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Real-World pharmacovigilance analysis of drug-related conjunctivitis using the FDA adverse event reporting system database

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Drug-related conjunctivitis can compromise ocular health and quality of life. To evaluate its epidemiology, we analyzed reports from the FDA Adverse Event Reporting System (FAERS) spanning January 2004 to June 2024. The control group in this study comprised individuals using non-target drugs, while the experimental group consisted of individuals using target drugs. Using disproportionality analysis, we identified drugs with a positive signal for conjunctivitis and stratified their risk levels; we also examined induction periods to assess the speed of onset. Among 38 drugs most frequently reported for conjunctivitis, two ophthalmic agents—brimonidine (ROR = 23.04) and latanoprost (ROR = 10.55)—and eight non-ophthalmic drugs, including tralokinumab (ROR = 83.3), dupilumab (ROR = 18.92), and allopurinol (ROR = 5.04), were associated with positive signals. Tralokinumab, brimonidine, dupilumab, and latanoprost were identified as high-association medications. Notably, ophthalmic agents had a significantly shorter induction period than non-ophthalmic drugs (mean 125.9 vs. 298.4 days). These findings underscore the need for vigilant pharmacovigilance and further investigation into the etiology and prevention of drug-related conjunctivitis.

Keywords Conjunctivitis, FAERS database, Real-world study, Disproportional analysis, Pharmacovigilance study

Abbreviations

FDA	U.S. Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
READUS-PV	The Reporting of A Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance
ROR	Ratio of Odds Ratios
PRR	Proportional Reporting Ratio
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
DEMO	Demographic Record
REAC	Adverse Event Record
DRUG	Drug Record
OUTC	Outcome Record
RPSR	Report Source Record
THER	Therapy Record
INDI	Indication Record

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PS	Primary Suspected cases
BCPNN	Bayesian Confidence Propagation Neural Network
MGPS	Multi-Item Gamma Poisson Shrinker
CI	Confidence Interval
MDs	Medical doctors
PHs	Pharmacists
AD	Atopic dermatitis
IL	Interleukin
RR	Risk Ratio
OX40	CD134, TNFRSF4
BAC	Benzalkonium chloride
HLA-DR	Human Leukocyte Antigen- DR isotype
SJS	Stevens-Johnson syndrome
TEN	Toxic Epidermal Necrolysis

The conjunctiva, a thin and semi-transparent membrane, covers the anterior part of the sclera and the inner side of the eyelids. Inflammation or infection of the conjunctiva leads to the dilation of its vessels, resulting in congestion and edema. This condition, often accompanied by ocular discharge, is known as conjunctivitis[1]. Various factors, including infectious agents such as viruses and bacteria, as well as non-infectious agents like allergies, chemical irritants, and inflammation secondary to certain autoimmune diseases, can trigger conjunctivitis[2]. Medications may also cause a conjunctival reaction termed drug-related conjunctivitis, which can result from the direct toxic effects of the drugs or allergic reactions to their components[3]. Although this reaction may be induced by topical medications, such as eye drops, it is also associated with systemically administered drugs[4]. For instance, benzalkonium chloride, a common preservative in eye medications, frequently triggers drug-related conjunctivitis[5].

Conjunctivitis is a widespread condition that imposes substantial health, economic, and social burdens. It is estimated that approximately 6 million people in the United States are affected by acute conjunctivitis annually[6]. The cost of treating bacterial conjunctivitis alone is estimated to range from $377 million to $857 million per year[7]. Additionally, many U.S. state health departments require students to receive topical antibiotic eye drops, regardless of the underlying cause of conjunctivitis, before they can return to school[8]. Despite its clinical prevalence, systematic research on drug-related conjunctivitis is relatively scarce, primarily derived from individual case reports. This scarcity limits our comprehensive understanding of its pathogenesis, epidemiological characteristics, and clinical management. Furthermore, the continuous introduction of new medications and diversification of medication practices may alter the spectrum of drugs causing drug-related conjunctivitis and the associated disease patterns, necessitating ongoing monitoring and research to update and refine our knowledge.

The FDA Adverse Event Reporting System (FAERS), a comprehensive database, collects spontaneous adverse event reports following the use of medical products. As a crucial component of drug safety monitoring, FAERS provides essential data support for epidemiological studies of drug adverse reactions and post-market drug regulation[9]. This research evaluates the association of drug-related conjunctivitis associated with the use of these data in a large-scale real-world setting, encompassing both topical ocular and systemic medications. The study aims to enhance pharmacovigilance and guide individualized medication use in clinical practice. Moreover, this research may reveal potential association of drug-related conjunctivitis not yet mentioned on some drug labels[10].

Materials and methods

Data source and study design

This study employs a retrospective observational pharmacovigilance analysis utilizing the publicly accessible FAERS database. All methods and protocols of this study were conducted in compliance with the relevant guidelines and regulations outlined in "The Reporting of A Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV)[11]. Since the FAERS database is publicly accessible and patient records are anonymized, this study does not require informed consent or ethical approval. Managed by the U.S. Food and Drug Administration, FAERS is a spontaneous reporting system that compiles adverse event reports from healthcare providers, patients, pharmaceutical manufacturers, and other stakeholders[12]. The FAERS data used in this study are available at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Adverse event symptoms are encoded using the Medical Dictionary for Regulatory Activities (MedDRA), an internationally standardized and clinically validated tool. The Open Vigil 2.1-MedDRA software, accessible through provided links, supports the retrieval and extraction of relevant data. To ensure data accuracy and reliability, this analysis includes only cases reported by healthcare professionals (medical doctors and pharmacists, coded as MD, PH). Between January 2004 and June 2024, a total of 21,035,995 original entries were recorded in the FAERS database; after the elimination of duplicate reports, 17,785,793 entries remained. Additionally, deduplication of drug names listed under commercial brands reduced the number of unique drugs to 1,300. The data cleaning process is illustrated in Fig. 1.

