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# EMERGING CAUSES OF DRUG-INDUCED DRY EYE DISEASE: A REVIEW OF DRY EYE-ASSOCIATED REPORTS IN THE FDA ADVERSE EVENT REPORTING SYSTEM

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## ABSTRACT

Dry Eye Syndrome (DES) is a chronic condition which affects patients of all ages, ethnicities, and sex. The range of symptoms can vary from mild to severe. Much research has been dedicated into better understanding DES etiology. However, there has been little research into the prevalence of drug-induced or drug-associated DES in patients beyond the typically known candidates such as antihistamines and anticholinergics. The aim of this manuscript is to investigate and compare the top 50 systemic and ophthalmic drug causes for DES noted in the publicly-available FDA Adverse Event Reporting System (FAERS).

Investigating the FAERS database, we uncovered several drugs associated with a high incidence of DES development that were not widely known previously, such as Monoclonal Antibodies and Chemotherapy Agents. Among the top 50 drugs associated with DES, 70.46% of reports were from females with 80.65% of reports originating in the US. The median age of individuals reporting was 56. Monoclonal Antibodies were significantly more widely reported compared to other identified drug categories, comprising 26.17% of total reports.

The findings from this study have the potential to inform and raise awareness among clinicians about emerging drug-induced causes of DES.

*Keywords*: Dry eye; drug induced dry eye; visual disturbance; blurry vision

## INTRODUCTION

Dry Eye Syndrome (DES), also known as keratoconjunctivitis sicca, is a multifactorial disease characterized by a loss of homeostasis of the tear film, leading to ocular discomfort, visual disturbance, and potential damage to the ocular surface.[1] This condition affects millions of individuals worldwide, significantly impairing quality of life by causing symptoms such as pain, discomfort, foreign body sensation, irritation, burning sensation, and fluctuating visual acuity. DES prevalence increases significantly as people age and is more common in

females.[1,2] DES can be classified as either "aqueous deficient" or "hyperevaporative." Aqueous deficient dry eye is characterized by the deterioration of the aqueous tear film layer secondary to lacrimal gland insufficiency, while hyperevaporative dry eye manifests from increased evaporation of tear film. Aqueous deficient dry eye comprises around one-tenth of total DES cases, with hyperevaporative dry eye accounting for the rest.[1] The pathophysiology of DES involves a complex interplay between tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities, which can be triggered or exacerbated by various intrinsic and extrinsic factors.

Clinically, DES presents with a broad spectrum of manifestations ranging from mild, transient irritation to severe, persistent symptoms that can substantially impact daily activities. Common signs include conjunctival hyperemia, punctate epithelial erosions, and filamentary keratitis.[3,4] The management of DES typically involves a combination of approaches aimed at alleviating symptoms, restoring tear film stability, and addressing underlying etiologies. Treatment options include artificial tears, topical anti-inflammatory medications, tear conservation strategies, and in severe cases, surgical interventions such as punctal occlusion and amniotic membrane grafting.[4]

A critical aspect of managing DES is identifying and mitigating potential contributing factors, which can source from environmental triggers such as air pollution and high temperatures or from poor work conditions such as prolonged screen time and light exposure.[4,5] Underlying disease pathology such as meibomian gland dysfunction, thyroid disease, Sjogren's syndrome, or mucous membrane pemphigoid to name a few can also be additive to DES (Table 1).[1,4,6] However, while much of the research surrounding dry eye focuses on pathophysiology and new treatment modalities, relatively less attention is being paid to newer systemic drug causes, and this aspect is also relatively less recognized by many clinicians. Numerous drugs have been implicated in the development or exacerbation of DES, often as a result of their pharmacological effects on tear production and composition, or their influence on the ocular surface and adnexal structures. Medications commonly associated with dry eye include antihistamines, antidepressants, anticholinergics, beta-blockers, and isotretinoin, among others (Table 2).[1,4] Recent pharmacovigilance studies have highlighted an increasing number of emerging drugs linked to DES, reflecting the expanding scope of pharmacotherapy and the growing awareness of drug-induced ocular surface disorders.[7] However, there has not yet been a study to rank and classify the leading causes of drug-induced dry eye reports on a global level.

The global prevalence of DES was estimated to be 9.12% in 2021.[10] The global market for pharmaceuticals treating DES was valued at over 5.53 billion USD in 2022 (nearly 15% of the total global market for ophthalmic drugs) with estimated increases of 7.85% year-over-year from 2023 to

**TABLE 1.** Causes of Dry Eye Syndrome.[8,9]

| | |
|---|---|
| Aqueous Defcient | Aging<br>Autoimmune conditions (Sjogren's syndrome, lupus, scleroderma, rheumatoid arthritis)<br>Blepharitis<br>Graft versus host disease<br>Thyroid disorders<br>Allergic eye disease<br>Corneal nerve desensitization (from contact lens wear or prior refractive surgery) |
| Evaporative | Meibomian gland dysfunction<br>Infrequent blinking (from Parkinson's, computer use, driving, reading)<br>Entropion/ectropion<br>Pollution and low air humidity |

**TABLE 2.** Risk Factors for Dry Eye Syndrome.[8,9]

| | |
|---|---|
| Modifiable | Androgen, vitamin A, omega-3 fatty-acid deficiency<br>Screen time<br>Contact lens wear<br>History of refractive surgery<br>Hormone replacement therapy<br>Hematopoietic stem cell transplant<br>Residing in a dry or polluted environment<br>Antihistamines, antidepressants, anticholinergics, beta-blockers, diuretics, isotretinoin |
| Non-Modifiable | Age, particularly above 50<br>Female, especially during pregnancy or menopause<br>Asian race<br>Diabetes<br>Rosacea |

2030.[11,12] With such a large proportion of the global population afflicted and financially affected by DES, it becomes crucial to reduce preventable DES development and exacerbation from all causes, especially previously unknown or little known drug-induced adverse reactions. This manuscript aims to provide a comprehensive overview of the top 50 emerging drugs associated with DES, examining their mechanisms of action, clinical implications, and potential management strategies. By elucidating the relationship between these drugs and DES, we aim to enhance clinician awareness, improve patient care, and contribute to the broader understanding of DES in the context of modern pharmacotherapy.

