Original Research

A systematic analysis and data mining of opioid-related adverse events submitted to the FAERS database

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Impact Statement

The potent efficacy of opioids in pain management is accompanied by a spectrum of adverse effects. The prevailing opioid epidemic, marked by escalating usage and overdose fatalities, presents a critical nationwide crisis, impacting public health, socio-economic stability, and overall well-being in the United States. While researchers have delved into comprehending opioid-linked adverse events (AEs), a comprehensive inquiry encompassing diverse opioids remains absent. This study employs Empirical Bayes Geometric Mean (EBGM), a widely endorsed Bayesian technique for disproportionality analysis, to unearth potential AE signals within FDA Adverse Events Reporting System (FAERS) concerning distinct opioid classes. By scrutinizing these safety cues, we undertake a comparative assessment to furnish a panoramic outline of opioid-associated AEs across all 13 Food and Drug Administration (FDA)-approved prescription opioid classes. Through data mining and comparative analysis, distinctive patterns of correlated AEs emerge within varied opioid categories. These insights hold promise for refining pain management by offering guidance in the selection of appropriate opioid medications within clinical realms.

Abstract

The opioid epidemic has become a serious national crisis in the United States. An indepth systematic analysis of opioid-related adverse events (AEs) can clarify the risks presented by opioid exposure, as well as the individual risk profiles of specific opioid drugs and the potential relationships among the opioids. In this study, 92 opioids were identified from the list of all Food and Drug Administration (FDA)-approved drugs, annotated by RxNorm and were classified into 13 opioid groups: buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol. A total of 14,970,399 AE reports were retrieved and downloaded from the FDA Adverse Events Reporting System (FAERS) from 2004, Quarter 1 to 2020, Quarter 3. After data processing, Empirical Bayes Geometric Mean (EBGM) was then applied which identified 3317 pairs of potential risk signals within the 13 opioid groups. Based on these potential safety signals, a comparative analysis was pursued to provide a global overview of opioid-related AEs for all 13 groups of FDA-approved prescription opioids. The top 10 most reported AEs for each opioid class were then presented. Both network analysis and hierarchical clustering analysis were conducted to further explore the relationship between opioids. Results from the network analysis revealed a close association among fentanyl, oxycodone, hydrocodone, and hydromorphone, which shared more than 22 AEs. In addition, much less commonly reported AEs were shared among dihydrocodeine, meperidine, oxymorphone, and tapentadol. On the contrary, the hierarchical clustering analysis further categorized the 13 opioid classes into two groups by comparing the full profiles of presence/absence of AEs. The results of network analysis and hierarchical clustering analysis were not only consistent and cross-validated each other but also provided a better and deeper understanding of the associations and relationships between the 13 opioid groups with respect to their adverse effect profiles.

Keywords: Prescription opioids, AEs, FAERS, data mining, potential safety signals

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Introduction

Opioids such as morphine, oxycodone, and methadone have been commonly prescribed to treat various types of pain from short-term to chronic and opioid use disorder (OUD) as well. Prescription opioid use (POU) may cause a variety of adverse events (AEs) ranging from mild to serious illness (including overdose deaths). Different from other common painkillers such as ibuprofen or acetaminophen, opioids can produce euphoria in addition to pain relief. This imparts a high potential risk for addition to opioids which can lead to misuse or overdose.[1] The National Institute on Drug Abuse

(NIDA) reported that there were nearly 80,411 opioid overdose deaths in 2021 in the United States alone.[2] Moreover, the Centers for Disease Control and Prevention (CDC) estimated that prescription opioid misuse has cost the US $78.5 billion/year in economic loss due to health-care, lost productivity, addiction treatment, and criminal justice involvement.[3] Therefore, the consistent increase in opioid use and overdose deaths (https://www.cdc.gov/opioids/basics/epidemic.html) makes the current opioid epidemic a serious national crisis that affects public health as well as the social and economic welfare in the United States.