Data extraction

We identified reports of conjunctivitis from the Adverse Drug Reaction (REAC) file using the preferred terms and associated codes: "Conjunctivitis" (code = 10,010,741), "Conjunctivitis Infective" (code = 10,010,741), "Conjunctivitis Allergic" (code = 10,010,744), "Noninfective Conjunctivitis" (code = 10,074,701), "Giant Papillary Conjunctivitis" (code = 10,018,258), "Photoelectric Conjunctivitis" (code = 10,063,669), and "Ligneous Conjunctivitis" (code = 10,071,570). We extracted the number of reports and their corresponding PRIMARYIDs.

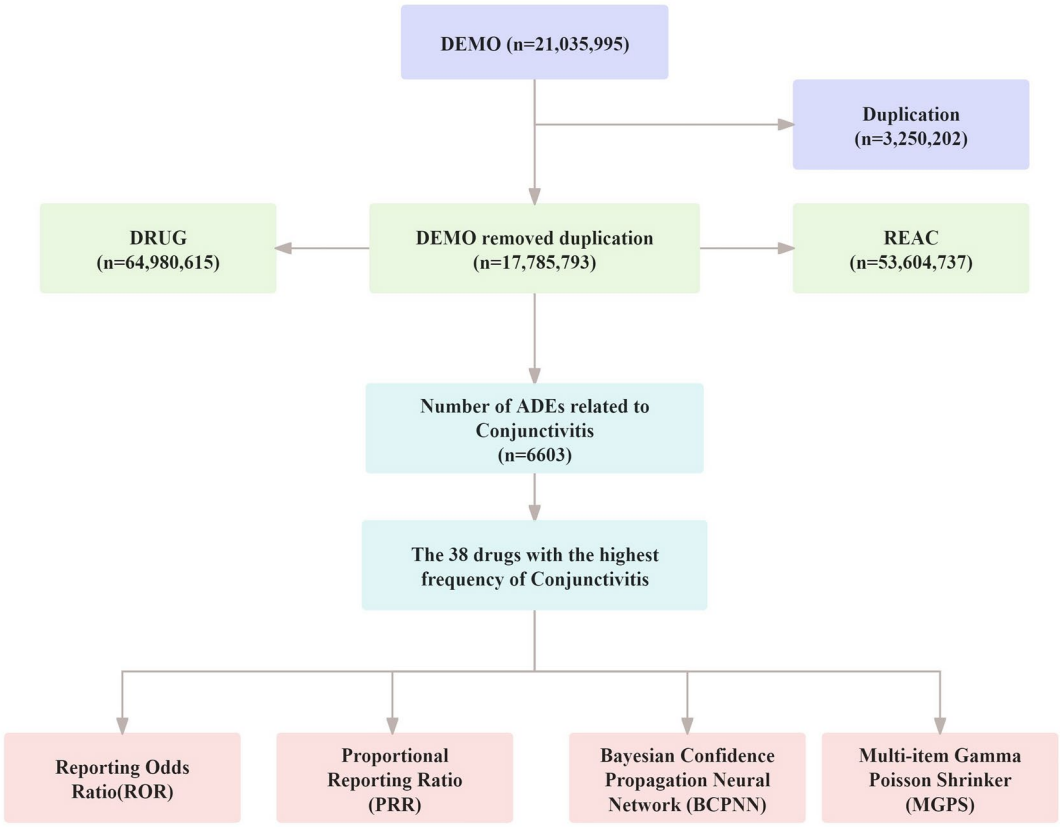

Fig. 1. The flow diogram of screening reports containing conjunctivitis elicited by diverse agents from the FAERS database.

Utilizing these IDs, we retrieved additional data, including Individual Safety Reports (ISR), demographic information [patient age, gender, and reporter country from the Demographic Record (DEMO) file], adverse event records, medication usage details, report timestamps, and treatment outcome records. Our analysis focused exclusively on drugs primarily suspected of causing these events. We excluded drugs categorized as "concomitant medication," "secondary suspected drugs," and "interaction drugs" due to the significant uncertainty regarding their association with the adverse events.

Statistical analysis

The control group in this study comprised individuals using non-target drugs, while the experimental group consisted of individuals using target drugs. To identify potential adverse event signals, we employed four disproportionality analysis methods: the Reporting Odds Ratio (ROR)[13], Proportional Reporting Ratio (PRR)[14], Bayesian Confidence Propagation Neural Network (BCPNN)[15], and Multi-item Gamma Poisson Shrinker (MGPS)[16]. The criteria for identifying positive signals are as follows: (1) For ROR, the criteria are a ≥ 3 and a 95% confidence interval (CI) for the ROR (ROR 95% CI lower limit) > 1; (2) for PRR, the criteria are a ≥ 3 and a PRR 95% CI lower limit > 1; (3) for BCPNN, the criterion is that the lower limit of the 95% CI for the information component ($IC_{0.25}$) > 0; (4) and for MGPS, the criteria are a > 0 and the empirical Bayesian geometric mean lower 95% CI for the posterior distribution ($EBGM_{0.5}$) ≥ 2. For more specific information, please refer to Supplementary Tables 1 and 2. We considered a signal valid only if it met the criteria across all four disproportionality analysis methods, thereby indicating a potential association between the drug and conjunctivitis. Furthermore, we analyzed the duration of drug use prior to the onset of drug-induced conjunctivitis and compared onset times across various medications. Employing the BCPNN algorithm, we categorized the association of conjunctivitis linked with different drugs into four quartiles and evaluated the duration of these adverse reactions.

