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Drug-Induced Conjunctivitis: Analysis of the FDA Adverse Event Reporting System Database

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Abstract

Conjunctivitis is a highly prevalent condition of diverse etiology affecting around 2 percent of the world's population, with cases ranging from mild to severe. Previous studies have focused on the pathogenic, environmental, and preservative-induced causes of conjunctivitis. However, little research has examined drug-associated risk factors for conjunctivitis, especially outside of eye drops. The goal of this study is to identify and elicit trends among the top 50 medications associated with conjunctivitis in the FDA Adverse Event Reporting System (FAERS) and their respective drug categories.

Investigating the FAERS database, we uncovered several drug categories associated with high incidence of conjunctivitis, such as Monoclonal Antibodies and Disease-modifying Antirheumatic Drugs (DMARDs). Among the top 50 drugs associated with conjunctivitis, 55.34% of reports were from females with 62.41% of reports originating in the US. The median age of individuals reporting was 52. Monoclonal Antibodies were significantly more widely reported compared to other identified drug categories, comprising 39.41% of total reports. The findings from this study have the potential to educate clinicians about emerging drug-related causes of conjunctivitis.

Keywords: conjunctivitis; drug reaction; adverse event; ocular surface disease

Introduction

Conjunctivitis is a highly prevalent and multifaceted disease with many different etiologies and causes. It is characterized by inflammation or swelling of the conjunctival tissue that can result in associated pain and ocular discharge [1]. This disease affects millions of people worldwide with over 2 percent of the world's population affected, resulting in mild-to-severe symptoms and worsened quality of life [2]. Its etiologies include bacterial, viral, allergic, and drug-induced conjunctivitis. Conjunctivitis can develop as a direct result of a multitude of factors which include the quality of the surrounding environment and levels of pollution [3].

Drug-induced or "Toxic" conjunctivitis is a specific form that results from adverse reaction to topical or systemic medications that oftentimes contain preservatives. These preservatives are used to extend the shelf life of certain eye drops and topical drugs, and they contain antimicrobials that might irritate the ocular surface [1]. Although useful in limiting potential for bacterial, mycotic, and amoebal eye infections, preservatives have numerous ocular side effects that can impact a person's quality of life such as stinging, dry eye, and tearing [4, 5]. Discomfort due to eye drops can lead to noncompliance and patients discontinuing treatment, potentially worsening other ocular pathology. Symptoms increase with dose and length of medication for preservative eye drops. Patients with chronic diseases such as glaucoma or dry eye syndrome are more likely to have these side effects due to prolonged or repeated exposure to preservative medications [4]. Preservatives are known to cause irritation and adverse side effects to the ocular surface, with one study finding that preservatives can cause two to three times more likelihood to develop blepharitis, eczema, conjunctival hyperemia, follicles, and superficial punctate keratitis [6]. In addition to decreased stability of the tear film, preservative use can lead to conjunctival inflammation, fibrosis, squamous metaplasia, and subconjunctival fibrosis [5]. Depending on the specific preservative used in the medication, a patient may experience an allergic or cytotoxic reaction, leading to conjunctival scarring or drug-induced pemphigoid [5, 7, 8]. Fortunately, symptoms of preservative eye drops are oftentimes alleviated through quick cessation of irritant usage, such as making a shift to preservative-free eye drops if available. Although oftentimes more expensive and inconvenient as they are packaged in single-use vials, preservative-free eye drops can significantly reduce or remove any symptoms or irritation that a patient experiences while on preservative medication. Hence, it is critical that physicians find a right balance that minimizes the symptoms of preservative topical eye drops and the chances of infection while allowing the primary condition to be treated.

Although abundant literature has discussed the effects of preservative eye drops on the ocular surface, few studies show the effect of other systemic medications on conjunctivitis. With the growing prevalence of antibody therapies to treat diseases like cancers, new literature is constantly uncovering side effects of these treatment regimens. One possible side effect is conjunctival inflammation, with antibodies such as Dupilumab and Rituximab, commonly used in the treatment of atopic dermatitis and non-Hodgkin's lymphoma respectively, having been shown to cause conjunctivitis [9, 10]. However, these side effects could partly be due to immunosuppression or chemotherapy agents resulting in irritation or increasing the likelihood for conjunctival infection [9]. Drugs that weaken the immune system such as chemotherapy agents, immunomodulators, DMARDs, and certain monoclonal antibodies may also increase risk for conjunctival infections caused by bacterial, viral, and fungal organisms.

