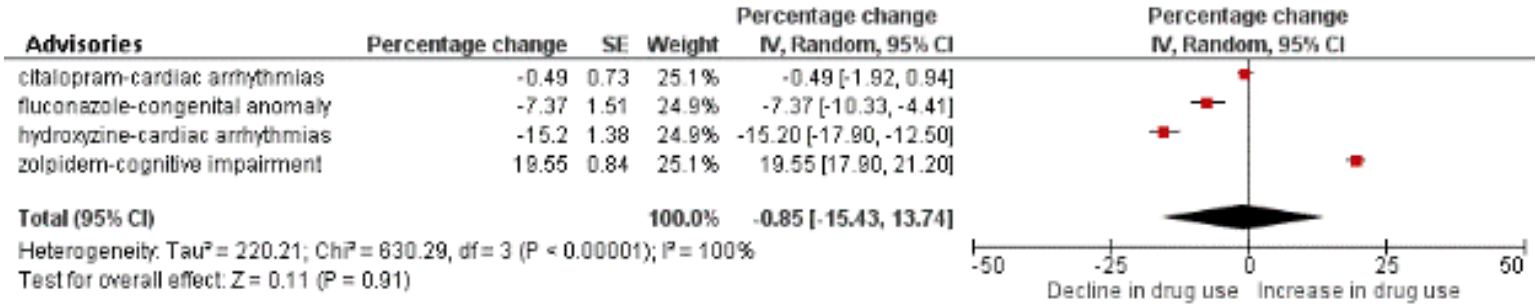
Created by the authors. *Y=yes N=no NA=not applicable

Figure S1. Crude actual versus predicted percentage change in the number of prescriptions per 100,000 population following drug safety advisories without dose-related advice* (unadjusted by change in controls without an advisory)



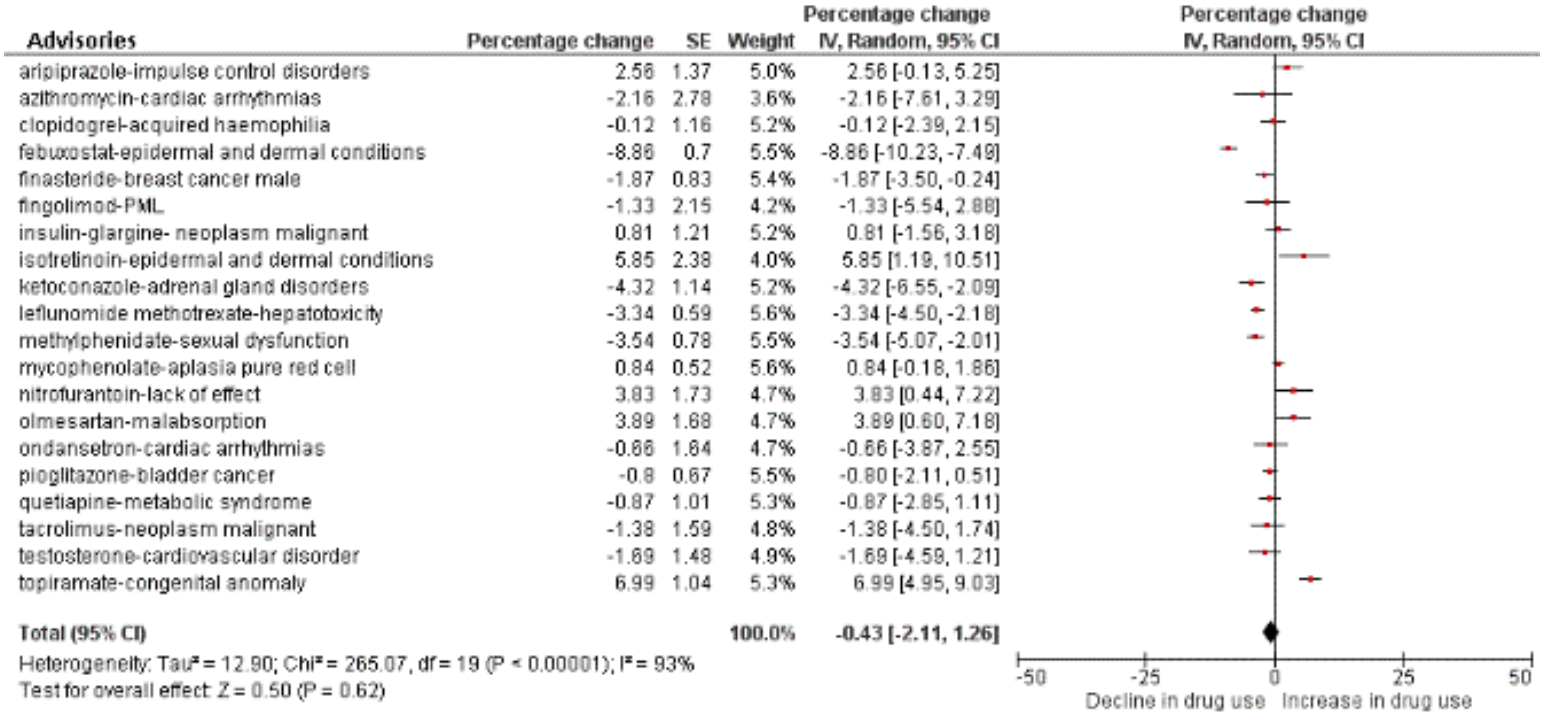
*Actual versus predicted percentage change in the number of prescriptions prescribed or dispensed per 100,000 population during an 11-month period following the month a drug advisory was issued. Dose-related advice was defined as advice that revised the recommended or maximum dose of a drug or warned about risk associated with higher doses. Created by the authors. SE=standard error IV=inverse variance CI=confidence interval PML=progressive multifocal leukoencephalopathy df=degrees of freedom