Indepth analyses of POU-related AEs have been conducted using different data sources.[4–9] For example, a study on millions of medical reports in the Premier database revealed that POU could increase cardiopulmonary and respiratory arrest risks.[6] Meanwhile, the US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) has been an important data source for analyzing different aspects of POU-related AEs such as age and sex of patients and year and type of AE reports.[4,7] FAERS is the largest AE database containing over 16 million reports from 1969 to the present to support the FDA's postmarketing safety surveillance program.[10–13] AE reports for currently marketed US drugs and therapeutic biologic products are submitted mandatorily by pharmaceutical companies and voluntarily by patients, health-care professionals, and the general public. Numerous studies have been conducted on the database to assess postmarketing reporting rates for drug safety review and risk assessments.[14–18] In addition, FAERS offers vast opportunities for researchers to apply data mining and machine learning algorithms to monitor and predict AEs, as well as identify the hidden associations between various drugs and AEs.[19] Currently, no comprehensive study has provided a global view of AEs with various opioids from the available postmarketing databases. Therefore, this study initiated data mining of the FAERS database to clarify the similarities/differences between AEs reported for different types of opioids (e.g. morphine, oxycodone, and fentanyl).

Data mining is essential to support data processing in the FAERS, transforming data into meaningful knowledge to inform product safety and identify new AE signals. Disproportionality analysis approaches are generally used to discover potential safety signals from large databases such as FAERS.[20–24] These approaches quantify the "unexpectedness" of a drug and AE association, where the "unexpectedness" is calculated by comparing the observed reporting rates between each drug-event pair to an expected reporting rate derived from the combination of all drugs and AEs in the database. In this work, the FDA-approved opioid drugs in FAERS were normalized and grouped into 13 classes, identified as buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol. The Empirical Bayes Geometric Mean (EBGM),[20] a representative Bayesian statistical method widely used for disproportionality analysis, was then applied to detect potential significant AE signals for the different opioid classes. Thousands of drug-AE pairs were identified as potential safety signals, with the top 10 most frequently observed AEs for each opioid class reported. Network analysis and hierarchical clustering of the AEs further revealed differences and similarities between the opioid classes. The results provide a systematic view of the potential AEs associated with different opioid classes and might be beneficial for determining the appropriate prescription and safe use of opioids by clinicians and patients.

Materials and Methods

Data retrieval and pre-processing

First, the list of all FDA-approved drugs[25] was downloaded, and then 92 opioids were identified which were categorized into 13 opioid groups: buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol (Supplemental Table S-1). All the AE reports in FAERS from 2004, Quarter 1 to 2020, Quarter 3[13] were then downloaded and the drug-AE extracted. Every case of an AE that was associated with a drug was considered a pair, and the duplicated pairs were eliminated. AEs were coded as Preferred Terms (PTs) in MedDRA.[26] RxNorm,[27,28] produced by the National Library of Medicine, was applied to provide a standardized nomenclature for clinical drugs. Finally, the extracted opioid-AE pairs were used to construct the data set.

Potential safety signal detection

To identify potential safety signals from the collected data set, EBGM,[20] a representative Bayesian method for signal detection, was utilized. In EBGM, the co-occurrence numbers of drug-AE pairs are considered independent Poisson random variables. Specifically, the variable's mean for ith drug and jth AE is defined as $\mu_{ij} = \lambda_{ij} \times E_{ij}$, where λ_{ij} denotes the reporting ratio RR_{ij} and E_{ij} denotes the expected co-occurrence number under the null hypothesis H_0: $\lambda_{ij} = 1$.[19] Therefore, the Reporting Ratio (RR), a commonly used statistics method for signal detection,[21,23] is based on the degree of disproportionate reporting of an AE for a product of interest (e.g. drug) compared to this same event for all other products in the given data set, the EBGM calculation is conceptually similar to that of the RR but uses Bayesian shrinkage and stratification.

For implementation, the same approaches as in previous work were applied.[19] Specifically, the R package "mederrRank" was used to calculate the maximum likelihood estimation (MLE) in the EBGM.[29] The ending condition used for the MLE procedure was when the difference of log-likelihoods after two successive iterations was less than 0.01 or the number of iterations in the MLE procedure was greater than 1000. An extra function in the "mederrRank" package was also implemented to compute EB05 values, which were the lower bounds of the two-sided 90% confidence interval (CI) around EBGM values.[30] The potential safety signals were identified when the co-occurrence for a drug-AE pair was greater than or equal to 3 and the EB05 value was greater than 1 instead of 3,[19] to avoid missing any potential signals. The identified potential signals were then analyzed and compared.

