Impact of drug safety-related regulatory actions in South Korea

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Background

Due to constraints in sample size and the relatively short duration of pre-approval clinical trials, the effectiveness and safety of new drugs are not fully assessed at the time of market approval[1]. Therefore, unexpected safety issues can emerge in the post-market period. When new safety concerns arise, regulatory authorities employ drug safety-related regulatory actions to keep clinicians and patients updated.

In Korea, the Ministry of Food and Drug Safety (MFDS) implements a variety of safety-related regulatory actions. When serious safety issues are identified, the MFDS publishes the safety alert to healthcare professionals to disseminate new safety information and recommendations. Another well-established safety-related intervention is the drug utilization review (DUR) system. The DUR is a nationwide real-time system in Korea that sends alerts to the prescribers at the time of prescription based on predefined DUR criteria.

Although regulatory authorities implement regulatory interventions to change prescribing patterns and ultimately improve patients' clinical outcomes, the overall effect of safety-related actions remains unclear[2,3]. Thus, this study aimed to assess the impact of safety-related regulatory actions on clinical practice using a nationwide claims database in Korea.

Methods

We used the Health Insurance Review and Assessment Service Covid-19 Observational Medical Outcomes Partnership (HIRA Covid-19 OMOP) database from January 2018 to December 2021[4]. This database includes patients who were selected by age/sex-stratified extraction of 20% of the total patients eligible for National Health Insurance in 2021.

In this cross-sectional study, we defined safety-related regulatory actions as the issuance of safety alert or introduction of DUR by the MFDS. Table 1 shows the list and detailed information of selected drugs included in this study.

Table 1. List of drugs and information on safety-related regulatory actions in Korea

Drug	Introduction date	Type of regulatory actions	Note
Fluoroquinolones	21 December 2018	Safety alert	Reason for alert: Increased risk of aortic aneurysm and dissection

			Recommendations: Avoiding prescriptions for high-risk patients
Febuxostat	25 February 2019	Safety alert	Reason for alert: Increased risk of all-cause mortality Recommendations: Limiting the use to patients who are experience severe side effects from allopurinol or not treated effectively with allopurinol
Nizatidine	22 November 2019	Safety alert	Reason for alert: Detection of N-nitrosodimethylamine (NDMA), a probable human carcinogen Recommendations: Suspension of the marketing authorization
Tramadol	22 May 2019	DUR	Contraindication for younger than age 12 years
Chlorpheniramine	24 September 2020	DUR	Requiring attention when prescribed to older adults, aged ≥ 65 years
Dimenhydrinate			
Hydroxyzine			
Propiverine			
Solifenacin			

DUR, drug utilization review.

We included patients who were prescribed drugs subject to safety-related regulatory actions. For DUR-related drugs, only patients who met the specific DUR criteria for each drug were included. The exposure was defined as the introduction of safety-related regulatory actions. Since we extracted the prescription pattern on a monthly basis, the start of the exposure period was defined as the next month of the introduction date of safe-related regulatory actions. The outcome of interest was the average daily number of prescriptions per month.

To investigate whether prescribing patterns changed before and after the introduction of safety-related regulatory actions, we conducted interrupted time series analyses using segmented linear regression models. In the regression models, we included time as a continuous variable to indicate baseline trend, a binary indicator variable indicating before or after the exposure to measure the level change, and the continuous variable that counted the number of months after the exposure to measure the changes in the trend. Additionally, we included a month variable to adjust for seasonality. The dependent variable, average daily number of prescriptions per month, was log-transformed to normalize

its distribution and calculate the relative change. To test for first-order autocorrelation in the model, we examined the Durbin-Watson statistic. If first-order autocorrelation was detected, we used Prais-Winsten generalized least squares regression. Otherwise, we used ordinary least squares regression with Newey-West standard errors to account for potential autocorrelation. We used fixed- or random-effects meta-analyses to estimate the pooled relative change in level and trend. A two-tailed value of *p*-value less than 0.05 was considered statistically significant.

Definitions and codes used of this study are available at https://github.com/ohdsi-studies/SAGE.

Results

The changes in prescription patterns before and after the introduction of safety-related regulatory actions are shown in Table 2 and Figure 1. Regarding safety alert, the average level change in the number of prescriptions was – 8%, while there was no significant trend change (level change [95% CI]: 0.92 [0.90 – 0.94], trend change [95% CI]: 1.00 [0.98 – 1.03]). For tramadol, a DUR-listed drug for contraindication on age, the number of prescriptions immediately decreased by 93% after the introduction of DUR system. Among DUR-registered drugs which require caution when prescribed to older adults, the average level change in the number of prescriptions was -7% (level change [95% CI]: 0.93 [0.91 – 0.95], trend change [95% CI]: 0.99 [0.99 – 1.00]).