Figure S2. Crude actual versus predicted percentage change in the number of defined daily doses per 100,000 population following dose-related drug safety advisories* (unadjusted by change 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 were those with dose-related advice, where 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. Created by the authors. SE=standard error IV=inverse variance CI=confidence interval df=degrees of freedom

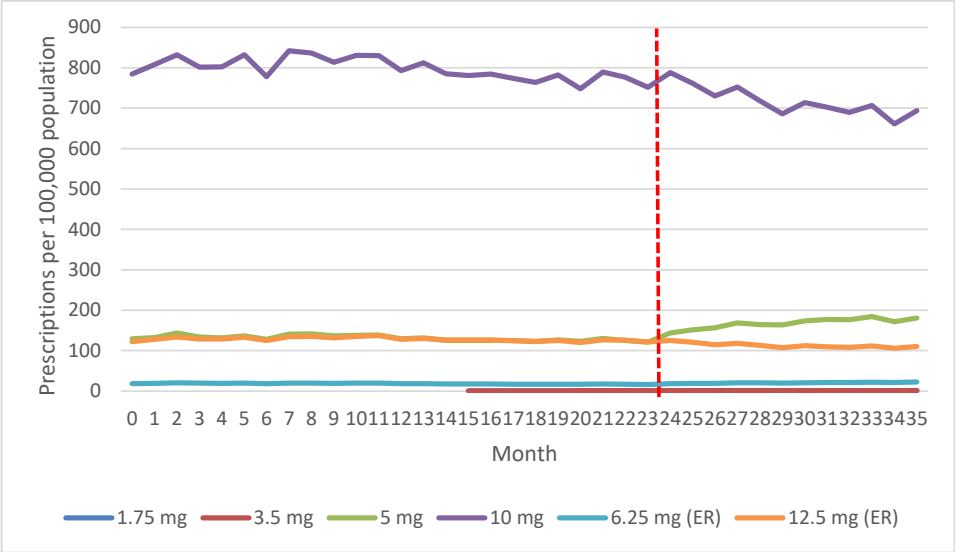
Figure S3. Percentage change in the number of prescriptions per 100,000 population among controls for the analysis of advisories without dose-related advice*