Results

Basic information of patients with drug-related conjunctivitis

From 2004 to 2022, there was a consistent increase in the number of reports concerning drug-related conjunctivitis. By June 2024, a total of 6,603 patients had reported adverse events linked to this condition, with the peak occurring in 2022, accounting for 923 cases [Fig. 2A]. The average age of these patients was approximately 47.41 ± 22.84 years, as detailed in Table 1. Notably, the age distribution of these patients approximated a normal curve, initially increasing before decreasing, with the most reports found in the 61–65 age group [Fig. 2B]. The majority of the reports originated from the United States, which accounted for 57.10% of the total (n = 3770)

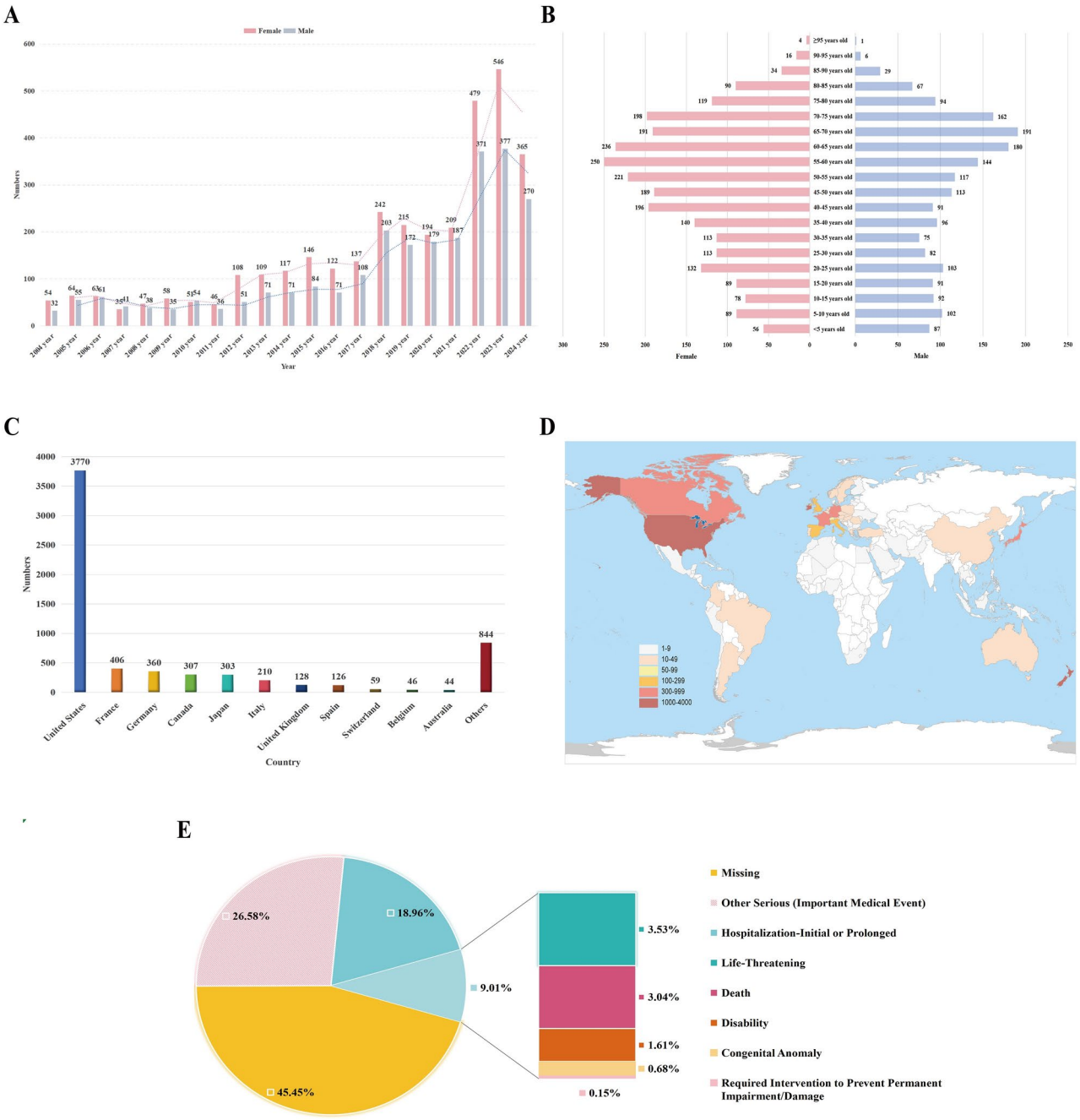

Fig. 2. Characteristics of reports involved in drug-related conjunctivitis from the FAERS database. (**A**) displays a timeline chart showing the distribution of reported adverse events of conjunctivitis over time. (**B**) Depicts a pyramid chart of age distribution among patients reporting adverse events of conjunctivitis, categorized by gender. (**C**) presents a histogram of the distribution of reported adverse events of conjunctivitis by country. (**D**) showcases a heatmap of the distribution of reported adverse events of conjunctivitis by country. (**E**) illustrates a pie chart representing the distribution of outcomes among patients experiencing adverse events of conjunctivitis.

[Figs. 2C and 2D]. Excluding cases with missing data, nearly 26.58% of the reports indicated other serious outcomes, including a significant number of hospitalizations (either initial or prolonged) [Fig. 2E]. For additional details, see Table 1.

Classification of drugs associated by therapeutic purpose

In light of the fact that some medications are prescribed to treat conditions associated with conjunctivitis yet may show positive signals due to insufficient efficacy, we excluded these drugs from our analysis. We also verified the brand and generic names of these medications. After screening the 1,300 drugs in our database, we identified

Variables	Value
Age (year)	47.41 ± 22.84
Weight (Kg)	68.61 ± 27.07
Gender	
Female	3396 (51.43%)
Male	2554 (38.68%)
Missing	653 (9.89%)
Outcome	
Other Serious (Important Medical Event)	1755 (609.89%)
Hospitalization -Initial or Prolonged	1252 (309.89%)
Disability	106 (209.89%)
Death	201 (109.89%)
Life-Threatening	201 (109.89%)
Required Intervention to Prevent Permanent Impairment/Damage	10 (709.89%)
Congenital Anomaly	45 (9.89%)
Missing	3001 (509.89%)
Country	
United States	3770 (57.10%)
France	406 (6.15%)
Germany	360 (5.45%)
Canada	307 (4.65%)
Japan	303 (4.59%)
Italy	210 (3.18%)
United Kingdom	151 (1.94%)
Missing	128 (2.29%)
Others	968 (14.66%)

