TFOS DEWS II iatrogenic report

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ABSTRACT

Dry eye can be caused by a variety of iatrogenic interventions. The increasing number of patients looking for eye care or cosmetic procedures involving the eyes, together with a better understanding of the pathophysiological mechanisms of dry eye disease (DED), have led to the need of a specific report about iatrogenic dry eye within the TFOS DEWS II.

Topical medications can cause DED due to their allergic, toxic and immuno-inflammatory effects on the ocular surface. Preservatives, such as benzalkonium chloride, may further aggravate DED. A variety of systemic drugs can also induce DED secondary to multiple mechanisms. Moreover, the use of contact lens induces or is associated with DED. However, one of the most emblematic situations is DED caused by surgical procedures such as corneal refractive surgery as in laser-assisted in situ keratomileusis (LASIK) and keratoplasty due to mechanisms intrinsic to the procedure (i.e. corneal nerve cutting) or even by the use of postoperative topical drugs. Cataract surgery, lid surgeries, botulinum toxin application and cosmetic procedures are also considered risk factors to iatrogenic DED, which can cause patients' dissatisfaction, visual disturbances and poor surgical outcomes.

This report also presents future directions to address iatrogenic DED, including the need of deeper epidemiological studies about the risk factors, development of less toxic medications and preservatives, as well as new techniques for less invasive eye surgeries. Novel research into detection of early dry eye prior to surgeries, efforts to establish appropriate therapeutics and a greater attempt to regulate and oversee medications, preservatives and procedures should be considered.

1. Introduction

Iatrogenic disease is defined as an adverse clinical condition resulting from medical treatment by a health professional. The word iatrogenic is derived from Greek *iatros*, physician, *genein*, to

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produce. Iatrogenic disease is thus a condition caused by the commission, rather than the omission, of treatment. It affects a large number of patients worldwide in all areas of medicine [1].

Dry eye can be caused by a variety of iatrogenic interventions, including topical or systemic drugs, the use of contact lenses, and ophthalmic surgical and non-surgical procedures. Recognized as important causes of dry eye disease (DED), these iatrogenic factors were addressed in the 2007 Tear Film Ocular Surface (TFOS) Dry Eye Workshop (DEWS) definition and classification report [2].

The ever-increasing number of patients undergoing ophthalmic (and non-ophthalmic) procedures, together with a better understanding of the pathophysiological mechanisms of DED, have highlighted the need for a deeper analysis of iatrogenic dry eye, and thus, the 2017 TFOS DEWS II has a dedicated report on this topic [3].

In addition to providing updated scientific information regarding iatrogenic dry eye, the 2017 DEWS II report aims to increase awareness in the medical and non-medical communities with regard to preventing, or at least decreasing, the effects of iatrogenic dry eye on the ocular surface, vision, and quality of life of our DED patients.

2. Goals of the TFOS DEWS II iatrogenic subcommittee

The goals of the TFOS DEWS II Iatrogenic Dry Eye Subcommittee were to: 1) define iatrogenic dry eye; 2) identify the most important iatrogenic mechanisms of dry eye and propose an etiological classification; 3) present an updated epidemiological analysis and a comprehensive and evidence-based review of each type of iatrogenic dry eye; 4) discuss prophylaxis and recommendations for management; and 5) propose areas for future research.

3. Classification of iatrogenic dry eye

Iatrogenic dry eye can be classified as shown in Table 1.

4. Major causes of iatrogenic dry eye

4.1. Systemic drug-induced DED

4.1.1. Incidence and prevalence

Among the top 100 best-selling systemic drugs in the US in 2009, 22 of them possibly cause dry eye [4]. Of the 9 systemic drugs known to be secreted into the tear film, 8 have been associated with causing dry eye [4]. Most of the studies available on systemic drug-induced DED only analyze the classes of drugs, but not individual prescription drugs [4]. Overall, systemic drugs may cause dry eye secondary to decreased tear production, altered nerve input and reflex secretion, inflammatory effects on secretory glands, or direct irritation effects through secretion into the tears [5]. However, not every drug does actually reach the ocular surface structures, but rather certain drug properties and kinetics play a role in determining which drugs penetrate intraocularly, namely, lipid solubility, molecular weight, ionic state, plasma protein binding and total blood concentration [6].

Schein et al. attributed 62% of DED cases in the elderly to systemic drying medications, including nonsteroidal anti-inflammatory drugs (NSAIDs; odds ratio [OR] 1.30), diuretics (OR 1.25), vasodilators (OR 1.37), analgesics/antipyretics (OR 1.28), antiulcer agents (OR 1.44), sulfonylureas (OR 1.3), cardiac glycosides (OR 1.28), anxiolytics/benzodiazepines (OR 2.35), anti-infectives (OR 1.88), antidepressants/antipsychotics (OR 2.54), hypotensive agents (OR 1.98), and antihistamines (OR 1.67) [7].

The Beaver Dam population-based, age-adjusted, cumulative 10-year dry eye study in 3722 subjects recognized the use of systemic antihistamines and diuretics as risk factors for DED [8]. The

Table 1
Classification of iatrogenic dry eye.

- I. Drug-induced
  - o A. Systemic
  - o B. Topical
- II. Contact lens-induced
- III. Ophthalmic surgery
  - o A. Refractive surgery
  - o B. Keratoplasty (PK, LK and EK)
  - o C. Cataract surgery
  - o D. Lid surgery
  - o E. Other surgeries
    - ■ 1. Conjunctival surgery
    - ■ 2. Glaucoma surgery
    - ■ 3. Vitreoretinal surgery
    - ■ 4. Strabismus surgery
    - ■ 5. Intrastromal corneal ring segment(s) implantation
    - ■ 6. Others
- IV. Non-surgical ophthalmic procedures
  - o A. Botulinum toxin
  - o B. Crosslinking (CXL)
  - o C. Cosmetic procedures
  - o D. Others
- V. Non-ophthalmic conditions
  - o A. Graft-versus-host disease (GVHD)
  - o B. Others

Beaver Dam Offspring Study analyzing the prevalence of dry eye in 3275 individuals included inhaled steroid use as an additional risk factor (OR 2.04) [9]. Systemic hormones were associated with a 71% increase in the likelihood of dry eye symptoms in women under the age of 50 years (OR 1.71), as well as multi-vitamin use (OR 1.43) [9]. In all subjects 50 years and older, the use of benzodiazepines was also associated with dry eye (OR 2.25) [9]. Hormone replacement therapy, especially estrogen use alone (OR 1.69), was added as a risk factor for DED by the Women's Health Study, which analyzed over 25,000 postmenopausal women [10]. The Extension Blue Mountains Eye Study, which included 1174 participants aged 50 or older in Australia, confirmed corticosteroids (OR 1.6), antidepressants (OR 1.7), and hormone replacement therapy (OR 1.6) as risk factors for DED in the elderly [11]. In 25,444 US men aged 50 years and older, antidepressants (OR 1.90), anti-hypertensives (OR 1.15), and medications used to treat benign prostatic hyperplasia (OR 1.35) were associated with an increased risk of DED [12]. A small case-control study in male subjects taking anti-androgen therapy for prostatic disorders confirmed its added risk for the development of MGD-associated DED [13].

In the National U.S. Veterans Affairs Administration database, which includes over 2 million patients, the use of antidepressant medications (OR 1.97) and antianxiety medications (OR 1.74) was associated with an increased risk of DED [14]. The use of systemic beta-blockers was associated with worsening of dry eye in nearly 800 participants of the Women's and Physicians Health studies [15].

