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Impact of Regulatory Post-Market Safety Advisories on Prescribing Practices: An Interrupted Time Series Analysis

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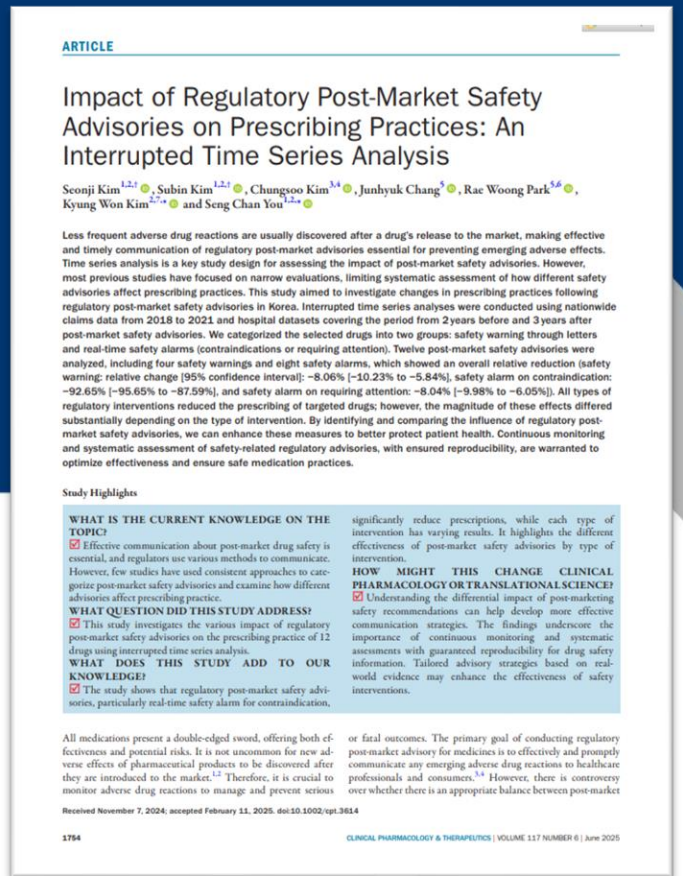

ARTICLE

Impact of Regulatory Post-Market Safety Advisories on Prescribing Practices: An Interrupted Time Series Analysis

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Less frequent adverse drug reactions are usually discovered after a drug's release to the market, making effective and timely communication of regulatory post-market advisories essential for preventing emerging adverse effects. Time series analysis is a key study design for assessing the impact of post-market safety advisories. However, most previous studies have focused on narrow evaluations, limiting systematic assessment of how different safety advisories affect prescribing practices. This study aimed to investigate changes in prescribing practices following regulatory post-market safety advisories in Korea. Interrupted time series analyses were conducted using nationwide claims data from 2018 to 2021 and hospital datasets covering the period from 2 years before and 3 years after post-market safety advisories. We categorized the selected drugs into two groups: safety warning through letters and real-time safety alarms (contraindications or requiring attention). Twelve post-market safety advisories were analyzed, including four safety warnings and eight safety alarms, which showed an overall relative reduction (safety warning: relative change [95% confidence interval]: −8.06% [−10.23% to −5.84%], safety alarm on contraindication: −92.65% [−95.65% to −87.59%], and safety alarm on requiring attention: −8.04% [−9.98% to −6.05%]). All types of regulatory interventions reduced the prescribing of targeted drugs; however, the magnitude of these effects differed substantially depending on the type of intervention. By identifying and comparing the influence of regulatory post-market safety advisories, we can enhance these measures to better protect patient health. Continuous monitoring and systematic assessment of safety-related regulatory advisories, with ensured reproducibility, are warranted to optimize effectiveness and ensure safe medication practices.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Effective communication about post-market drug safety is essential, and regulators use various methods to communicate. However, few studies have used consistent approaches to categorize post-market safety advisories and examine how different advisories affect prescribing practice.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study investigates the various impact of regulatory post-market safety advisories on the prescribing practice of 12 drugs using interrupted time series analysis.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The study shows that regulatory post-market safety advisories, particularly real-time safety alarm for contraindication, significantly reduce prescriptions, while each type of intervention has varying results. It highlights the different effectiveness of post-market safety advisories by type of intervention.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Understanding the differential impact of post-marketing safety recommendations can help develop more effective communication strategies. The findings underscore the importance of continuous monitoring and systematic assessments with guaranteed reproducibility for drug safety information. Tailored advisory strategies based on real-world evidence may enhance the effectiveness of safety interventions.