Modeling many preceding studies, the publicly available FDA Adverse Event Reporting System (FAERS) was used to access data on specific drugs and their relation to DES.[13,14] FAERS provides cases of drug-associated adverse event reports related to a queried search item (either a drug or symptom of interest) from the total repository of adverse events reported to the FDA by healthcare providers, consumers, and drug manufacturers.[15] Healthcare providers and consumers submit reports on a voluntary basis, while manufacturers are required to report any adverse event cases they receive. The database provides large-scale datasets containing variables such as time of reporting, gender, age, drug class, country of report, amongst many others. However, reports related to a specific drug active ingredient do not necessarily imply causation as burden of proof is not required for a drug to be included within an adverse event report and multiple drugs may be implicated within a single report.[15] Numerous studies have employed the FAERS platform to identify drug-related adverse events across a range of diseases and health conditions; however, there has yet to be a study that investigates which drugs are most commonly reported in connection with DES.

Despite significant advancements in understanding the pathophysiology and treatment of DES, recognition of newer systemic drugs as potential contributors to this condition remains limited. Through this analysis, we aim to fill the existing knowledge gap concerning medication-induced dry eye, offering valuable insights that can guide both clinical practice and future research in this important area of ophthalmology.

## METHODS

To evaluate cases of drug-associated DES reported to the FDA, we reviewed the publicly available FAERS database using the search term "dry eye."[15] A table of all results returned by the "dry eye" query, with each row being a separate

adverse event case report, was downloaded into an Excel file using the Listing of Cases analysis tool from FAERS. Columns included in the downloaded table were "Case ID," "Suspect Product Names," "Suspect Product Active Ingredients," "Reason for Use," "Reactions," "Serious," "Outcomes," "Sex," "Event Date," "Latest FDA Received Date," "Case Priority," "Patient Age," "Patient Weight," "Sender," "Reporter Type," "Report Source," "Concomitant Product Names," "Latest Manufacturer Received Date," "Initial FDA Received Date," "Country where Event occurred," "Reported to Manufacturer?," "Manufacturer Control Number," "Literature Reference," and "Compounded Flag." Afterwards, an R script was utilized to exclude cases (each delineated by a row in the file) outside the study period of 2004 to 2023. If a single case involved multiple drugs listed in the table column "Suspect Product Active Ingredients," the R script would read and log each active ingredient, with that case counting towards the reported total for each constituent drug. For example, if a report with Case ID 123 included the active ingredients drug 1 and drug 2, the report would be added as an additional tally for both drug 1 and drug 2.

The top 50 drugs associated with DES from 2004 to 2023 were determined based upon the total counts of unique reports associated with a single generic drug name and active ingredient. The reports were then categorized by country where the event occurred, gender of the affected individual, and functional class. Functional classes were based on guidelines from the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system, which organizes drug active ingredients based on anatomical target, therapeutic use, and pharmacological structure.[16] The top 50 drugs were organized following these ATC principles into the functional classes of: Antibiotics, Chemotherapy Agents, Dermatological Agents, Disease-modifying Antirheumatic Drugs (DMARDs), Endocrine and Metabolic Agents, Excipients, Monoclonal Antibodies, Neurological Agents, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Ophthalmology Agents, Respiratory Agents, and Urological Agents. The drug active ingredients Methotrexate, Methotrexate Sodium, and Lenalidomide were classified as DMARDs due to their primary uses in treating autoimmune diseases such as rheumatoid arthritis despite possessing secondary applications as Chemotherapy Agents. Propylene Glycol was classified as an Excipient due to its role as a lubricant and solvent facilitating the delivery of therapeutic agents. Year-over-year trends in the proportional representation of each functional drug class were assessed using time series plots and linear regression. Additionally, the top 10 drugs associated with DES were determined for the six countries reporting the most DES cases in FAERS.

## RESULTS

In the study period from 2004 to 2023, there were a total of 25,430,281 adverse event reports listed in FAERS, with 34,114 (0.13%) of those being related to DES. The median age of patients in reports for all adverse events related to DES was 57 while 70.05% of reported events involved female patients.

The top 50 drugs associated with DES globally are seen in Table 3 and Figure 1. These top 50 drugs make up 57.12% of total reports related to DES during the study period. Interestingly, US reports of the top 50 drugs totaled 15,637, comprising 80.24% of total adverse events reports for the top 50 drugs during the study timeframe. The most prevalent drug to be included in DES reports was Dupilumab, possessing 5,956 reports (17.46% of total reports across all drugs) with 98.39% of its reports originating from the US. Within the top 50, drugs with over 70% of their DES adverse events reported from the US were Dupilumab, Cyclosporine, Lifitegrast, Polyethylene Glycol 400\Propylene Glycol, Tofacitinib Citrate, Lenalidomide, Bimatoprost, Brimonidine Tartrate, Latanoprost, Onabotulinumtoxina, Belantamab Mafodotin, Palbociclib, Sodium Oxybate, Tiotropium Bromide Monohydrate, Ibrutinib, Alendronate Sodium, Erlotinib Hydrochloride,