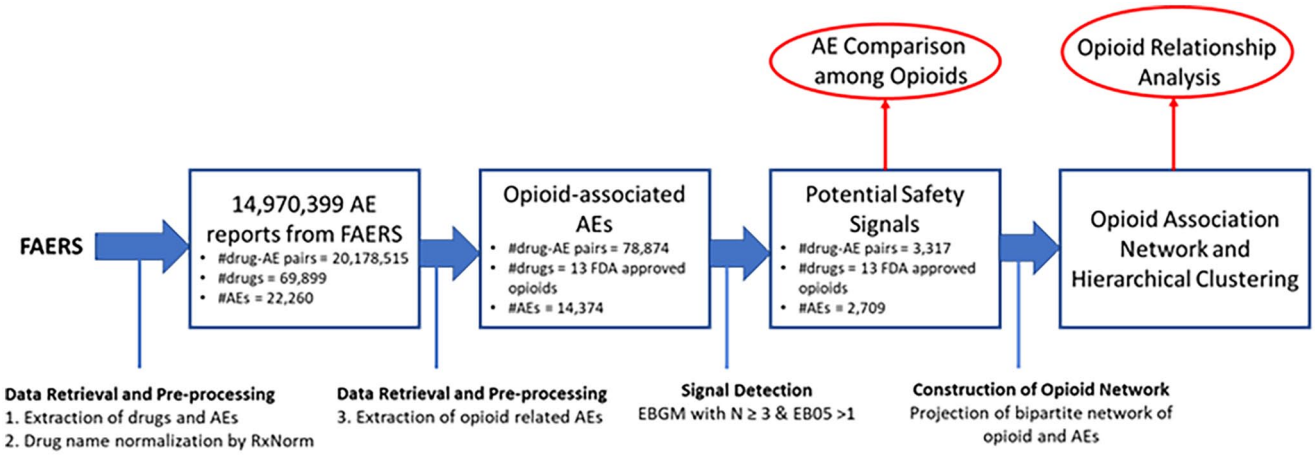

Figure 1. Study flowchart.

Association network and hierarchical clustering

The opioid association network was built on the identified potential safety signals using the same approach described in previous work.[19] Briefly, the "graph.constructor" function in the R package "igraph"[31] was first used to build the opioid-AE association network. This network was an unweighted and undirected bipartite graph, where two different types of vertices were opioids and AEs while edges connected opioids and their paired AEs. The "bipartite.projection" function was then applied to build the opioid association network. This was a weighted but undirected graph, where vertices were opioids and a weighted edge connected two opioids if they shared the same AEs, with the weight indicated as the number of their shared AEs.

To explore the relationship between opioids based on their whole AEs, the hierarchical clustering analysis was conducted on an "opioid-profile" matrix, which was a binary matrix with a 1/0 representing the presence/absence of an AE for a given opioid. The Jaccard distance and the average linkage method were used to calculate the distance between opioids. The cluster dendrogram of opioids was finally generated by an agglomerative clustering algorithm in the R package. Opioids sharing more AE presences/absences were clustered together.

Results

Overall statistics of data retrieval

The flowchart of this study is shown in Figure 1. A total of 14,970,399 AE reports were retrieved and downloaded from FAERS from 2004, Quarter 1 to 2020, Quarter 3. After normalizations, 20,178,515 pairs of drug AEs were obtained, originating from 69,889 unique drugs and 22,260 AEs. The number of drug-AE pairs was larger than the number of reports since there could be multiple drug-AE pairings in one AE report. Next, 78,874 pairs of opioid-AEs were extracted, encompassing 13 FDA-approved opioid groups and 14,374 unique AEs. Among these 78,874 pairs, only 3317 pairs were identified as the potential safety signals according to the results of EBGM and EB05 analysis, which included 13 FDA-approved opioid groups and 2709 unique AEs.

Table 1. AE statistics for 13 FDA-approved opioid groups.

	Prescription opioids	AE reports	%	Unique AEs
Natural	Codeine	19,200	5.3	264
	Morphine	25,047	6.9	318
Semi-synthetic	Dihydrocodeine	1106	0.3	73
	Hydrocodone	56,126	15.6	494
	Hydromorphone	39,229	10.9	350
	Oxycodone	129,800	36.0	510
	Oxymorphone	4553	1.3	52
Synthetic	Buprenorphine	11,125	3.1	188
	Fentanyl	28,109	7.8	416
	Meperidine	458	0.1	57
	Methadone	5442	1.5	191
	Tapentadol	2215	0.6	91
	Tramadol	38,035	10.6	313
	Total	360,445	100	2709

AE: adverse event; FDA: Food and Drug Administration.

