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.

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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

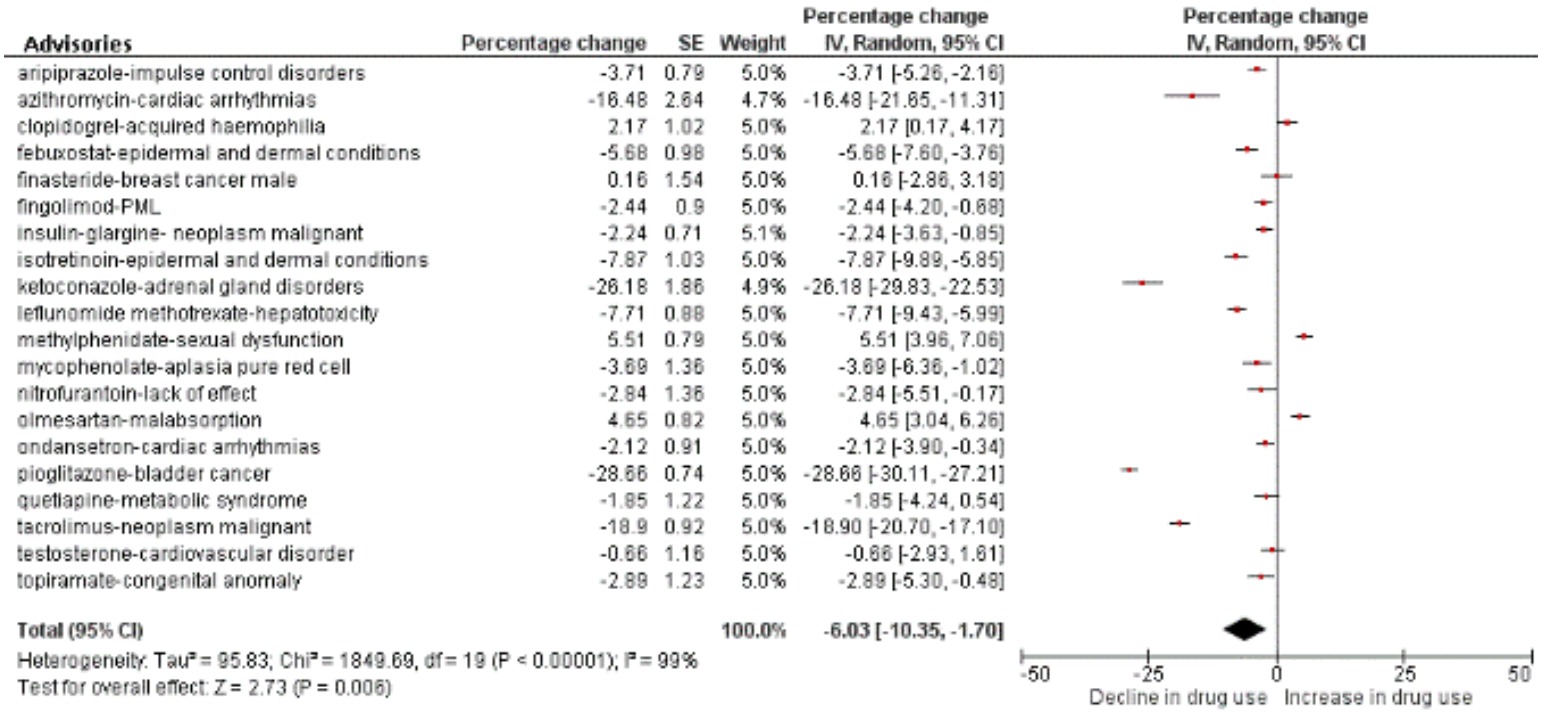
Advisory	Index advisory	Prescribing advice restricted to a small subgroup of patients (Y/N/NA)*	Quotation from the advisory to support this answer, if needed	Note to support this answer, if needed
aripiprazole-impulse control disorders	Canada	NA		
azithromycin-cardiac arrhythmias	United States	N		-While 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.

