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Effect of acid suppressant medications on the laxative action of magnesium preparations in patients with opioid-induced constipation: A pharmacovigilance analysis of the FDA Adverse Event Reporting System

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Objective: Magnesium oxide is widely used for treating opioid-induced constipation, a serious analgesic-associated problem. Opioid analgesic users are often prescribed non-steroidal anti-inflammatory drugs, which are sometimes combined with acid suppressants to prevent gastrointestinal adverse events. Magnesium preparations combined with acid suppressants may diminish magnesium preparations' laxative effect. This study was aimed at evaluating the effect of magnesium preparations combined with acid suppressants on the incidence of opioid-induced constipation by using the Food and Drug Administration Adverse Event Reporting System. **Methods:** Adverse events were defined per the Medical Dictionary for Regulatory Activities; the term 'constipation (preferred term code: 10010774)' was used for analysis. After adjusting for patient background factors using propensity score matching, acid suppressants' effect on constipation incidence was evaluated in opioid users prescribed magnesium preparations alone as laxatives by using a test for independence. **Key Findings:** The Food and Drug Administration Adverse Event Reporting System contains 14,475,614 reports for January 2004 to December 2021. Significantly increased constipation incidence was related to magnesium preparations combined with acid suppressants, especially proton pump inhibitors ($P < 0.0001$, McNemar's test). **Conclusion:** Magnesium preparations combined with acid suppressants may diminish magnesium preparations' laxative effect; healthcare professionals should pay attention to this issue.

1. Introduction

When left untreated, pain diminishes all aspects of a patient's quality of life (QoL) (Katz 2002). Opioid analgesics are used for the management of cancer pain and chronic non-cancer pain in clinical practice. They cause opioid-induced bowel dysfunction, such as nausea, vomiting, abdominal distention, and opioid-induced constipation (OIC) (Muller et al. 2017). Unlike nausea and vomiting, OIC requires long-term management because the affected patients do not develop tolerance to the condition (Kumar et al. 2014). In a multi-center prospective observational cohort study of patients with cancer in Japan, approximately half of the patients developed OIC (Tokoro et al. 2019). In another study, more than half of the eligible patients experienced moderate-to-severe abdominal symptoms, such as bloating, due to constipation, and patients with constipation symptoms tended to have a lower QoL than did those without constipation (Christensen et al. 2016). The management of OIC, therefore, is important for maintaining good QoL in patients receiving opioid analgesics for pain management. Treatment for OIC generally includes exercise, fiber/fluid intake, and laxative use (Mesia et al. 2019). Laxatives have been recommended for preventing and treating OIC in several guidelines and by expert consensus (Fallon et al. 2018; Crockett et al. 2019; Farmer et al. 2019). Clinical guidelines for cancer pain management published by the Japanese Society for Palliative Medicine recommend osmotic or stimulant laxatives for the treatment of OIC (Mawatari et al. 2022). Osmotic laxatives, such as magnesium oxide (MgO), are widely used in Japan because of their long-term safety, low drug price, and effectiveness in the management of OIC (Ishihara et al. 2012; Mori et al. 2021).

The World Health Organization advocates a three-step analgesic ladder for the selection of analgesics according to pain intensity. In the first step of this ladder, non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), which cause gastrointestinal adverse events (AEs), are recommended. To prevent gastrointestinal AEs, acid suppressant medications (ASMs) such as proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H₂RAs) are generally prescribed in combination with NSAIDs. Patients whose pain has been controlled with opioid analgesics often use NSAIDs in combination with ASMs. MgO has a laxative effect under acidic conditions in the stomach. It is converted into magnesium chloride (MgCl₂) under acidic conditions. MgCl₂ is converted into magnesium bicarbonate, Mg(HCO₃)₂, by sodium hydrogen carbonate (NaHCO₃) contained in the pancreatic juice secreted from the duodenum and finally becomes magnesium carbonate (MgCO₃). Mg(HCO₃)₂ and MgCO₃ increase the osmotic pressure of the intestinal lumen fluid, promote the transfer of water into the intestinal lumen, and increase the water content and stool volume. Water-containing stool stimulates the intestinal wall and intestinal movement (Mori et al. 2021). Therefore, the co-administration of ASMs that inhibit gastric acid secretion may diminish the effects of MgO. This was evidenced in a previous study using retrospective results from a single institution, where ASMs increased the incidence of constipation in patients receiving low-dose MgO (< 2000 mg/day) (Ibuka et al. 2016). However, the aforementioned study was conducted in a single institution, had a limited sample size, and did not account for potential bias that may have resulted from other background factors that could influence the incidence of OIC; thus, further