Table 1. Baseline Data of Conjunctivitis Patients Reported in the FAERS Database. Continuous numerical variables are expressed as mean ± standard deviation, and categorical variables are presented as n(%).

the top 38 drugs with the highest number of reported cases. These drugs were primarily categorized into six classes, with dupilumab reporting the highest incidence, as outlined in Table 2 and illustrated in Fig. 3. Signal calculations were performed for these 38 drugs using four disproportionality analysis methods. Ten of these drugs met the positive criteria across all disproportionality analysis methods. The drugs with the highest ROR were tralokinumab (83.30, 95%CI = 47.78—145.20), brimonidine(23.04, 95%CI = 17.99—29.52), dupilumab (18.92, 95%CI = 17.97—19.92), latanoprost(10.55, 95%CI = 7.36—15.12) and allopurinol(5.04, 95%CI = 3.40—7.46) , with detailed data provided in Table 2.

Drug classification by association degree

We utilized the BCPNN algorithm to assess the association of drug-related conjunctivitis. The BCPNN values are categorized as follows: values less than 3 indicate a low association, while values greater than 3 signify a high association. Applying this framework, we evaluated the association for drugs that tested positive across all disproportionality analysis methods. Tralokinumab, brimonidine, and dupilumab emerged as the top three drugs with relatively high association, recording BCPNN values of 6.32, 4.50, and 3.56, respectively. Conversely, drugs such as erlotinib, lamotrigine, and canakinumab showed relatively lower association, with BCPNN values of 1.69, 2.07, and 2.16, detailed in Fig. 4.

Comparison of drug-related onset times between ophthalmic and non-ophthalmic medications

We categorized the drugs based on their primary therapeutic uses into two groups: ophthalmic medications (2 drugs) and non-ophthalmic medications (8 drugs). Comprehensive data on the onset times of drug-related effects were collected, and differences between these groups were analyzed using cumulative risk curves. The analysis revealed that ophthalmic medications tend to exhibit a shorter time to onset of drug-related effects compared to non-ophthalmic medications. Specifically, the average onset time for ophthalmic medications was 125.9 days, while it extended to 298.4 days for non-ophthalmic medications. For a detailed breakdown of these findings, refer to Table 3 and Fig. 5.

Discussion

Our study reviewed nearly two decades of anonymized conjunctivitis reports from the FAERS database, providing a comprehensive overview of medications potentially associated with conjunctivitis. From 6,603 reports, we identified the top 38 drugs frequently linked to conjunctivitis and applied disproportionality analysis

Medications	Drug	N	ROR(95%Cl)	PRR(χ^2)	EBGM(EBGM05)	IC(IC025)
Anticancer drugs	Pembrolizumab	15	0.52 (0.32—0.87)	0.52 (6.43)	0.53 (0.34)	-0.93 (-2.59)
Anticancer drugs	Cetuximab	16	**4.94 (3.02—8.08)**	**4.93 (50.07)**	**4.92 (3.26)**	**2.30 (0.63)**
Anticancer drugs	Capecitabine	19	0.84 (0.54—1.32)	0.84 (0.56)	0.84 (0.58)	-0.25 (-1.91)
Anticancer drugs	Afatinib	19	2.88 (1.84—4.53)	2.88 (23.29)	2.88 (1.97)	1.52 (-0.14)
Anticancer drugs	Docetaxel	19	1.10 (0.70—1.73)	1.1 (0.19)	1.1 (0.76)	0.14 (-1.52)
Anticancer drugs	Lenalidomide	22	0.30 (0.20—0.46)	0.3 (34.77)	0.31 (0.22)	-1.7 (-3.37)
Anticancer drugs	Trastuzumab	26	0.86 (0.59—1.27)	0.86 (0.58)	0.86 (0.62)	-0.21 (-1.88)
Anticancer drugs	Rituximab	28	0.39 (0.27—0.56)	0.39 (27.09)	0.39 (0.29)	-1.36 (-3.03)
Anticancer drugs	Imatinib	29	1.16 (0.81—1.68)	1.16 (0.67)	1.16 (0.86)	0.22 (-1.45)
Anticancer drugs	Fluorouracil	32	3.18 (2.25—4.50)	3.18 (47.49)	3.16 (2.37)	1.66 (0)
Anticancer drugs	Nivolumab	41	1.47 (1.08 – 2.00)	1.47 (6.18)	1.47 (1.14)	0.56 (-1.11)
Anticancer drugs	Erlotinib	44	**3.26 (2.42—4.38)**	**3.25 (68.19)**	**3.24 (2.52)**	**1.69 (0.03)**
Anticancer drugs	Methotrexate	54	0.69 (0.53—0.90)	0.69 (7.46)	0.69 (0.55)	-0.53 (-2.20)
Immunomodulator	Palivizumab	7	2.17 (1.04—4.57)	2.17 (4.43)	2.17 (1.17)	1.12 (-0.55)
Immunomodulator	Tralokinumab	13	**83.30 (47.78—145.20)**	**79.91 (1011.36)**	**79.74 (50.09)**	**6.32 (4.64)**
Immunomodulator	Abatacept	16	1.02 (0.62—1.67)	1.02 (0.01)	1.02 (0.68)	0.03 (-1.64)
Immunomodulator	Canakinumab	21	**4.49 (2.92—6.90)**	**4.48 (56.64)**	**4.47 (3.12)**	**2.16 (0.49)**
Immunomodulator	Ocrelizumab	23	1.41 (0.94—2.13)	1.41 (2.76)	1.41 (1.00)	0.5 (-1.17)
Immunomodulator	Tocilizumab	29	0.90 (0.62—1.30)	0.9 (0.32)	0.9 (0.66)	-0.15 (-1.82)
Immunomodulator	Fingolimod	30	0.82 (0.57—1.18)	0.82 (1.14)	0.82 (0.61)	-0.28 (-1.95)
Immunomodulator	Rofecoxib	44	0.58 (0.43—0.77)	0.58 (13.64)	0.58 (0.45)	-0.79 (-2.45)
Immunomodulator	Secukinumab	57	1.76 (1.36—2.29)	1.76 (18.56)	1.75 (1.41)	0.81 (-0.86)
Immunomodulator	Adalimumab	81	0.62 (0.50—0.78)	0.63 (17.98)	0.63 (0.52)	-0.67 (-2.33)
Immunomodulator	Infliximab	86	0.94 (0.76—1.16)	0.94 (0.36)	0.94 (0.78)	-0.09 (-1.76)
Immunomodulator	Etanercept	148	0.45 (0.39—0.53)	0.45 (94.82)	0.47 (0.41)	-1.1 (-2.76)
Immunomodulator	Dupilumab	2389	**18.92 (17.97—19.92)**	**18.81 (24,446.90)**	**11.8 (11.30)**	**3.56 (1.89)**
Musculoskeletal drugs	Zoledronic Acid	52	1.72 (1.31—2.26)	1.72 (15.63)	1.72 (1.37)	0.78 (-0.89)
Musculoskeletal drugs	Alendronate	58	1.09 (0.85—1.42)	1.09 (0.47)	1.09 (0.88)	0.13 (-1.54)
Ophthalmic medications	Ranibizumab	27	2.29 (1.57—3.34)	2.28 (19.43)	2.28 (1.66)	1.19 (-0.48)
Ophthalmic medications	Latanoprost	30	**10.55 (7.36—15.12)**	**10.5 (256.66)**	**10.45 (7.73)**	**3.39 (1.72)**
Ophthalmic medications	Brimonidine	64	**23.04 (17.99—29.52)**	**22.79 (1319.68)**	**22.56 (18.33)**	**4.5 (2.83)**
Other medications	Amlodipine	16	0.66 (0.41—1.08)	0.66 (2.72)	0.66 (0.44)	-0.59 (-2.26)
Other medications	Pregabalin	18	0.41 (0.26—0.65)	0.41 (15.03)	0.41 (0.28)	-1.27 (-2.94)
Other medications	Allopurinol	25	**5.04 (3.40—7.46)**	**5.03 (80.32)**	**5.01 (3.60)**	**2.32 (0.66)**
Other medications	Ondansetron	40	**4.51 (3.30—6.15)**	**4.5 (108.18)**	**4.48 (3.45)**	**2.16 (0.50)**
Other medications	Ibuprofen	47	1.91 (1.44—2.55)	1.91 (20.32)	1.91 (1.50)	0.93 (-0.74)
Other medications	Lamotrigine	91	**4.26 (3.47—5.25)**	**4.26 (223.43)**	**4.21 (3.54)**	**2.07 (0.41)**
Respiratory system medications	Budesonide	25	1.92 (1.29—2.84)	1.91 (10.88)	1.91 (1.38)	0.93 (-0.73)