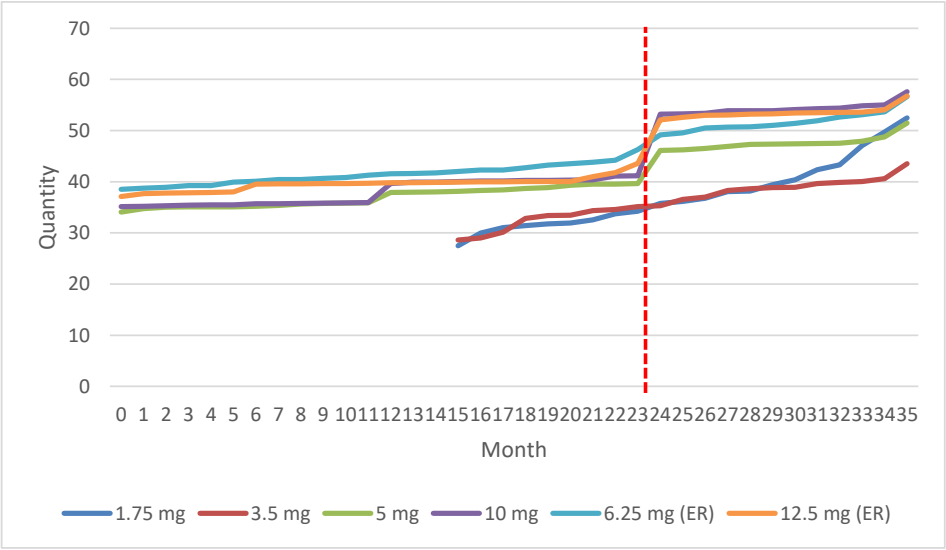
*Percentage change in the number of prescriptions prescribed or dispensed per 100,000 population among controls during an 11-month period following the month a drug advisory was issued in the index country (for concurrent controls) or during an analogous 11-month period (for historical controls). Dose-related advice was defined as advice that revised the recommended or maximum dose of a drug or warned about risk associated with higher doses. Created by the authors. SE=standard error IV=inverse variance CI=confidence interval PML=progressive multifocal leukoencephalopathy df=degrees of freedom

Figure S4. Zolpidem utilization before and after cognitive impairment advisory in US (sensitivity analysis)

(a) Number of prescriptions dispensed per 100,000 population before and after cognitive impairment advisory in the US,* by strength, including extended release (ER) medications