Table 1: Patient demographics in reports in which opioid analgesics were prescribed

		Number of patients [n (%)]	
<i>Total</i>		285,744	
<i>Sex</i>	Male	116,862 (50.2)	
	Female	115,903 (49.8)	
<i>Age (years)</i>	0–69	85,693 (83.2)	
	≥ 70	17,289 (16.8)	
<i>Type of opioid analgesics</i>	Fentanyl	79,877 (16.5)	
	Hydrocodone	68,968 (14.3)	
	Hydromorphone	45,755 (9.5)	
	Methadone	14,672 (3.0)	
	Morphine	75,771 (15.7)	
	Oxycodone	135,709 (28.1)	
	Oxymorphone	21,835 (4.5)	
	Tapentadol	1,574 (0.3)	
	Tramadol	39,068 (8.1)	
	<i>Combination of laxative</i>	Presence	1,807 (0.6)
Absence		283,937 (99.4)	
<i>Laxative</i>	MPs [†] alone	447 (24.7)	
	Combination of MPs [†] and sennoside	112 (6.2)	
	PAMORAs [‡] alone	207 (11.5)	
	Sennoside alone	1,038 (57.4)	
	Combination of sennoside and PAMORA [‡]	3 (0.2)	
<i>Combination of ASMs[§]</i>	Presence	8,215 (2.9)	
	Absence	277,529 (97.1)	
<i>Type of ASMs[§]</i>	Proton pump inhibitors	Esomeprazole	1,893 (23.0)
		Lansoprazole	1,416 (17.2)
		Omeprazole	3,777 (46.0)
		Rabeprazole	363 (4.4)
	Histamine 2 receptor antagonist	Cimetidine	97 (1.2)
		Famotidine	479 (5.8)
		Ranitidine	1,129 (13.7)
		Roxatidine	3 (0.0)

[†]MPs: Magnesium preparations including magnesium citrate, magnesium hydroxide, magnesium oxide, and magnesium sulfate

[‡]PAMORA: Peripheral-acting mu-opioid receptor antagonist

[§]ASMs: Acid suppressant medications

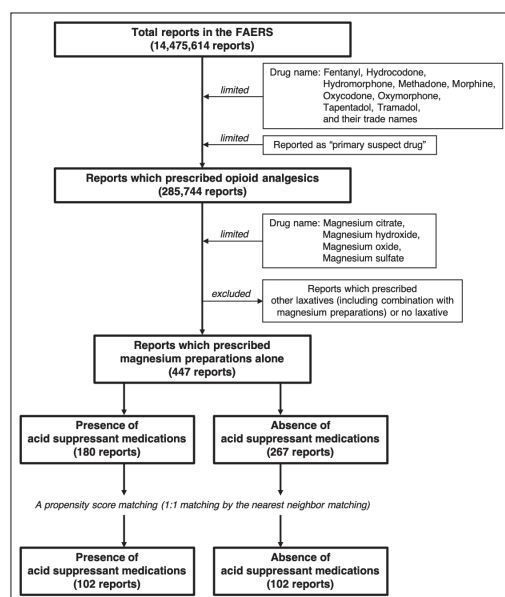


Fig. 1: Flowchart of data analysis

validation is needed regarding the external validity of the finding suggesting that ASMs diminish the laxative effect of MgO. Spontaneous reporting systems (SRSs) consist of large real-world datasets and can play a major role in the detection of novel and severe AEs that were not detected during pre-market clinical trials (Kasliwal 2012). The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is the largest primary database, with more than 15 million reports available to regulatory authorities for pharmacovigilance and represents an opportunity to investigate data that reflect the realities of clinical practice. Recently, propensity score (PS) matching has been used as an effective statistical method to reduce bias by equating groups based on possible confounders in SRS databases (Akimoto et al. 2016; Wang et al. 2020; Nakao et al. 2021). We reasoned that utilizing PS matching could provide a more accurate assessment of the impact of ASMs on reducing laxative effects of magnesium preparations (MPs) in patients who use opioids by adjusting for background factors that may influence OIC. This study aimed to evaluate the effect of the combination of MPs, including MgO, and ASMs on the incidence of OIC by using the FAERS database.