Other medications that can be taken orally or intravenously such as Bisphosphonates, which are used to treat and prevent osteoporosis and similar diseases, and Phenothiazine, a class of antipsychotic medications, have also been reported to cause conjunctivitis [11]. COX-2 inhibitors, which are often used to treat acute pain and arthritis, are a form of Nonsteroidal Anti-Inflammatory Drug (NSAID) and have been associated with blurred vision and conjunctivitis. A proposed mechanism for this is through drug elimination by tear secretion, with small amounts of medicine secreted in the tears triggering adverse reactions or inflammation of the conjunctiva [12]. This mechanism has also been attributed to many other drug classes such as chemotherapy agents like Cytosine Arabinoside [9, 13]. Furthermore, herbal medications such as chamomile, which is used in a form of tea to treat various conditions, can cause severe conjunctivitis due to the tea being made with *Matricaria chamomilla* pollen, resulting in possible allergic conjunctivitis [12, 14]. Another herbal and dietary supplement used to treat conditions such as the common cold is *Echinacea purpurea*, which has also been associated with allergic conjunctivitis through anaphylactic reaction and activation of the body's autoimmune response [12, 15].

This study used data from the publicly available FDA Adverse Event Reporting System (FAERS) to analyze the specific drugs linked with conjunctivitis. FAERS contains various reports from manufacturing agencies, healthcare providers, and consumers. In addition to the actual report, specific variables such as time, gender, and country of origin are gathered as well. Still, these reports do not imply causation since many of the cases have a combination of drugs in the treatment regimen [16]. With the ever-growing pharmaceutical market and increasing usage of novel drug categories, recognition of conjunctivitis-associated adverse drug events remain limited. The goal of this study is to build upon the current understanding of drug-induced conjunctivitis by highlighting drugs with the strongest potential associations, further informing clinicians' treatment plans.

Methods

The publicly available FAERS database was reviewed using the search term "conjunctivitis." [16] Using R statistical analysis software and Excel, cases within our study period of 2004 through 2023 were isolated and sorted by generic drug name.

The top 50 drugs associated with conjunctivitis from 2004 to 2023 were determined based upon the total counts of unique adverse event reports associated with a single generic drug name and active ingredient. After identifying the top 50 drugs, the reports were then categorized by variables such as country of origin, gender, and class of drug. The classes of drugs were based on the top 50 drugs found, where a class was eligible to be formed if three or more drugs that fit in the category were present. Drug types that were present less than three times were classified under the "Other" category. Yearly trends in the proportional representation of each functional drug class were assessed using linear regression.

Results

In the study period from 2004 to 2023, there were a total of 25,430,281 adverse event reports listed in FAERS, with 14,257 (0.06%) of those being related to conjunctivitis. The median age of patients in reports for all adverse events related to conjunctivitis was 52 while 55.34% of reported events involved female patients.

	Drug Name and Rank	***Total Adverse Event Reports***	***Conjunctivitis Reports***	***(% of Total Adverse Event Reports)***	***US Conjunctivitis Reports***	***(% of Drug Specific Conjunctivitis Reports)***	***Maximum Conjunctivitis Reports in a Year***	***(Year)***	***Median Year***	***Reported Female***	***% Female Drug Specific***	***Age Median***
	Overall Database from 2004-2023	25430281	14257	0.06%	7793	54.66%	1843	2023	2019	7890	55.34%	52
	Top 50 Drugs Combined	5178916	9095	0.18%	5676	62.41%	1179	2023	2019	5040	55.42%	48
1	Dupilumab	201403	3,761.0	1.87%	3,548	94.34%	861	2023	2021	1701	45.23%	40
2	Adalimumab	619162	522.0	0.08%	308	59.00%	70	2016	2016	385	73.75%	46
3	Etanercept	549442	430.0	0.08%	302	70.23%	46	2016	2015	351	81.63%	52
4	Lamotrigine	68720	338.0	0.49%	60	17.75%	26	2009	2014	192	56.80%	33
5	Methotrexate	168637	270.0	0.16%	42	15.56%	45	2022	2020	195	72.22%	47
6	Infliximab	178857	215.0	0.12%	21	9.77%	49	2023	2020	137	63.72%	44
7	Secukinumab	131889	206.0	0.16%	93	45.15%	45	2020	2020	131	63.59%	55
8	Rituximab	159725	205.0	0.13%	26	12.68%	35	2022	2020	121	59.02%	53.5
9	Sulfamethoxazole\ Trimethoprim	38183	201.0	0.53%	36	17.91%	44	2023	2019	114	56.72%	44
10	Ibuprofen	99639	188.0	0.19%	26	13.83%	26	2019	2018	68	36.17%	13
11	Prednisone	139832	186.0	0.13%	29	15.59%	39	2022	2020	115	61.83%	44
12	Tocilizumab	82197	177.0	0.22%	10	5.65%	34	2022	2020	152	85.88%	47
13	Allopurinol	20771	173.0	0.83%	7	4.05%	33	2018	2018	103	59.54%	66.5
14	Zoledronic Acid	66583	169.0	0.25%	66	39.05%	29	2013	2013	130	76.92%	60.5
15	Acetaminophen	130114	166.0	0.13%	15	9.04%	30	2023	2019	92	55.42%	44
16	Fluorouracil	60855	163.0	0.27%	13	7.98%	24	2018	2018	54	33.13%	66
17	Lenalidomide	351254	158.0	0.04%	112	70.89%	20	2021	2019	83	52.53%	64.5