All of the following analyses were pursued on these identified potential safety signals.

The statistics of the retrieved AE reports for the 13 opioid groups is shown in Table 1. The 13 opioid groups belonged to three categories: natural, semi-synthetic, and synthetic.[32,33] The number of retrieved AE reports with potential significance varied largely. Among 360,445 reports, 129,800 (36.0%) were documented with oxycodone covering 510 unique AEs; while 56,126 (15.6%) with hydrocodone covering 494 unique AEs, 39,229 (10.9%) with hydromorphone covering 350 unique AEs, and 38,035 (10.6%) with tramadol consisting of 313 unique AEs. Meperidine had the smallest number of reports (458 or 0.1%) with potential significance, and only 57 unique AEs were reported.

AE comparison among opioids

Table 2 lists the top 10 most reported AEs for each of the 13 opioids. The columns "*N*" and "%" are the numbers and percentages of the reported AEs with potential significance. Note that for all 13 opioids, the top 10 AEs occupy almost 50% of the total number of reports (i.e. 168,743 out of 360,445), indicating the importance of these major AEs derived from

Table 2. Top 10 frequently reported AEs for each opioid group.

	N	%		*N*	%
Buprenorphine			**Methadone**		
Vomiting	2919	26.24	Convulsion	389	7.15
Convulsion	839	7.54	Thrombocytopenia	242	4.45
Withdrawal syndrome	747	6.71	Agitation	217	3.99
Abortion spontaneous	453	4.07	Myocardial infarction	205	3.77
Irritability	449	4.04	Lethargy	185	3.4
Premature delivery	435	3.91	Premature delivery	178	3.27
Nervousness	300	2.7	Blood glucose increased	155	2.85
Cardiac arrest	244	2.19	Nystagmus	147	2.7
Joint swelling	229	2.06	Muscular weakness	145	2.66
Alcohol abuse	225	2.02	Sedation	136	2.5
Codeine			**Morphine**		
Drug abuse	1683	8.77	Anxiety	2563	10.23
Erythema	1053	5.48	Abdominal pain	1857	7.41
Alanine aminotransferase increased	952	4.96	Confusional state	1851	7.39
Migraine	817	4.26	Gait disturbance	1169	4.67
Suicidal ideation	720	3.75	Condition aggravated	1126	4.5
Hyponatremia	614	3.2	Bone disorder	1066	4.26
Swelling face	586	3.05	Neuropathy peripheral	848	3.39
Renal failure acute	576	3	Mental status changes	686	2.74
Neutropenia	554	2.89	Memory impairment	621	2.48
Hypercalcemia	527	2.74	Hypersensitivity	600	2.4
Dihydrocodeine			**Oxycodone**		
Fatigue	135	12.21	Fall	10,647	8.2
Renal failure acute	74	6.69	Pneumonia	9427	7.26
Premature baby	68	6.15	Constipation	9425	7.26
Depressed level of consciousness	50	4.52	Pruritus	5060	3.9
Chest pain	41	3.71	Cough	4861	3.74
Palpitations	41	3.71	Muscle spasms	4809	3.7
Pulmonary edema	41	3.71	Infection	4635	3.57
Emotional distress	33	2.98	Chronic kidney disease	4112	3.17
Aggression	29	2.62	Gastroesophageal reflux disease	3540	2.73
Contraindicated product administered	29	2.62	Pleural effusion	3197	2.46
Fentanyl			**Oxymorphone**		
Emotional distress	1370	4.87	Drug dependence	2525	55.46
Serotonin syndrome	1055	3.75	Accidental overdose	1193	26.2
Pulmonary edema	1026	3.65	Crying	135	2.97
Hemoglobin decreased	925	3.29	Fall	93	2.04
Platelet count decreased	882	3.14	Muscle spasms	70	1.54
Hallucination	849	3.02	Loss of consciousness	61	1.34
Atrial fibrillation	825	2.94	Pulmonary edema	55	1.21
Hypokalemia	766	2.73	Confusional state	47	1.03
Gastroesophageal reflux disease	742	2.64	Intentional drug misuse	42	0.92
Convulsion	702	2.5	Amnesia	37	0.81
Hydrocodone			**Tapentadol**		
Diabetes mellitus	2432	4.33	Headache	270	12.19
Amnesia	2305	4.11	Medication error	230	10.38
Hemoglobin decreased	2257	4.02	Depression	217	9.8
Sleep apnea syndrome	1713	3.05	Anxiety	184	8.31
Tachycardia	1658	2.95	Condition aggravated	104	4.7
Hemorrhage	1629	2.9	Dehydration	73	3.3
Cardiomegaly	1570	2.8	Peripheral swelling	67	3.02
Surgery	1551	2.76	Heart rate increased	61	2.75
Dental caries	1454	2.59	Inappropriate schedule of drug administration	52	2.35
Drug effect decreased	1406	2.51	Respiratory depression	50	2.26
Hydromorphone			**Tramadol**		
Overdose	16,574	42.25	Malaise	5147	13.53
Pneumonia	2620	6.68	Toxicity to various agents	4016	10.56
Emotional distress	1068	2.72	Rash	3340	8.78
Feeling abnormal	1003	2.56	Loss of consciousness	2378	6.25
Synovitis	802	2.04	Contusion	1717	4.51