Table 2: Tests of independence for constipation and each factor before propensity score matching in reports in which magnesium preparations alone were prescribed

		Presence of constipation	Absence of constipation	P-values
<i>Number of patients</i>		68	379	
<i>Sex</i>	Male	21 (34.4%)	150 (45.0%)	0.1240 ^a
	Female	40 (65.6%)	183 (55.0%)	
<i>Age</i>	0–69	26 (52.0%)	167 (65.5%)	0.0704 ^a
	≥ 70	24 (48.0%)	88 (34.5%)	
<i>Fentanyl</i>	+	19 (27.9%)	153 (40.4%)	0.0524 ^a
	-	49 (72.1%)	226 (59.6%)	
<i>Hydrocodone</i>	+	2 (2.9%)	30 (7.9%)	0.2008 ^b
	-	66 (97.1%)	349 (92.1%)	
<i>Hydromorphone</i>	+	3 (4.4%)	24 (6.3%)	0.7823 ^b
	-	65 (95.6%)	355 (93.7%)	
<i>Methadone</i>	+	3 (4.4%)	39 (10.3%)	0.1740 ^b
	-	65 (95.6%)	340 (89.7%)	
<i>Morphine</i>	+	33 (48.5%)	96 (25.3%)	0.0001 ^{a*}
	-	35 (51.5%)	283 (74.7%)	
<i>Oxycodone</i>	+	38 (55.9%)	128 (33.8%)	0.0005 ^{a*}
	-	30 (44.1%)	251 (66.2%)	
<i>Tapentadol</i>	+	2 (2.9%)	24 (6.3%)	0.4004 ^b
	-	66 (97.1%)	355 (93.7%)	
<i>Tramadol</i>	+	4 (5.9%)	53 (14.0%)	0.0751 ^b
	-	64 (94.1%)	326 (86.0%)	
<i>Combination of acid suppressant medications</i>	+	37 (54.4%)	143 (37.7%)	0.0098 ^{a*}
	-	31 (45.6%)	236 (62.3%)	
<i>Proton pump inhibitors</i>	+	31 (45.6%)	102 (26.9%)	0.0019 ^{a*}
	-	37 (54.4%)	277 (73.1%)	
<i>H₂ receptor antagonists</i>	+	7 (10.3%)	52 (13.7%)	0.4421 ^a
	-	61 (89.7%)	327 (86.3%)	

^a Chi-squared test, ^b Fisher's exact test, *P < 0.05

2. Investigations and results

The FAERS database contains 14,475,614 reports submitted from January 2004 through December 2021. There were 285,744 reports of opioid analgesic prescription (Table 1). Oxycodone (n = 135,709 [28.1%]) was the most common opioid analgesic in these reports, followed by fentanyl (n = 79,877 [16.5%]) and morphine (n = 75,771 [15.7%]). There were 1,807 reports of laxative use (sennoside alone, n = 1,038 [57.4%]; MPs alone, n = 447 [24.7%]; and peripherally acting mu-opioid receptor antagonists (PAMORAs) alone, n = 207 [11.5%]). Further, there were 112 (6.2%) and 3 (0.2%) reports of MPs used in combination with a sennoside and a sennoside used in combination with PAMORAs, respectively. We identified 8,215 reports of ASM use. Regarding PPIs, the numbers of reports for omeprazole and esomeprazole were 3,777 (46.0%) and 1,893 (23.0%), respectively. As for H₂RAs, the numbers of reports for ranitidine and famotidine were 1,129 (13.7%) and 479 (5.8%), respectively.

On the basis of a previous study (Ibuka et al. 2016), we defined a subgroup in which an MP was prescribed alone as a laxative (Fig. 1). As a preliminary examination, a test of independence was performed with the presence of constipation as the dependent variable and patient background factors, such as age (0–69 years or ≥ 70 years), sex (male or female), presence of each opioid analgesic, and presence of ASMs as independent variables (Table 2). Presence of morphine (P = 0.0001), oxycodone (P = 0.0005), and ASMs (P = 0.0098), especially PPIs (P = 0.0019), was significantly associated with the incidence of constipation. Logistic regression analysis was performed with the presence or absence of ASMs as

the dependent variable and age, sex, and presence or absence of each opioid analgesic as the independent variables, and PS was calculated. The C-statistic was 0.65054 (data not shown). Based on the calculated PS, the nearest neighbor matching was performed, and 102 pairs (N = 204) were matched. Table 3 shows the comparison of the number of reports for each factor before and after PS matching. Standardized differences were slightly greater than 0.1 for tapentadol and hydrocodone but less than 0.1 for the other factors. After PS matching, a corresponding test was performed for the presence or absence of constipation and ASMs, and a significant association was observed (P < 0.0001) (Table 4). Moreover, when ASMs were classified into PPIs and H₂RAs and analyzed, a significant association was observed in PPIs (P < 0.0001).