Table 2. Interrupted time series analyses of the impact of the safety-related regulatory actions on drug utilization in South Korea

Type of regulatory actions		**Drug**	**Pre-intervention trend**	**Level change (95% CI)**	**Trend change (95% CI)**
Safety alert		Fluoroquinolones	0.99	1.01 (0.85 – 1.19)	1.00 (0.96 – 1.03)
		Febuxostat	1.03	0.92 (0.90 – 0.94)*	0.99 (0.98 – 0.99)*
		Nizatidine	1.00	0.89 (0.79 – 1.01)	1.02 (1.01 – 1.03)*
DUR	Contraindication for younger than age 12 years	Tramadol	0.98	0.07 (0.04 – 0.12)*	0.98 (0.93 – 1.03)
	Requiring attention when prescribed to older adults, aged ≥ 65 years	Chlorpheniramine	0.99	0.72 (0.55 – 0.95)*	1.01 (0.98 – 1.04)
		Dimenhydrinate	1.00	0.96 (0.91 – 1.01)	1.00 (0.99 – 1.00)
		Hydroxyzine	1.00	0.89 (0.84 – 0.94)*	0.99 (0.99 – 1.00)*

		Propiverine	1.01	0.95 (0.92 – 0.99)*	0.99 (0.99 – 1.00)*
		Solifenacin	1.01	0.91 (0.87 – 0.95)*	0.99 (0.99 – 1.00)*

* *p*-values less than 0.05

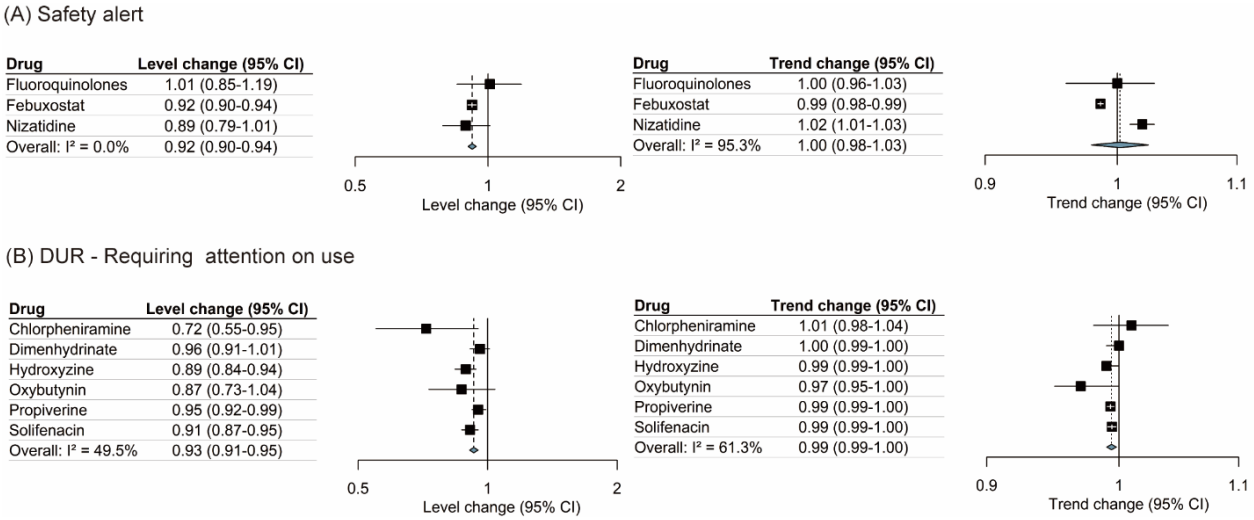

Figure 1. Results of meta-analyses to estimate the change in drug utilization patterns according to regulatory intervention type. DUR, drug utilization review.

Conclusion

The impacts of safety-related regulatory actions varied by type of intervention. For safety alerts, the effects differed according to the contents and recommendations of the safety alert letter. Providing the DUR information to prescribers led to a significant reduction in prescribing patterns in Korea. Given the varying effects, continuous monitoring and reproducibility assessment of safety-related regulatory actions are warranted. Conducting similar analyses across diverse countries would provide valuable insights and learnings to improve the effectiveness of such interventions on a global scale.

References

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