(Continued)

Table 2. (Continued)

	N	%		N	%
Hypersensitivity	779	1.99	Hypokalemia	1058	2.78
Coma	688	1.75	Coronary artery disease	953	2.51
Product use issue	616	1.57	Burning sensation	892	2.35
Atrial fibrillation	614	1.57	Cognitive disorder	714	1.88
Intervertebral disk protrusion	595	1.52	Tinnitus	688	1.81
Meperidine					
Febrile neutropenia	60	13.1			
Pulmonary embolism	43	9.39			
Muscle spasms	27	5.9			
Anaphylactic reaction	18	3.93			
Dehydration	17	3.71			
Balance disorder	16	3.49			
Malignant neoplasm progression	16	3.49			
Pneumonia aspiration	15	3.28			
Dry eye	12	2.62			
Sedation	12	2.62			

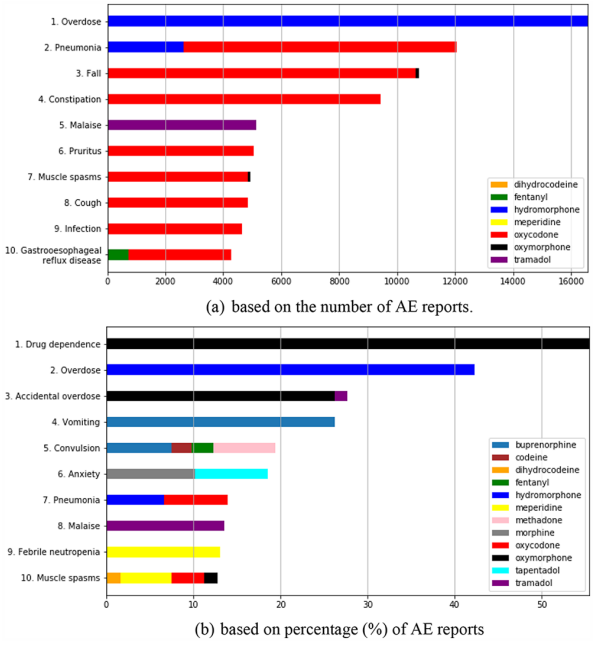

Figure 2. Breakdown by opioids within the top 10 AEs based on (a) number of reports and (b) percentage of AE reports.

the opioid exposure. Some of the opioids had the same AEs among the top 10. For example, pneumonia was identified as the second top AE for both oxycodone and hydromorphone, while emotional distress appeared as the top AE for fentanyl, hydromorphone, and dihydrocodeine. However, quantitatively there were only 24 AEs overlapping among the top 10 for all 13 opioids (i.e. 24 out of 130). This AE-overlap ratio remained the same for the whole opioid data set (i.e. 608 out of 3317). In general, it means that most AEs were different for each opioid exposure. This might provide support to an individualized approach of opioid prescriptions for patients, especially patients with underlying health conditions.