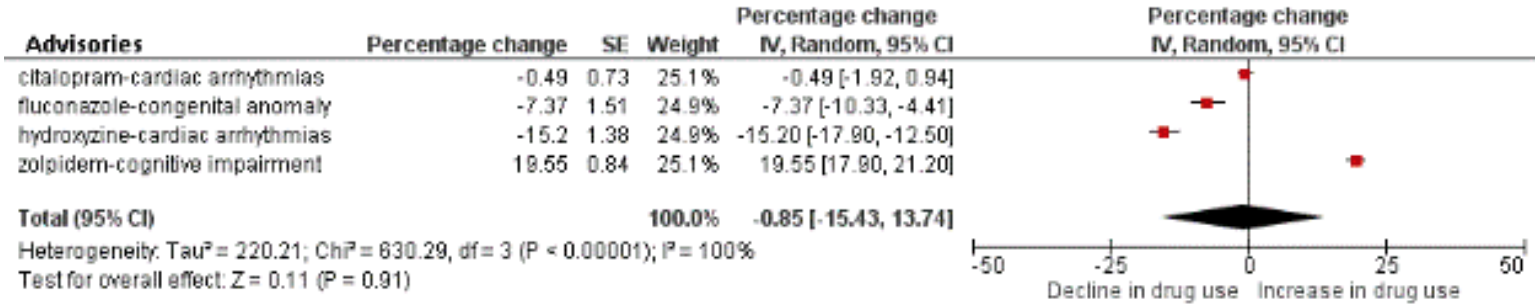
Created by the authors. *Y=yes N=no NA=not applicable

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)



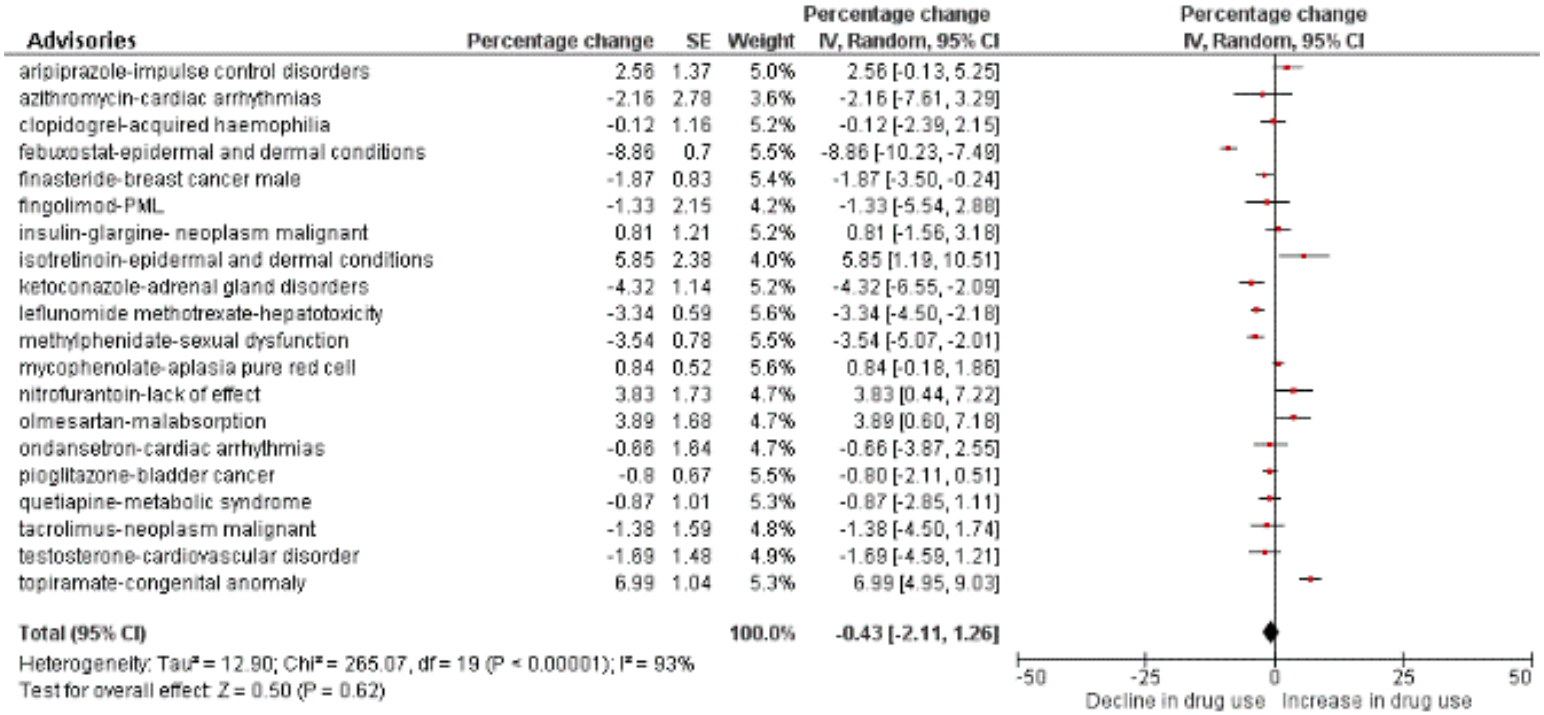
*Actual versus predicted percentage change in the number of prescriptions prescribed or dispensed per 100,000 population during an 11-month period following the month a drug advisory was issued. Dose-related advice was defined as advice that revised the recommended or maximum dose of a drug or warned 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