Table 2. Statistical Values and Distribution of Drug-Related Conjunctivitis.

to determine 10 drugs with significant associations. This analysis represents the most comprehensive list to date of medications potentially inducing conjunctivitis.

The drugs were categorized into six classes: immunomodulators, musculoskeletal drugs, anticancer drugs, ophthalmic medications, respiratory system medications, and others. Importantly, while some drugs, such as dupilumab and lamotrigine, were frequently reported, the high number of reports does not necessarily equate to a stronger association due to varying real-world usage rates[17–19].

Using four disproportionality analysis methods—ROR, PRR, BCPNN, and MGPS—we identified ten drugs meeting positive signal criteria across all methods. These were further classified into high-association (e.g., tralokinumab, brimonidine, dupilumab, and latanoprost) and low-association categories, based on ROR values. This approach enhances our understanding of drug-related conjunctivitis and provides valuable insights for individualized medication strategies.

Tralokinumab, a fully human IgG4 monoclonal antibody targeting Interleukin-13 (IL-13), neutralizes the activity of IL-13 by inhibiting its binding to the receptor, thereby aiding in alleviating symptoms of atopic dermatitis (AD). It received approval in the United States in December 2021[20]. A case report highlighted a 61-year-old male, without a history of rheumatic diseases or prior ophthalmic conditions, who experienced significant improvement in his AD symptoms since initiating tralokinumab treatment. However, he reported worsening bilateral eye redness, irritation, tearing, and photosensitivity starting six weeks after the initiation of tralokinumab injections. His ocular symptoms did not improve with the use of artificial tears[21]. A meta-analysis