To overview the status of the opioids and the distribution of the top 10 AEs, either the total number of reports for each AE for each of the opioids (Figure 2(a)) or the percentage of a certain AE for each of the opioids (Figure 2(b)) was calculated. For example, considering the absolute number of reports, the AE of "overdose" was reported the most, occurring over 16,000 times and mostly for hydromorphone (blue). Tramadol users (purple) mostly reported "malaise" while fentanyl (green) was closely associated with "gastroesophageal reflux disease." The number of reports for the 13 groups of opioids diverged greatly. For example, oxycodone was the opioid with the most unique AEs reported (36% or 510 AEs), while meperidine had only 0.1% (57 AEs) (Table 1). Therefore, we looked at the distribution of the top 10 AEs by their percentages (Figure 2(b)). Compared to Figure 2(a), the top 10 percentage of AEs (Figure 2(b)) were reported in most of the opioids with the only exception being hydrocodone. The top 10 percentage of AEs (Figure 2(b)) was partly different from the top 10 number of AEs (Figure 2(a)), with only four AEs the same but exhibited in a different order. Specifically, for over 2709 opioid-related AEs, overdose, pneumonia, malaise, and muscle spasms were reported multiple times both in terms of frequencies and percentages. Although the first and third highest percentage of AEs "drug dependence" and "accidental overdose" did not appear in Figure 2(a) as a top 10 AE, they were the dominant AEs with oxymorphone (55.46% and 26.20%, Table 2). The same phenomena occurred with the fourth highest percent AE of "vomiting," which was the leading AE of buprenorphine, and the ninth highest percent AE of "febrile neutropenia" with meperidine (Table 2). The top sixth highest percent AE "anxiety" was attributed to morphine (10.23%) and tapentadol (8.31%) (Table 2). The data in Tables 1 and 2 as well as Figure 2(a) and (b) may provide some insights into understanding of AE profiles for the most popularly prescribed opioids on the market. It should be noted that the results were based on the self-reporting system of FAERS only, the causality and the accuracy need to be further validated by clinical electronic health records (EHRs).

Opioid relationship analysis

To further compare the 13 opioids, network analysis on the pairs of opioid-AEs was applied, with the results shown in Figure 3. The size of each node (i.e. opioid) in Figure 3 represents its weight, determined by the numbers of the AEs

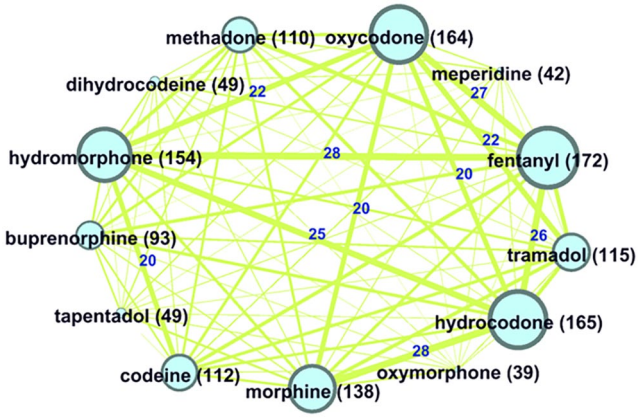

Figure 3. Opioid association network.
Each node represents an opioid, and the number next to each node represents the total number of AEs shared between that opioid with all other opioids. The numbers on the edges connecting two opioids represent the significant number of AEs shared between those two opioids.

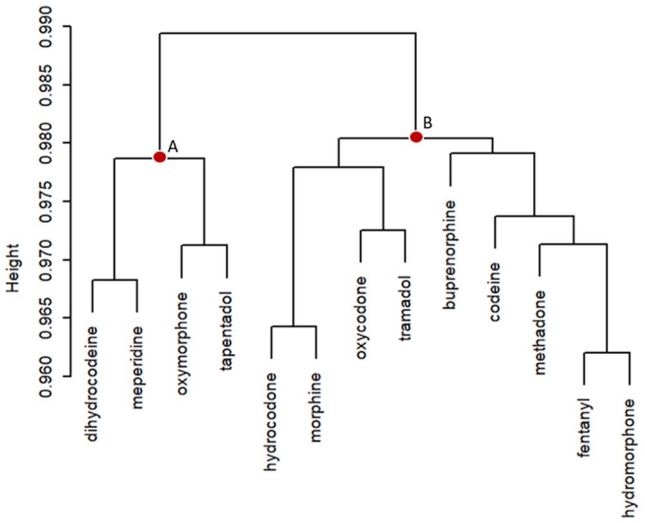

Figure 4. Dendrogram of the hierarchical clustering based on all opioids' AEs. The Jaccard distance and the average linkage method were used to calculate the distance between opioids. The opioids which shared similar profiles for AE presence/absence were clustered together. The 13 opioids were classified into two main groups (A and B).

