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Analyzing adverse event signals of aprepitant using FAERS database data in real-world settings

Broadening the adverse event spectrum of aprepitant and its clinical implications

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Abstract

Aprepitant, a neurokinin-1 receptor antagonist approved by the US FDA for chemotherapy- and postoperative-induced nausea and vomiting, has limited real-world safety data; we therefore interrogated the FDA Adverse Event Reporting System from Q1 2004 to Q3 2023 to systematically characterize aprepitant-associated adverse drug events. After extracting 8271 reports on 3033 patients, we applied a combined signal detection framework – reporting odds ratio, proportional reporting ratio and the Bayesian confidence propagation neural network with multi-item gamma Poisson shrinker – and analyzed demographics, reporter profiles and temporal trends. Women represented 54.10% of cases, the 45 to 65-year age group 27.86%, and healthcare professionals filed 65.64% of reports; the United States, France, Japan, the United Kingdom, and China contributed most cases, peaking during 2013 to 2019. While labeled toxicities were confirmed, novel high-strength signals emerged, including joint deposition, oral mucosal roughening, encephalopathy, dysplasia, febrile myelodysplasia, small cell lung cancer and tonic-clonic movements, whereas dyspnea and nausea remained the 2 most frequently reported events. These findings corroborate known risks and unveil previously under-recognized aprepitant related adverse reactions, providing actionable safety guidance for clinicians and suggesting that the strong joint deposition signal warrants prospective investigation of aprepitant in arthritic disorders.

Abbreviations: ADE = adverse drug event, BCPNN = Bayesian confidence propagation neural network, FAERS = FDA Adverse Event Reporting System, FDA = US Food and Drug Administration, MGPS = multi-item gamma Poisson shrinker, PRR = proportional reporting ratio, ROR = reporting odds ratio.

Keywords: adverse event, aprepitant, data mining, FAERS, NK-1RA, pharmacovigilance, real-world study

1. Introduction

According to the most recent worldwide cancer data from the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases were reported in 2022, along with 9.7 million fatalities due to cancer.[1] For the majority of cancer patients, chemotherapy continues to be the primary treatment method. However, it has numerous negative side effects, one of the most clinically relevant being chemotherapy-induced nausea and vomiting (CINV).[2,3] A large real-world study based on a Chinese oncology population showed that the incidence of CINV throughout chemotherapy was as high as 83%,[4] and although much progress has been made in controlling CINV, the control rate is not ideal, with 40% of patients still not being treated satisfactorily throughout the entire cycle of chemotherapy.[5] CINV significantly reduces the quality of life of patients and their adherence to anticancer therapy, and poorly controlled or severe CINV can result in dose reductions or cycle delays, compromising chemotherapy efficacy.[6–9]

With the development and marketing of relevant drugs, acute CINV has been effectively prevented and controlled, but the effective prevention and control of delayed CINV remains an unmet clinical need for current tumor patients. Research

FC, DC, and HW contributed to this article equally

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The datasets generated during and/or analyzed during the current study are publicly available.

This study did not require ethical approval as it involved the use of publicly available datasets and did not involve human participants or animal subjects. The data were anonymized and did not contain any personally identifiable information.

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indicates that, even when acute CINV is absent in patients undergoing chemotherapy, 23% to 24% of them still experience delayed CINV.[10] It has been discovered that the development of CINV involves numerous neurotransmitters, with 5-hydroxytryptamine 3 (5-HT3) and substance P (SP) identified as crucial ones.[11] Substance P (SP) is the primary neurotransmitter in the central nervous system, responsible for triggering neurokinin-1 (NK-1), a factor linked to late-onset vomiting.[12] Aprepitant, recognized globally as the inaugural NK-1 receptor antagonist (NK-1RA), has received approval to prevent CINV triggered by highly emetogenic chemotherapy or moderately emetogenic chemotherapy. It achieves this by attaching to the NK-1 receptor in the central nervous system, thereby inhibiting the discharge of SP.[10,13] Furthermore, clinical research has shown the significance of NK-1RA, exemplified by aprepitant, in managing postoperative nausea, vomiting, and antitumor,[14,15] among other therapies. There is also a study indicating the possible use of aprepitant in treating chronic refractory pruritus.[16]

The adverse event reporting system (FAERS) of the US Food and Drug Administration gathers unsolicited reports of adverse events and medication mistakes following global drug administration. This system helps to offset the drawbacks of specification delays, uncertainty, and incompleteness, and it aids in the post-marketing monitoring of drugs and therapeutic biologics.[17] In this research, we employed the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) techniques to sift through and extract information from the data gathered from FAERS. The aim was to examine the indications of potential adverse drug events (ADEs) related to aprepitant in real-world scenarios, thereby offering guidance for the clinical choice and secure application of aprepitant.

2. Materials and methods

2.1. Study design and data source

The initial information was sourced from the FAERS database on the US FDA's official website (https//fis.fda.gov/extensions/FPDQDE-FAERS/FPD-QDE-FAERS.html). This database has been accessible to the public from the first quarter of 2004 and is updated and published every 3 months. The data can be downloaded in 2 formats, ASCII packet and XML packet. Primarily, it consists of self-reported drug-related safety reports gathered from patients or healthcare professionals. For data mining and statistical analysis, 79 quarterly ASCII packets were gathered from the FAERS database, spanning from the initial quarter of 2004 through to the third quarter of 2023, as per this research.