The systemic drugs identified by large epidemiological studies as increasing the risk for DED together with their associated ORs are listed in Table 2.

4.1.2. Systemic drugs with a known or suspected link to dry eye symptoms

The list of systemic drugs with a known or suspected link to dry eye symptoms is quite extensive. Table 3 presents a compilation of known or suspected systemic agents that have been reported to induce or exacerbate dry eye. Among other sources, this listing of drugs has been compiled from a series of extensive reviews [17–23], epidemiological studies and the key database from Fraunfelder and colleagues, published in both peer-reviewed

journals and every 4–5 years in book form [24,25]. In addition to collecting spontaneous reports from clinicians, the registry accumulates data from spontaneous reports sent to the World Health Organization's (WHO's) Uppsala Monitoring Center (Uppsala, Sweden), the Food and Drug Administration (Rockville, MD), pharmaceutical companies and screening of the world's literature. The registry has applied the WHO Causality Assessment Guide of Suspected Adverse Reactions to classify causality as either "Certain", i.e., determined by withdrawal and rechallenge with drug; "Probable", relying on response to drug withdrawal without rechallenge; or "Possible" where the clinical event is mainly judged based on its occurrence within a reasonable time sequence from drug administration.

Using a similar approach to define systemic drug and dry eye relationships, Stapleton and colleagues [26] reviewed 23 large cohort and record analysis dry eye prevalence studies and classified the level of evidence for dry eye risk factors according to "Mostly Consistent" (where mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data), "Suggestive" (where suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal), or "Unclear" (where evidence is either directly conflicting information in peer-reviewed publications or inconclusive, but with some basis for biological rationale).

4.1.3. Mechanisms

Multiple different mechanisms have been proposed to describe the effect of drugs on dry eye symptoms and are unique to the particular class of drug being administered. A large segment of systemic drugs that have an effect on dry eye symptoms are those with anticholinergic activity. More specifically, G-protein coupled muscarinic receptors in the lacrimal gland acini and conjunctival mucus-producing cells can be affected [27], thereby reducing aqueous and mucous tear component production and resultant tear film stability [28]. Moreover, functional cholinergic receptors have been identified in human meibomian gland epithelial cells and these receptors would also be impacted by anti-cholinergic agents [29]. The anti-cholinergic class comprises a wide range of therapeutic drug categories including antidepressants, antipsychotics or neuroleptics, anti-Parkinson's, H1 antihistamines, decongestants and antispasmodics. Additionally, adrenergic agents, including both beta-blockers and alpha agonists, elicit changes in both tear production and tear film quality (i.e., mucus and protein secretion) likely mediated by protein kinase C production and intracellular Ca^{++} concentration [30,31].

Several drugs such as amiodarone, aspirin, bisphosphonates, chloroquine, ibuprofen and clofazimine are secreted in the tears and may aggravate existing sicca conditions, due to either mechanical irritation or an increased evaporative form of dry eye caused by the presence of drug crystals or deposits in the tears or cornea [32,33]. Alcohol is also secreted in tears and can contribute to dry eye via hyperosmolarity and shortened tear film breakup time [34].

Certain chemotherapeutic agents such as methotrexate, mitomycin C and busulfan have been reported to cause alterations in the quality of the tear film [35] or affect reflex tear secretion [36]. In addition, dysfunctional tear syndrome has been associated with epidermal growth factor inhibitors such as erlotinib and cetuximab based on a hospital chart review of 69 patients [37].

Normal vitamin A is needed for corneal epithelial differentiation, increasing corneal wound healing and strength and reducing corneal and conjunctival epithelial keratinization [38]. Excess retinoic acid (RA) is used in the treatment of severe acne, cancer chemotherapy and anti-aging cosmetics. However, too much RA can cause dry eye and blepharitis; as isotretinoin is secreted in tears by the lacrimal gland and is attributed to inducing atrophy of the meibomian glands, it can lead to changes in lipid secretion, tear osmolality and tear film stability [39,40].

In terms of the mechanism of high-dose RA-induced dry eye, there are several possible ocular surface target tissues, including the lacrimal glands, meibomian glands, cornea and conjunctiva. High-dose RA is known to cause meibomian gland atrophy, reduced quality of meibum, reduced tear film breakup time, increased tear osmolarity and dry eye symptoms [41]. It induces tissue necrosis and keratinization in adult animal meibomian glands [42] and disrupts meibomian gland development if given during prenatal developmental period [43]. At the molecular and cellular level, RA inhibits meibomian gland epithelial cell proliferation, increases cell death, alters the expression of more than 6000 genes including IL-1β and matrix metalloproteinase 9 (MMP-9) and inactivates AKT signaling pathway that is important for cell survival and proliferation [44]. Similarly, high-dose RA also inhibits rat lacrimal gland epithelial cell proliferation and down-regulates androgen receptors [45,46]. However, RA does not appear to affect human lacrimal gland secretion clinically. One study found that Schirmer test scores were not significantly different before or after 2 months of Accutane treatment, even though reduced TBUT, increased blepharitis and subjective dryness, itching and CL intolerance did increase significantly after Accutane treatment [47]. This indicates that dry eye induced by RA is more likely secondary to MGD rather than reduced lacrimal gland secretion. It is not clear why the clinical data show discrepancies from the animal and cell experimental data on the effect of high-dose RA on lacrimal glands. However, it appears that MGD is a major mechanism of RA-induced dry eye in both human, animal and cell culture studies. In terms of the cornea and conjunctiva, high-dose RA has been used to promote corneal wound healing and reduce conjunctiva keratinization; these tissues seem to be quite tolerable to high levels of RA and therefore not contributory to dry eye induced by RA [38].

While benzodiazapines may depress salivary (and potentially tear) secretion via binding to muscarinic receptors, the antigenic potential of this drug category also plays a major role in causing dry eye symptoms as a side effect related to development of Stevens-Johnson syndrome [48]. A type I immune response to the desmethyldiazepam metabolite is responsible for the cross-reactivity of the various benzodiazepines and derivatives. Beyond this category, Fraunfelder and colleagues [24] identified more than 150 drugs that may have a possible relationship with Stevens-Johnson syndrome and the associated dry eye symptoms.

Because of interactions that may occur following therapy with multiple drugs, the exact mechanisms by which combinations of drugs may act in concert to produce dry eye symptoms becomes complex [4]. From a broad perspective, Schein and colleagues uncovered an increasing adjusted positive odds ratio for each additive drug therapeutic used with symptoms of dry eye and dry mouth [7], suggesting a combined effect of drugs. The use of five or more prescription drugs (polypharmacy) and the addition of OTC medications are thought to increase the risk for iatrogenic DED [4].

In consideration together with the results of epidemiological studies showing effects of multiple medications on the prevalence of dry mouth symptoms [49,50], there is good cause for caution when considering similar drugs with potential for development of dry eye. Further discussion of iatrogenic mechanisms can be found in the Report of the Pathophysiology Committee [51].

Table 2
Systemic Drugs Identified by Large Epidemiological Studies and Associated Odds Ratios for risk of Dry Eye Disease (DED).