3. Discussion

MgO is widely used as a first-line treatment for OIC in Japan; however, it has been reported that the combined use of ASMs may attenuate the laxative effect of MgO (Yamasaki et al. 2014; Ibuka et al. 2016). To the best of our knowledge, this is the first study to demonstrate the effect of ASM on reducing laxative effects of MPs in patients with OIC using real-world data from an SRS database based on the PS matching technique. Our findings reinforce those of previous studies in terms of external validity and covariate adjustment.

According to the reports in the FAERS database, the most prescribed laxative is sennoside, which is a common stimulant laxative that promotes peristalsis in the small and large intestines,

Table 3: Comparison of the number of reports for each factor before and after propensity score matching

		Before propensity score matching			After propensity score matching				
		ASM [†] (+)	ASM [†] (-)	P-values	Standardized	ASM [†] (+)	ASM [†] (-)	P-values	Standardized
		N=180	N=267		Difference	N=102	N=102		Difference
Age	≥ 70	58 (45.67)	54 (30.34)	0.0062 ^a	0.3198	37 (36.27)	41 (40.20)	0.5644 ^a	0.0809
	0–69	69 (54.33)	124 (69.66)			65 (63.73)	61 (59.80)		
Sex	Male	60 (37.50)	111 (47.44)	0.0507 ^a	0.2021	48 (47.06)	46 (45.10)	0.7788 ^a	0.0393
	Female	100 (62.50)	123 (52.56)			54 (52.94)	56 (54.90)		
Fentanyl	+	61 (33.89)	111 (41.57)	0.1015 ^a	0.1589	39 (38.24)	35 (34.31)	0.5602 ^a	0.0818
	-	119 (66.11)	156 (58.43)			63 (61.76)	67 (65.69)		
Hydrocodone	+	14 (7.78)	18 (6.74)	0.6768 ^a	0.0401	7 (6.86)	4 (3.92)	0.5374 ^b	0.1305
	-	166 (92.22)	249 (93.26)			95 (93.14)	98 (96.08)		
Hydromorphone	+	14 (7.78)	13 (4.87)	0.2055 ^a	0.1198	6 (5.88)	5 (4.90)	1.0000 ^b	0.0434
	-	166 (92.22)	254 (95.13)			96 (94.12)	97 (95.10)		
Methadone	+	14 (7.78)	28 (10.49)	0.3357 ^a	0.0942	12 (11.76)	14 (13.73)	0.6746 ^a	0.0591
	-	166 (92.22)	239 (89.51)			90 (88.24)	88 (86.27)		
Morphine	+	63 (35.00)	66 (24.72)	0.0186 ^a	0.2261	26 (25.49)	23 (22.55)	0.6230 ^a	0.0689
	-	117 (65.00)	201 (75.28)			76 (74.51)	79 (77.45)		
Oxycodone	+	69 (38.33)	97 (36.33)	0.6672 ^a	0.0414	47 (46.08)	48 (47.06)	0.8884 ^a	0.0196
	-	111 (61.67)	170 (63.67)			55 (53.92)	54 (52.94)		
Tapentadol	+	12 (6.67)	14 (5.24)	0.5284 ^a	0.0605	4 (3.92)	2 (1.96)	0.6828 ^b	0.1162
	-	168 (93.33)	253 (94.76)			98 (96.08)	100 (98.04)		
Tramadol	+	26 (14.44)	31 (11.61)	0.3783 ^a	0.0842	12 (11.76)	14 (13.73)	0.6746 ^a	0.0591
	-	154 (85.56)	236 (88.39)			90 (88.24)	88 (86.27)		