18	Alendronate Sodium	40805	146.0	0.36%	92	63.01%	40	2012	2013	119	81.51%	52.5
19	Panitumumab	12054	140.0	1.16%	14	10.00%	17	2020	2018	37	26.43%	69
20	Amoxicillin	31841	138.0	0.43%	5	3.62%	17	2022	2018	79	57.25%	40
21	Cetuximab	26593	137.0	0.52%	56	40.88%	16	2017	2014	39	28.47%	66
22	Carbamazepine	35221	135.0	0.38%	4	2.96%	22	2018	2015	78	57.78%	54
23	Abatacept	102419	129.0	0.13%	26	20.16%	22	2023	2020	117	90.70%	50
24	Brimonidine Tartrate	12231	126.0	1.03%	70	55.56%	14	2017	2017	68	53.97%	74
25	Aspirin	112371	125.0	0.11%	10	8.00%	33	2018	2018	75	60.00%	71
26	Tofacitinib Citrate	134458	122.0	0.09%	55	45.08%	22	2020	2020	111	90.98%	53
27	Cyclosporine	74984	111.0	0.15%	59	53.15%	14	2016	2016	73	65.77%	59
28	Certolizumab Pegol	85860	106.0	0.12%	27	25.47%	23	2023	2020	92	86.79%	47
29	Pantoprazole Sodium	46452	105.0	0.23%	1	0.95%	19	2018	2019	76	72.38%	48
30	Ondansetron Hydrochloride	8169	105.0	1.29%	101	96.19%	26	2020	2019	51	48.57%	0
31	Human Immunoglobulin G	64820	104.0	0.16%	62	59.62%	20	2023	2019	59	56.73%	40.5
32	Bimatoprost	20413	104.0	0.51%	90	86.54%	13	2021	2015	94	90.38%	56
33	Dexamethasone	112317	103.0	0.09%	23	22.33%	20	2021	2020	31	30.10%	69
34	Prednisolone	75309	101.0	0.13%	5	4.95%	20	2021	2019	58	57.43%	49
35	Natalizumab	167672	101.0	0.06%	92	91.09%	21	2011	2012	83	82.18%	41.5
36	Nivolumab	73062	99.0	0.14%	16	16.16%	23	2021	2019	37	37.37%	68
37	Oxaliplatin	58445	98.0	0.17%	7	7.14%	14	2023	2019	26	26.53%	69
38	Cyclophosphamide	132725	98.0	0.07%	21	21.43%	12	2022	2018	64	65.31%	52.5
39	Omalizumab	52370	97.0	0.19%	19	19.59%	19	2020	2020	73	75.26%	42.5
40	Isotretinoin	48686	92.0	0.19%	67	72.83%	12	2013	2013	55	59.78%	20
41	Erlotinib Hydrochloride	29038	91.0	0.31%	37	40.66%	17	2012	2012	47	51.65%	70
42	Golimumab	57458	90.0	0.16%	3	3.33%	20	2023	2021	71	78.89%	52
43	Pregabalin	140027	87.0	0.06%	21	24.14%	17	2023	2019	62	71.26%	44
44	Ocrelizumab	41411	85.0	0.21%	22	25.88%	35	2023	2022	71	83.53%	48
45	Fingolimod Hydrochloride	82085	83.0	0.10%	39	46.99%	12	2019	2017	72	86.75%	47.5
46	Montelukast Sodium	30286	81.0	0.27%	4	4.94%	19	2021	2021	42	51.85%	35
47	Unspecified Ingredient	54515	79.0	0.14%	25	31.65%	11	2010	2010	51	64.56%	58
48	Irinotecan	19551	79.0	0.40%	11	13.92%	15	2018	2017	26	32.91%	65
49	Trastuzumab	45818	78.0	0.17%	10	12.82%	15	2022	2018	66	84.62%	50
50	Ribavirin	82187	77.0	0.09%	32	41.56%	19	2015	2014	31	40.26%	52

Table 1: Top 50 Medications Associated with Reports of Conjunctivitis to the FDA from 2004 to 2023.