shared with the other opioids, so as the size of the interconnecting lines between two opioids. Note that fentanyl, oxycodone, hydrocodone, and hydromorphone have larger nodes and thicker lines connecting each other, indicating the significant numbers of shared AEs with other opioids. Figure 3 also shows that the most weighted connections are among these four opioids or closely related to them, such as the two strong connections between hydrocodone and morphine ($w=28$) and between oxycodone and tramadol ($w=22$). On the contrary, dihydrocodeine, meperidine, oxymorphone, and tapentadol nodes are much smaller than the other opioids, indicating it was less common for AEs to be shared with the other opioids. The results in Figure 3 and Table 2 were well confirmed by the listing of top 10 AEs (Table 2) and provided the information on the opioid associations with the potential AEs.

As described in the previous section, most of the AEs differed for each opioid. To further explore the relationship between opioids, hierarchical clustering analysis was conducted on an "opioid-AEs profile" matrix, which is a binary matrix with a 1 or 0 representing the presence or absence of an AE for a given opioid, respectively. The cluster dendrogram of all 13 opioids is shown in Figure 4. The opioids which shared similar profiles for AE presence/absence were clustered together. For example, fentanyl and hydromorphone had 1999 AEs (out of 2709 unique AEs) exhibiting the similar presence/absence profiles, among which 28 AEs were same, including "emotional distress" and "premature baby." Hydrocodone and morphine had 1953 AEs with the similar presence/absence profiles, among which the two opioids shared 28 AEs including "gastrointestinal toxicity" and "hypertonic bladder." Dihydrocodeine and meperidine had 2587 AEs with the similar presences/absences; however, these two opioids only shared four AEs, "aggression," "hepatomegaly," "impaired healing," and "muscle spasms." In the same way, oxymorphone and tapentadol had 2574 AEs with the similar presence/absence profiles, but only shared four AEs, "apathy," "application site pain," "tooth loss," and "pulmonary edema." It is apparent that the results shown in Figures 3 and 4 reflected the relationships between the 13 groups of opioids from two different angles. The network analysis highlighted the associations between the 13 opioids through common AEs (Figure 3), while the hierarchical clustering analysis focused on the relationships between the opioids based on the full AE profiles, including not only the commonly present AEs but also the features based on the presence/absence of AEs (Figure 4). For example, fentanyl and hydromorphone shared 28 AEs and had a close association between each other in the network analysis (Figure 3), while they were the nearest two opioids and were clustered together in the hierarchical clustering analysis (Figure 4). Both results depicted the high similarity between fentanyl and hydromorphone on the potential safety signals of the AEs. The same could be said for the clustering of hydrocodone/morphine and oxycodone/tramadol. On the contrary, dihydrocodeine/meperidine and oxymorphone/tapentadol had only four common AEs present in each group but were clustered together due to the similar profiles of absent AEs. In Figure 4, the 13 opioids were classified into two main groups (A and B): each of the four opioids in group A had less than 50 shared AEs with the other opioids; while each opioid in group B had a higher number (>90) of AEs shared with the other opioids. The results are also reflected and validated by those shown in Figure 3. Network analysis and hierarchical clustering analysis provided a clearer and deeper understanding of the association and relationships of the 13 opioids. The results may be potentially applied to improving pain treatment and management.

Discussion

The long-term use of opioids has increased markedly, prompting researchers to pay more attention to the AEs associated with opioid exposure.[4,7,31] In this work, 17 years of AE reports were retrieved from FAERS, and a comprehensive study was conducted on AEs associated with FDA-approved opioids. To the best of our knowledge, this study was the first to provide a global overview on the potential safety issues of various prescription opioids and explored

the associations between the 13 classes of opioids by data mining methods.