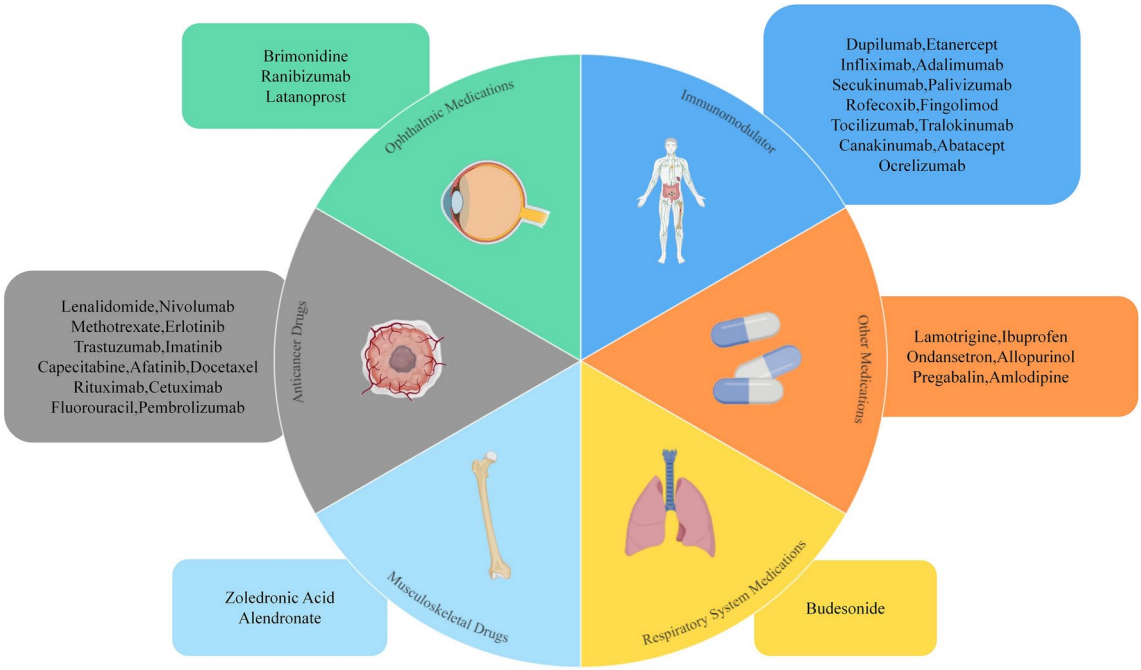

Fig. 3. The identification and classification of drugs associated with conjunctivitis.

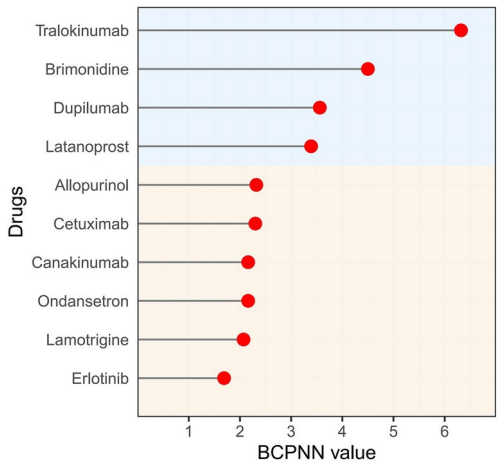

Fig. 4. Forest plots of different agents inducing conjunctivitis under BCPNN classification. Ten drugs were ranked according to their BCPNN values, allowing us to classify them into two association categories: high and low. High association drugs include tralokinumab, brimonidine, dupilumab and latanoprost. Low association drugs include allopurinol, cetuximab, canakinumab, ondansetron, lamotrigine and erlotinib.

indicated that the use of tralokinumab increases the risk of conjunctivitis compared to placebo (Odds Ratio [OR] = 2.46 [95% CI 1.60—3.77])[21]. Furthermore, an analysis of five clinical trials found a higher incidence of conjunctivitis adverse events in the tralokinumab-treated group (7.5%) than in the placebo group (3.2%) among patients with AD[22]. The exact pathophysiological mechanism of tralokinumab-induced conjunctivitis is not fully understood, but some studies suggest that these monoclonal antibodies, by binding to IL-4Rα and thus inhibiting IL-4 and IL-13, prevent the activation of conjunctival goblet cells, leading to underdevelopment and decreased mucin production. This affects the stability of the tear film and the function of the mucosal epithelial barrier, thereby inducing conjunctivitis[23,24]. Frequently studied alongside tralokinumab, dupilumab is a fully human monoclonal antibody that binds to and inhibits signaling through the IL-4receptor, blocking the action of pro-inflammatory cytokines. This antibody is primarily used for treating eczema, allergic reactions, and sinusitis, among other atopic or allergic conditions[25]. A meta-analysis of dupilumab and conjunctivitis showed that dupilumab users exhibited a higher risk of conjunctivitis compared to placebo users (Risk Ratio [RR] = 1.89; 95% CI = 1.34–2.67)[26]. The mechanism of conjunctivitis in patients treated with dupilumab is not completely understood, but several hypotheses have been proposed: reduced ocular cytokines provide

Classification	Drug	Mean (day)	Q1 (day)	Q3 (day)	BCPNN
Non-Ophthalmic Drugs	Latanoprost	364.86	9.50	130.50	3.39
Non-Ophthalmic Drugs	Canakinumab	340.42	98.75	395.00	2.16
Non-Ophthalmic Drugs	Dupilumab	145.56	0	111.25	3.56
Non-Ophthalmic Drugs	Erlotinib	108.62	20.00	121.00	1.69
Non-Ophthalmic Drugs	Tralokinumab	101.40	10.00	180.00	6.32
Non-Ophthalmic Drugs	Cetuximab	64.50	23.75	91.50	2.30
Non-Ophthalmic Drugs	Allopurinol	14.09	12.00	20.00	2.32
Ophthalmic Remedy	Brimonidine	273.90	21.50	266.50	4.50
Ophthalmic Remedy	Lamotrigine	26.71	9.00	20.75	2.07

Table 3. Drug-Related Time Distribution of Drug-Related Conjunctivitis Caused by Different Drugs.