**TABLE 3.** Top 50 drugs associated with DES reports in FAERS from 2004–2023

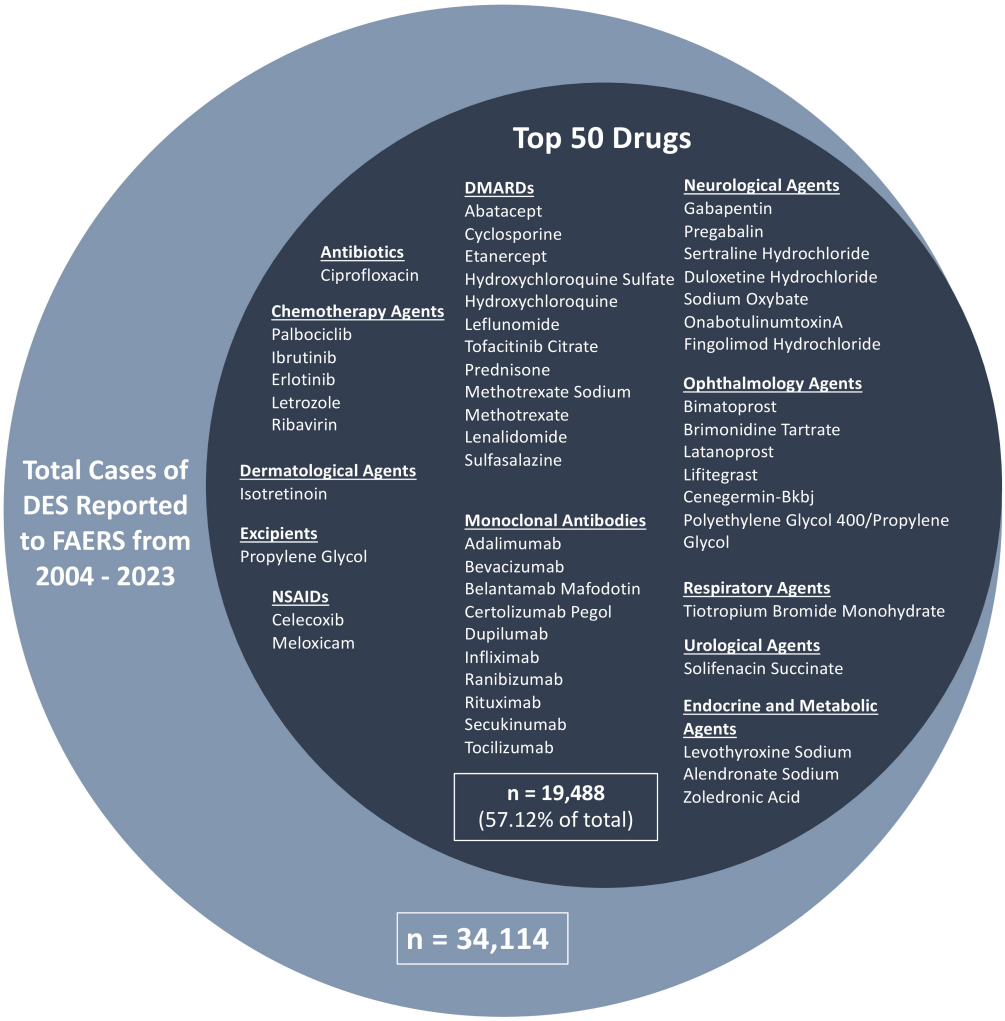
| | Drug Name and Rank | Functional Class | Total Adverse Event Reports | Dry Eye Reports | (% of Total Adverse Event Reports) | US Dry Eye Reports | (% of Drug-Specific Dry Eye Reports) | Maximum Dry Eye Reports in a Year | (Year) | Median Year | Reported Female | Female % | Age Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall Database from 2004-2023 | | 2,54,30,281 | 34,114 | 0.13% | 25,591 | 75.02% | 4,868 | 2023 | 2019 | 23,898 | 70.05% | 57 |
| | Top 50 Drugs Combined | | 46,30,097 | 20,785 | 0.45% | 16,764 | 80.65% | 3,968 | 2023 | 2020 | 14,646 | 70.46% | 56 |
| 1 | Dupilumab | Monoclonal Antibodies | 2,01,403 | 5,956 | 2.96% | 5,860 | 98.39% | 2,100 | 2023 | 2022 | 3,572 | 59.97% | 45 |
| 2 | Adalimumab | Monoclonal Antibodies | 6,19,162 | 1,419 | 0.23% | 891 | 62.79% | 174 | 2020 | 2018 | 1,152 | 81.18% | 56 |
| 3 | Etanercept | DMARDs | 5,49,442 | 1,378 | 0.25% | 941 | 68.29% | 125 | 2017 | 2015 | 1,121 | 81.35% | 58 |
| 4 | Cyclosporine | DMARDs | 74,984 | 1,298 | 1.73% | 1,167 | 89.91% | 230 | 2017 | 2017 | 1,032 | 79.51% | 62 |
| 5 | Liftegrast | Ophthalmology Agents | 12,156 | 931 | 7.66% | 924 | 99.25% | 241 | 2022 | 2021 | 778 | 83.57% | 65 |
| 6 | Polyethylene Glycol 400\Propylene Glycol | Ophthalmology Agents | 4,444 | 803 | 18.07% | 789 | 98.26% | 541 | 2016 | 2016 | 460 | 57.29% | 68 |
| 7 | Isotretinoin | Dermatological Agents | 48,686 | 768 | 1.58% | 537 | 69.92% | 94 | 2013 | 2015 | 424 | 55.21% | 22 |
| 8 | Methotrexate | DMARDs | 1,68,637 | 674 | 0.40% | 108 | 16.02% | 214 | 2020 | 2020 | 533 | 79.08% | 58 |
| 9 | Tofacitinib Citrate | DMARDs | 1,34,458 | 632 | 0.47% | 500 | 79.11% | 152 | 2017 | 2019 | 547 | 86.55% | 59 |
| 10 | Lenalidomide | DMARDs | 3,51,254 | 597 | 0.17% | 556 | 93.13% | 103 | 2021 | 2020 | 389 | 65.16% | 67.5 |
| 11 | Bimatoprost | Ophthalmology Agents | 20,413 | 581 | 2.85% | 555 | 95.52% | 89 | 2021 | 2016 | 522 | 89.85% | 58 |