[†] ASM: Acid suppressant medication

^a Chi-squared test, ^b Fisher's exact test, ^c P < 0.05

Table 4: Tests of independence after propensity score matching in reports in which magnesium preparations alone were prescribed

		Presence of constipation	Absence of constipation	P-values
<i>Combination of acid suppressant medications</i>	+	18 (60.00)	84 (48.28)	< 0.0001 ^c
	-	12 (40.00)	90 (51.72)	
<i>Proton pump inhibitors</i>	+	13 (43.33)	61 (35.06)	< 0.0001 ^c
	-	17 (56.67)	113 (64.94)	
<i>H₂ receptor antagonists</i>	+	6 (20.00)	27 (15.52)	0.6744 ^c
	-	24 (80.00)	147 (84.48)	

^c McNemar's test, * P < 0.05

followed by MPs. This study showed an increase in the incidence of constipation associated with the combined use of ASMs and MPs, and this result is consistent with that of a previous study (Ibuka et al. 2016). As mentioned in the introduction, stomach acid is necessary for MgO to be effective as a laxative. Yamasaki et al. (2014) reported that among patients who had undergone surgery, defecation control was worse in patients using MgO and ASMs than in those using MgO alone and that MgO had lower solubility in a weakly acidic environment than in a strongly acidic environment in *in vitro* conditions. This mechanism is consistent with our results.

Our results specifically indicate that the combined use of MPs and PPI may diminish the laxative effect of MPs. H₂RAs specifically inhibit histamine 2 receptors in the gastric acid secretory pathway. In contrast, PPIs inhibit the proton pump, the final secretory pathway of gastric acid, and thus exhibit potent antacid effects. The more potent antacid effect of PPIs may be related to our findings. Further fundamental and epidemiologic studies are needed to clarify this mechanism; however, healthcare professionals need to be more careful when MPs and PPIs are used together.

Incidence of AEs and poor laxative efficacy have been reported in the case of osmotic or stimulant laxative use for the treatment of OIC (Emmanuel et al. 2017). PAMORAs are a new type of laxative that fundamentally improves OIC by specifically binding to mu-opioid receptors in the intestinal tract. In a randomized

controlled trial conducted among patients using opioid analgesics in Japan, PAMORAs users showed better complete defecation rates and QoL than did MgO user (Ozaki et al. 2022). Several guidelines have recommended the use of PAMORAs for patients in whom conventional laxatives fail (Fallon et al. 2018; Crockett et al. 2019; Mawatari et al. 2022). However, the long-term safety of PAMORAs has not yet been established. Therefore, MgO use may continue in the treatment of OIC, and its appropriate use remains an important topic in Japanese clinical practice.

This study has several limitations. An SRS, such as the FAERS database, is subject to various biases, including a lack of information on the total number of patients to whom medicines were administered, lack of a clear denominator, under-reporting, over-reporting, and missing data. For example, Alatawi and Hansen (2017) evaluated the under-reporting in FAERS and reported that the range varies widely depending on the nature of the drug. This high under-reporting rate is a limitation of the FAERS analysis. Therefore, careful attention should be paid to the interpretation of the results of our study. In this study, PS matching was performed to mitigate the effect of confounding factors and enhance the robustness of the results. However, it is important to note the presence of unmeasured confounders because only factors that can be obtained from FAERS can be included. Recent approaches have yielded multiple techniques to address these challenges in high-dimensional contexts (Hripsak et al. 2016; Schuemie et al. 2018; Tian

et al. 2018). However, utilizing these novel analytical methods is deemed a topic of future concern. In addition, the FAERS database has accumulated reports from the U.S. and other countries around the world. Nevertheless, the U.S. accounts for the majority of the reports, with Japan accounting for only a small percent of the total. It should be noted that MgO has been widely used as a laxative in East Asian countries, including Japan (Mori et al. 2021), and this trend of use may not be in line with that in Western countries. This study suggests that ASMs, especially PPIs, may attenuate the laxative effect of MPs in patients with OIC. Because the combination of MgO and ASMs in opioid users is a frequent occurrence in Japanese clinical practice, the results of this study indicate that healthcare professionals should pay attention to constipation management in patients receiving opioids for pain control.