Medication	Author/Year	Study population (Study; number; age)	Odds Ratio
NSAIDS[a]	Schein et al. [7]	2481; 65–84 yr	1.30
Diuretics			1.25
	Moss et al. [16] [Beaver Dam Eye study]	3722; 48–91 yr	none available, p = 0.02
Vasodilators	Schein et al. [7]	2481; 65–84 yr	1.37
Analgesics/antipyretics			1.28
Antiulcer agents			1.44
Sulfonylureas			1.30
Cardiac glycosides			1.28
Anxiolytics/benzodiazepines			2.35
	Paulsen et al. [9] [Beaver Dam Offspring]	3275; 21–84 yr.	2.25
	Galor et al. [14] [Veterans Affairs database]	2,454,485; 21–100yr	1.74
Anti-infectives	Schein et al. [7]	2481; 65–84 yr	1.88
Antidepressants/antipsychotics	Schein et al. [7]	2481; 65–84 yr	2.54
	Chia et al. [11]	3654; >49 yr	1.70
	Schaumberg et al. [12]	25,444; >49 yr	1.90
	Galor et al. [14]	2,454,485; ages	1.97
Antihypertensives	Schein et al. [7]	2481; 65–84 yr	1.98
	Schaumberg et al. [12]	25,444; >49 yr	1.15
Antihistamines	Schein et al. [7]	2481; 65–84 yr	1.67
	Moss et al. [16]	3722; 48–91 yr	none available; p = 0.01
Inhaled steroid use	Paulsen et al. [9]	3275; 21–84 yr.	2.04
Systemic corticosteroids	Chia et al. [11]	3654; >49 yr	1.60
Systemic hormones (in women <50 yr)	Paulsen et al. [9]	3275; 21–84 yr.	1.71
Hormone replacement therapy (HRT)	Schaumberg et al. [10] (estrogen alone)	postmenopausal women; 25,665, 45–84 yr.	1.69
	Chia et al. [11]	3654; >49 yr	1.60
Antiandrogen therapy/medications to treat benign prostate hyperplasia	Schaumberg et al. [12]	25,444; >49 yr	1.35
Multi-vitamins	Paulsen et al. [9]	3275; 21–84 yr.	1.43
	Moss et al. [8]	3722; 48–91 yr	1.41

[a] Nonsteroidal anti-inflammatory drugs.

4.1.4. Recommendations for management

Identification of the offending medication can be predicated upon knowledge of recognized systemic medications certain to cause dry eye as described in Table 3. However, an approach providing even better certainty would be to withdraw and rechallenge with the drug or food of interest. When that is not possible, a response to drug or food withdrawal without rechallenge is in order, although in certain cases the relationship of the dry eye onset might be inferred directly from the time of first dosing of the drug or upon specific instances of food ingestion. In accordance with the patient's health needs, simply discontinuing the medication may not be acceptable. As such, when possible, switching to medications with alternative mechanisms may permit continued therapy with the possibility of eliminating the ocular side effect. However, it may be possible to adjust the dosage of the offending medication to still allow for adequate therapy with reduced side effects. Also, if symptoms are not too severe and the patient's condition warrants continuation of the specific drug, it may be possible to simply add on lubricants or other ocular topical therapies [52,53].

Ideally, elimination of systemic drug effects comes from better drug design. As a first step, increased specificity for target receptors and elimination of non-specific receptor binding would be the goal. In particular, the elimination of extraneous binding to muscarinic receptors would no doubt broaden the field of drugs that could be used without dry eye side effects. Second, chemical modifications (such as pro-drugs or hydrophobicity) that affect absorption or permeation into ocular tissues without adversely affecting distribution to target tissues could provide value. Third, the development of controlled or sustained delivery systems that impact the kinetics and/or distribution of the drug could have a dramatic impact on the levels that actually reach the eye. Finally, changes to the dose form and administration method could lead to reductions in the concentrations of drug in ocular tissue; highly localized administration methods near a disease locus might allow for less systemic circulation of a drug.

4.2. Topical drug-induced DED

4.2.1. Incidence and prevalence

The evaluation of DED induced by topical drugs is complicated, as clinical trials typically exclude patients prone to ocular surface disease (OSD), and thus, dry eye symptoms may not be interpreted and reported as such. Most available epidemiological data regard the prevalence of OSD among patients treated over the long term for glaucoma or ocular hypertension. Randomized clinical trials (RCTs) show good overall tolerance of glaucoma treatments, with only a few patients withdrawn due to local intolerance, dry eye, or allergy. However, there are several major differences between clinical trials and real life: clinical trials are usually of short duration; most patients only receive one drug and possible interactions or additive toxic effects of various compounds are not addressed; for ethical reasons, patients with known hypersensitivity to the active molecule or the preservative and those with active concomitant diseases, in particular active or severe dry eye, blepharitis or allergy, are not included.

A multicenter cross-sectional epidemiologic survey in four European countries including 9658 glaucoma patients revealed symptoms of "stinging or burning," "foreign body sensation," or "dry eye sensation" in 47.5%, 41.9%, and 34.9%, respectively, of patients, using preserved glaucoma medications. These complaints were reduced to 19.6%, 14.8%, and 16.0%, respectively, with the use of preservative-free eye drops [106]. Corneal staining was present in 25.6% versus 8.9% of patients using preserved versus nonpreserved glaucoma medications. In a German registry of 20,506 glaucoma patients from 900 centers, the prevalence of dry eye was 56.9% in women and 45.7% in men. Dry eye occurred in decreasing

Table 3
Known or suspected systemic medications causing, contributing to, or aggravating dry eye.

Category	Subcategory	Systemic Drugs Identified or Implicated in Dry Eye[a]	Representative References[b]
Analgesic	Antirheumatic	Aspirin*, Ibuprofen*	[32,54–56]
	Cannabinoid	Dronabinol*, Tetrahydrocannabinol*	[57]
	Opioid	Buprenorphine, Fentanyl, Methadone, Morphine*, Opium*, Oxymorphone, Tapentadol	[58,59]
Anesthesia		Ether*, Nitrous Oxide*	[58,60]
Anticholinergic (antimuscarinic)	Antiarrythmic/Bronchodilating	Atropine*, Diphenhydramine, Disopyramide, Homatropine, Ipratropium*, Methscopolamine, Scopolamine*, Tiotropium, Tolterodine	[61,62]
	Antihistamine	Azelastine, Brompheniramine*, Carbinoxamine*, Cetirizine*, Chlorpheniramine*, Clemastine*, Cyproheptadine*, Desloratidine*, Dexchlorphenamine*, Diphenhydramine*, Doxylamine*, Epinastine, Fexofenadine*, Hydroxyzine, Ketotifen, Loratidine*, Olopatadine, Promethazine, Pseudoephedrine, Tripelennamine*, Triprolidine*	[26,63–67]
	Antidepressant	Agomelatine, Amitriptyline, Bupropion, Chlomipramine, Cialopram, Desipramine, Doxepin, Duloxetine, Fluoxetine, Fluvoxamine, Imipramine, Mianserine, Mirtazapine, Nortripty, Paroxetine, Reboxetine, Sertraline, Tianeptine, Trazodone, Venlafaxine	[11,67–72]
	Anti-Parkinson's	Benapryzine, Benzhexol, Benztropine, Bornaprine, Levodopa, Methixine, Orphenadrine, Pamipexole, Procyclidine	[73,74]
	Antipsychotic	Aiprasidone, Aripiprazole, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine, Clozapine, Cyproheptadine, Dexchlorphiniramine, Fluphenazine, Haloperidol, Lithium carbonate, Olanzepine, Perphenazine, Promethazine, Quetiapine, Risperidone, Sulpiride, Thiethylperazine, Thioridazine Thiothixene, Trifluoperazine	[75–79]
	Antispasmodic	Fesoterodine, Homatropine*, Oxybutynin, Propantheline, Propiverine, Solifenacin, Tolterodine*, Trospium	[62,80,81]
	Decongestant	Oxymetazoline, Phenylephrine, Phenylpropanolamine, Pseudoephedrine, Xylometazoline	[23,82]
Antihypertensive	Adrenergic blocking	Acebutolol, Atenolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Pindolol, Clonidine*, Prazosin, Oxprenolol*, Propranolol*	[30,31,83,84]
	Na$^+$Cl$^-$ Co-transporter (diuretic)	Bendroflumethiazide, Chlorothiazide, Chlortalidone, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Trichlormethiazide	[26,66,85,86]
Antileprosy		Clofazimine*	[87]
Antimalarial		Chloroquine*, Hydrochloroquine*	[88]
Antineoplastic		Busulfan, Cetuximab*, Cyclophosphamide*, Docetaxel, Erlotinib*, Gefitinib*, Interferon, Methotrexate, Mitomicin C, Panitumumab*, Vinblastine*, Vertiporphin*	[17,35,36,89,90]
Anxiolytic/hypnotic		Alprazolam*, Diazepam*, Eszopiclone, Lorazepam*, Zolpidem, Zopiclone	[69,72,91]
Chelator/Calcium Regulator		Methoxsalen, Alendronate, Pamidronate, Risedronate	[92,93]
Depressant		Ethanol*	[34]
Herbal and Vitamins		Isotretinoin*, Niacin, Echinacea, Kava	[23,94–97] For complete references on Isoretinoin refer to the Report of Sex, Hormones and Genders Subcommittee [98]
Hormonal	Antiandrogen/Estrogen replacement	Alfuzosin, Doxazosin, Finasteride*, Leuprorelin*, Tamsulosin, Terazosin, Estrogen/progesterone, Medroxyprogesterone	[72,99–102] For complete references refer to the Report of Sex, Hormones and Genders Subcommittee [98]
Neurotoxin		Botulinum A* or B	[103] [104],
Sedative		Primidone, Phenylbarbitol	[105]