The top 50 drugs associated with conjunctivitis globally are seen in Table 1. These top 50 drugs (9,095) make up 63.8% of total reports related to conjunctivitis during the study period. Interestingly, US reports of the top 50 drugs totaled 5,676, which made up 62.41% of total adverse events reports for the top 50 drugs during the study timeframe. The most prevalent drug to be included in conjunctivitis reports was Dupilumab, possessing 3,761 reports (26.4% of total reports across all drugs) with 94.34% of its reports originating from the US. Within the top 50, drugs with over 70% of their conjunctivitis adverse events reported from the US were Dupilumab, Etanercept, Lenalidomide, Ondansetron Hydrochloride, Bimatoprost, Natalizumab, and Isotretinoin. The top 50 drugs with fewer than 10% of their total reports from the US included Infliximab, Tocilizumab, Allopurinol, Acetaminophen, Fluorouracil, Amoxicillin, Carbamazepine, Aspirin, Pantoprazole Sodium, Prednisolone, Oxaliplatin, Golimumab, and Montelukast Sodium. When grouped into functional classes, Monoclonal Antibodies are by far the most listed in FAERS in association with conjunctivitis.

Drug Class	***Conjunctivitis Reports***	***(% of Total Conjunctivitis Reports)***	***US Conjunctivitis Reports***	***(% of Drug Specific Conjunctivitis Reports for US)***	***Maximum Conjunctivitis Reports in a Year***	***Median Year***	***Reported Female***	***% Female Drug Specific***	***Age Median***	***Average % Change Per Year (95% CI), P value***
Anti-Cancer Medications	382	2.68%	74	19.37%	53	2017	177	46.34%	66	-0.03 (-0.16, 0.09), P = 0.57
Anticonvulsants	558	3.91%	85	15.23%	55	2015	330	59.14%	41	-0.42 (-0.55, -0.29), P < 0.001
Corticosteroids	376	2.64%	55	14.63%	63	2020	201	53.46%	47	0.11 (0.02, 0.20), P = 0.02
DMARDs	995	6.98%	533	53.57%	85	2017	732	73.57%	55	0.06 (-0.18, 0.31), P = 0.60
Immunomodulators	408	2.86%	187	45.83%	78	2020	311	76.23%	52	0.25 (0.17, 0.33), P < 0.001
Monoclonal Antibodies	5619	39.41%	4164	74.11%	1060	2020	2898	51.58%	46	3.06 (2.42, 3.71), P < 0.001
NSAIDs and Acetaminophen	414	2.90%	44	10.63%	62	2018	209	50.48%	40	-0.13 (-0.25, -0.01), P = 0.04
Other	1494	10.48%	646	43.24%	135	2017	914	61.18%	53	-0.45 (-0.74, -0.16), P = 0.005
Overall Database from 2004-2023	14257	100.00%	7793	54.66%	1843	2019	7890	55.34%	52	

Table 2: Drug Categories Associated with Reports of Conjunctivitis to the FDA from 2004 to 2023.

Monoclonal Antibodies comprised 39.41% of total conjunctivitis reports in the study period. This was followed by the "Other" category (10.48%), DMARDs (6.98%), Anticonvulsants (3.91%), NSAIDs and Acetaminophen (2.90%), Immunomodulators (2.86%), Anti-cancer Medications (2.68%), and Corticosteroids (2.64%). The US was the primary source of drug-induced conjunctivitis reports for Monoclonal Antibodies and DMARDs. Monoclonal Antibodies had the highest percentage of reports coming from the US (74.11%), while NSAIDs and Acetaminophen had the lowest percentage of US reports (10.63%).