ADEs were categorized and standardized using the preferred system organ classification (SOC) and preferred terminology (PT) from the adverse drug reaction terminology set of the international medical dictionary of terms (MedDRA), as per the data normalization standards.[18]

2.2. Data extraction and mining

In our research, we employed ROR, PRR, BCPNN, and MGPS for signal detection. These 4 algorithms are based on a 4-grid table (see Table 1). A signal was suggested to be generated when the following conditions were met simultaneously: the report count was 3 or more, the lower boundary of the 95% confidence interval for ROR exceeded 1, PRR was 2 or higher, the chi-square value was 4 or above, IC-2SD was >0, and the threshold for EBGM05 was above 2 (see Table 2).[19] A sign suggested a statistical correlation between the medication and the intended ADE. A higher value for the lower boundary of the 95% confidence interval of the ROR signified a more robust link between the intended medication and the ADE.[20] Statistical analysis was conducted using Microsoft Excel 2019 and SAS 9.4 software.

Table 1

Four-grid table.

	Aprepitant related ADEs	Non-aprepitant related ADEs	Total
Aprepitant	a	b	$a + b$
Non-aprepitant	c	d	$c + d$
Total	$a + c$	$b + d$	$N = a + b + c + d$

ADE = adverse drug event.

Table 2

ROR, PRR, BCPNN, and EBGM methods, formulas, and thresholds.

Method	Formula	Threshold
ROR	$ROR = \frac{a/c}{b/d} = \frac{ad}{bc}$	$a \geq 3$ and 95% CI (lower limit) > 1
	$95\%\ CI = e^{\ln(ROR) \pm 1.96\sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$	
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	$a \geq 3$, PRR ≥ 2 and $2 \geq 4$
	$2 = \frac{(a+b+c+d)(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)}$	
BPCNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025 > 0 (IC025: the lower bound of 95% CI)
	$95\%\ CI = E(IC) \pm 2\times\sqrt{V(IC)}$	
EBGM	$EBGM = (aN)/[(a + b)(a + c)]$	EBGM05 > 2 (EBGM05: the lower bound of 95% CI)
	$95\%\ CI = e^{\ln(EGBM) \pm 1.96\sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}}$	

BPCNN = Bayesian confidence propagation neural network, EBGM = empirical Bayesian geometric mean, PRR = proportional reporting ratio, ROR = reporting odds ratio.

3. Results

3.1. Descriptive analysis

From the first quarter of 2004 to the third quarter of 2023, 79 quarters of ADE reports for aprepitant were pulled from the FAERS database. Doubtful and repetitive data were eliminated, leaving 3033 adverse events reports and 8271 adverse events induced by target drug as "primary suspicion (PS)" (Fig. 1). The report indicated that the majority of patients were women, making up 54.10% (n = 1641) of the total. The median age of the patients was 58.00 years, with an average age of 54.67 years. The largest age group was 45 to 65 years, comprising 27.86% (n = 845) of the patients. The most reports came from consumers (n = 930, 30.66%) and physicians (n = 748, 24.66%). United States, France, Japan, United Kingdom, and China topped the list of top 5 reporting countries (as shown in Fig. 2). The number of reports was high during 2013 to 2019, followed by a decreasing trend. (Detailed basic information is shown in Table 3.)

3.2. Classification of system organs involved in ADEs

According to the conditions to be met, the screened aprepitant ADE signals were statistically analyzed, and the PTs with signals were classified using the MedDRA system organ classification to finally obtain the valid signal PTs and the corresponding SOCs. A total of 108 significant aprepitant-associated ADE signals were screened (Wayne's plots, Fig. 3), involving 23 SOCs (Table 2). The signals under each SOC were arranged in descending order, with the 3 highest being general disorders and administration site conditions (26 signals), respiratory, thoracic and mediastinal disorders (10 signals), and investigations (9 signals). In comparison with the drug insert, there were 9 SOCs that did not appear in the insert (see Table 4).

3.3. Ranking of the top 30 ADEs

We arranged the valid signals in a descending sequence according to the count of reports and the lower limit value of ROR 95% CI, respectively. Consequently, we identified the top 30 signals based on the quantity of reports (Table 5) and signal strength (Table 6). Comparison of the screened signal PTs with the drug insert for aprepitant revealed that there were 6 signals among the top 30 ADEs in terms of number of reports that did not appear in the insert: erythema, back pain, encephalopathy, dysphagia, bone marrow failure, and Throat tightness. Seven of the top 30 ADEs in signal strength that did not appear in the drug insert were joint deposit, oral mucosal roughening, encephalopathy, aplasia, febrile bone marrow aplasia, small cell lung cancer, and tonic-clonic movements. The results provide a reference for further updating the adverse drug reactions in the aprepitant drug insert.

4. Discussion

Our research revealed that female patients were more likely to experience aprepitant-associated ADEs. Apart from taking into account the varying prevalence of chemotherapy-induced nausea and vomiting in males and females, it's equally crucial to examine if the adverse drug reactions linked to aprepitant are gender-specific, a subject that hasn't been explored yet. In the observed age demographics, the largest proportion of individuals aged 45 to 65 years is seen. Aprepitant is primarily indicated for patients with malignant tumors, considering that it may be related to the higher incidence of tumors in middle-aged and elderly people.[21] As for the reporting countries, the United States accounted for the largest proportion (58.26%), in addition to geographical differences in the recognition and utilization of the drug, it cannot be ruled out that it is related to the differences in the incidence of ethnicity. The data in this study is deemed fairly reliable, as indicated by the fact that 65.64% of the adverse reaction reports were submitted by professionals with a relevant medical background. Consumers made up the largest percentage of reporters (30.66%), followed by doctors (24.66%), other healthcare professionals (23.01%), and pharmacists (17.97%). The annual number of reports decreased after 2019, which should be closely related to the increasing level of awareness of the drug in all aspects after its widespread use.