[a] Drugs marked with an asterisk are classified as having a *certain* causative relationship to dry eye symptoms as described by Fraunfelder and colleagues [24]. "Certain" is defined as… "A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory rechallenge procedure if necessary." For listed drugs, the scope of terms searched for relation to or implication in dry eye symptoms included side effect categories of burning sensation, keratoconjunctivitis sicca, lacrimation-decreased, meibomian gland changes, sicca-ocular, Stevens-Johnson syndrome, tears-drug found in.
[b] References listed in the table represent selected or illustrative drugs in the category.

frequencies in patients with pseudoexfoliation glaucoma, primary open-angle glaucoma, and pigmentary glaucoma [107].

In one large epidemiological survey, conducted in 4107 glaucoma patients [108], the frequency of signs and symptoms increased with the number of preserved eye drops used and was significantly lower for all criteria in a group of patients treated with unpreserved betablockers. More recently, an observational survey confirmed the high prevalence of dry eye in glaucoma patients with

a clear relationship with the number of eyedrops; 39% and 43% had dry eye with two and three drugs, respectively, whereas dry eye was only found in only 11% of patients receiving one eyedrop; based on a score of ocular surface symptoms, severe dry eye was found in 8.7% and 15% of patients receiving two and three eyedrops, respectively [109]. Another study showed a clear relationship between the number of medications, irrespective of their family, which may suggest that a common compound leads to such sides effects, namely the preservative, the only component common to all eyedrops [110].

Other risk factors for the development of DED in glaucoma patients are the duration of treatment, higher intraocular pressure, glaucoma severity, and the use of BAK-containing eye drops [107,110–113]. The risk for DED is probably independent from the pressure-lowering drug used [114], with contradictory evidence existing concerning ethnicity, age and sex as risk factors [107,110,111], Interestingly, a recent survey showed that almost 38% of glaucoma patients were using tear substitutes, more than half of them being preserved. This finding illustrates the lack of knowledge on the iatrogenic cause of DED in glaucoma, the additive strategy to manage DED consisting of treatments to alleviate symptoms rather than considering the cause and the illogical use of preservative-containing eyedrops [115].

Baudouin et al. reported an observational cross-sectional study in 516 patients with glaucoma or ocular hypertension receiving antiglaucomatous eye drops. Symptoms of dry eye in this population included burning (47.3%), eye dryness (44.0%), foreign body sensation (39.9%), itching (39.1%), tearing (31.6%) as well as signs such as conjunctival hyperemia (60.3%), eyelid margin redness (46.7%), corneal (34.7%) or conjunctival (28.3%) staining, and a decreased tear breakup time (TBUT) below 5 s (20.9%) [110]. The prevalence of dry eye complaints evaluated prospectively by the U.S. Dry Eye Ocular Surface Disease Index (OSDI) questionnaire in 630 glaucoma/ocular hypertension patients on topical anti-glaucoma treatment was 48.4% from 10 sites, and the OSDI scores indicated mild (21.3%), moderate (13.3%), or severe (13.8%) OSD [111].

In their cross-sectional study in 101 patients on anti-glaucoma medications from California, Leung et al. reported dry eye symptoms in 59% of patients (severe in 27%), decreased Schirmer test values in 61%, decreased TBUT in 78%, and ocular surface staining in 22% of the subjects [112]. In Australia, 39% of patients with glaucoma suffered from significant DED, and the associated economic burden was calculated to be 330.5 million AU$ per year [116].

4.2.2. Topic drugs considered as causing dry eye

Many topical drugs and excipients have been considered as causing DED [4], (Tables 4 and 5), but specific data on the active compounds are mostly lacking as ophthalmic preparations are most often tested in preserved formulations, which may hinder interpretation on the respective role of the drug, preservatives and excipients. In healthy volunteers, Ishibashi et al. demonstrated that preserved timolol caused significantly higher tear film instability and disruption of corneal barrier function than did preservative-free timolol [117]. Similar results were found in healthy volunteers when comparing preservative-free and BAK-containing carteolol, with no visible effect of the unpreserved betablocker [118]. However, Kuppens et al. found that tear turnover remained at a lower level than normal with unpreserved timolol, even though values were better than with preserved timolol [119]. Recently, in an experimental model, differences between epinastine and olo-patadine that could not be attributed to BAK were noticed, favoring epinastine, which did not reduce tear volume [120]. On the other hand, another study in a mice model of dry eye found no statistical difference in aqueous tear production when comparing epinastine

and olopatadine and that both medications did not cause significant damage to the compromised ocular surface [121].

Other common excipients in ophthalmic formulations (solutions, ointments, suspensions, and emulsions) could also contribute to dry eye symptoms (Table 5). Additionally, the chemical properties of the formulation, such as iso/hypotonicity and pH, may also impact the tear film and local tolerance upon instillation.

4.2.3. Mechanism

Topical drugs may act at the level of the ocular surface through various mechanisms, exerting allergic, toxic and/or immuno-inflammatory effects or by chemical interactions with the lacrimal film, either by disrupting the lipid layer through detergent tensioactive effects, by reducing aqueous secretion or damaging: goblet cells; the conjunctival and corneal epithelia; corneal nerves through neurotoxic effects; or even eyelids at the skin or meibomian gland level. The most studied detergent compounds are quaternary ammoniums, which are highly hydrosoluble bipolar compounds that have surfactant properties. They act mainly via their detergent properties, which dissolve lipids and destroy the bacterial walls and cell membranes. Labbe et al. demonstrated a clear relationship between cumulative amounts of benzalkonium chloride (BAK) and disruption of the tear film measured by tear film osmolarity [122].

Indirect effects may also occur if drug-induced chronic inflammation stimulates cornified envelope precursors [123]. causing goblet cell content entrapment and squamous metaplasia. Eyelid margin keratinization may further result in meibomian gland dysfunction. Additionally, destruction and/or dysfunction of goblet

Table 4
Topical drugs considered to cause or aggravate DED [4].