All medications present a double-edged sword, offering both effectiveness and potential risks. It is not uncommon for new adverse effects of pharmaceutical products to be discovered after they are introduced to the market.[1,2] Therefore, it is crucial to monitor adverse drug reactions to manage and prevent serious or fatal outcomes. The primary goal of conducting regulatory post-market advisory for medicines is to effectively and promptly communicate any emerging adverse drug reactions to healthcare professionals and consumers.[3,4] However, there is controversy over whether there is an appropriate balance between post-market

Received November 7, 2024; accepted February 11, 2025. doi:10.1002/cpt.3614

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Importance of monitoring ADRs

- All medications present a double-edged sword, offering **both effectiveness and potential risks**
- In United States, **adverse drug reaction (ADR)** is estimated to cause over 2 million hospitalizations and more than 100,000 deaths each year
- Thus, it is important to **monitor the effectiveness and safety of drugs** before and after the approval

ADR Group	No. of Studies	Total Patients Studied	Incidence of ADRs, %	95% CI
ADRs in Patients While in the Hospital (ADRIn)				
All severities	18	34 463	10.9	7.9-13.9
Serious	12	22 502	2.1	1.9-2.3
Fatal	10	28 872	0.19	0.13-0.26
Patients Admitted to the Hospital Due to an ADR (ADRAd)				
Serious†	21	28 017	4.7	3.1-6.2
Fatal	6	17 753	0.13	0.04-0.21

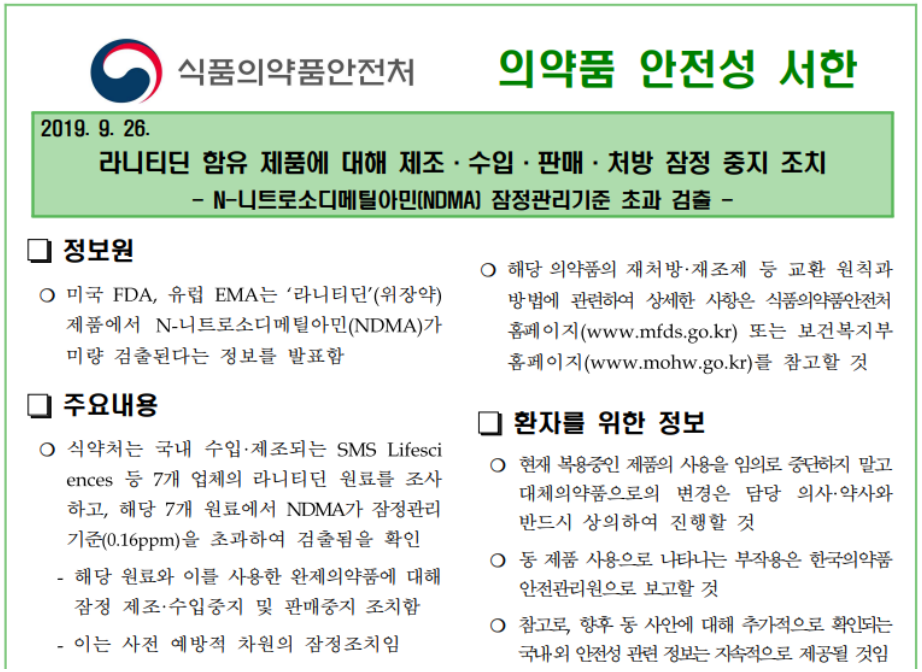
Needs for post-marketing drug surveillance

- To evaluate the effectiveness and safety of drugs, pre-approval clinical trials are widely conducted
- However, **pre-approval trials** are sometimes limited due to the **low generalizability** and the **lack of information on long-term effects**
- For about 10% of all drugs, **new and serious safety issues** are **identified after market approval**; It underscores the importance of post-marketing drug surveillance