The present study coupled 4 algorithms for signaling detection and found that the strongest ADE signaling of aprepitant was joint deposition (n = 3, ROR = 435.03 [134.81, 1403.79]). Ko et al proposed that the use of antagonists to block NK1R

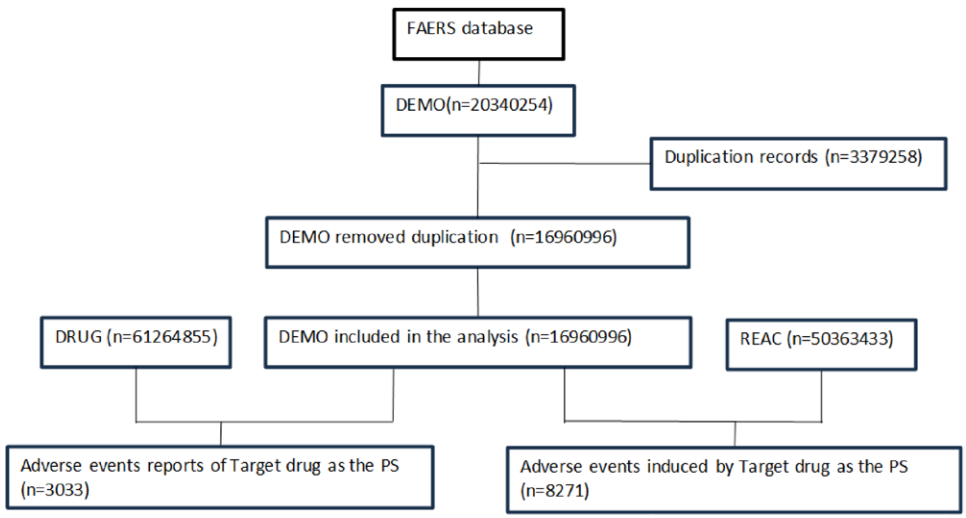

Figure 1. Data processing flowchart for adverse event analysis from the FAERS database. The flowchart illustrates the data extraction and processing steps from the FDA Adverse Event Reporting System (FAERS) database. The initial DEMO dataset contained 2,03,40,254 records. After removing 33,79,258 duplication records, 1,69,60,996 records were included in the analysis. The DRUG and REAC datasets contained 6,12,64,855 and 5,03,63,433 records, respectively. Among these, 3033 adverse event reports identified the target drug as the primary suspect (PS), corresponding to 8271 specific adverse events induced by the target drug as the PS. DEMO = demographic data, DRUG = drug information, FAERS = FDA Adverse Event Reporting System, PS = primary suspect, REAC = adverse reaction data.

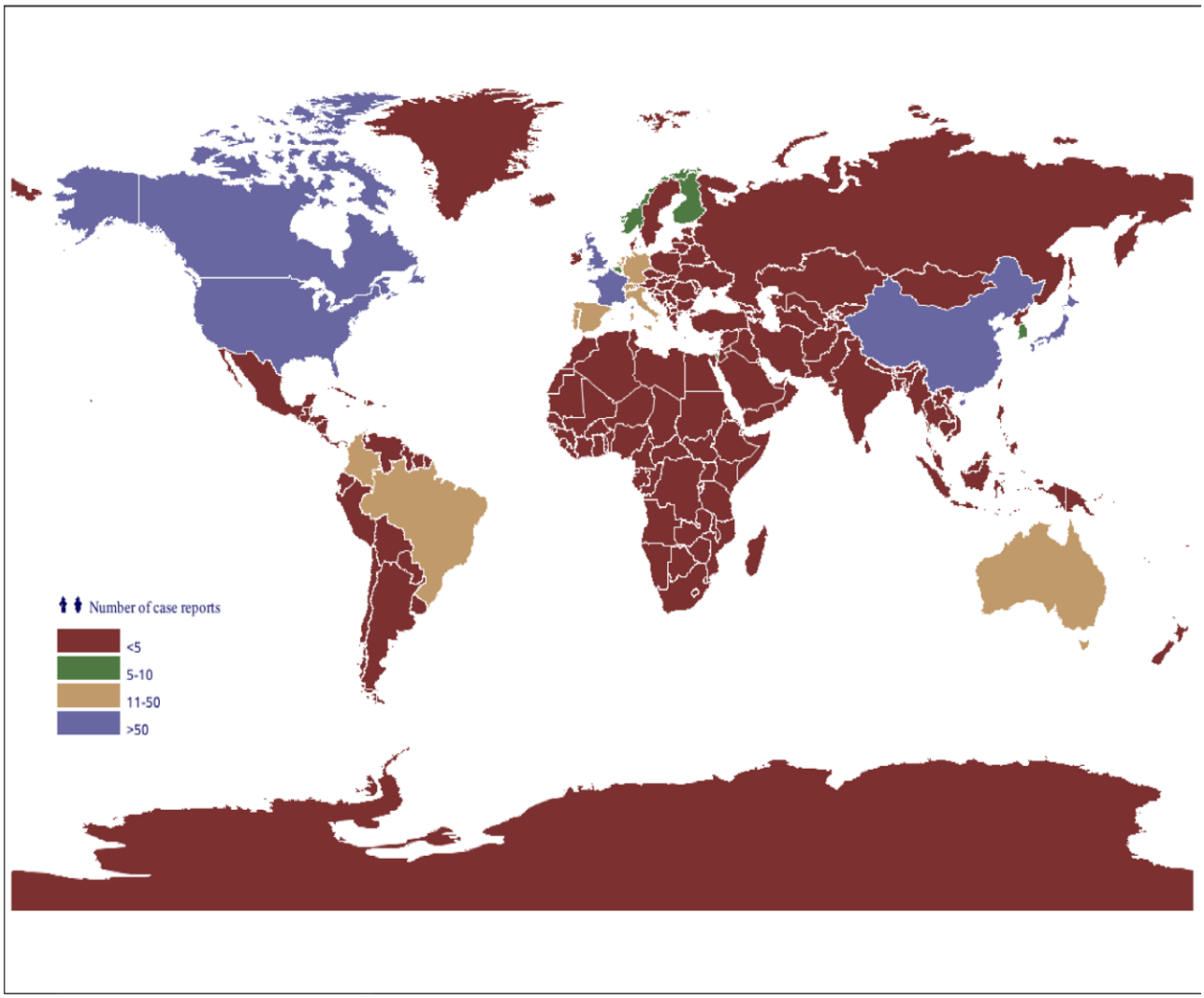

Figure 2. Global distribution of case reports for the target drug. Choropleth map depicting the worldwide distribution of case reports per country, categorized into 4 quantitative ranges: <5 cases (dark red), 5 to 10 cases (green), 11 to 50 cases (tan), and >50 cases (purple). The map highlights significant geographic disparities in reporting number.