Class	Examples
Agents used to treat glaucoma	
Betablocking agents	Betaxolol
	Carteolol
	Levobunolol
	Metipranolol
	Timolol
Adrenergic agonist drugs	Apraclonidine
	Brimonidine
	Dipivefrin
Carbonic anhydrase inhibitors	Brinzolamide
	Dorzolamide
Cholinergic agents	Pilocarpine
	Ecothiopate
Prostaglandins	Bimatoprost
	Latanoprost
	Travoprost
	Unoprostone
Agents used to treat allergies	Emedastine
	Olopatadine
Antiviral agents	Aciclovir
	Idoxuridine
	Trifluridine
Decongestants	Naphazoline
	Tetryzoline
Miotics	Dapiprazole
Mydriatics and cyclopegics	Cyclopentolate
	Tropicamide
	Hydroxyamfetamine
Preservatives	Benzalkonium chloride
Topical and local anesthetics	Cocaine
	Proxymetacaine
	Tetracaine
Topical ocular NSAIDs	Bromfenac
	Diclofenac
	Ketorolac
	Nepafenac

cells cause loss of the immunosuppressive properties driven by mucin-secreting cells, which may further enhance chronic inflammation by loss of their negative feedback to dendritic cells [124].

Clinically, it remains difficult to discriminate between spontaneous changes in OSD and iatrogenic effects. Symptoms and timing of conjunctival allergy induced by the instillation of eyedrops can be evocative, but simple conjunctival congestion or papillary conjunctivitis may be observed with or without eczema. Delayed allergic reactions can also occur, often mimicking blepharitis with low-grade inflammation. Similarly, it can be very difficult to differentiate corneal staining due to DED, either preexisting or iatrogenic, from toxic epitheliopathy or corneal melting, like those induced by overuse of anesthetics or NSAIDs. With so many confounding factors, the relationships between eyedrops and ocular inflammation, tear instability or ocular surface staining, are often difficult to assess, especially when the treatment is mandatory for a severe sight-threatening condition. This is particularly the case in glaucoma, when long-term, often life-long, treatments are required.

4.2.3.1. Role of preservatives and excipients. The Pharmacopoeia recommends that eyedrops contain a preservative to prevent microbial proliferation after the bottle is opened. Preservatives used in ophthalmic preparations belong to a variety of chemical families, including mercury derivatives, alcohols, parabens, EDTA, and chlorhexidine, but quaternary ammonium compounds, due to their low allergenic effects and apparently good safety profiles, have progressively become the major preservatives in use today. BAK is

Table 5
Ophthalmic product excipients that might contribute to dry eye symptoms. Source of ingredients from approved FDA Inactive Ingredient List 2016 [148].

Ophthalmic Excipient Category	Ingredient
Surfactants/Co-solubilizers	Glyceryl monostearate
	Lauroyl sarcosine
	Nonoxynol-9
	Octoxynol-40
	Octylphenol polymethylene
	Poloxamer 188
	Poloxamer 407
	Polyethylene glycol 300
	Polyethylene glycol 400
	Polyethylene glycol 4000
	Polyethylene glycol 8000
	Polyoxyethylene-polyoxypropylene 1800
	Polyoxyl 35 castor oil
	Polyoxyl 40 hydrogenated castor oil
	Polyoxyl 40 stearate
	Polypropylene glycol
	Polysorbate 20
	Polysorbate 60
	Polysorbate 80
	Propylene glycol
	Sorbitan monolaurate
	Tocophersolan
	Triton 720
	Tyloxapol
Preservative Aids	Benzyl alcohol
	Cetyl alcohol
	Chlorobutanol
	Edetate disodium
	Methylparaben
	Phenylethyl alcohol
Antioxidants	Sodium sulfate
	Sodium sulfite
	Sodium bisulfate
	Sodium bisulfate
	Sodium metabisulfite
	Sodium thiosulfate

an alkylbenzyldimethylammonium chloride mixture composed of C12 and C14 chains, commonly used at concentrations ranging from 0.004 to 0.02%. A large number of clinical and experimental investigations using *in vitro* or animal models have suggested that BAK has cytotoxic effects on several structures of the eye, with a threshold of toxicity found at about 0.005%, i.e. below the concentration used in most eyedrops [125]. It is a well-known irritant in dermatological and allergological investigations, but rarely recognized as the main allergen responsible for contact dermatitis [126].

BAK may cause or aggravate DED through various mechanisms such as its toxic and proinflammatory effects, as well as detergent properties, which have been well demonstrated in numerous experimental and clinical investigations [125]. Goblet cells produce soluble mucins and participate on tear film stability and immune defenses. These cells are extremely sensitive to toxic and inflammatory stress, decreased in density in humans after short exposure to BAK or BAK-containing timolol [127]. MUC1 and MUC16 were found to be reduced after exposure to BAK in human corneal and limbal epithelial cells. Transmission electron microscopy revealed alteration of the mucus layer after exposure to 0.01% BAK for 5 or 15 min, whereas more prolonged exposure (60 min) to 0.01% BAK destroyed the mucus layer [128]. These toxic effects were also found by Kahook and Noecker, who reported significantly lower densities of goblet cells in animals receiving BAK-containing latanoprost compared to preservative-free artificial tears, even though the specific effects of latanoprost alone were not addressed [129].

In addition, as a tensioactive compound, BAK is also a detergent for the lipid layer of the tear film. Thus, while an unpreserved betablocker did not impact tear stability, decreased TBUT was observed with a preserved betablocker [118]. Increased tear osmolarity was also observed in patients receiving preserved eyedrops compared to those who received unpreserved topical medication [122]. Following the loss of its protective properties, the impaired tear film not only causes dry eye symptoms and corneal damage, but also may convey cytotoxic inflammatory mediators throughout the ocular surface. Hence, increased corneal epithelial permeability was shown in dry eye with additional impairment when using artificial tears containing BAK compared to non-preserved eyedrops [130]. Tear film alterations may therefore stimulate a series of biological changes in the ocular surface, leading to subsequent neurogenic inflammation and further impairment of the tear film, creating a vicious cycle [131].

BAK causes disruption of the tight junctions of the corneal epithelium, an effect that has led to BAK being considered an enhancer of drug penetration into the anterior chamber [125]. The cytotoxic effects of BAK have been shown to be increased experimentally when cells were previously submitted to a hyperosmotic stress mimicking dry eye *in vitro*; therefore, BAK can cause some level of toxicity in normal or glaucomatous eyes, which can be compensated by tissue defenses, but to a much greater level in dry eyes, which is consistent with clinical findings. However, as BAK may progressively cause tear instability and hence hyperosmolarity, this compound is likely to change the conditions of it is own tolerance and result in increasing toxicity levels [132].

Additionally BAK has shown neurotoxic effects to the trigeminal nerve endings [133], which is consonant with a large study comparing the effects of preserved and unpreserved antiglaucoma drugs on corneal nerves using *in vivo* confocal microscopy (IVCM) [134]. The density of superficial epithelial cells and the number of sub-basal nerves were reduced in the preservative-containing groups, and stromal keratocyte activation and bead-like nerve shaping were higher in the glaucoma preservative therapy groups than in the control and preservative-free groups. Moreover, this study identified a decreased corneal sensitivity, based on

esthesiometry, in all preserved groups compared to control or unpreserved prostaglandins and betablockers. This neurotoxic property of BAK could thus contribute to the apparently good comfort of some patients receiving BAK-containing eyedrops.