4. Experimental

4.1. Data source

FAERS data from January 2004 to December 2021 are publicly available and can be downloaded from the FDA website (www.fda.gov). The data are anonymized, and personal information is deleted from FAERS reports. Each report was given an identification (ID) number to distinguish each individual when recorded in the database. Therefore, it is not possible to identify the individual being reported. The database comprises seven files: DEMO, DRUG, REAC, OUTC, RPSR, INDI, and THER. DEMO contains basic patient information such as sex, age, date of AE occurrence or initiation, and country where the event occurred; DRUG contains information such as drug name, route of administration, and dosage; REAC contains AE names; OUTC contains case outcomes; RPSR contains AE information sources; INDI contains indications; and THER contains information such as the start date of administration, end date of administration, and duration of therapy. The seven data tables were imported into the relational database (FileMaker Pro Advanced 17 (FileMaker, Santa Clara, CA, USA)). FDA recommendations (www.fda.gov) to exclude duplicate reports for patients were followed, and the most recent case numbers were used to identify and exclude such records from the analysis.

4.2. Definition of AEs and drug selection

AEs were identified using their preferred terms (PTs) determined according to the Medical Dictionary for Regulatory Activities (MedDRA). Since this study focused on constipation as an AE, the term 'constipation (PT code: 10010774)' was used as a PT. Depending on the role of drugs in AEs, drugs are classified as 'primary suspect drug', 'secondary suspect drug', 'concomitant', and 'interacting' in the FAERS. Reports in which opioid analgesics were registered as primary suspect drugs were extracted for this study. The FAERS database contains both generic and trade names. To extract reports from the FAERS database, generic and trade names of 27 opioid analgesics listed as common opioid analgesics used for cancer pain by the American Cancer Society (www.cancer.org) were used. The generic names for (PAMORAs) were those listed as commonly used PAMORAs in a review article (Mesia et al. 2019), and the corresponding trade names were obtained by referring to Drug@FDA (www.fda.gov), which contains information about drugs, including biological products, approved for human use in the United States. The generic names of the ASMs used in this analysis were obtained from a previous study (Ibuka et al. 2016), and their trade names were obtained by referring to Drug@FDA. MgO is the most commonly used magnesium preparation in East Asian countries such as Japan, China, and Taiwan, whereas magnesium hydroxide is most commonly used in Korea and the United States. On the other hand, in European countries, magnesium citrate, magnesium hydroxide, magnesium sulfate, and MgO are used as salt laxatives (Mori et al. 2021). Since this study used FAERS, which accumulates reports from all over the world, 'magnesium citrate', 'magnesium hydroxide', and 'magnesium sulfate' as well as 'MgO' were included in this study. These preparations are collectively defined as MPs in this manuscript.

4.3. Statistical analysis

Data analyses were performed using JMP Pro 16.0 (SAS Institute, Cary, NC, USA). In observational studies, background factors often differ between groups receiving a particular treatment and those not receiving it. Rosenbaum and Rubin defined PS as the probability of treatment assignment conditional on the baseline covariate (Rosenbaum et al. 1983). The PS is a balancing score, and for participants with the same PS, the distribution of observed baseline covariates is consistent between the groups that receive a particular treatment and those that do not. PS matching can estimate the average treatment effect for the treated by matching patients in the treated and non-treated groups with approximate PSs (Peter 2011). Logistic regression analysis was performed to calculate the PS considering the use of ASMs as the dependent variable, and patient background factors (age, sex, and type of co-administered opioids) that could be collected from FAERS as independent variables. The nearest neighbor-matching method was used for 1:1 matching, and the caliper value was set at 0.2. The standardized difference was used for checking the balance of patient background before and after PS matching. A standardized difference of < 0.1 was considered an appropriate covariate balance. Chi-square test or Fisher's exact test was used to evaluate the independence for the non-corresponding 2×2 contingency tables. The McNemar test was used to assess corresponding data. The significance level was set at 0.05.

4.4. Ethical approval

Ethical approval was not sought because this was an observational study without any research participants. All results were obtained from data openly available online from the website of the FDA (www.fda.gov). All data from the FAERS database were fully anonymized by the regulatory authority before we accessed them. No consent to participate was required owing to the retrospective nature of this study.

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Author contributions: MM, AS, and MN contributed to the overall concept and design of the study. MM and MN wrote the main manuscript text. MM, MI, RS, WW, KO, FG, KM, and SH conducted data extraction and statistical analysis. MI, TS, HT, SN, and SS contributed to the data validation process. MN, AS, and KI revised the article critically for important intellectual content. All authors have reviewed the manuscript.

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