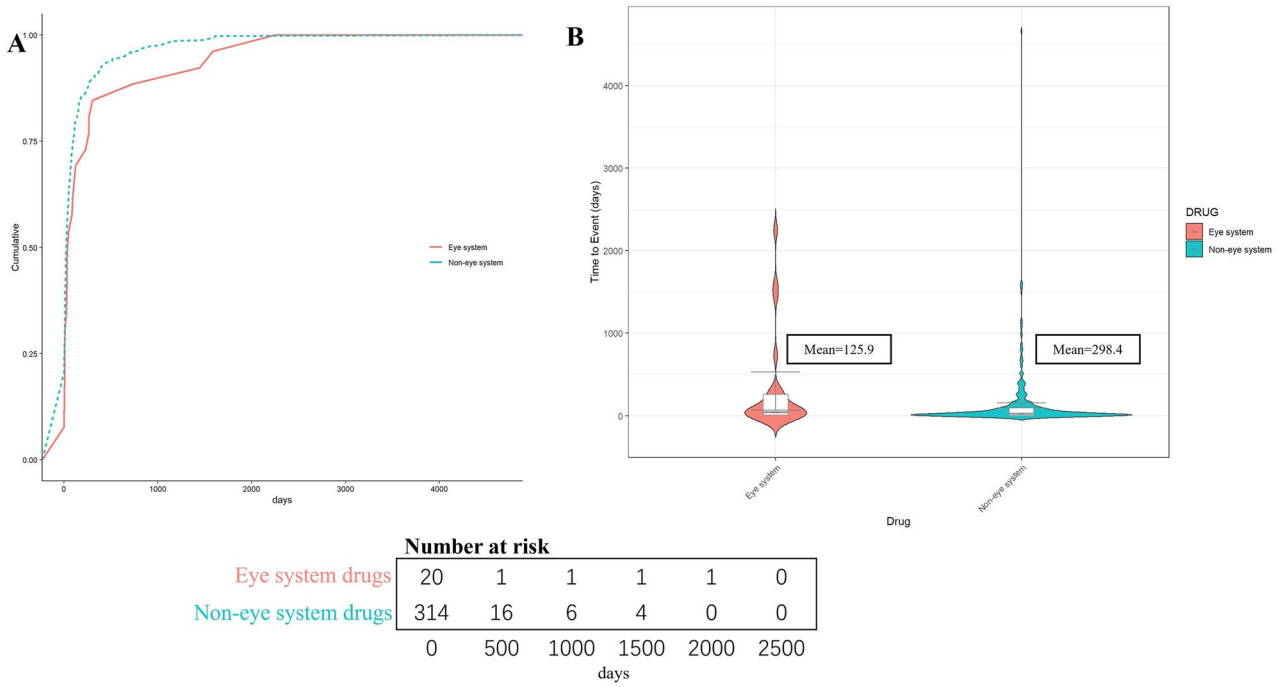

Fig. 5. Time to event onset of conjunctivitis elicited by various drugs. (**A**) shows a cumulative risk timeline of drug induction for eye system drugs and non-eye system drugs. (**B**) exhibits a violin plot for time disparities in two group induction.

a favorable environment for the growth of Demodex mites, leading to an IL-17 mediated inflammatory response[22]; eosinophilia following dupilumab treatment[15]; increased downstream activity of CD134, TNFRSF4 (OX40) ligand in the eye[27]; and systemic suppression of IL-13 indirectly causing a reduction in conjunctival goblet cells and mucin production[24]. Bakker and colleagues found a significant lack of conjunctival goblet cells, accompanied by T-cell and eosinophil infiltration after performing diagnostic biopsies on the inferior fornix conjunctiva of patients with AD complicated by dry eye associated conjunctivitis. The study suggested that a lack of mucin leads to increased ocular surface irritation, thus triggering conjunctivitis[23,28]. In our study, dupilumab was the most frequently reported drug (n = 2389; ROR = 18.92), and timely identification and intervention are crucial for patients with AD using dupilumab and tralokinumab.

Brimonidine, an α-2 adrenergic agonist primarily used for treating glaucoma and ocular hypertension, has been confirmed to exhibit potential ocular toxicity in several studies. Bae et al. reported two cases of atypical conjunctival lesions in patients using brimonidine, both of which resolved after discontinuation of the drug[29]. Hwang et al. also found that after long-term use of 0.15% brimonidine, 19 patients with an average medication duration of 29 months were suspected of developing conjunctival lymphoproliferative lesions[30]. This may be related to an allergic reaction to brimonidine itself, a side effect that has also been confirmed[31].

Latanoprost, the first topical prostaglandin F2α analogue used for treating glaucoma, has been found to have better tolerability compared to timolol. However, latanoprost eye drops typically contain preservatives, which are generally considered a major factor causing ocular surface side effects. Preservatives used in latanoprost eye drops, such as benzalkonium chloride (BAC), can cause or exacerbate dry eye disease through various

mechanisms, such as toxicity, pro-inflammatory effects, and detergent properties, as has been extensively demonstrated in numerous experimental and clinical studies[32]. Several clinical studies have shown that switching from preserved latanoprost eye drops to a preservative-free formulation can significantly alleviate ocular surface damage and ocular symptoms[33]. The contribution of latanoprost itself to adverse ocular surface reactions remains controversial. One clinical trial showed that patients using latanoprost eye drops containing 0.02% BAC exhibited higher ocular surface inflammation markers Human Leukocyte Antigen- DR isotype (HLA-DR) expression in the conjunctiva compared to patients using an unpreserved alternative tear solution with the same concentration of BAC, suggesting that latanoprost itself might induce ocular surface inflammation[34]. On the other hand, an experiment conducted on cultured human corneal epithelial sheets indicated that preservative-free latanoprost eye drops impaired corneal epithelial barrier function after 6 h of exposure[35]. Clinicians should consider the individual ocular condition of patients when choosing ophthalmic medications and weigh the benefits against potential side effects to minimize adverse effects from treatment.

While low-association drugs demonstrate a slightly weaker clinical association with drug-induced conjunctivitis compared to high-association drugs, their role remains significant. This category primarily includes allopurinol (BCPNN value = 2.32), cetuximab (BCPNN value = 2.30), ondansetron (BCPNN value = 2.16), canakinumab (BCPNN value = 2.16), lamotrigine (BCPNN value = 2.07), and erlotinib (BCPNN value = 1.69). In clinical practice, it has been observed that xanthine oxidase inhibitors, targeted therapies, and anti-inflammatory drugs exhibit a certain correlation with the association of developing conjunctivitis, particularly in susceptible individuals. Allopurinol, primarily used to treat hyperuricemia, has recently been strongly associated with the occurrence of Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), where conjunctivitis is often one of the initial symptoms[36]. Similarly, lamotrigine, an antiepileptic drug, has been implicated in multiple cases of SJS, with specific genetic markers, including HLA, playing a crucial role in its pathogenesis. These HLA alleles present antigens to T cells, activating the immune response[37]. It is noteworthy that HLA gene typing varies among ethnicities, and HLA typing screening is clinically significant for minimizing exposure to adverse reactions[38]. Targeted therapy drugs such as cetuximab and erlotinib, which are widely used to inhibit the EGFR signaling pathway and suppress cancer cell proliferation, can potentially increase the incidence of mucosal inflammation and subsequent conjunctivitis due to damage to the epithelial mucosa. A randomized controlled study indicated that 10% of patients developed conjunctivitis after taking cetuximab[39]. Moreover, a case report documented that conjunctivitis occurred just four days after initiating a daily dose of 300 mg of erlotinib[40], highlighting the importance of monitoring the dosage of targeted medications in clinical settings. Canakinumab, targeting interleukin-1β to regulate chronic inflammation, may play a therapeutic role in autoimmune conjunctivitis but could also heighten the association of infectious conjunctivitis due to immunosuppression[41]. Ondansetron, commonly prescribed for nausea, is less frequently associated with ocular inflammatory reactions; however, a case report of an ophthalmic crisis in a child post-administration, mediated by dopamine receptor inhibition, suggests a potential link to ocular conditions[42]. The suppression of dopamine receptors can exacerbate inflammation, indicating their critical role in maintaining ocular surface homeostasis[42]. Given the diverse mechanisms through which these drugs can induce conjunctivitis, current research is increasingly focused on exploring their inflammatory pathways in depth. This is crucial for early identification and the development of prevention strategies for high- association patients.