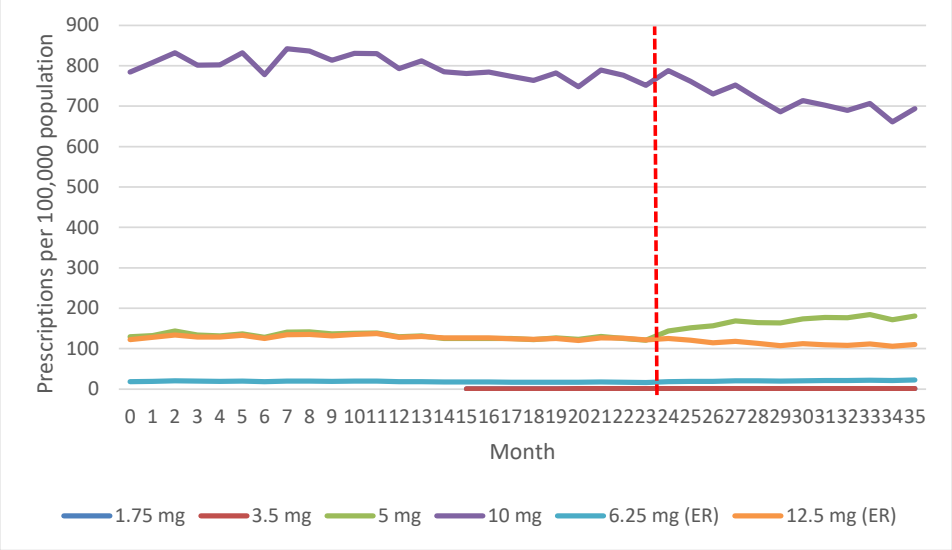
Figure S3. Percentage change in the number of prescriptions per 100,000 population among controls for the analysis of advisories without dose-related advice*



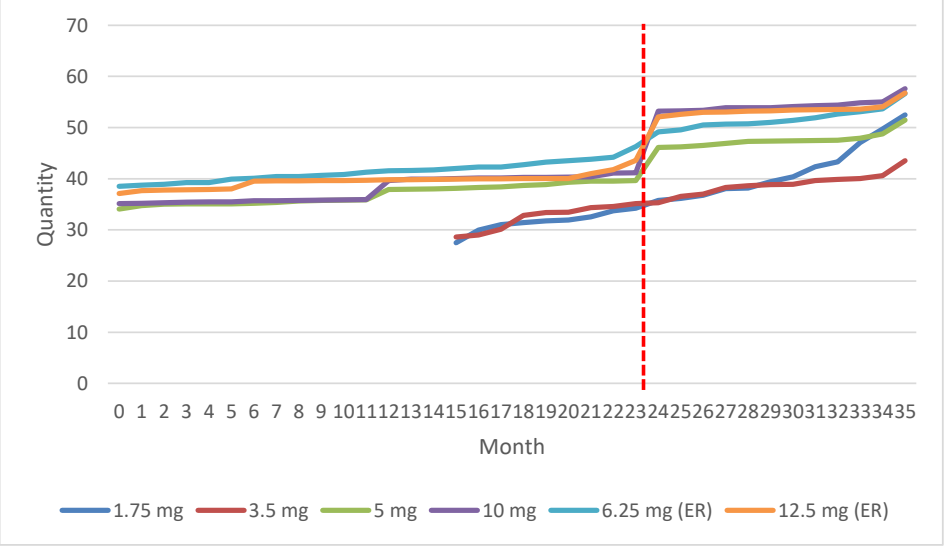
*Percentage change in the number of prescriptions prescribed or dispensed per 100,000 population among controls during an 11-month period following the month a drug advisory was issued in the index country (for concurrent controls) or during an analogous 11-month period (for historical controls). Dose-related 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