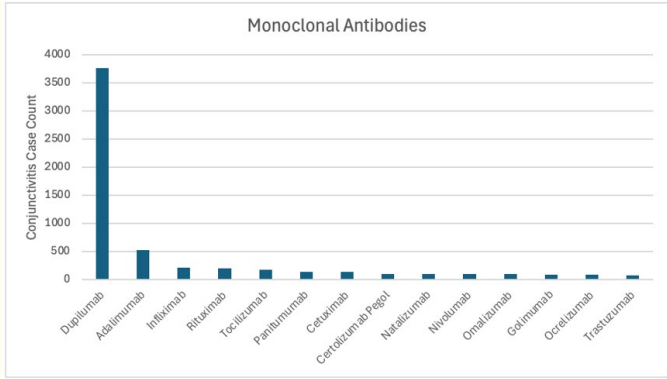


Figure 1

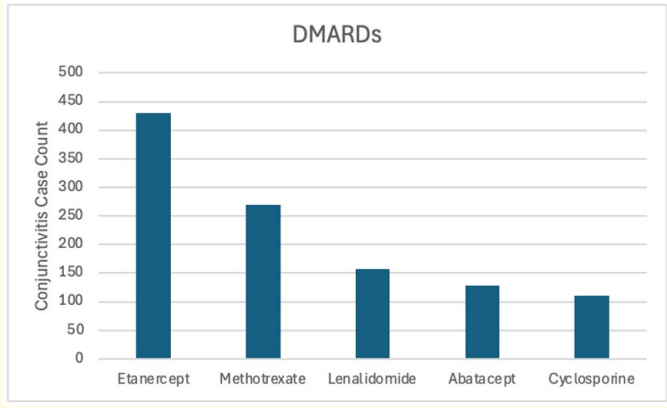


Figure 2

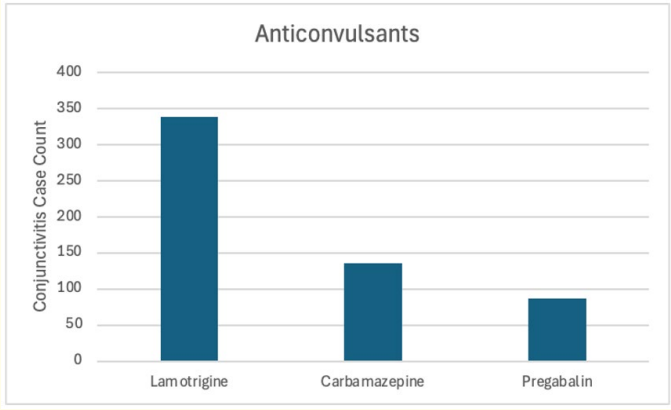


Figure 3

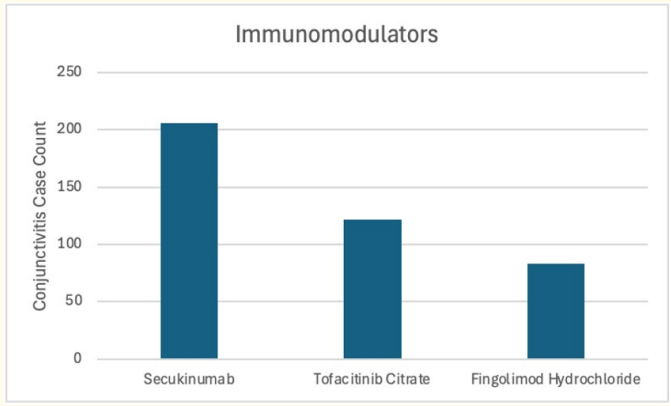
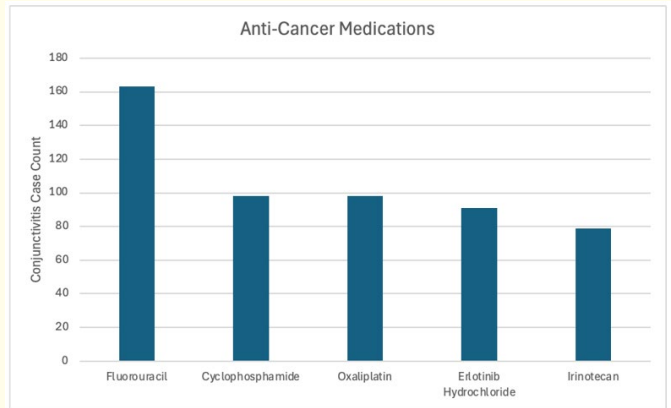


Figure 4



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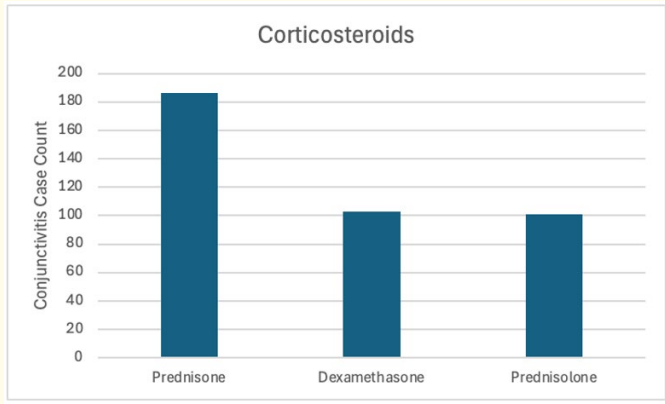

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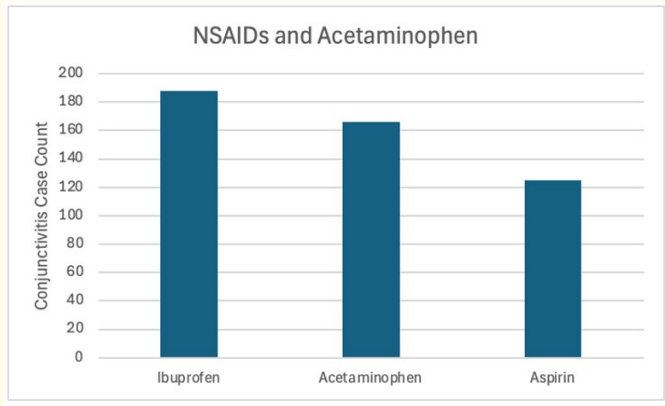