| 12 | Brimonidine Tartrate | Ophthalmology Agents | 12,231 | 473 | 3.87% | 445 | 94.08% | 157 | 2019 | 2019 | 336 | 71.04% | 66.5 |
| 13 | Latanoprost | Ophthalmology Agents | 21,160 | 447 | 2.11% | 326 | 72.93% | 57 | 2010 | 2015 | 315 | 70.47% | 72 |
| 14 | Tocilizumab | Monoclonal Antibodies | 82,197 | 446 | 0.54% | 42 | 9.42% | 148 | 2020 | 2020 | 394 | 88.34% | 67 |
| 15 | Abatacept | DMARDs | 1,02,419 | 436 | 0.43% | 94 | 21.56% | 135 | 2020 | 2020 | 393 | 90.14% | 67 |
| 16 | Pregabalin | Neurological Agents | 1,40,027 | 434 | 0.31% | 228 | 52.53% | 46 | 2010 | 2016 | 350 | 80.65% | 58 |
| 17 | Onabotulinumtoxina | Neurological Agents | 57,833 | 392 | 0.68% | 317 | 80.87% | 39 | 2018 | 2017 | 360 | 91.84% | 50 |
| 18 | Rituximab | Monoclonal Antibodies | 1,59,725 | 378 | 0.24% | 35 | 9.26% | 90 | 2023 | 2021 | 256 | 67.72% | 51 |
| 19 | Belantamab Mafodotin | Monoclonal Antibodies | 2,128 | 355 | 16.68% | 322 | 90.70% | 186 | 2022 | 2022 | 82 | 23.10% | 66.5 |
| 20 | Leflunomide | DMARDs | 48,122 | 337 | 0.70% | 27 | 8.01% | 116 | 2020 | 2020 | 273 | 81.01% | 67 |
| 21 | Palbociclib | Chemotherapy Agents | 79,308 | 296 | 0.37% | 248 | 83.78% | 60 | 2022 | 2020 | 276 | 93.24% | 65 |
| 22 | Prednisone | DMARDs | 1,39,832 | 274 | 0.20% | 90 | 32.85% | 55 | 2023 | 2020 | 190 | 69.34% | 51 |
| 23 | Gabapentin | Neurological Agents | 87,695 | 263 | 0.30% | 78 | 29.66% | 63 | 2020 | 2020 | 215 | 81.75% | 72 |
| 24 | Sulfasalazine | DMARDs | 32,917 | 261 | 0.79% | 21 | 8.05% | 93 | 2020 | 2020 | 205 | 78.54% | 66 |
| 25 | Hydroxychloroquine Sulfate | DMARDs | 30,475 | 259 | 0.85% | 28 | 10.81% | 77 | 2020 | 2020 | 216 | 83.40% | 67 |
| 26 | Cenegermin-Bkbj | Ophthalmology Agents | 6,470 | 255 | 3.94% | 53 | 20.78% | 131 | 2023 | 2023 | 195 | 76.47% | 68 |
| 27 | Fingolimod Hydrochloride | Neurological Agents | 82,085 | 237 | 0.29% | 149 | 62.87% | 46 | 2019 | 2018 | 185 | 78.06% | 48 |

