

Influence of drug safety advisories on drug utilization: an international interrupted time series and metaanalysis study



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BACKGROUND AND AIMS

Regulatory drug safety advisories represent a key strategy for managing risk from drug harms. We aimed to evaluate the impact of drug advisories on drug utilization in Australia, Canada, the US, the UK and Denmark.

METHODS

Data and study population:

• We used a database of advisories compiled from regulatory agencies' websites for the Safer

 Table 2. Index countries and controls for dose-related advisories

US*
US*
CA
US*

*historical controls CA=Canada

Fig 2. Actual versus predicted percentage change in the number of prescriptions per 100,000 population in index country in the 11 months following drug safety advisories without dose-related advice, in comparison to control without an advisory

Advisories Framework for Effective Risk-communication (SAFER) project, and we used administrative health data from Australia, Canada, the US, the UK and Denmark.

Study design and analysis:

- Interrupted time series design, including 24 months prior to each advisory and 11 months post-advisory (the month of advisory was considered a transition period).
- Outcomes: (a) monthly prescriptions dispensed per 100,000 population, or (b) for doserelated advisories, monthly defined daily doses (DDDs) dispensed per 100,000 population.

Statistical analysis:

- For each advisory drug-risk group (e.g., advisories on pioglitazone and bladder cancer), we deemed the first advisory issued by one of the 5 countries as the index advisory, and selected a control country without an advisory (or a historical control if necessary).
- We used interrupted time series models, adjusted for a linear time trend, seasonality and autocorrelation, to estimate the actual vs predicted change in drug utilization rates for index advisories, adjusted by the change in control countries (or historical controls as applicable).
- We conducted a random effects meta-analysis of changes in drug utilization, for advisories unrelated to dose and dose-related advisories, to estimate the average effect size.

Fig I. Selection of advisories flowchart



				Percentage change	Percentage change
Study or Subgroup	Percentage change	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
aripiprazole-impulse control disorders	-6.26	1.63	5.0%	-6.26 [-9.45, -3.07]	_ _
azithromycin-cardiac arrhythmias	-14.32	3.96	4.6%	-14.32 [-22.08, -6.56]	_
clopidogrel-acquired haemophilia	2.29	1.59	5.0%	2.29 [-0.83, 5.41]	+
febuxostat-epidermal and dermal conditions	3.17	1.21	5.1%	3.17 [0.80, 5.54]	
finasteride-breast cancer male	2.04	1.72	5.0%	2.04 [-1.33, 5.41]	
fingolimod-PML	-1.56	2.46	4.9%	-1.56 [-6.38, 3.26]	—
insulin-glargine- neoplasm malignant	-3.61	1.41	5.1%	-3.61 [-6.37, -0.85]	
isotretinoin-epidermal and dermal conditions	-13.72	2.53	4.9%	-13.72 [-18.68, -8.76]	_
ketoconazole-adrenal gland disorders	-21.86	2.21	5.0%	-21.86 [-26.19, -17.53]	_
leflunomide methotrexate-hepatotoxicity	-4.37	1.09	5.1%	-4.37 [-6.51, -2.23]	
methylphenidate-sexual dysfunction	9.04	1.11	5.1%	9.04 [6.86, 11.22]	
mycophenolate-aplasia pure red cell	-4.53	1.48	5.1%	-4.53 [-7.43, -1.63]	
nitrofurantoin-lack of effect	-6.67	2.22	5.0%	-6.67 [-11.02, -2.32]	_ _
olmesartan-malabsorption	0.74	1.91	5.0%	0.74 [-3.00, 4.48]	_ -
ondansetron-cardiac arrhythmias	-0.82	1.96	5.0%	-0.82 [-4.66, 3.02]	_
pioglitazone-bladder cancer	-28.36	0.94	5.1%	-28.36 [-30.20, -26.52]	
quetiapine-metabolic syndrome	-0.98	1.6	5.0%	-0.98 [-4.12, 2.16]	
tacrolimus-neoplasm malignant	-17.52	1.76	5.0%	-17.52 [-20.97, -14.07]	_
testosterone-cardiovascular disorder	-0.56	2.44	4.9%	-0.56 [-5.34, 4.22]	— -
topiramate-congenital anomaly	-9.88	1.61	5.0%	-9.88 [-13.04, -6.72]	_ _
Total (95% CI)			100.0%	-5.84 [-10.94, -0.74]	-
Heterogeneity: Tau ^z = 131.63; Chi ^z = 1013.31, o Test for overall effect: Z = 2.24 (P = 0.02)	f = 19 (P < 0.00001); I² =	: 98%			-50 -25 0 25 50 Decline in drug use Increase in drug use

Fig 3. Actual versus predicted percentage change in the number of defined daily doses per 100,000 population in the 11 months following dose-related drug safety advisories, in comparison to controls without an advisory.