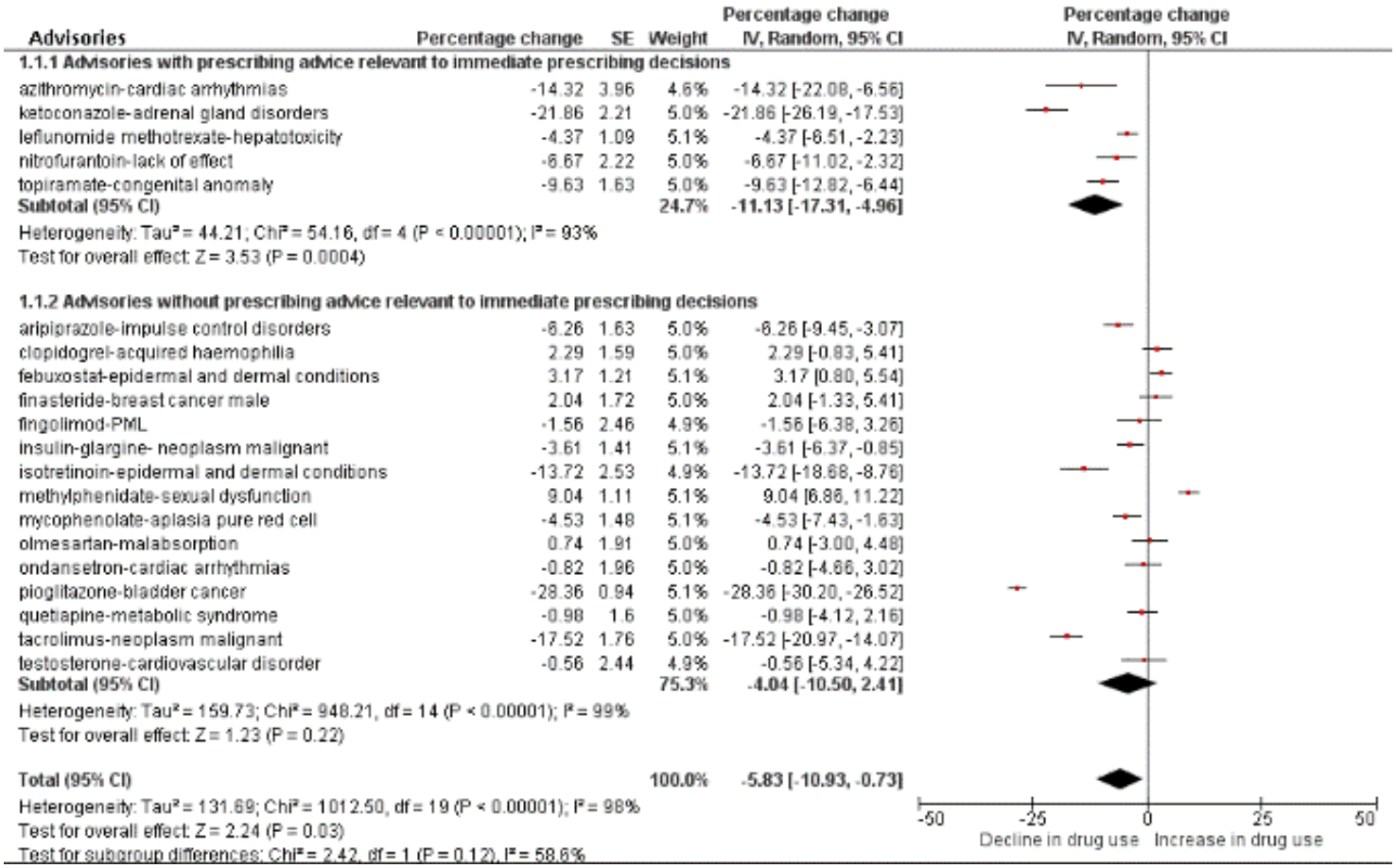


(b) Average quantity of zolpidem dispensed monthly before and after cognitive impairment advisory in the US,* by medication strength, including extended release (ER) medications



*individuals <65 years with private health coverage or >=65 years with Medicare and supplemental health coverage in US IBM MarketScan Research Databases. Created by the authors.

Figure S5. Actual versus predicted percentage change in the rate of prescriptions, following advisories with vs without prescribing advice relevant to immediate prescribing decisions.*



*Compared advisories with vs without prescribing advice relevant to immediate prescribing decisions and not restricted to a small subgroup. This analysis included only advisories without 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. Created by the authors. SE=standard error IV=inverse variance CI=confidence interval PML=progressive multifocal leukoencephalopathy df=degrees of freedom

We asked two practising physicians to review the advisories in our subgroup analysis, including a general practitioner who agreed to assist the study for this purpose (JAL) and an emergency department physician from our research team (JL). We asked each physician to review each of the advisories and consider the question: "From your perspective as a practising physician, does this advisory contain prescribing advice relevant to an immediate prescribing decision?" In addition, the physician reviewers could provide a supporting quotation from an advisory or comment to explain their views. The purpose of this assessment was to provide qualitative data about how practising physicians view prescribing advice in drug safety advisories.

A descriptive analysis of assessments of these advisories by two physician reviewers indicated their views of prescribing advice in the advisories differed. One physician identified advisories as containing prescribing advice only if they contained information about a change in indication or contraindication, or in one case a reminder about appropriate use of a medication. In contrast, the other physician's assessments suggested information about drug risk in an advisory could represent implicit prescribing advice. This physician cited information from advisories about label changes and drug risks as evidence that an advisory contained prescribing advice, while reasons an advisory was deemed not to contain prescribing advice included the unpredictability of an adverse effect, inconsistency of evidence about a medication's risk, and information that risk was primarily associated with prolonged use. The latter physician's assessments suggested information about drug risk may be interpreted as prescribing advice if it provides guidance on which patients should receive the medication and is perceived to be reliable.

Box S1. Descriptive analysis of physician views of prescribing advice in drug safety advisories

Created by the authors.

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