Experimental data also demonstrated direct proinflammatory effects of BAK with the release of inflammatory cytokines or increased expression of receptors to chemokines and cytokines [135,136]. Additionally, BAK breaks down conjunctival immunological tolerance in a murine model [137]. In humans, using immunocytological and flow cytometry methods, higher expression of HLA-DR, a marker of inflammation, occurred in impression cytology specimens over the ocular surface with preserved eyedrops [138]. Other inflammation-related markers, such as ICAM-1, interleukin (IL)-6, IL-8, IL-10, CCR4 or CCR5, were also found to be overexpressed in glaucoma patients and even more with multiple therapy and preserved eyedrops [139]. A significant infiltration of the central cornea with dendritic inflammatory cells is observed with IVCM in healthy volunteers receiving BAK-containing eye drops compared to a non-preserved solution [140].

New preservatives recently developed as alternatives to BAK, like Polyquad®, Purite® and sofZia®, result in significantly lower cytotoxic effects [125,136,141–143]. However, their possible effects on the tear film and tolerance in dry eye patients have not been fully investigated.

4.2.3.2. Switch studies. Several studies have shown that switching from a preserved to nonpreserved formulation significantly improved the ocular surface and reduced symptoms. This was noticed with betablockers, where a 50% reduction in signs and symptoms was found, resulting in levels similar to those expected in the general population [106,144]. These results are important as they indicate that betablockers in a nonpreserved formulation seem not to induce any additional sign of dry eye and that their use is not apparently associated with an increased rate of DED. In addition, the change from preserved to nonpreserved glaucoma medications significantly reduced the discomfort upon instillation (43% vs. 17%), burning/stinging (40% vs. 22%), foreign body sensation (31% vs. 14%), dry eye sensation (23% vs. 14%), tearing (21% vs., 14%) and eyelid itching (18% vs. 10%) [108]. Similar results were also found when switching from a preserved prostaglandin, latanoprost, to a nonpreserved formulation of another prostaglandin analog [145]. The same group also reported that after switching from preserved latanoprost to preservative free tafluprost, patients reported a reduction in symptoms and signs that was correlated with improvement in the tear fluid proteome. Schirmer test results were increased significantly with increases in lysozyme, lacritin, and prolactin-inducible protein, whereas Schirmer test results were significantly lowered with increased levels of S100A6 (calcyclin), S100A11 (calgizzarin) and enolase 1 [146]. Interestingly, in those studies, reversibility of inflammatory lesions can be obtained rapidly, as also shown with dendritic cell numbers returning to normal levels in less than 1 month [140]. In an Australian survey in 375 patients, switching to unpreserved antiglaucoma eyedrops resulted in decreased use of tear substitutes by the patients, improvement in quality of life questionnaire results, decreased numbers of patients with abnormal tear instability and no effect on intraocular pressure control [147].

4.2.4. Recommendations for management
The subtraction strategy is always preferable when considering iatrogenic effects. The first step is the identification of the drug role, which may be very difficult when side effects occur late after the introduction of the treatment, when several drugs and components are used, when the ocular surface is concomitantly impaired, or when the treatment cannot be interrupted without endangering

the eye condition. The use of eye drops to alleviate symptoms of dry eye may be necessary, but adding preserved eyedrops to an eye with dryness induced by other eyedrops, and likely the preservative, may be ineffective and also cause further aggravation. Whenever the drug is identified, efforts should be made to stop the treatment/preservative if possible. As BAK toxicity is dose-dependent, reducing the number of preserved eyedrops may be helpful and may reduce the burden of side effects to acceptable levels [106,147]. Additionally, laser trabeculoplasty or surgery may be options to consider when the ocular surface is severely impaired and quality of life is decreased.

Alternatively, low toxicity preservatives have been developed and showed little if no effects to the ocular surface [129,136]. They can be proposed in a way to subtract or reduce the most toxic compounds. In cases of dry eye, they could provide safer options than those with BAK, but long-term clinical investigations are necessary to prove this concept.

4.3. Contact lens (CL)-related DED

4.3.1. Incidence and prevalence
No prospective epidemiological study is available to document the natural occurrence and evolution of CL-related DED. However, CL use was reported as a risk factor for dry eye in several epidemiological studies on dry eye. In the Canadian Dry Eye Epidemiology Study (CANDEES), 50.1% of the CL wearers experienced dry eye compared to 21.7% of non-CL wearers [149]. Current CL use was recognized as a risk factor for dry eye in the Beaver Dam Offspring Study with an OR of 2.39 in those under 50 years of age [9]. In 3443 high school students, CL wear was associated with an increased risk for symptoms of dry eye in boys (OR 4.14) and girls (OR 4.68) [150]. A study from China reported a prevalence of dry eye symptoms in 8.4% of the 1885 evaluated high school students compared to 32.8% of the 122 CL wearers [151]. However, Young et al. [152] reported that 23% of CL wearers with dry eye symptoms did not exhibit typical clinical signs of dryness.

The report of the Subcommittee on Epidemiology of the TFOS International Workshop on Contact Lens Discomfort discussed extensively the difficulty of disambiguating symptoms of dryness and discomfort reported by CL wearers [153]. To illustrate this overlap, Begley et al. [154] reported a prevalence of dryness of 37% and evening discomfort during CL wear of 37% in a population of 83 patients in a private optometry office in Toronto, Canada. When they repeated this study with a much larger cohort of 367 CL wearers [155], ocular discomfort was reported by 79% of respondents and dryness by 77%.

Dry eye in CL wearers has been identified as a growing public health problem [156]. Many papers have been published on the prevalence of symptoms of dry eye during CL wear [153], with the apparent presumption by many of the authors that they are documenting DED. However, according to the consensus reported by the TFOS DEWS II diagnostic methodology subcommittee, objective signs must be demonstrated to confirm the existence of dry eye [157]. While papers reporting CL dryness symptoms in CL wear are important to characterize and define the extent of this troubling complaint [153], they cannot claim to be defining DED.

To assist ongoing interpretation of the literature, two definitions of dryness related to CL wear are proposed: CL-induced dry eye (CLIDE) and CL-associated dry eye (CLADE).

CLIDE can be defined as the existence of signs and symptoms of dry eye during CL wear, whereby such signs and symptoms did not exist prior to CL wear. Very few studies have assessed the incidence of CLIDE according to this definition; one example where this has been done is the study of Alzahrani et al. [158] who reported that, of 60 people free of DED prior to CL wear, 25 (42%) developed CLIDE by

1 week after commencing wear of daily disposable hydrogel CLs.

CLADE can be defined as the existence of signs and symptoms of dry eye during CL wear. According to this definition, the possibility that the DED observed in CL wearers is due to a pre-existing dry eye condition cannot be discounted. Two studies have essentially assessed CLADE. Pult et al. [159] recruited 20 symptomatic and 13 asymptomatic CL wearers (who were not pre-screened for DED) and assessed symptoms using the CLDEQ and a range of signs over a 4-week period, concluding that assessment of non-invasive TBUT, lid parallel conjunctival folds and the OSDI could best predict future dry eye symptoms. Nichols and Sinnott [160] recruited 415 CL wearers (who were not pre-screened for DED) and assessed symptoms using the CLDEQ and a range of signs in a cross-sectional study; factors shown to be significantly related to dry eye status in multivariate modeling were female sex, lenses with higher nominal water content, rapid prelens tear film thinning time, frequent usage of over-the-counter pain medication, limbal injection and increased tear film osmolality.