		Percentage change		Percentage change	Percentage change
Study or Subgroup	Percentage change	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
citalopram-cardiac arrhythmias	-0.99	1.22	25.1%	-0.99 [-3.38, 1.40]	
fluconazole-congenital anomaly	-8.86	2.05	24.8%	-8.86 [-12.88, -4.84]	
hydroxyzine-cardiac arrhythmias	-15.84	1.7	25.0%	-15.84 [-19.17, -12.51]	
zolpidem-cognitive impairment	17.77	1.1	25.1%	17.77 [15.61, 19.93]	

- Alert or Direct Health Professional Communication
- Must have been on market 2 years prior and 1 year post index advisory
- Drug frequently used and had stable use in a 2-year pre-advisory period
- 24 advisories, including 23 for drugs with highest use and 1 to increase the number of advisories for newer drugs (on market <6 years prior to advisory)

RESULTS

- 24 advisories met the inclusion criteria, including 20 advisories without dose-related advice (Table I) and 4 dose-related advisories (Table 2).
- Advisories without dose-related advice were associated with a decline of -5.84% (-10.94, -0.74) in prescriptions per 100,000 population (Fig 2). Dose-related advisories were not associated with a change in defined daily doses per 100,000 population (Fig 3)
- One quarter of advisories in each analysis were followed by a decline in drug use of >10%.
- Meta-analyses showed a high degree of heterogeneity of effect among advisories.

Table 1. Index country and controls for advisories without dose-related advice

Advisory (drug-risk group)	Index country	Control
aripiprazole-impulse control disorders	CA	DK
azithromycin-cardiac arrhythmias	US	US*
clopidogrel-acquired haemophilia	DK	AU
febuxostat-epidermal and dermal conditions	UK	US*
finasteride-breast cancer male	UK	CA
fingolimod-PML	US	CA
insulin-glargine-neoplasm malignant	US	DK
isotretinoin-epidermal and dermal conditions	CA	DK
ketoconazole-adrenal gland disorders	US	US*
leflunomide-hepatotoxicity	US	AU
methylphenidate-sexual dysfunction	US	US*
mycophenolate-aplasia pure red cell	UK	US*
nitrofurantoin-lack of effect	UK	AU†
olmesartan-malabsorption	US	AU†
ondansetron-cardiac arrhythmias	US	AU†
pioglitazone-bladder cancer	US	US*
quetiapine-metabolic syndrome	UK	UK*
tacrolimus-neoplasm malignant	DK	CA
testosterone-cardiovascular disorder	CA	UK
topiramate-congenital anomaly	DK	CA

Total (95% Cl)100.0%-1.93Heterogeneity: Tau² = 236.96; Chi² = 347.26, df = 3 (P < 0.00001); l² = 99%</td>Test for overall effect: Z = 0.25 (P = 0.80)



CONCLUSIONS

- The association between regulatory drug safety advisories and changes in drug utilization was highly variable, and the average change in drug use was small.
- If the goal of regulatory drug safety advisories is to influence prescribing to minimize drug harms, current risk communication strategies will likely need to be enhanced.
- It would be valuable to better understand the factors which contribute to changes in drug utilization following drug safety advisories

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REFERENCES

- I. Perry LT, Bhasale A, Fabbri A, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. JAMA Intern Med 2019;179:982–4. doi:10.1001/jamainternmed.2019.0294
- 2. Dormuth C, Morrow R. Influence of safety advisories on drug utilization: an international interrupted time series analysis. Amsterdam, The Netherlands: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance 2019 (EUPAS30098). http://www.encepp.eu/encepp/viewResource.htm?id=30099

*historical controls +concessional beneficiaries (e.g., seniors and individuals with low income) CA=Canada DK=Denmark AU=Australia

3. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309.





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