Figure 7

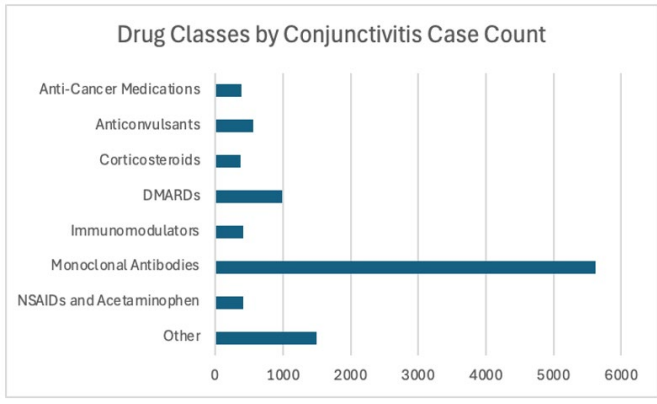

Figure 8

Linear regression was performed to determine significance of change in the proportional representation of drug categories among conjunctivitis adverse event reports over the study period. Monoclonal Antibodies showed a statistically significant ($P < 0.001$) increase in proportional reporting with an average annual increase of 3.06% from 2004 to 2023 (95% CI: 2.42, 3.71). Linear regression on Immunomodulators highlighted a significantly increasing trend (0.25%) during the study period ($P < 0.001$, 95% CI: 0.17, 0.33). The Corticosteroids category also exhibited a statistically significant ($P = 0.02$) annual increase of 0.11% (95% CI: 0.02, 0.20). On the other hand, the "Other" and Anticonvulsant categories showed statistically significant ($P = 0.005$ and $P < 0.001$, respectively) decreases of roughly 0.45% (95% CI: -0.74, -0.16) and 0.42% (95% CI: -0.55, -0.29) respectively over the study period. NSAIDs and Acetaminophen also showed an annual decrease in proportional reporting of 0.13% ($P = 0.04$, 95% CI: -0.25, -0.01). However, DMARDs and Anti-cancer Medications did not display a statistically significant average percent change per year.

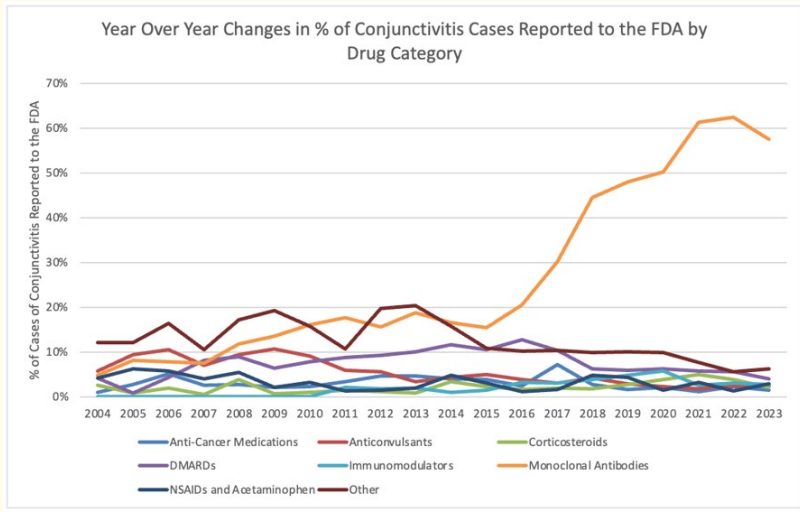

Figure 9

1. United States			***2. France***			***3. Canada***		
Drug Name	Conjunctivitis Reports	% of Total Country Conjunctivitis Reports	Drug Name	Conjunctivitis Reports	% of Total Country Conjunctivitis Reports	Drug Name	Conjunctivitis Reports	% of Total Country Conjunctivitis Reports
Total Country Conjunctivitis Reports	7793		Total Country Conjunctivitis Reports	798		Total Country Conjunctivitis Reports	715	
Dupilumab	3548	45.53%	Lamotrigine	69	8.65%	Infliximab	126	17.62%
Adalimumab	308	3.95%	Ibuprofen	37	4.64%	Methotrexate	107	14.97%
Etanercept	302	3.88%	Valproate Sodium	37	4.64%	Prednisone	97	13.57%
Lenalidomide	112	1.44%	Amoxicillin	35	4.39%	Tocilizumab	88	12.31%
Ondansetron Hydrochloride	101	1.30%	Rituximab	29	3.63%	Rituximab	78	10.91%
Secukinumab	93	1.19%	Amoxicillin\ Clavulanate Potassium	28	3.51%	Montelukast Sodium	67	9.37%