could be a potential treatment approach for rheumatoid arthritis and osteoarthritis. This could be due to the immunomodulatory function of the SP-NK1R pathway in inflammatory conditions.[22] SP is extensively dispersed in the human body, contributing significantly to numerous physiological and pathophysiological activities, including inflammation, angiogenesis, and pain. The abnormal expression of the SP-NK1R pathway in various inflammatory diseases suggests its potential role in inflammatory processes.[23] Lam et al[24] found that injection of an NK1R antagonist into the knee joint of a rat model of arthritis induced by 125 μL of Freund's complete adjuvant led to a reduction in arthritic pain and knee swelling in rats. Meanwhile, Liu et al[25] conducted an experiment on fibroblast-like synoviocytes (FLSs), which were obtained from the knee joint's synovial tissue of both healthy individuals and those suffering from rheumatoid arthritis (RA). They were exposed to an NK1R antagonist (aprepitant). The study discovered that the expression of NK1R was notably higher in FLSs from RA patients compared to those from healthy subjects. Furthermore, the data indicated that NK-1R inhibition by aprepitant reduced the secretion of inflammatory substances in RA-FLSs. These 2 studies suggest that aprepitant may be effective in treating arthritis through direct action on the joints. Our research findings indicated a significant correlation between the use of aprepitant and the formation of joint deposits. This could potentially offer fresh proof to endorse the therapeutic application of aprepitant in arthritis treatment.

Aprepitant is used as a capsule for oral administration and as a prodrug of fosaprepitant for intravenous administration.[10] Our current research revealed that general disorders and administration site conditions were found to be the SOC with the highest number of signals (n = 26). In addition, among the top 30 PTs in terms of signal strength, PTs related to infusion site reactions also accounted for the highest proportion (11/30), as well as a larger number of reports. The ADEs encompassed infusion site phlebitis, infusion site irritation, infusion site hives, and infusion site pain. When a medication seeps out of the vein, it can lead to injection site adverse reactions (ISAE), which may manifest as pain at the infusion location, redness, inflammation, and/or vein inflammation. The use of harsh drugs can lead to transient discomfort, constriction, and inflammation of the vein or the area of injection, with the possibility of a localized inflammatory reaction. If medications that cause blisters are administered, there's a risk of blister formation and tissue death, necessitating procedures like wound cleaning, grafting, or other surgical treatments.[26] Infusion site reactions not only induce immediate discomfort and suffering for the patient, but the leakage and subsequent tissue death may result in severe

Table 3

Basic information on adverse event reports related to aprepitant.

Characteristics	Case number, n	Case proportion, %
Gender		
Female	1641	54.10
Male	931	30.70
Not specified	461	15.20
Age		
<18	85	2.80
18≤ and <45	321	10.58
45≤ and <65	845	27.86
65≤ and <75	441	14.54
≥75	138	4.55
Not Specified	1203	39.66
Age (quantitative)		
N (missing)	1830 (1203)	
Mean (SD)	54.67 (16.67)	
Median (Q1, Q3)	58.00 (46.00, 66.00)	
Min, max	0.00, 92.00	
Reporter		
Consumer	930	30.66
Lawyer	1	0.03
Not specified	67	2.21
Other health-professional	742	24.46
Pharmacist	545	17.97
Physician	748	24.66
Reported countries (top 5)		
United States	1767	58.26
France	508	16.75
Japan	173	5.70
Not specified	139	4.58
United Kingdom	75	2.47
Outcome		
Life-threatening	228	7.52
Hospitalization – initial or prolonged	808	26.64
Disability	102	3.36
Death	294	9.69
Congenital anomaly	1	0.03
Required intervention to prevent permanent impairment/damage	5	0.16
Other	1009	33.27

Q1 = lower quartile, Q3 = upper quartile, SD = standard deviation.

lasting harm, such as persistent pain, nerve damage, functional or mobility impairment, and aesthetic disfigurement.[27] This finding suggests the need for vigilance and close monitoring of patients for any signs of infusion site reactions when applying aprepitant intravenously. The issues related to the drug itself and the accuracy of its administration process must not be overlooked, including checking the syringe's appearance, its handling, selecting the injection site, providing care, and taking precautions after the injection. In clinical work, healthcare professionals should follow up on medication instruction and education.

Moreover, this research discovered several previously unmentioned ADEs in the drug's insert, including roughening of the oral mucosa, encephalopathy, dysplasia, febrile bone marrow aplasia, small cell lung cancer, and tonic-clonic movements. To the best of the author's knowledge, no scientific studies indicate that aprepitant may lead to encephalopathy. However, there have been reports of encephalopathy induced by isocyclophosphamide following its combined use with aprepitant.[28] The way aprepitant works might be associated with its suppressive impact on CYP3A4. The occurrence of encephalopathy caused by isocyclophosphamide varies between 5% and 30% in patients who are administered with isocyclophosphamide infusion.[29,30] The clinical signs of this condition can range from slight sleepiness or vertigo to experiencing hallucinations, seizures, falling into a coma, and in extreme cases, death. In the present study, encephalopathy was reported in 71 cases with an ROR value of 21.89 (95% CI: 17.32–27.66), which is a high signal strength and therefore needs to be taken seriously by clinicians. Vazirian et al observed no meaningful statistical correlation between the onset of encephalopathy induced by isocyclophosphamide and the administration of aprepitant.[31] To sum up, additional clinical research is required to establish the link between aprepitant and encephalopathy, including encephalopathy triggered by isocyclophosphamide.