(*Continues*)

**TABLE 3.** Continued.

| | Drug Name and Rank | Functional Class | Total Adverse Event Reports | Dry Eye Reports | (% of Total Adverse Event Reports) | US Dry Eye Reports | (% of Drug-Specific Dry Eye Reports) | Maximum Dry Eye Reports in a Year | (Year) | Median Year | Reported Female | Female % | Age Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | Secukinumab | Monoclonal Antibodies | 1,31,889 | 232 | 0.18% | 94 | 40.52% | 60 | 2023 | 2021 | 159 | 68.53% | 54 |
| 29 | Sodium Oxybate | Neurological Agents | 60,317 | 230 | 0.38% | 210 | 91.30% | 59 | 2016 | 2017 | 195 | 84.78% | 45 |
| 30 | Ribavirin | Chemotherapy Agents | 82,187 | 228 | 0.28% | 137 | 60.09% | 64 | 2015 | 2013 | 140 | 61.40% | 53 |
| 31 | Tiotropium Bromide Monohydrate | Respiratory Agents | 72,965 | 227 | 0.31% | 187 | 82.38% | 25 | 2009 | 2011 | 174 | 76.65% | 70 |
| 32 | Solifenacin Succinate | Urological Agents | 12,877 | 217 | 1.69% | 151 | 69.59% | 29 | 2013 | 2014 | 176 | 81.11% | 68 |
| 33 | Ciprofloxacin | Antibiotics | 36,499 | 205 | 0.56% | 30 | 14.63% | 34 | 2023 | 2018 | 101 | 49.27% | 46 |
| 34 | Meloxicam | NSAIDs | 10,787 | 203 | 1.88% | 25 | 12.32% | 58 | 2022 | 2021 | 178 | 87.68% | 67 |
| 35 | Levothyroxine Sodium | Endocrine and Metabolic Agents | 52,390 | 202 | 0.39% | 83 | 41.09% | 54 | 2018 | 2018 | 171 | 84.65% | 55.5 |
| 36 | Ibrutinib | Chemotherapy Agents | 68,031 | 200 | 0.29% | 184 | 92.00% | 34 | 2020 | 2020 | 121 | 60.50% | 69 |
| 37 | Alendronate Sodium | Endocrine and Metabolic Agents | 40,805 | 192 | 0.47% | 137 | 71.35% | 33 | 2012 | 2014 | 163 | 84.90% | 56 |
| 38 | Methotrexate Sodium | DMARDs | 69,834 | 191 | 0.27% | 79 | 41.36% | 46 | 2017 | 2019 | 168 | 87.96% | 58 |
| 39 | Duloxetine Hydrochloride | Neurological Agents | 57,515 | 190 | 0.33% | 97 | 51.05% | 52 | 2015 | 2015 | 167 | 87.89% | 51 |
| 40 | Celecoxib | NSAIDs | 53,406 | 189 | 0.35% | 50 | 26.46% | 69 | 2020 | 2020 | 158 | 83.60% | 75 |
| 41 | Ranibizumab | Monoclonal Antibodies | 23,421 | 186 | 0.79% | 87 | 46.77% | 37 | 2015 | 2015 | 124 | 66.67% | 77 |
| 42 | Erlotinib Hydrochloride | Chemotherapy Agents | 29,038 | 185 | 0.64% | 160 | 86.49% | 104 | 2017 | 2017 | 151 | 81.62% | 69 |
| 43 | Hydroxychloroquine | DMARDs | 29,576 | 181 | 0.61% | 14 | 7.73% | 71 | 2020 | 2020 | 136 | 75.14% | 67 |
| 44 | Bevacizumab | Monoclonal Antibodies | 94,415 | 165 | 0.17% | 100 | 60.61% | 39 | 2015 | 2016 | 111 | 67.27% | 67 |
| 45 | Infliximab | Monoclonal Antibodies | 1,78,857 | 164 | 0.09% | 53 | 32.32% | 31 | 2023 | 2021 | 114 | 69.51% | 48 |
| 46 | Letrozole | Chemotherapy Agents | 29,805 | 159 | 0.53% | 42 | 26.42% | 33 | 2022 | 2020 | 136 | 85.53% | 64 |
| 47 | Propylene Glycol | Excipients | 1,431 | 155 | 10.83% | 155 | 100.00% | 119 | 2016 | 2016 | 100 | 64.52% | 55 |
| 48 | Certolizumab Pegol | Monoclonal Antibodies | 85,860 | 155 | 0.18% | 85 | 54.84% | 42 | 2023 | 2021 | 127 | 81.94% | 52 |
| 49 | Zoledronic Acid | Endocrine and Metabolic Agents | 66,583 | 153 | 0.23% | 98 | 64.05% | 37 | 2014 | 2014 | 123 | 80.39% | 63 |
| 50 | Sertraline Hydrochloride | Neurological Agents | 71,946 | 151 | 0.21% | 43 | 28.48% | 25 | 2023 | 2018 | 100 | 66.23% | 50 |

**FIG. 1.** Top 50 drugs associated with DES reports in FAERS from 2004–2023 listed by functional classes, with relative size of circles correlating with percentage of total reported cases.




and Propylene Glycol. The top 50 drugs with fewer than 10% of their total reports from the US included Tocilizumab, Rituximab, Leflunomide, Sulfasalazine, Hydroxychloroquine.

When grouped into functional classes, Monoclonal Antibodies are the most listed in FAERS in association with DES comprising 26.17% of total DES reports in the study period. This was followed by Ophthalmology Agents (10.06%), DMARDs (10.03%), Neurological Agents (4.91%), Chemotherapy Agents (3.49%), Dermatological Agents (2.25%), Endocrine and Metabolic Agents (1.57%), NSAIDs (1.13%), Antibiotics (1.08%), Respiratory Agents (0.67%), Urological Agents

**TABLE 4.** Top 50 drugs associated with DES reports in FAERS from 2004–2023 – Drug Functional Classes.

| Drug Class | Dry Eye Reports | (% of Total Dry Eye Reports) | US Dry Eye Reports | (% of Drug-Specific Dry Eye Reports) | Maximum Dry Eye Reports in a Year | Median Year | Reported Female | Female % | Age Median | Average % Change Per Year |
|---|---|---|---|---|---|---|---|---|---|---|
| Antibiotics | 369 | 1.08% | 83 | 22.49% | 65 | 2019 | 215 | 58.27% | 47 | 0.03 (0.002, 0.05), P = 0.03 |
| Chemotherapy Agents | 1,192 | 3.49% | 758 | 63.59% | 160 | 2018 | 916 | 76.85% | 64 | 0.05 (–0.07, 0.17), P = 0.38 |
| Dermatological Agents | 768 | 2.25% | 537 | 69.92% | 94 | 2015 | 424 | 55.21% | 22 | –0.27 (–0.39, –0.14), P < 0.001 |
| DMARDs | 3,423 | 10.03% | 2,292 | 66.96% | 441 | 2018 | 2,663 | 77.80% | 59 | 0.25 (–0.02, 0.52), P = 0.07 |
| Endocrine and Metabolic Agents | 534 | 1.57% | 308 | 57.68% | 69 | 2016 | 446 | 83.52% | 57 | –0.02 (–0.15, 0.11), P = 0.78 |
| Excipients | 155 | 0.45% | 155 | 100.00% | 119 | 2016 | 100 | 64.52% | 55 | 0.03 (–0.06, 0.12), P = 0.52 |
| Monoclonal Antibodies | 8,929 | 26.17% | 7,434 | 83.26% | 2,503 | 2022 | 5,659 | 63.38% | 51 | 2.24 (1.47, 3.01), P < 0.001 |
| Neurological Agents | 1,676 | 4.91% | 1,063 | 63.42% | 182 | 2017 | 1,413 | 84.31% | 54 | –0.11 (–0.31, 0.10), P = 0.28 |
| NSAIDs | 385 | 1.13% | 73 | 18.96% | 122 | 2020 | 330 | 85.71% | 67 | 0.05 (–0.03, 0.12), P = 0.20 |
| Ophthalmology Agents | 3,433 | 10.06% | 3,043 | 88.64% | 658 | 2019 | 2,563 | 74.66% | 65 | 0.53 (0.10, 0.95), P = 0.02 |
| Respiratory Agents | 227 | 0.67% | 187 | 82.38% | 25 | 2011 | 174 | 76.65% | 70 | –0.26 (–0.32, –0.19), P < 0.001 |
| Urological Agents | 217 | 0.64% | 151 | 69.59% | 29 | 2014 | 176 | 81.11% | 68 | –0.10 (–0.18, –0.02), P = 0.02 |
| Overall Database from 2004–2023 | 34,114 | 100.00% | 25,591 | 75.02% | 4,868 | 2019 | 23,898 | 70.05% | 57 | |