Type of study	Strengths	Weaknesses
Randomized clinical trials	Best for studying an intervention Randomized High internal validity Unbiased distribution of confounders Evaluates efficacy	Expensive: time and money Short follow-up Volunteer bias Low generalizability to different or real-world population

Safety-related regulatory actions

- In response to postmarket drug surveillance, regulatory authorizations implement **safety-related regulatory actions** to **inform the updated safety information** to clinicians and patients
- Implementing **safety-related regulatory actions** can lead to **changes in prescribing patterns** or clinical practices



식품의약품안전처

의약품 안전성 서한

2019. 9. 26.

라니티딘 함유 제품에 대해 제조 · 수입 · 판매 · 처방 잠정 중지 조치

- N-니트로소디메틸아민(NDMA) 잠정관리기준 초과 검출 -

❑ 정보원

○ 미국 FDA, 유럽 EMA는 '라니티딘'(위장약) 제품에서 N-니트로소디메틸아민(NDMA)가 미량 검출된다는 정보를 발표함

❑ 주요내용

○ 식약처는 국내 수입·제조되는 SMS Lifesciences 등 7개 업체의 라니티딘 원료를 조사하고, 해당 7개 원료에서 NDMA가 잠정관리기준(0.16ppm)을 초과하여 검출됨을 확인

- 해당 원료와 이를 사용한 완제의약품에 대해 잠정 제조·수입중지 및 판매중지 조치함
- 이는 사전 예방적 차원의 잠정조치임

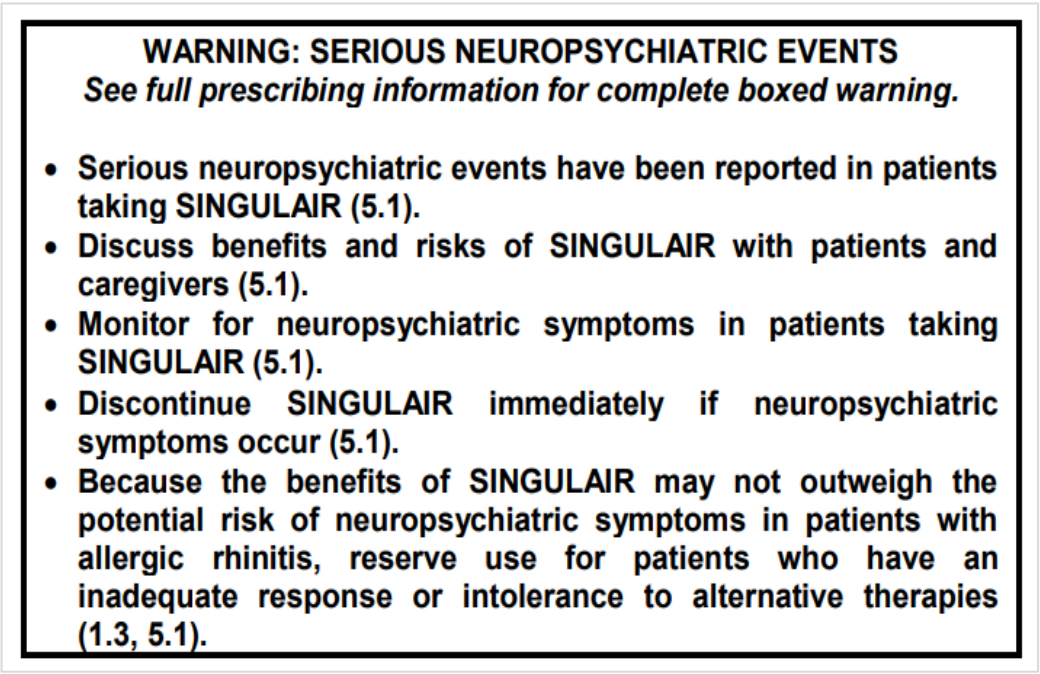
○ 해당 의약품의 재처방·재조제 등 교환 원칙과 방법에 관련하여 상세한 사항은 식품의약품안전처 홈페이지(www.mfds.go.kr) 또는 보건복지부 홈페이지(www.mohw.go.kr)를 참고할 것