The FAERS database has been used as an important source for reporting and detecting drug AEs, with a significant number of reports specifically related to various opioids. The limitations and drawbacks[34] of FAERS might be partially overcome by the size of the data set, such as what Sakaeda *et al*.[35] mentioned: "a report in the FAERS database is a story, sometimes only a rumour, but numerous reports can reflect reality." We have retrieved close to 15 million AE reports from 2004, Quarter 1 to 2020, Quarter 3 from the FAERS database. We expected the size of the data and the data mining methods applied in this study might have improved the causal relationship between opioid exposure and reported events, reduced the heterogeneity in the reports due to individual reporting, therefore lowering the inflation of risk attributable to a medication based on FAERS pharmacovigilance. However, as a spontaneous reporting system, FAERS data have the limitation on determining causality and drawing comparative conclusions. The results from FAERS in this study need to be further validated.

One challenge point is the heterogeneity of drug names appearing in the database, which is a mixture of generic and trade names of drugs.[4,7,36] Historically, this was either unsolved by searching for specific drug names[4,36] or partly solved using a regular expression package to address spelling errors.[7] This resulted in many AEs being excluded from previous analysis. In this work, we attempted to overcome this issue systematically using RxNorm for drug name normalization before proceeding with data processing. RxNorm has been considered the standard vocabulary tool to represent medicines in the United States and is able to provide normalized names for clinical drugs and link these names to many commonly used drug vocabularies in pharmacy management.[27,28] In this study, the data set retrieved from FAERS has close to 15 million reports covering 69,889 drugs and 22,260 AEs. We applied RxNorm and successfully classified the drugs into 13 opioid classes. The top three most reported opioids during a period of 17 years (2004, Quarter 1 to 2020, Quarter 3) were the classes of oxycodone, hydrocodone, and hydromorphone, and all of which are semi-synthetic opioids that accounted for over 60% of the AE reports (Table 1).

Pharmacovigilance is designated as the detection, assessment, understanding, and prevention of AEs,[37] with special attention to the potential safety signal analysis. Starting from close to 15 million FAERS reports over 17 years, we have excavated and analyzed the huge data set sequentially and identified 3317 pairs of opioid-AEs as potential safety signals from a total of 78,874 pairs by applying EBGM and EB05 algorithms. Table 2 and Figure 2 show the status and comparative analysis of the top 10 potential AEs with risks for each of the 13 opioids. These mined potential safety signals could be used for multiple investigations as well as by health-care experts for drug safety assessment. It was reported that the FAERS data have contributed to more than 50% of all postmarket safety-related label changes.[38] In this study, we also successfully identified some AEs for which details were not previously listed in DailyMed. For example, 73 tapentadol-related cases reported "dehydration" and 67 cases reported "peripheral swelling." In addition, some of the opioids have their dominant AE(s) (the AE with more than 10% reports) and the dominant AEs vary among the opioids. For example, 55.46% of the reports of oxymorphone exposures reported the side effect of "drug dependence," while the most occurring AE of hydromorphone was "overdose." In addition, we found that the overlapping of AEs of the 13 opioids was around 18.4%. We believe that these results may provide valuable references for physicians, health-care experts, and patients to choose appropriate opioid(s) that avoid or reduce the risks of some serious AEs, especially for patients with existing medical conditions. When combining the results from Table 1 and Figures 3 and 4, we noticed that hydrocodone, hydromorphone, oxycodone, and fentanyl were not only the top five most reported prescription opioids with the most (top four) unique AEs, but they also had more common AEs (Figure 3) and had similar profiles on AEs presence/absence (Figure 4). Except for the synthetic opioid fentanyl, the other three are semi-synthetic opioids with similar chemical structures. Further research is expected to reveal the association of AE development with the chemical structures of prescription opioids and opioid receptors to help develop potentially safer and less addictive pain medications. We are also planning to identify the sex and race disparities on prescription opioid-related AEs.

AUTHORS' CONTRIBUTIONS

HL performed all the calculations and data analysis and wrote the first draft of the manuscript. This work was established primarily by WZ in developing the methods, conceiving the original idea, and guiding the data analysis and presentation of results. HL, HH, HF, PR, WG, and WZ participated in the data set construction and the resulting figures. HF and BL-C provided FDA product center subject matter expert consultation. BL-C, HH, and WT joined WZ for project management and result interpretation. All authors contributed to data verification, approach evaluation, and assisted with writing the manuscript. All authors read and approved the final manuscript.

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DECLARATION OF CONFLICTING INTERESTS

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SUPPLEMENTAL MATERIAL

Supplemental material for this article is available online.

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