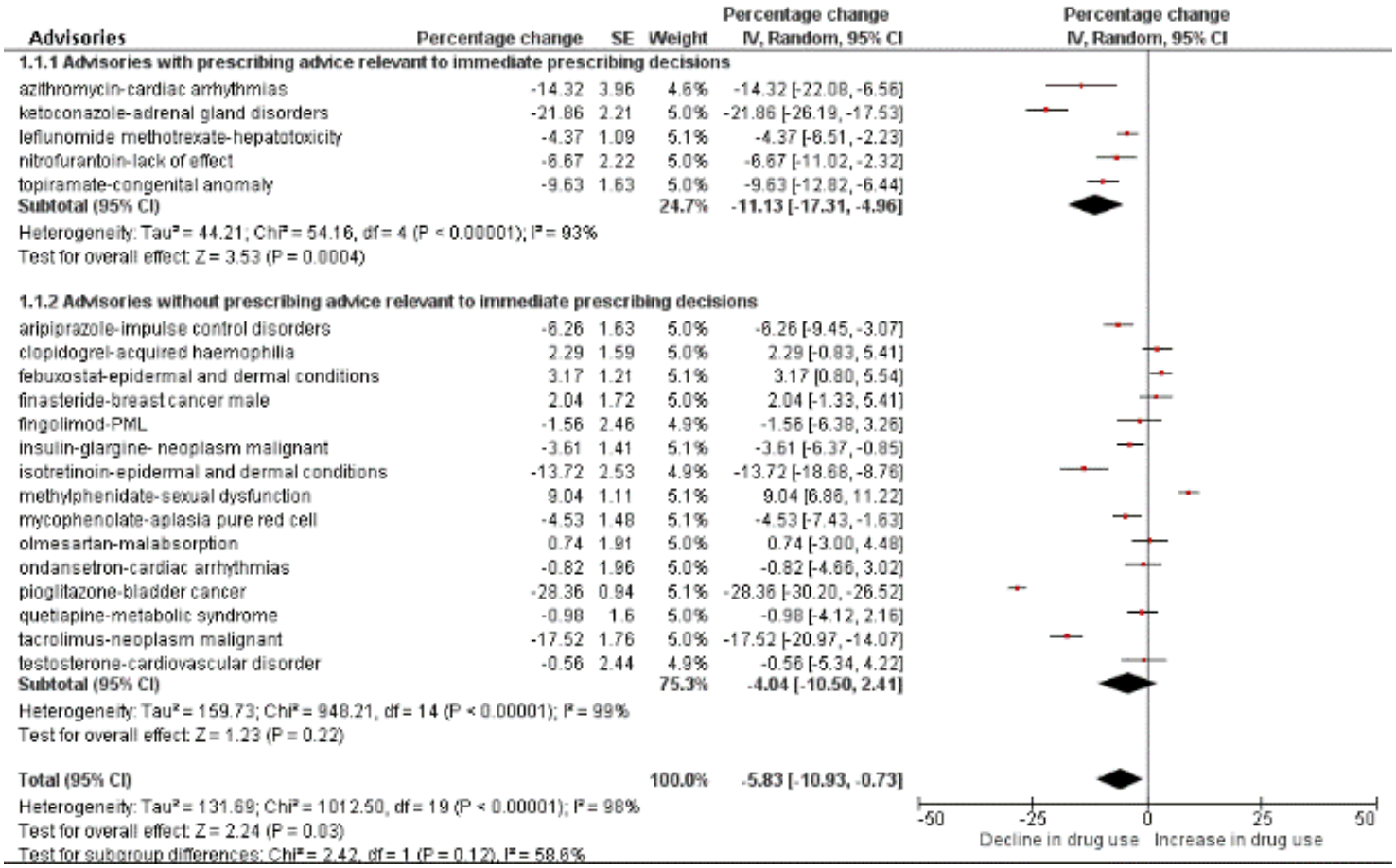


(b) Average quantity of zolpidem dispensed monthly before and after cognitive impairment advisory in the US,* by medication strength, including extended release (ER) medications



*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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