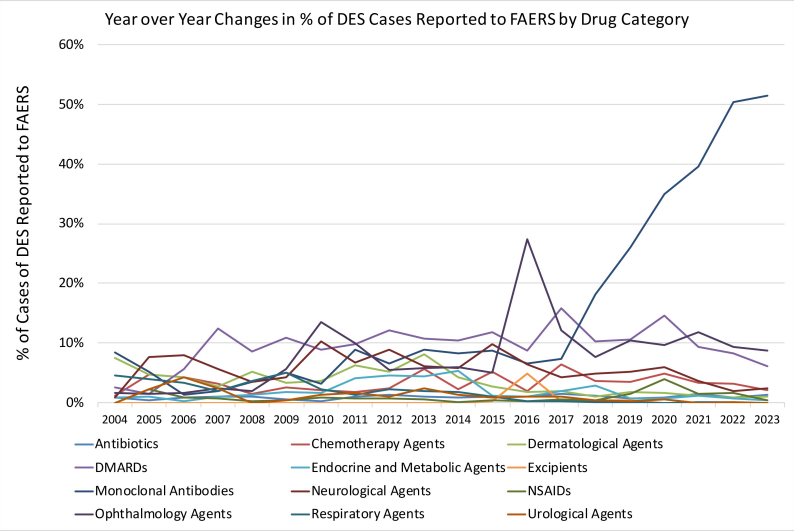
(0.64%), and Excipients (0.45%) in descending order of frequency (Table 4). The US was the primary source of drug-induced DES reports for all drug categories except Antibiotics and NSAIDs which had Canada as the most represented country and primary source respectively. Excipients had the highest percentage of reports coming from the US (100.00%), while NSAIDs had the lowest percentage of US reports (18.96%).

Linear regression was performed to determine significance of change in the proportional representation of drug categories among DES 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 2.24% (95% CI: 1.47, 3.01) from 2004 to 2023. Ophthalmology Agents and Antibiotics also showed statistically significant average annual increases in proportional representation of 0.53% (95% CI: 0.10, 0.95; $P = 0.02$) and 0.03% (95% CI: 0.002, 0.05; $P = 0.03$) respectively. Dermatological Agents, Respiratory Agents, and Urological Agents showed statistically significant average annual decreases of –0.27% (95% CI: –0.39, –0.14; $P < 0.001$), –0.26% (95% CI: –0.32, –0.19; $P < 0.001$), and –0.10% (95% CI: –0.18, –0.02; $P = 0.02$) respectively. However, Chemotherapy Agents, DMARDs, Endocrine and Metabolic Agents, Excipients, Neurological Agents, and NSAIDs did not display a statistically significant average percent change per year. A more detailed breakdown of year over year changes in the proportional representation of each drug category within DES case reports can be found in Figure 2.

While the majority of DES cases are being reported from the US, it remains critical to elucidate other major international contributors to the DES reports. Aside from the US, the next five countries with the most reported DES adverse events were, in descending order: Canada, United Kingdom, Germany, France, and Brazil. For those countries, the top 10 drugs associated with DES were reported in Table 5.

DMARDs comprised 6 of the top 10 drugs associated with DES in Canada and 4 of the top 10 drugs in the US. DMARDs were also present in the top 10 drugs for Germany, France, and Brazil. Monoclonal Antibodies comprised 4 of the top 10 drugs reported by Brazil in association with DES. Ophthalmology Agents comprised 3 of the top 10 drugs reported

**FIG. 2.** The percentage of DES cases reported to FAERS in association with each drug functional class for study years 2004–2023.



by the US in association with DES, and were also present in the top 10 for Brazil. Additionally, Neurological Agents comprised 4 of the top 10 drugs reported by France in association with DES, and were also present in the UK and Germany. The remaining countries displayed a more varied list of categories among the top 10 drugs associated with DES. Interestingly, Corticosteroids were only in the top 10 for Germany and France, with NSAIDs only in the top 10 for Canada and Germany.

**TABLE 5.** Top 6 countries associated with DES reports in FAERS from 2004–2023 – Top 10 Drugs.

| Drug Rank | Drug Name | Dry Eye Reports | (% of Total County Reports) |
|---|---|---|---|
| **1. United States** | | | |
| Total Country Dry Eye Reports | | 25,591 | |
| 1 | Dupilumab | 5,860 | 22.90% |
| 2 | Cyclosporine | 1,167 | 4.56% |
| 3 | Etanercept | 941 | 3.68% |
| 4 | Lifitegrast | 924 | 3.61% |
| 5 | Adalimumab | 891 | 3.48% |
| 6 | Polyethylene Glycol 400\Propylene Glycol | 789 | 3.08% |
| 7 | Lenalidomide | 556 | 2.17% |
| 8 | Bimatoprost | 555 | 2.17% |
| 9 | Isotretinoin | 537 | 2.10% |
| 10 | Tofacitinib Citrate | 500 | 1.95% |
| **2. Canada** | | | |
| Total Country Dry Eye Reports | | 1,536 | |
| 1 | Methotrexate | 411 | 26.76% |
| 2 | Tocilizumab | 328 | 21.35% |
| 3 | Etanercept | 288 | 18.75% |
| 4 | Abatacept | 277 | 18.03% |
| 5 | Leflunomide | 275 | 17.90% |
| 6 | Rituximab | 249 | 16.21% |
| 7 | Adalimumab | 243 | 15.82% |
| 8 | Sulfasalazine | 221 | 14.39% |
| 9 | Hydroxychloroquine Sulfate | 209 | 13.61% |
| 10 | Meloxicam | 160 | 10.42% |
| **3. United Kingdom** | | | |
| Total Country Dry Eye Reports | | 1,140 | |
| 1 | Ciprofloxacin | 76 | 6.67% |
| 2 | Sertraline Hydrochloride | 62 | 5.44% |
| 3 | Isotretinoin | 56 | 4.91% |