Alendronate Sodium	92	1.18%	Allopurinol	25	3.13%	Etanercept	59	8.25%
Natalizumab	92	1.18%	Carbamazepine	25	3.13%	Mepolizumab	55	7.69%
Bimatoprost	90	1.15%	Cyclophospha-mide	24	3.01%	Tofacitinib Citrate	55	7.69%
Brimonidine Tartrate	70	0.90%	Dupilumab	24	3.01%	Adalimumab	54	7.55%
4. Germany			***5. Japan***			***6. Italy***		
Drug Name	Conjunc-tivitis Reports	% of Total Country Conjunctivitis Reports	Drug Name	Conjunc-tivitis Reports	% of Total Country Conjunctivitis Reports	Drug Name	Conjunc-tivitis Reports	% of Total Country Conjunctivitis Reports
Total Country Conjunctivitis Reports	712		Total Country Conjunctivitis Reports	362		Total Country Conjunctivitis Reports	351	
Aspirin	62	8.71%	Bacillus Calmette-Guer-in Substrain Connaught Live Antigen	37	10.22%	Fluorouracil	61	17.38%
Furosemide	52	7.30%	Lamotrigine	34	9.39%	Oxaliplatin	39	11.11%
Dupilumab	47	6.60%	Dupilumab	22	6.08%	Allopurinol	37	10.54%
Carbamaze-pine	45	6.32%	Bacillus Calmette-Guerin Antigen, Unspeci-fied Substrain	17	4.70%	Panitumumab	36	10.26%
Pantoprazole Sodium	45	6.32%	Brimonidine Tartrate	12	3.31%	Irinotecan	23	6.55%
Clopidogrel Bisulfate	42	5.90%	Panitumumab	12	3.31%	Cetuximab	22	6.27%
Diazepam	41	5.76%	Nivolumab	10	2.76%	Cyclophospha-mide	16	4.56%
Allopurinol	39	5.48%	Prednisolone	10	2.76%	Lamotrigine	16	4.56%
Torsemide	39	5.48%	Cyclosporine	9	2.49%	Paclitaxel	16	4.56%
Prednisolone	38	5.34%	Cetuximab	8	2.21%	Carboplatin	13	3.70%

Table 3: Top 10 Drugs for Each of the Top 6 Countries Associated with Reports of Conjunctivitis from 2004 to 2023.

Aside from the US, the next five countries with the most reported conjunctivitis adverse events were, in descending order: France, Canada, Germany, Japan, and Italy. For those countries, the top 10 drugs associated with conjunctivitis were reported in Table 3.

Anti-cancer Medications comprised 6 of the top 10 drugs reported by Italy in association with conjunctivitis and were also present in the top 10 for France. Monoclonal Antibodies comprised 5 of the top 10 drugs associated with conjunctivitis in Canada, and were also present four times in the top 10 drugs for Japan and three times for the US. The remaining countries displayed a more varied list of categories among the top 10 drugs associated with conjunctivitis.

Interestingly, Corticosteroids were only present once in the top 10 for Japan, Germany, and Canada. The NSAIDs and Acetaminophen category was only in the top 10 for France and Germany while Immunomodulators were only in top 10 for Canada and US (Table 3).

Discussion

In our review of the FAERS, we found important themes related to adverse event reports of drug-induced conjunctivitis. Out of all identified drug categories, Monoclonal Antibodies comprised a significant amount of reports during the study period (39.41%). Interestingly, Dupilumab, which is commonly used to treat atopic dermatitis, comprised a large portion of all top 50 drug related conjunctivitis reports (41.4%) associated with Monoclonal Antibodies. The top 2 monoclonal antibodies (Dupilumab and Adalimumab) are humanized monoclonal antibodies. Additionally, Monoclonal Antibodies saw a significant year-over-year increase in proportional reports (3.06%), which was far greater in magnitude compared to the rest of the categories.

This heavy reporting of Monoclonal Antibodies, especially in the United States, can be attributed to the steep increase in usage of various related therapies across medicine. Monoclonal Antibodies are being used in various sectors of healthcare to treat cancer, chronic inflammatory disease, and infection [17]. Monoclonal Antibodies are increasing in scope of application as well, with many new products being marketed for conditions such as asthma, age-related macular degeneration, multiple sclerosis, osteoporosis, Alzheimer's disease, metabolic disease, migraines, and other diseases [17]. The rapid rise in Monoclonal Antibody usage in the late 2010s and early 2020s could be attributed to their usage in treating COVID-19 as well [18].

The high prevalence of Dupilumab in conjunctivitis reports correlates with current literature, with previous studies reporting that conjunctivitis was more frequent with Dupilumab treatment in atopic dermatitis patients [19, 20]. Moreover, clinical trials studying the long term management of atopic dermatitis with Dupilumab resulted in higher incidences of conjunctivitis in the treatment group given Dupilumab plus topical corticosteroids. Symptoms of Dupilumab-induced conjunctivitis include predominant involvement of the conjunctiva, hyperemia of the limbus, redness, itching, and conjunctival cicatrisation and follicular changes [10, 21]. Hence, it is crucial that patients with history of ocular surface disease consult with eye care professionals before starting Dupilumab therapy.