❑ 환자를 위한 정보

○ 현재 복용중인 제품의 사용을 임의로 중단하지 말고 대체의약품으로의 변경은 담당 의사·약사와 반드시 상의하여 진행할 것

○ 동 제품 사용으로 나타나는 부작용은 한국의약품안전관리원으로 보고할 것

○ 참고로, 향후 동 사안에 대해 추가적으로 확인되는 국내외 안전성 관련 정보는 지속적으로 제공될 것임



WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

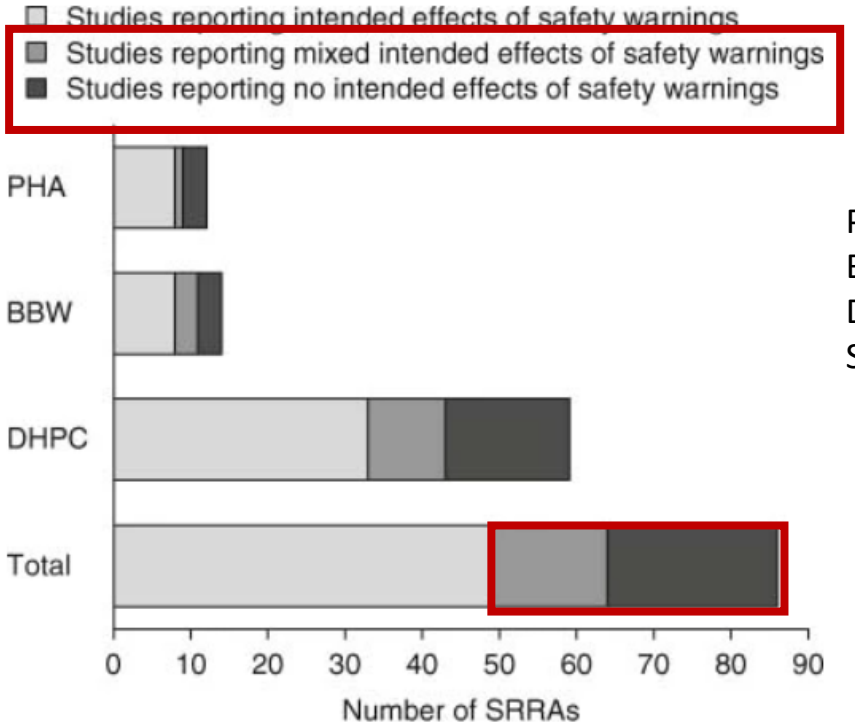
See full prescribing information for complete boxed warning.

- **Serious neuropsychiatric events have been reported in patients taking SINGULAIR (5.1).**
- **Discuss benefits and risks of SINGULAIR with patients and caregivers (5.1).**
- **Monitor for neuropsychiatric symptoms in patients taking SINGULAIR (5.1).**
- **Discontinue SINGULAIR immediately if neuropsychiatric symptoms occur (5.1).**
- **Because the benefits of SINGULAIR may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3, 5.1).**

Safety-related regulatory actions

- However, the **effectiveness of regulatory actions for drug surveillance is unclear** and their impact can vary by clinical indication or method of dissemination

- Thus, our study aims to access the **impact of the drug safety-related regulatory decisions on the changes in the prescribing patterns** using the nationwide claims data and multi-center electronic medical records (EMR) in Korea



PHA = Public Health Advisories;
BBW = Black Box Warning;
DHPC = Direct Healthcare Professional Communications;
SRRA = Safety-related regulatory actions

Piening, Sigrid et al. Drug safety, 2012.