(*Continues*)

## DISCUSSION

In our review of publicly available FAERS data, we found a multitude of important themes regarding the prevalence and characteristics of DES reports associated with multiple drug classes which have been summarized below.

### *Prevalence and Drug Classes*

The data indicates that Monoclonal Antibodies are the functional class with the highest proportion of DES reports, with 26.17% of the total DES reports. This is followed by Ophthalmology Agents at 10.06% and DMARDs at 10.03%. These findings suggest that Monoclonal Antibodies, Ophthalmology Agents, and DMARDs are significant contributors to drug-induced DES, which may be due to their widespread use and potential impacts on tear production and ocular surface integrity. Previous studies have identified dry eye as a side effect of Monoclonal Antibodies such as Dupilumab, Ophthalmology Agents such as Latanoprost, and DMARDs such as Methotrexate.[7,17] Dupilumab and Monoclonal Antibodies have been hypothesized to cause DES via reducing aqueous tear and mucin production while also creating local immunodeficiency resulting in increased ocular bacterial and viral infection.[18] As DMARDs are also known for their related effects in reducing inflammation, Methotrexate-associated ocular irritation may have a similar pathophysiology. In mice models, preservative-free Latanoprost eye drops were found to reduce tear production, disrupt the

**TABLE 5.** Continued.

| Drug Rank | Drug Name | Dry Eye Reports | (% of Total County Reports) |
|---|---|---|---|
| 4 | Simvastatin | 42 | 3.68% |
| 5 | Mirtazapine | 38 | 3.33% |
| 6 | Letrozole | 33 | 2.89% |
| 7 | Trastuzumab | 28 | 2.46% |
| 8 | Finasteride | 25 | 2.19% |
| 9 | Levofloxacin | 22 | 1.93% |
| 10 | Docetaxel\Docetaxel Anhydrous | 22 | 1.93% |
| **4. Germany** | | | |
| Total Country Dry Eye Reports | | 503 | |
| 1 | Ribociclib | 43 | 8.55% |
| 2 | Letrozole | 42 | 8.35% |
| 3 | Ciprofloxacin | 37 | 7.36% |
| 4 | Ranibizumab | 36 | 7.16% |
| 5 | Adalimumab | 32 | 6.36% |
| 6 | Prednisolone | 25 | 4.97% |
| 7 | Mirtazapine | 20 | 3.98% |
| 8 | Ibuprofen | 19 | 3.78% |
| 9 | Cyclosporine | 18 | 3.58% |
| 10 | Finasteride | 17 | 3.38% |
| **5. France** | | | |
| Total Country Dry Eye Reports | | 498 | |
| 1 | Levothyroxine Sodium | 89 | 17.87% |
| 2 | Levonorgestrel | 27 | 5.42% |
| 3 | Dexamethasone | 18 | 3.61% |
| 4 | Levothyroxine\ Levothyroxine Sodium | 16 | 3.21% |
| 5 | Aripiprazole | 16 | 3.21% |
| 6 | Lamotrigine | 16 | 3.21% |
| 7 | Lenalidomide | 14 | 2.81% |
| 8 | Pregabalin | 13 | 2.61% |
| 9 | Gabapentin | 13 | 2.61% |
| 10 | Ixazomib | 12 | 2.41% |

(*Continues*)

**TABLE 5.** Continued.

| Drug Rank | Drug Name | Dry Eye Reports | (% of Total County Reports) |
|---|---|---|---|
| **6. Brazil** | | | |
| Total Country Dry Eye Reports | | 330 | |
| 1 | Adalimumab | 43 | 13.03% |
| 2 | Latanoprost | 31 | 9.39% |
| 3 | Isotretinoin | 15 | 4.55% |
| 4 | Rituximab | 14 | 4.24% |
| 5 | Travoprost | 12 | 3.64% |
| 6 | Secukinumab | 12 | 3.64% |
| 7 | Etanercept | 12 | 3.64% |
| 8 | Ribociclib | 12 | 3.64% |
| 9 | Zoledronic Acid | 10 | 3.03% |
| 10 | Tocilizumab | 9 | 2.73% |

corneal epithelial barrier, and promote cell apoptosis as well as inflammation.[19] Given commonalities in chemical structure, such findings could be extrapolated to explain the mechanism of DES from prostaglandin analogs in general. However, many exact mechanisms of these associations between drug classes and DES have not yet been elucidated, a gap that can be addressed through future research. The remaining functional classes each comprised less than 5% of total DES reports.

### *Temporal Trends*

The data highlights that the year with the highest number of DES reports was 2023, with a maximum of 4,868 reports. Notably, Monoclonal Antibodies and Antibiotics both peaked in their maximum reports in 2023, while each of the other categories peaked in maximum reports 2020 or earlier. Monoclonal Antibodies comprised 51.41% of drug-associated DES reports in 2023, making them the key driver in the rising quantity of DES cases, reflecting the burgeoning increase in recognition and usage of these drugs in recent years.[20] The stark increase in Monoclonal Antibody reporting

might have been further propelled due to the class of medications being used to treat COVID-19.[21] Furthermore, increasing DES reports could also result from rising public awareness and use of FAERS as a reporting platform. The median year of reporting for most drug classes seems to center around the late 2010s to early 2020s, indicating a recent surge in awareness and reporting of drug-induced DES for newer drugs being introduced near the end of that timeframe. The COVID-19 pandemic did not have a marked effect on overall DES adverse event reporting.