Our study revealed that ophthalmic medications, particularly brimonidine and latanoprost, induce adverse reactions significantly faster than non-ophthalmic drugs, with an average onset time of 125.9 days compared to 298.4 days. This disparity is likely attributable to the localized administration and unique pharmacological properties of these medications. Brimonidine is commonly associated with ocular discomfort and congestion, whereas latanoprost, a prostaglandin analog, is frequently linked to allergic eye reactions. The direct application of these drugs to ocular tissues results in a rapid elevation of local drug concentrations, thereby increasing the likelihood of side effects such as conjunctivitis within a shorter time frame. By contrast, systemic drugs generally manifest adverse effects on major organs, including the heart, liver, and kidneys, prior to receiving regulatory approval. Consequently, the potential for ocular side effects, particularly those affecting the conjunctiva, tends to receive less emphasis during evaluation. Our cumulative risk analysis underscores the importance of healthcare providers closely monitoring patients' ocular responses, especially during the initial stages of treatment with ophthalmic medications. Timely management of adverse effects, such as conjunctivitis, is crucial to safeguarding patient safety and optimizing therapeutic outcomes.

In this study, reports from the United States accounted for 57.10% of the total, raising concerns about potential reporting bias. This phenomenon can be attributed to several factors. From the perspective of population size and healthcare infrastructure, the large population base and advanced healthcare system in the United States facilitate the detection and reporting of drug-related adverse events. Additionally, in terms of reporting awareness, healthcare providers, patients, and pharmaceutical companies in the United States generally place a greater emphasis on adverse event reporting, leading to more frequent submissions to the FAERS database. To mitigate the impact of this bias, our study design focused on drugs primarily suspected of causing conjunctivitis, while excluding concomitant medications and drugs with uncertain associations. This approach minimizes interference caused by variations in reporting practices. Furthermore, we uniformly applied four disproportionality analysis methods, which are independent of the geographic origin of reports, ensuring the reliability and robustness of the results. Future research could incorporate subgroup analyses to compare reporting differences across regions, thereby exploring the influence of geographic factors on study outcomes. Moreover, systematically investigating variations in reporting practices across countries—including differences in processes, incentives, and regulatory frameworks—would provide deeper insights into how these factors affect data collection and presentation. Such efforts would ultimately enable more accurate evaluations of the association between drugs and conjunctivitis.

This study has several limitations. First, the FAERS database is a spontaneous reporting system that relies on voluntarily submitted adverse event reports. This reliance on spontaneous reporting may lead to underreporting of mild or common events, such as mild cases of conjunctivitis, while severe or unusual events may be overreported. Second, ophthalmic drugs are more likely to be associated with earlier detection and reporting of conjunctivitis, potentially introducing bias into the analysis. Third, the underlying conditions treated with certain drugs may predispose patients to conjunctivitis, acting as a confounding factor. Furthermore, establishing causality in pharmacovigilance and observational cohort studies is inherently challenging due to the lack of complete information in FAERS cases, such as dosage, frequency, duration of exposure, patient comorbidities, onset times, and other critical clinical details. This missing information limits the ability to fully analyze potential associations. Additionally, the exclusion of concomitant medications, secondary suspected drugs, and interaction drugs in our analysis may overlook significant contributing factors. The type of conjunctivitis (e.g., allergic, infective) is also not specified in the FAERS data, reducing the clarity and specificity of the outcomes. Consequently, our data mining results should be interpreted with caution, and conclusions should be drawn through comprehensive, evidence-based evaluations.

Conclusion

Through a comprehensive analysis of the FAERS database, we identified medications potentially associated with conjunctivitis, underscoring the necessity of implementing tailored pharmacovigilance strategies. For immune system modulators, it is crucial to enhance monitoring of ocular adverse events during both clinical trials and post-marketing surveillance. For ophthalmic drugs, prioritizing formulation optimization and strengthening patient education are essential to reducing the incidence of adverse reactions. For drugs targeting the metabolic system, individualized monitoring within specific populations is warranted. These findings highlight the importance of continuous pharmacovigilance and further research, which are vital for advancing the understanding of drug-related conjunctivitis. In the long term, such insights could improve medication safety protocols, inform clinical practices, and ultimately enhance patient outcomes.

Data availability

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: FAERS Publish Dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard).

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Author contributions
Xiang Li conceived the research idea. Xiang Li ,Yi-qing Sun and Miao-miao Liu conducted data cleaning and literature review. Xiang Li and Yi-qing Sun contributed to drafting and critically revising the work for intellectual content. Xiang Li and Yi-qing Sun conducted the analysis and created the figures and tables. Jia-feng Tang provided a critical review of the manuscript. All authors have read and approved the manuscript.

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Declaration

Competing interests
The authors declare no competing interests.

Ethical approval
Considering that the FAERS database is publicly accessible, and patient records are anonymous and de-identified, it does not involve informed consent or ethical approval.

Additional information
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