In cancer patients, dyspnea is a prevalent and troubling symptom, with an occurrence rate ranging from 20% to 70%,[32] as noted by Hui et al.[33] The life quality of cancer patients and their families can be significantly diminished by dyspnea, a potentially terrifying complication.[34,35] A study by Yoshinobu Matsuda et al found that coughing may exacerbate dyspnea, and 1 study suggests that aprepitant may be a new pharmacologic treatment option for cough.[36] Nonetheless, the research only encompassed patients suffering from a cough related to lung cancer, and the limited number of participants (n = 20) along with the brief period of the study restricted the inferences regarding the broad usability of aprepitant in cough treatment. The current research discovered that dyspnea was the most frequently occurring ADE, implying that there might be a need for additional, extended, and more comprehensive randomized controlled trials to further assess the safety and effectiveness of aprepitant in treating cough. In clinical practice, more attention should also be paid to dyspnea in patients with preexisting respiratory diseases when using aprepitant to prevent chemotherapy-related nausea and vomiting. In addition, the second most frequent ADE is nausea. Chemotherapy frequently results in both nausea and vomiting; however, the neuropharmacological mechanisms behind them differ. Moreover, nausea can manifest on its own.[37] The effectiveness of NK-1 receptor antagonists in significantly reducing vomiting related to chemotherapy has been demonstrated[12,38]; however, their role in preventing nausea is not as clear. There are no conclusions regarding the definitive effectiveness of NK-1RA in the prevention or treatment of chemotherapy-associated nausea.[39] More research and better antiemetic regimens are needed to improve nausea control.

Although this study leveraged the FDA Adverse Event Reporting System, which aggregates spontaneous reports from approximately 130 countries, its geographical coverage is uneven. Consequently, the generalizability of our findings is constrained by 3 main factors. First, the analyzed cohort predominantly comprises middle-aged women receiving highly emetogenic chemotherapy – a demographic that mirrors the approved indication of aprepitant – so the derived safety profile is most directly applicable to this core oncology population. Second, 55.5% of reports originated from the United States, indicating disproportionate representation of high-income regions; this limits external validity for low- and middle-income countries, where genetic backgrounds and comorbidity patterns may differ. Third, pediatric (<18 years) patients accounted for only 3.0% of reports and geriatric (>75 years) patients for even fewer, warranting caution when extrapolating the observed signals to these extreme age groups. Multi-database collaborations that integrate EudraVigilance, VigiBase and regional pharmacovigilance repositories (e.g., JADER, KIDS-KAERS) are therefore needed to assess geographic and ethnic effect modification and to enhance the broader applicability of these results.

5. Data limitations and future research directions

5.1. Limitations

This real-world mining study of FDA Adverse Event Reporting System data can detect post-marketing safety signals early, yet several inherent limitations call for cautious interpretation.[40] Under-reporting, duplicate submissions and the absence of denominator data preclude estimation of true incidence rates. Geographic imbalance – 58.26% of reports originate from the

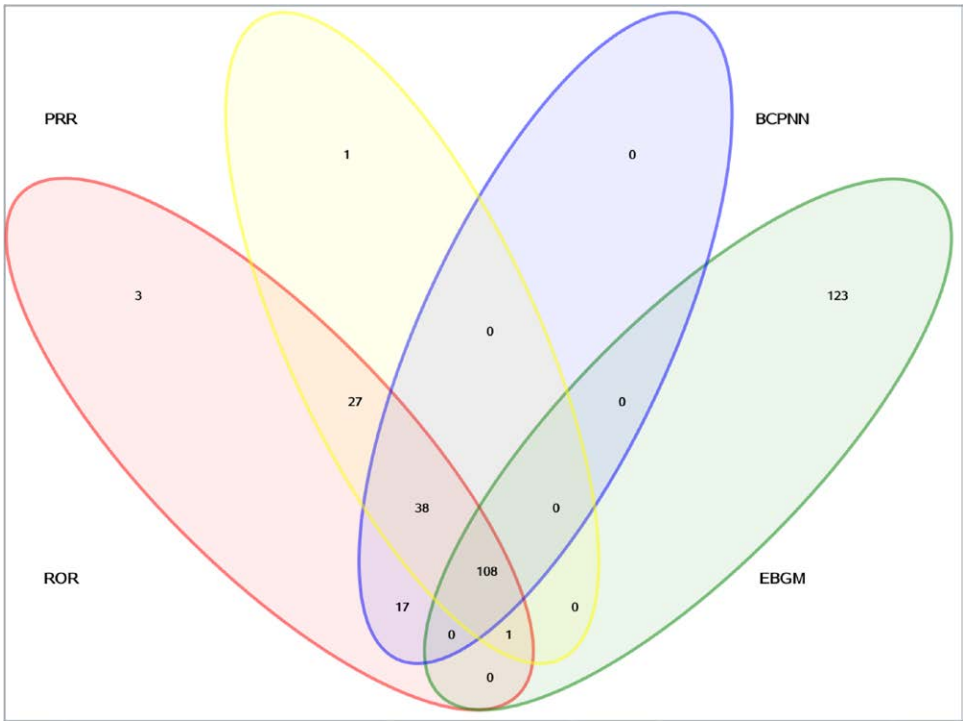

Figure 3. Venn diagram of adverse event signals detected by 4 disproportionality analysis methods. The diagram illustrates the number of unique and overlapping signals generated by 4 distinct algorithms: proportional reporting ratio (PRR, yellow), Bayesian confidence propagation neural network (BCPNN, purple), reporting odds ratio (ROR, red), and empirical Bayes geometric mean (EBGM, green). The numbers in the diagram represent the count of signals uniquely detected by each method or shared among them, with 108 signals detected by all 4 methods together. BCPNN = Bayesian confidence propagation neural network, EBGM = empirical Bayes geometric mean, PRR = proportional reporting ratio, ROR = reporting odds ratio.