4.3.2. Mechanism

CL-induced biophysical changes to the tear film in CL wearers with dry eye symptoms include: a thinner, patchy lipid layer with poor wettability and impaired spreading capability [161]; tear film instability, indicated by reduced non-invasive TBUT [162]; increased tear evaporation rate [163]; lower basal tear turnover rate [164]; increased tear osmolarity [160]; and decreased tear film meniscus volume [165]. CL-induced biochemical changes to the tear film in CL wearers with dry eye symptoms include: elevated cholesterol levels [166]; increased level of secretory phospholipase A2 degradation products malondialdehyde and 4-hydroxynonenal [167]; decreased levels of beta-2-microglobulin, proline-rich protein-4, lacritin and secretoglobin 1D1 [168]; increased concentrations of secretoglobin 2A2, albumin, 'deleted in malignant brain tumor' (DMBT)-1 and prolactin-inducible protein [168]; and decreased levels of the mucin MUC5AC [169].

Several CL-induced ocular changes have potential significance in the etiology of CLIDE as has been previously reviewed [170]. Ocular responses that have attracted attention in relation to CLIDE are alterations to Langerhans cells, conjunctival goblet cell density and lid wiper epitheliopathy [171]. Langerhans cell density is higher in the cornea after 1 week of CL wear in those with CLIDE (55 ± 7 cells/mm^2) versus those without CLIDE (43 ± 4 cells/mm^2) and non CL-wearing controls (27 ± 4 cells/mm^2) [158]. Goblet cell density has been found to be reduced in CL wearers with CLIDE versus those without CLIDE [172–175]. Alterations or deficits in mucin produced by goblet cells could adversely affect lubrication of the interface between ocular and CL surfaces [169]. Meibomian glands can also be affected by CL use. Expressibility, number of plugged and expressed orifices, and gland dropout can be induced during the first 2 years of CL wear [176]. In vivo confocal microscopy of the meibomian glands shows significantly decreased basal epithelial cell density, lower acinar unity diameters, higher glandular orifices diameters and greater secretion reflectivity [177]. Early studies claimed to have demonstrated increased levels of severity of lid wiper epitheliopathy in CL wearers reporting dry eye/discomfort symptoms [159,169,178–181], but more recent investigations have failed to replicate those original observations [182–185]. Furthermore, lid wiper epitheliopathy appears to be of little value in predicting symptoms of dryness and discomfort in CLADE [159].

Environmental factors may exacerbate CLADE. Kojima et al. [186] reported that 69 office workers who wore CLs and spent more than 4 h engaged in work on a visual display terminal had a lower tear meniscus volume with significant dry eye and visual symptoms triggered by environmental factors, compared with a control group of 102 age- and sex-matched non-CL wearers doing similar work.

4.3.3. Recommendations for management

Management strategies demonstrated to have some level of efficacy are: excluding the possibility of systemic and ocular disease; fitting daily disposable lenses [187]; fitting lenses containing internal wetting agents [188]; topical wetting agents [189–193]; hydroxypropyl cellulose ophthalmic inserts [194,195]; omega-3 [196] and omega-6 [197] fatty acids; punctal plugs [198–200]; azithromycin (antibiotic with anti-inflammatory properties) [201]; reducing wearing time or ceasing lens wear [202,203].

4.4. Surgically-induced DED

4.4.1. Corneal refractive surgery

4.4.1.1. Incidence and prevalence. The incidence of dry eye symptoms after laser in situ keratomileusis (LASIK) surgery vary widely, depending on the severity cut-off and whether dry eye was present before surgery [204–213] In 157 eyes of 109 patients dissatisfied with LASIK, poor vision (63.1%) and dry eye (19.1%) were the chief complaints 2.6 ± 2.8 years after surgery [207]. In a recent study, tear film dysfunction was identified as the most common diagnosis for referral to a tertiary eye clinic following refractive surgery [214].

There are studies suggesting that PRK induces less dry eye than LASIK [215,216], and vice versa [213,217]. Most surgeons would agree that PRK eyes tend to have more visual fluctuation at 1 month after surgery that could be related to induced dry eye [217], but that could also be attributable to prolonged central epithelial remodeling after the surface ablation procedure. Those arguing that PRK induces less dry eye than LASIK often cite damage only to the corneal nerve endings, leading to faster regeneration in PRK, but it is not clear whether there is retrograde degeneration of nerves following terminal injury in the cornea [215,216].

Several studies have suggested that there is less change in corneal sensation and nerve density as well as less postoperative dry eye after SMILE (small incision lenticule extraction) surgery to correct refractive errors than after LASIK. [208,218–220], attributed to relative sparing of more superficial nerve fibers in SMILE. Little has been published about the effects of corneal inlays on dry eye, but the inlay acts as a barrier to regrowth of severed corneal nerves [221,222]; this suggests more dry eye after inlay surgery than LASIK, but further studies are needed to explore this hypothesis.

Risk factors for OSD or dry eye symptoms after LASIK include Schirmer test values > 10 mm [213,223,224], long-term CL wear [225], use of intraoperative mitomycin-C (MMC) [226], Asian ethnicity, female sex, a greater ablation depth as well as a narrow flap hinge [206,210,223,224,227–230]. Most studies agree that LASIK dry eye recurs after re-lifting of the flap for retreatment [231,232], but a study in Japan did not confirm this effect [233].

4.4.1.2. Mechanism. Most dry eye symptoms prior to refractive surgery are attributable to evaporative DED due to obstructive MGD [2,8,16]. Chronic inflammation of the lacrimal functional unit resulting in inadequate tear film integrity and function plays an important role in aqueous deficient dry eye, which can also be associated with evaporative DED [234]. Following refractive surgery, a neurotrophic component to dry eye further compromises the function of the lacrimal functional unit, at least transiently [231]. Another common contributor to dry eye symptoms and signs after refractive surgery that has received considerably less attention is ocular rosacea [216]. The tendency to reduce TBUT and the resulting evaporative component of this disease tends to worsen the symptoms and signs of dry eye after surgery and should also be recognized and treated prior to refractive surgery [206].

Femtosecond laser flaps are associated with less dry eye than microkeratome flaps and studies suggest the difference is attributable to unknown factors beyond the thinner average thickness of

femtosecond laser flap [216,235], hinge position or hinge angle [235]. Studies vary on whether a superior hinge position triggers less LASIK-induced dry eye than a temporal hinge position, but more recent studies using a single instrument found no difference [235,236].

4.4.1.3. Recommendations for management. Detection and treatment of dry eye prior to surgery is always the optimal management for refractive surgery-induced dry eye [216,231,232]. Topical cyclosporine A has been found to be the most effective treatment [237], but nonpreserved artificial tears and ointments, dietary alpha omega fatty acids, maintaining a humidity >40–50%, punctal plugs and even autologous serum drops are helpful adjuvants [237]. It is also important to treat associated conditions such as ocular rosacea (manual compression, doxycycline, azithromycin, etc.) and blepharitis (lid hygiene, antibiotics) prior to surgery. In general, treatment of dry eye should continue for at least 6–8 months following surgery and any retreatment, when the neurotrophic component reduces [238]. Many patients without symptoms or signs of dry eye will develop transient dry eye following LASIK or PRK, probably due to the neurotrophic effects of surgery [206,231,238]. Retreatment surgery is often associated with recurrence of dry eye symptoms and signs and should be preceded by optimization with cyclosporine A and nonpreserved artificial tears and ointments, with consideration of punctal plugs and autologous serum drops, depending on the severity of the disease [206,231,238].