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Data sources

- 6 Observational Medical Outcomes Partnership-Common Data Model (OMOP-CDM) based databases from Korea

Database	Patients (millions)	History
Claims data		
Health Insurance Review and Assessment Service (HIRA)	10	2018-2022
Electronic medical records		
Ajou University School of Medicine (AUSOM)	2.8	1993-2023
Kangdong Sacred Heart Hospital (KDH)	1.7	1986-2023
Kangwon National University Hospital (KWMC)	0.6	2003-2023
Wonkwang University Hospital (WKUH)	1.4	1998-2023
Yonsei University Health System (YUHS)	5.4	1997-2023

Definition of regulatory actions

- We selected **12 drugs regulatory-related post-market safety advisories** from 2016 to 2020

  1. **Safety warning**: systemic fluoroquinolones (FQs), febuxostat, ranitidine, and nizatidine
  2. **real-time safety alarm (contraindications in specific populations)**: mirtazapine and tramadol
  3. **real-time safety alarm (requiring attention in elderly patients)**: haloperidol, chlorpheniramine, dimenhydrinate, hydroxyzine, propiverine, and solifenacin

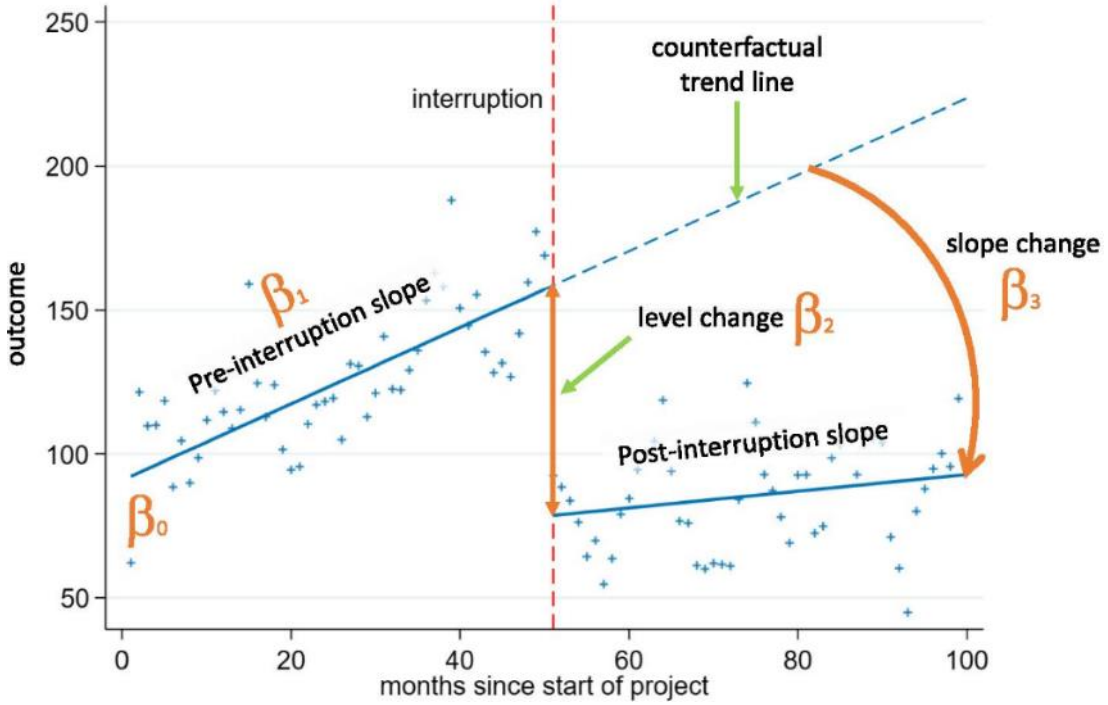
Study population and drug exposure

- The patients who were prescribed drugs with announced safety issues were included to compare the impact of post-market safety advisory
- The exposure was defined as the implementation of post-market safety advisories, with the intervention point defined as the next month of the introduction date of post-market safety advisories

Statistical analysis

- To assess changes in drug prescribing patterns before and after the regulatory decisions, we used **interrupted time series analyses using segmented linear regression model**

- The study period spanned from **January 2018 to December 2021 in the claims dataset**. For analysis using hospital data, we used data spanning **the 2 years before and 3 years after the publication of post-market safety advisories** for each drug



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Regulatory post-market advisories

- We selected **12 regulatory post-market advisories for analysis**, including four safety warnings issued via letter and eight real-time safety alarms during prescribing and dispensing (contraindications for specific populations or requiring attention for elderly patients)