There are many theories that postulate the mechanism of action for development of conjunctivitis after Dupilumab therapy. Possible mechanisms include Dupilumab blocking IL-13, leading to a reduction in goblet cells and mucin production and subsequent tear film instability, conjunctival inflammation, and eventual conjunctivitis [22]. Other mechanisms include eosinophilia, increased OX-40 ligand activity, and suppression of IL-4 and IL-3 activity resulting in an increased number of Demodex mites that cause IL-17 mediated inflammation [21, 23, 24]. It is possible the true mechanism is a combination of multiple proposed theories, but future studies need to continue to explore the cellular and molecular changes that result in conjunctivitis after Dupilumab therapy.

Aside from the Monoclonal Antibodies and "Other" Categories, the next most reported category was DMARDs (6.98%). Immunomodulators and DMARDs had more reports from females, 76.23% and 73.57% respectively. This is in line with literature highlighting elevated severity of symptomatic adverse events from immunotherapy (potentially due to pharmacokinetic differences) and arthritis prevalence in females [25, 26].

Domestic reports of drug-induced conjunctivitis were significantly greater in quantity compared to those from the following 5 top countries. This is particularly the case with Monoclonal Antibodies, where the US had the vast majority of conjunctivitis reports (74.11%). For the most reported monoclonal antibody, Dupilumab, the US was the origin of 94.34% of reports. The United States was also the source of the majority of DMARD reports as well (53.57%). The large discrepancy in geographical reports related to monoclonal antibodies can be attributed to the US, Canada, and Europe having the most access to monoclonal antibodies [27]. This US reporting bias is also due to the inherent limitation of the FAERS dataset, which is funded and run by the US government resulting in the majority of all reports coming from the US rather than other regions like Asia, Latin America, or Africa.

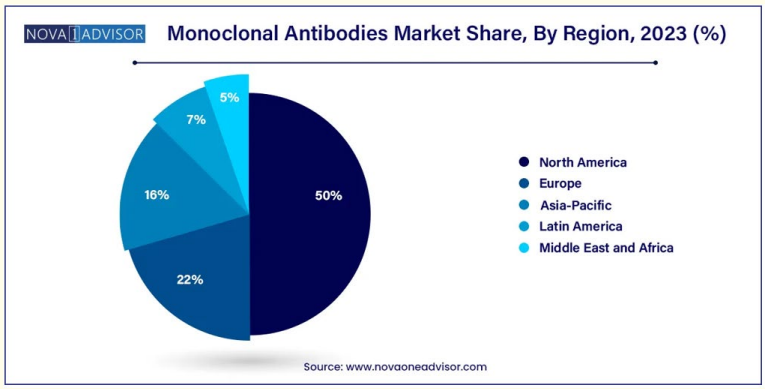

Figure 10: Monoclonal Antibodies Market Share, By Region, 2023 [27].

Limitations

Although the FAERS data set provides extensive and detailed reports on drug-associated adverse reactions, there are some limitations to the database. As noted before, FAERS cannot provide direct evidence of a causal relationship between a certain drug and its reported adverse event, as patients may include any medication they are taking at the time within a report and are usually involved in medication plans that incorporate a combination of different drugs once conjunctivitis is noticed. Patients may also mistakenly attribute worsening conjunctivitis to certain drugs despite their symptoms corresponding with expected disease progression or comorbidities. Additionally, a small minority of reports within the FAERS database were partially incomplete, omitting demographic information such as either age, gender, or country of origin [16]. FAERS also lacks key variables such as race/ethnicity data in addition to possessing a risk of consumer-based reporting biases. Because categorization was only performed for the top 50 drugs associated with conjunctivitis, values for percent representation of each drug class out of total FAERS database conjunctivitis reports are slightly diminished due to the exclusion of drugs falling outside the top 50. This study identified only the top 50 associated with reports for conjunctivitis, but there are many other causes for disease development. These results should be used to improve awareness of the side effects of certain drugs on the ocular surface.

Conclusion

This comprehensive analysis of the FAERS database highlights the most common drugs and drug categories associated with conjunctivitis adverse events and their respective temporal trends. Monoclonal Antibodies such as Dupilumab were highly reported and saw significant increases in their share of adverse event reports over time. By identifying these associations, healthcare providers can become more aware of the adverse conjunctival side effects of certain drugs, allowing them to become more vigilant to assure that patients receive the appropriate treatment for the eye disease. Additionally, understanding disease etiology and additional risk factors for specific medications will improve the informed consent process for both patients and physicians. It is important to educate physicians as well as patients about the main side-effects of all drugs, which will increase patient trust and understanding in the healthcare system and their treatment. Although this report highlights important associations between commonly used drugs and conjunctivitis, further research is needed to analyze the direct causative factors for specific medications on conjunctivitis.

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