Table 4

Distribution of aprepitant related ADEs at the SOC level.

SOC	SOC code	PT number	Case number	Composition of adverse event reports (%)
General disorders and administration site conditions	10018065	26	1608	19.44
Respiratory, thoracic and mediastinal disorders	10038738	10	591	7.15
Investigations*	10022891	9	515	6.23
Gastrointestinal disorders	10017947	8	913	11.04
Injury, poisoning and procedural complications*	10022117	7	617	7.46
Vascular disorders	10047065	7	403	4.87
Nervous system disorders	10029205	6	731	8.84
Immune system disorders	10021428	4	303	3.66
Blood and lymphatic system disorders	10005329	4	234	2.83
Neoplasms benign, malignant and unspecified (incl cysts and polyps)*	10029104	4	163	1.97
Hepatobiliary disorders*	10019805	4	123	1.49
Product issues*	10077536	4	106	1.28
Skin and subcutaneous tissue disorders	10040785	2	522	6.31
Musculoskeletal and connective tissue disorders	10028395	2	341	4.12
Metabolism and nutrition disorders	10027433	2	199	2.41
Surgical and medical procedures*	10042613	2	64	0.77
Psychiatric disorders	10037175	1	214	2.59
Infections and infestations	10021881	1	185	2.24
Cardiac disorders	10007541	1	167	2.02
Renal and urinary disorders*	10038359	1	106	1.28
Eye disorders*	10015919	1	81	0.98
Endocrine disorders	10014698	1	23	0.28
Congenital, familial and genetic disorders*	10010331	1	15	0.18

ADE = adverse drug event, PT = preferred terms, SOC = system organ class.
*Indicates that the SOC is not mentioned in the drug insert.

United States, with scant representation from Asia and Latin America – may understate ADE characteristics across different genetic backgrounds and comorbidity patterns. Pediatric (<18 years, 2.8%) and geriatric (>75 years, <5%) patients are markedly under-represented, restricting extrapolation of signals to these age extremes. Unmeasured confounders such as chemotherapy regimens, tumor progression and concomitant medications cannot be fully adjusted for, making it difficult to attribute

Table 5

Top 30 PTs for number of ADE reports related to aprepitant.

PT	Case number	ROR (95% CI)	PRR (95% CI)	Chi-square	IC (95% CI)	EBGM (95% CI)
Dyspnoea	268	3.58 (3.17, 4.05)	3.50 (3.11, 3.94)	482.68	1.81 (1.61, 1.97)	3.50 (3.10, 3.95)
Nausea	246	2.35 (2.07, 2.67)	2.31 (2.04, 2.61)	185.13	1.21 (1.01, 1.39)	2.31 (2.10, 2.62)
Flushing	178	12.39 (10.68, 14.37)	12.14 (10.50, 14.04)	1819.70	3.60 (3.29, 3.73)	12.14 (12.10, 14.06)
Erythema*	148	5.21 (4.43, 6.13)	5.13 (4.38, 6.02)	494.03	2.36 (2.08, 2.56)	5.13 (5.10, 6.04)
No adverse event	124	6.15 (5.15, 7.34)	6.07 (5.10, 7.23)	525.81	2.60 (2.28, 2.80)	6.07 (6.10, 7.24)
Hypersensitivity	119	4.84 (4.04, 5.80)	4.78 (4.00, 5.72)	356.72	2.26 (1.95, 2.48)	4.78 (4.10, 5.73)
Back pain*	118	3.73 (3.11, 4.48)	3.69 (3.09, 4.42)	232.63	1.88 (1.59, 2.12)	3.69 (3.10, 4.43)
Adverse event	109	8.89 (7.36, 10.74)	8.78 (7.29, 10.59)	752.00	3.13 (2.76, 3.31)	8.78 (8.10, 10.60)
Drug interaction	85	3.95 (3.19, 4.89)	3.92 (3.17, 4.84)	184.96	1.97 (1.61, 2.23)	3.92 (3.10, 4.85)
Anaphylactic reaction	83	12.17 (9.80, 15.12)	12.06 (9.74, 14.94)	841.05	3.59 (3.09, 3.73)	12.06 (12.10, 14.95)
Chest discomfort	74	5.53 (4.40, 6.95)	5.49 (4.37, 6.89)	271.86	2.46 (2.04, 2.71)	5.49 (5.10, 6.90)
Encephalopathy*	71	21.89 (17.32, 27.66)	21.71 (17.22, 27.38)	1398.45	4.44 (3.73, 4.41)	21.71 (21.10, 27.35)
Infusion site pain	64	43.01 (33.60, 55.05)	42.69 (33.41, 54.53)	2587.77	5.41 (4.33, 5.06)	42.69 (43.10, 54.26)
White blood cell count decreased	49	3.36 (2.54, 4.45)	3.35 (2.53, 4.43)	80.85	1.74 (1.27, 2.09)	3.35 (3.10, 4.43)
Dysphagia*	44	3.33 (2.47, 4.48)	3.32 (2.47, 4.45)	71.21	1.73 (1.22, 2.09)	3.32 (3.10, 4.46)
Hiccups	43	40.19 (29.75, 54.29)	39.99 (29.65, 53.93)	1624.04	5.31 (3.96, 4.84)	39.99 (40.10, 53.67)
Hyponatraemia	42	5.44 (4.02, 7.37)	5.42 (4.01, 7.33)	151.37	2.44 (1.85, 2.74)	5.42 (5.10, 7.33)
Infusion related reaction	40	5.09 (3.73, 6.95)	5.07 (3.72, 6.91)	130.83	2.34 (1.75, 2.66)	5.07 (5.10, 6.92)
Phlebitis	38	52.19 (37.90, 71.87)	51.95 (37.78, 71.45)	1883.07	5.69 (4.02, 4.95)	51.95 (52.10, 70.96)
Feeling hot	37	4.35 (3.15, 6.00)	4.33 (3.14, 5.98)	94.86	2.11 (1.52, 2.46)	4.33 (4.10, 5.98)
Tachycardia	35	2.90 (2.08, 4.05)	2.89 (2.08, 4.03)	43.45	1.53 (0.98, 1.94)	2.89 (2.10, 4.03)
Anaphylactic shock	31	9.46 (6.65, 13.47)	9.43 (6.63, 13.40)	233.32	3.24 (2.39, 3.41)	9.43 (9.10, 13.40)
Febrile neutropenia	30	3.55 (2.48, 5.08)	3.54 (2.48, 5.06)	54.75	1.82 (1.19, 2.23)	3.54 (3.10, 5.07)
Bone marrow failure*	30	9.81 (6.86, 14.05)	9.78 (6.84, 13.99)	236.23	3.29 (2.41, 3.45)	9.78 (9.10, 13.98)
Oxygen saturation decreased	28	3.99 (2.75, 5.78)	3.98 (2.75, 5.76)	62.39	1.99 (1.31, 2.39)	3.98 (3.10, 5.76)
Neutrophil count decreased	24	4.68 (3.14, 6.99)	4.67 (3.13, 6.97)	69.26	2.22 (1.45, 2.60)	4.67 (4.10, 6.97)
Infusion site erythema	23	25.05 (16.62, 37.75)	24.98 (16.60, 37.61)	527.42	4.64 (3.05, 4.23)	24.98 (25.10, 37.50)
Hepatocellular injury	22	8.95 (5.89, 13.61)	8.93 (5.88, 13.56)	154.81	3.16 (2.13, 3.33)	8.93 (8.10, 13.56)
Throat tightness*	22	5.99 (3.94, 9.10)	5.97 (3.93, 9.07)	91.04	2.58 (1.69, 2.90)	5.97 (5.10, 9.07)
Mucosal inflammation	20	5.78 (3.73, 8.97)	5.77 (3.72, 8.94)	78.81	2.53 (1.60, 2.86)	5.77 (5.10, 8.94)