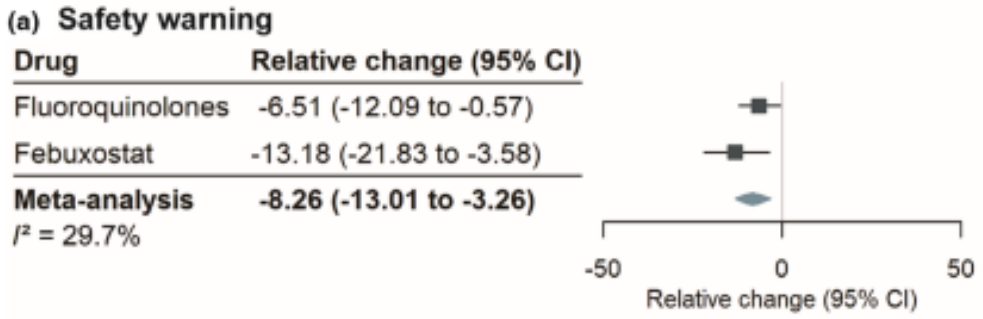
- Among the safety alarm, **75% of drugs required attention when prescribed to older adults**

Drug name	Date of post-market safety advisories	Types of post-market safety advisories
Fluoroquinolones	December 21, 2018	Safety warning (Aortic aneurysm and dissection)
Febuxostat	February 25, 2019	Safety warning (Death)
Ranitidine	September 26, 2019	Safety warning (Cancer – Excessive amounts of N-Nitrosodimethylamine)
Nizatidine	November 22, 2019	
Mirtazapine	December 30, 2016	Real-time safety alarm (contraindications in the younger than age 18 years)
Tramadol	22 May 2019	Real-time safety alarm (contraindications in the younger than age 12 years)
Haloperidol	August 31, 2018	Real-time safety alarm (Requiring attention when prescribed to older adults, aged ≥ 65 years)
Chlorpheniramine	September 24, 2020	
Dimenhydrinate		
Hydroxyzine		
Propiverine		
Solifenacin		

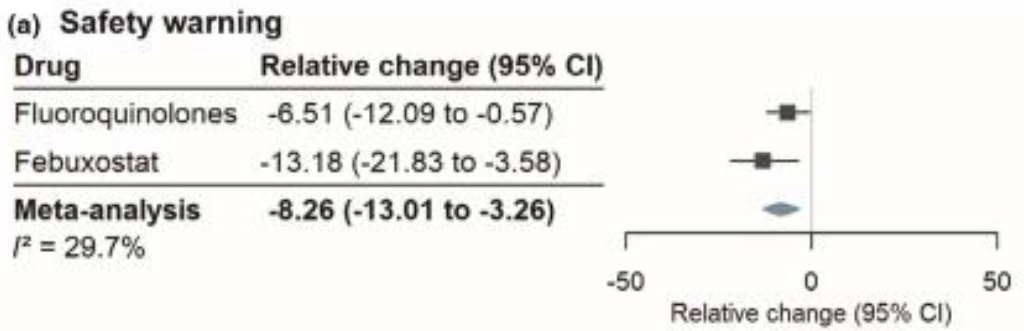
Changes in drug utilization related to safety warning

- The impact of **safety warning on drug utilization practice varied**, with effects ranging from −11% to +1%
- In the claims data, the result of meta-analysis indicated an average relative change in the number of prescriptions was −8% (95% confidence interval [CI] −10% to −6%)
- The results using meta-analysis showed the number of prescriptions decreased by −8% (95% CI −13.01% to −3.26% in the hospital