### *Demographic Insights*

Women appear to be disproportionately affected by drug-induced DES, with 70.05% of the overall reports involving female patients, which is consistent with previous literature that highlights elevated DES prevalence among females.[1,22,23] This disproportionate impact could possibly be attributed to hormonal differences in females such as lower androgen levels and menstruation cycles affecting ocular structure and tear film stability.[23] Females are also affected by DES-associated autoimmune diseases, such as Rosacea and Sjogren's syndrome, at higher rates than males.[23] The gender disparity could also result from higher reporting rates among female patients. The drug categories with the highest proportion of reports from females were NSAIDs (85.71%) and Neurological Agents (84.31%), while the lowest proportions were observed in Antibiotics (58.27%) and Dermatological Agents (55.21%). The individual drug with the highest proportion of female reports was Palbociclib (93.24%), while the lowest was Belantamab Mafodotin (23.10%).

### *Age Distribution*

The median age of patients reporting DES varies across drug classes, with the overall median age being 57 years. Notably, Chemotherapy Agents, Ophthalmology Agents, NSAIDs, Urological Agents, and Respiratory Agents have a higher median age of 60-70 years. These findings support the current understanding of older age being identified as a major risk factor for DES.[1,24,25] This suggests that older populations may be more susceptible to DES when using these medications, potentially due to age-related changes in tear production and ocular surface health or hormonal effects from menopause in older females. Underlying age-related disease pathology may contribute to DES manifestation through decreased tear production secondary to lacrimal gland dysfunction, increased tear evaporation secondary to abnormalities of the eyelids (causing prolonged corneal exposure), as well as increased inflammation and oxidative stress.[25] Systemic and topical eye medications are also major risk factors predisposing older populations to deficiencies in tear production and tear film composition.[25] According to the CDC, more than 76% of Americans aged 60 years or older use two or more prescription drugs, with 37% using 5 or more.[26] Medications commonly used amongst older patients such as antidepressants, diuretics, dopaminergic drugs, oral steroids, decongestants, antihistamines, and topical eye medications contain preservatives that increase risk for DES.[25,27]

### *Annual Change Rates*

The annual rates of change for DES reports show variability among drug classes. Monoclonal Antibodies had a significant rising trend in their proportion of DES-associated cases, increasing by an average of 2.24% annually within the 2004–2023 study period. This increase could be attributed to the growing prevalence of Monoclonal Antibodies (along with the approval of new agents) in treatment regimens for a variety of conditions such as cancer, autoimmune disease, and osteoporosis.[28,29] Ophthalmology Agents also had a significant increase in their proportional representation at an average of 0.53% annually. This increase could be attributed to the fact that the irritation side effects of artificial tears and ocular anti-inflammatory agents are known to manifest through long-term use.[30] Thus, as the patient population using Ophthalmology Agents for chronic DES increases over time, more cases will be reported. In contrast,

Dermatological Agents, Respiratory Agents, and Urological Agents were the only groups that displayed a statistically significant decrease in their proportion of DES reports with an average change of –0.27%, –0.26%, and –0.10% respectively. While significant, each of those functional classes have a relatively small magnitude of decrease and quantity of reports (with Dermatological Agents only comprising 2.25%, Respiratory Agents comprising 0.67%, and Urological Agents comprising 0.64% of total DES reports). These findings suggest that much of their decline can be attributed to the substantial increase in Monoclonal Antibody-related cases, with improved management practices or a shift in drug usage patterns acting as secondary factors.

## CLINICAL IMPLICATIONS

These findings highlight the necessity for clinicians to be vigilant about the potential for DES in patients prescribed Monoclonal Antibodies, Ophthalmology Agents, DMARDs, and other high-risk medications. The data emphasizes the need for regular ocular assessments and proactive management strategies in these patient populations. Furthermore, the gender and age disparities observed suggest that tailored approaches may be required to effectively address DES in different demographic groups.

## LIMITATIONS

Although the FAERS data set provides valuable and extensive detailed reports on drug-induced side effects, there are some limitations. As noted before, the database provides no 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 when DES is noticed. Additionally, patients may assume certain drugs to be the cause of worsening DES despite their symptoms being in line with expected disease progression or the influence of comorbidities. In addition, a small minority of reports within the FAERS database omitted certain demographic information such as age, gender, or country of origin.[15] FAERS also lacks key variables such as race/ethnicity data in addition to having a higher risk of reporting biases from the consumer-based reports that are included in the database. Because categorization was only performed for the top 50 drugs associated with dry eye, values for percent representation of each drug class out of total DES reports are slightly diminished due to the exclusion of drugs falling outside the top 50.

## CONCLUSION

This comprehensive analysis of FAERS data provides valuable insights into the etiology of drug-induced DES. The significant association of Monoclonal Antibodies, Ophthalmology Agents, and DMARDs with patient reports of DES underscores the need for heightened awareness and monitoring when prescribing DES patients such drugs. By identifying and understanding these associations, healthcare providers can improve patient outcomes through early identification and appropriate management of drug-induced DES. Future research should continue to explore the biological, physiological, environmental, and social mechanisms underlying these associations and develop targeted interventions to mitigate the impact of these medications on ocular health.

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## AUTHOR CONTRIBUTIONS

Conceptualization: KA, DP; Data Collection: EW, AV; Formal Analysis: EW, AV; Writing – Original Draft: EW, AV; Writing – Review & Editing: KA, EW, DP; Project Administration: KA, DP.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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