ADE = adverse drug event, BCPNN = Bayesian confidence propagation neural network, CI = confidence interval, EBGM = empirical Bayesian geometric mean, IC = information component, PRR = proportional reporting ratio, PT = preferred terms, ROR = reporting odds ratio.

*Indicates that the PT is not mentioned in the drug insert.

signals like "encephalopathy" solely to aprepitant. Although 4 disproportionality algorithms (ROR, PRR, BCPNN, MGPS) were combined, high-intensity signals – exemplified by joint deposition (ROR = 435.03) – still require clinical validation, while low-frequency preferred terms (<10 reports) risk false positivity from Bayesian shrinkage and the ≥3-report threshold may miss rare yet clinically critical ADEs in vulnerable subgroups. FAERS lacks original narratives, laboratory values and imaging data, preventing verification of encephalopathy grading, latency periods, dose–response relationships or the radiological features of joint deposition.

5.2. Future research directions

Future research should prioritize multinational collaboration and mechanistic validation to systematically address the identified safety signals. First, integrating multiple pharmacovigilance databases – including FAERS, EudraVigilance, VigiBase, and Asian repositories such as JADER and KIDS-KAERS – will enable quantification of geographic and ethnic effect modification across diverse healthcare systems, with particular attention to susceptibility differences in neurotoxicity among Asian populations, and further confirm the robustness of the joint deposition signal (ROR = 435.03). Second, preclinical studies using NK-1R knockout arthritis models should be conducted to elucidate the biological plausibility of joint deposition, thereby identifying novel therapeutic targets for inflammatory diseases. Finally, prospective surveillance of aprepitant use in pediatric (<18 years) and geriatric (>75 years) cohorts within oncology settings should be established to systematically evaluate the drug's safety profile in these vulnerable age groups.

6. Conclusion

To conclude, this research conducted a thorough disproportionality analysis using FAERS' real-world data to detect and pinpoint ADEs that have a strong correlation with aprepitant. The ADEs discovered in this research generally aligned with the side effects listed in the medication's leaflet. However, we also identified several new, highly significant ADEs, such as joint deposition, roughening of the oral mucosa, encephalopathy, dysplasia, febrile myeloid regenerative conditions, small cell lung cancer, and tonic-clonic movements. Among these, the strongest correlation was found to be joint deposition with aprepitant use, a discovery that could potentially offer novel evidence for the application of aprepitant in arthritis therapy. Furthermore, the research discovered that the 2 most frequent side effects of aprepitant were dyspnea and nausea. These findings provide guidance for the drug's safe application in clinical settings, aiding in reducing the potential risks associated with its use.

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Table 6

Top 30 PTs for ADE signal strength related to aprepitant.