Claims data



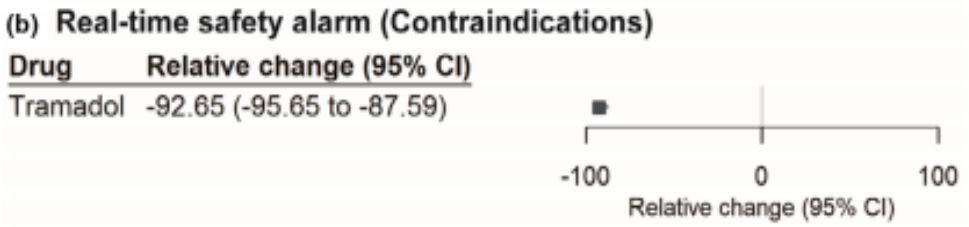
Hospital data



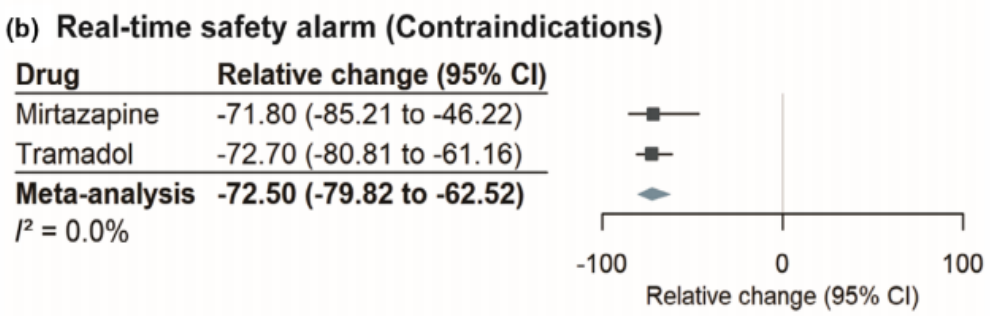
Changes in drug utilization related to safety alarm (Contraindication)

- In the case of nationwide claims data, the **number of prescriptions for tramadol** immediately **decreased by −93%** after the introduction of the real-time safety alarm
- In the hospital data, significant decreased in the number of prescriptions were observed in the meta-analysis (relative change [95% CI]: −73% [−80% to −63%]

Claims data



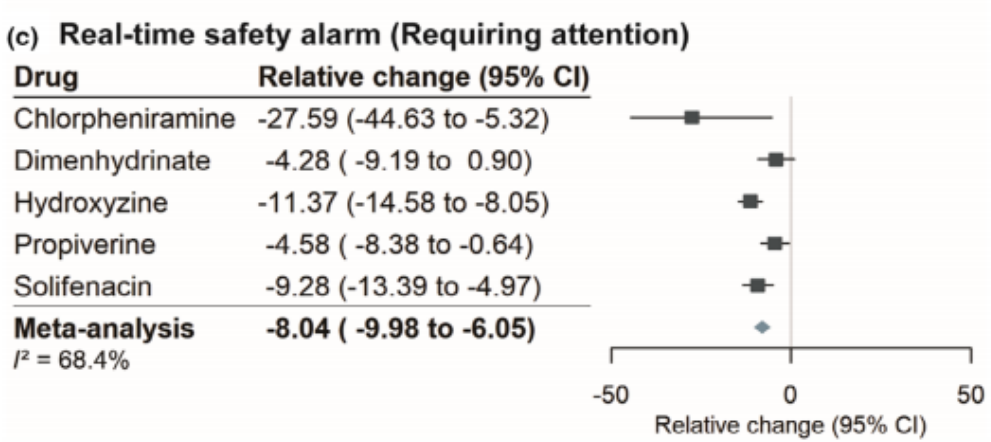
Hospital data



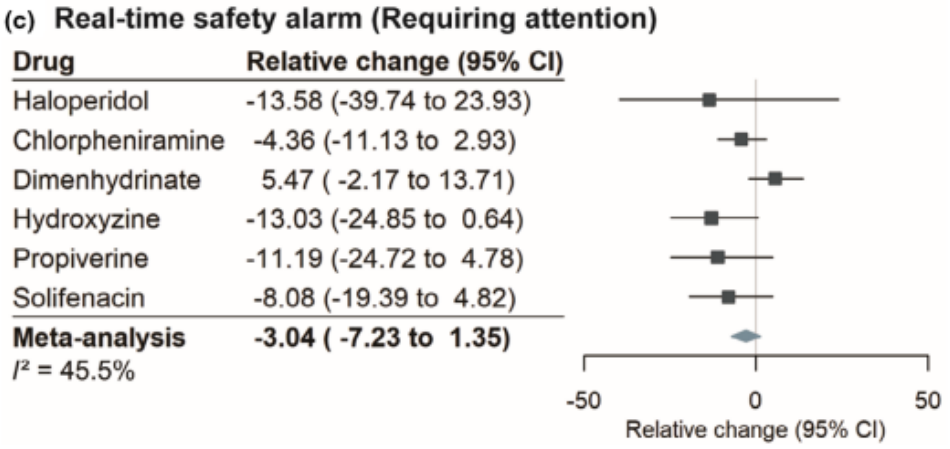
Changes in drug utilization related to safety alarm (Requiring attention)