PT	Case number	ROR (95% CI)	PRR (95% CI)	Chi-square	IC (95% CI)	EBGM (95% CI)
Joint deposit*	3	435.03 (134.81, 1403.79)	434.87 (134.82, 1402.72)	1212.04	8.67 (0.48, 3.49)	405.94 (125.80, 1309.94)
Infusion site phlebitis	6	186.51 (82.75, 420.34)	186.37 (82.82, 419.80)	1073.41	7.50 (1.65, 3.87)	180.87 (80.25, 407.63)
Infusion site irritation	16	118.88 (72.45, 195.06)	118.65 (72.82, 194.50)	1830.86	6.86 (3.19, 4.61)	116.40 (70.94, 191.00)
Infusion site urticaria	8	110.30 (54.80, 222.01)	110.19 (54.82, 221.65)	850.23	6.76 (2.09, 4.04)	108.25 (53.78, 217.89)
Infusion site rash	11	69.85 (38.54, 126.61)	69.76 (38.82, 126.34)	737.09	6.11 (2.53, 4.21)	68.98 (38.06, 125.03)
Phlebitis	38	52.19 (37.90, 71.87)	51.95 (37.82, 71.45)	1883.07	5.69 (4.02, 4.95)	51.52 (37.41, 70.96)
Infusion site pain	64	43.01 (33.60, 55.05)	42.69 (33.82, 54.53)	2587.77	5.41 (4.33, 5.06)	42.40 (33.12, 54.26)
Oral mucosal roughening*	3	99.30 (31.73, 310.80)	99.26 (31.82, 310.56)	287.14	6.61 (0.50, 3.41)	97.69 (31.21, 305.75)
Vein discoloration	5	75.77 (31.36, 183.08)	75.72 (31.82, 182.87)	364.16	6.23 (1.30, 3.68)	74.81 (30.96, 180.75)
Hiccups	43	40.19 (29.75, 54.29)	39.99 (29.82, 53.93)	1624.04	5.31 (3.96, 4.84)	39.73 (29.41, 53.67)
Injection site phlebitis	3	84.59 (27.06, 264.39)	84.56 (27.82, 264.19)	244.32	6.38 (0.49, 3.40)	83.41 (26.69, 260.72)
Infusion site reaction	13	45.48 (26.34, 78.51)	45.41 (26.82, 78.33)	560.43	5.49 (2.67, 4.22)	45.08 (26.11, 77.83)
Packaging design issue	3	77.75 (24.89, 242.86)	77.72 (24.82, 242.68)	224.34	6.26 (0.49, 3.40)	76.75 (24.57, 239.75)
Therapeutic product effective for unapproved indication	3	72.22 (23.13, 225.47)	72.19 (23.82, 225.30)	208.15	6.16 (0.49, 3.39)	71.36 (22.86, 222.78)
Product barcode issue	3	58.94 (18.90, 183.79)	58.92 (18.82, 183.65)	169.17	5.87 (0.48, 3.38)	58.36 (18.72, 181.99)
Encephalopathy*	71	21.89 (17.32, 27.66)	21.71 (17.82, 27.38)	1398.45	4.44 (3.73, 4.41)	21.64 (17.12, 27.35)
Infusion site erythema	23	25.05 (16.62, 37.75)	24.98 (16.82, 37.61)	527.42	4.64 (3.05, 4.23)	24.88 (16.51, 37.50)
Extravasation	15	25.46 (15.33, 42.30)	25.42 (15.82, 42.19)	350.40	4.66 (2.60, 4.05)	25.32 (15.24, 42.06)
Sense of oppression	5	29.98 (12.45, 72.20)	29.96 (12.82, 72.12)	139.29	4.90 (1.18, 3.54)	29.82 (12.38, 71.82)
Aplasia*	8	24.49 (12.22, 49.05)	24.46 (12.82, 48.97)	179.32	4.61 (1.80, 3.72)	24.37 (12.17, 48.81)
Febrile bone marrow aplasia*	11	20.56 (11.37, 37.17)	20.53 (11.82, 37.09)	203.70	4.36 (2.13, 3.80)	20.46 (11.32, 37.00)
Infusion site swelling	13	19.02 (11.03, 32.80)	18.99 (11.82, 32.72)	220.93	4.24 (2.28, 3.83)	18.94 (10.98, 32.66)
Flushing	178	12.39 (10.68, 14.37)	12.14 (10.82, 14.04)	1819.70	3.60 (3.29, 3.73)	12.12 (10.45, 14.06)
Infusion site induration	4	28.20 (10.56, 75.32)	28.19 (10.82, 75.25)	104.40	4.81 (0.83, 3.42)	28.06 (10.51, 74.95)
Anaphylactic reaction	83	12.17 (9.80, 15.12)	12.06 (9.82, 14.94)	841.05	3.59 (3.09, 3.73)	12.04 (9.70, 14.95)
Vein disorder	12	16.88 (9.57, 29.75)	16.85 (9.82, 29.69)	178.47	4.07 (2.12, 3.73)	16.81 (9.53, 29.63)
Procedural vomiting	3	29.28 (9.42, 91.05)	29.27 (9.82, 90.98)	81.52	4.86 (0.41, 3.31)	29.13 (9.37, 90.60)
Small cell lung cancer*	5	21.40 (8.89, 51.52)	21.39 (8.82, 51.46)	96.86	4.41 (1.10, 3.46)	21.32 (8.86, 51.32)
Infusion site discomfort	3	27.47 (8.84, 85.42)	27.47 (8.82, 85.36)	76.16	4.77 (0.40, 3.30)	27.35 (8.80, 85.03)
Tonic-clonic movements*	4	23.20 (8.69, 61.96)	23.19 (8.82, 61.90)	84.62	4.53 (0.80, 3.39)	23.11 (8.65, 61.70)

ADE = adverse drug event, BCPNN = Bayesian confidence propagation neural network, CI = confidence interval, EBGM = empirical Bayesian geometric mean, IC = information component, PRR = proportional reporting ratio, PT = preferred terms, ROR = reporting odds ratio.

*Indicates that the PT is not mentioned in the drug insert.

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