- Among the real-time safety alarm drugs requiring caution when prescribed to older adults, the average change in the number of prescriptions showed a relative decrease of −8% (95% CI −10% to −6%) in the claims data
- The average relative change of the regulatory decisions was not significant using hospital data (relative change [95% CI]: −3% [−7% to +1%])

Claims data



Hospital data



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Summary of the results

- In our study, **the regulatory post-market safety advisories**, including four safety warnings and eight real-time safety alarms, **had an overall immediate effect** (safety warning: relative change [95% CI]: −8% [−10% to −6%], safety alarm on contraindications: −93% [−96% to −88%], and safety alarm on requiring attention: −8% [−10% to −6%]).
- However, the **impacts of post-market safety advisories varied by type of intervention**, particularly for safety warnings.

Summary of the results

- The **real-time safety alarm proved to be more effective** than the safety warning
- **Variation in impact** between the same communication methods **is an important factor to consider**

Type of post-market safety advisories		Drug	Pre-intervention trend	Level change	Trend change	Absolute change (95% CI)[a]	Relative change (95% CI)[b]
Safety warning		Fluoroquinolones	−0.71	+0.82	+0.06	17.11 (−847.18 to 881.40)	+0.82 (−14.78 to +19.28)
		Febuxostat	+2.82	−8.14	−1.33	−94.81 (−125.98 to −63.63)*	−8.14 (−10.36 to −5.85)*
		Ranitidine	–	–	–	−30147.99 (−32648.20 to −27647.78)*	–
		Nizatidine	+0.26	−10.86	+1.75	−1566.92 (−3126.86 to −6.98)*	−10.86 (−21.39 to +1.08)
Real-time safety alarm	Contraindications—Younger than age 12 years	Tramadol	−2.02	−92.65	−2.18	−93.53 (−115.78 to −77.29)*	−92.65 (−95.65 to −87.59)*
	Requiring attention – Older adults (aged ≥65 years)	Chlorpheniramine	−0.88	−27.59	+0.80	−3734.80 (−7948.46 to 478.87)	−27.59 (−44.63 to −5.32)*
		Dimenhydrinate	+0.39	−4.28	−0.38	−73.28 (−160.79 to 14.24)	−4.28 (−9.19 to +0.90)
		Hydroxyzine	+0.43	−11.37	−0.66	−223.92 (−299.35 to −148.48)*	−11.37 (−14.58 to −8.05)*
		Propiverine	+0.94	−4.58	−0.68	−18.65 (−42.35 to 5.05)	−4.58 (−8.38 to −0.64)*
		Solifenacin	+1.36	−9.28	−0.57	−55.81 (−84.21 to −27.41)*	−9.28 (−13.39 to −4.97)*

CI, confidence interval. [a]The units are the number of monthly prescriptions. [b]The units are percentage.
*p-value lower than 0.05.

Conclusion

- **The impacts of regulatory post-market safety advisories varied** by type of intervention. Even within the same type of advisories, the effects differed according to the contents and recommendations
- Understanding the differential impacts of post-market safety advisories can **inform the development of more effective communication strategies**
- Given the varying effects,
  - ✓Continuous monitoring and reproducibility assessment of safety-related regulatory decisions should be warranted by **researchers**
  - ✓**Regulatory agency** should determine how to communicate the risk information in a timely and effective manner.

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Github: https://github.com/ohdsi-studies/SAGE

DOI: 10.1002/cpt.3614

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