4.4.2. Cataract surgery
4.4.2.1. Prevalence and incidence. The majority of cataract surgery is performed on older patients, a group with a higher incidence of pre-existing dry eye [16]. Cataract surgery has been shown to independently transiently induce or exacerbate dry eye [239–244]. Studies have shown that dry eye symptoms increase after uncomplicated phacoemulsification with a duration of about 3 months [240–242,245,246], although the increased symptoms duration, as assessed by the OSDI, may be shorter in patients using nonpreserved medications, artificial tears or topical cyclosporine A postoperatively [240]. The majority of studies show a decrease in TBUT and increased ocular surface vital dye staining after cataract surgery with resolution around 3 months or longer [240,242,245,247]. There were minimal changes in Schirmer 1 score [248,249] or tear meniscus height in some studies [246], but statistical changes in tear volume were found in others, with resolution by 2–3 months [240,242,245,247]. Diabetic patients undergoing cataract surgery appear to be more prone to dry eye; in comparison with non-diabetic patients, ocular symptoms and tear film stability are generally worsened over a more prolonged time period [250,251]. Cataract surgery also seems to be associated with detrimental changes in meibomian gland function (expressibility), but not structure (as observed using meibography) [246].

4.4.2.2. Mechanism. The purposed pathophysiological mechanisms underlying cataract-induced dry eye are multifactorial and include the use of topical anesthetics and desiccation, possible light toxicity from the operating microscope, nerve transection, elevation of inflammatory factors, goblet cell loss, and meibomian gland dysfunction [252]. Studies have shown that corneal denervation caused by intracapsular (ICCE) or extracapsular surgery (ECCE) could last up to 2 years [253] in comparison with 3 months with phacoemulsification [241]. Corneal sensation dropped centrally and temporally with temporal incision, but returned to baseline within 1 month with a 2.8-mm incision [241] and within 3 months with a 4.1-mm incision [254], and similar temporal changes were found in the TBUT. Corneal denervation associated with cataract

incisions and limbal relaxing incisions leads to the impairment of normal blinking and tearing reflexes and may result in damage to the corneal epithelium [245].

The surgical trauma inherent to cataract surgery is associated with the production of oxygen free radicals, proteolytic enzymes [255,256], prostaglandins, leukotrienes and inflammatory cytokines [245], which may affect corneal sensitivity, increase inflammation and contribute to tear film instability [245]. Of note, a marked decrease in conjunctival goblet cell density was observed following uncomplicated cataract surgery and conjunctival goblet cell density had not returned to baseline even at 3 months postoperatively [241,242,245]. The degree of goblet cell loss and associated conjunctival cell squamous metaplasia was related to operating room time [241] and the length of exposure to the operating microscope light [245].

The use of an aspirating lid speculum may exacerbate dry eye signs and symptoms during the early recovery from cataract surgery, but differences were no longer present at 1 month [257]. Similarly, grooved and longer incisions were associated with worse dry eye signs and symptoms, while there appeared to be little impact of incision location or shape [239]. Femtosecond laser-assisted cataract surgery (FLACS) seems to cause more fluorescein staining and higher initial dry eye stymptoms than conventional phacoemulsification surgery, although both forms of cataract surgery decreased TBUT and Schirmer I values with a peak impact at 1 week that had not returned to baseline at 1 month [258].

4.4.2.3. Recommendations for management. Even in the absence of DED, OSD should be managed before cataract surgery to optimize ocular biometry for optimum IOL power calculation as well as to minimize post-operative complications and complaints after cataract surgery [259]. Associated conditions such as ocular rosacea and blepharitis should be properly managed with lid hygiene, manual compression, and oral or topical antibiotics with an anti-inflammatory effect (eg doxycycline) [255,256]; however, care should be taken to avoid lid hygiene immediately prior or shortly after the surgery to prevent infectious complications. The use of topical drug-containing artificial tears, such as hyaluronate and carboxymethylcellulose, can improve TBUT, corneal staining and dry eye symptoms postoperatively [260,261]. Diquafosol 3% topical ophthalmic solution can further enhance TBUT, corneal staining, high order aberrations and Schirmer I test at 12 weeks after surgery [262]. Topical cyclosporine 0.05% may also improve signs and symptoms of DED in comparison to artificial tears alone after cataract surgery [249,263,264].

4.4.3. Lid surgeries
4.4.3.1. Incidence and prevalence. Lid surgery cause DED onset or worsen preoperative dry eye [265–269], which is common but underdiagnosed [270]. Prischmann et al. documented DED in 26.5% of 892 patients following blepharoplasty (the excision of skin, orbicularis oculi muscle and/or orbital fat) [271]. In a retrospective study by Saadat et al., only 5 of 60 patients (8.0%) with preoperative DED worsened following blepharoplasty [267]. Risk factors for dry eye symptoms following blepharoplasty include Bell phenomena, LASIK, concurrent upper and lower blepharoplasty, skin-muscle flap blepharoplasty, hormone therapy use, preoperative scleral show and postoperative lagophthalmos [271,272]. After ptosis surgery, both normal tear function [273–279] and dry eye [280–286] have been reported.

4.4.3.2. Mechanism. Close interaction of the eyelid/tear film/ocular surface makes lubrication susceptible to surgery-related changes in the eyelids' complex anatomical structure and function [266,270,287–289], hence a thorough knowledge of these is

mandatory to prevent inadvertent injury and to ensure effective tear film function post-surgery [269,290,291]. Lid surgery can seriously affect eyelid closure or position [288,292,293]. Symptoms occur secondary to exposure, leading to an increased tear evaporation rate and drying of the ocular surface, especially in poor Bell's phenomenon [291,294]. The cause of dysfunctional eyelid closure may be readily diagnosed in the presence of lagophthalmos, scleral show or ectropion [290,295]. Poor postoperative eyelid closure results from skin and/or muscle deficiency (anterior lamella) or intrinsic eyelid stiffness secondary to cicatricial changes within the middle and posterior lamella (orbital septum, lid retractors, conjunctiva) [290,291]. Eyelid dysfunction may also relate to the onset and persistence of chemosis and thus increase the risk of corneal and conjunctival exposure [288,296,297]. Dysfunction and/or dehiscence of the lateral canthus is another source of symptomatic eyelid closure disorder and an overlooked postblepharoplasty complication [288,295].

Although one study of 16 patients showed no significant compromise of eyelid kinematics following blepharoplasty [298], other authors have reported sluggish lid closure [299], incomplete reflex blink [269] and decreased blink rate [268] following partial resection of the orbicularis oculi with injury to the innervation. Blink alteration might account for reduced outflow of lipid secretion from the meibomian glands [41,300,301], for poor mechanical tear film distribution and for reduced tear drainage with impaired debris removal from the ocular surface [272,302]. After ptosis surgery, a widened palpebral fissure with a greater ocular surface exposure, increased efficacy of the lacrimal pump due to greater lid excursion, and altered ocular surface sensation influencing the blink reflex may predispose patients to or intensify dry eye [281,282,285,303].

The Fasanella-Servat procedure for ptosis correction involves tarsal resection and thus loss of meibomian glands [284,304]. Tumor resection and lid reconstruction using a modified Hughes tarsoconjunctival flap results in a complete loss of meibomian glands in the excision area of the lower eyelid and loss of glands in the tarsoconjunctival flap of the upper eyelid, as confirmed by meibography [305]. Injury during surgery can occur, especially to a prolapsed lacrimal gland [290,291], a condition observed in about 60% of patients undergoing blepharoplasty [306] and mostly in those with multiple previous eyelid surgeries [307,308]. Cosmetic lateral canthoplasty may cause outward redirection of normal lacrimal ductule orifices by externalization of conjunctival tissue or a direct injury to the lacrimal ductules, leading to fistula formation and lacrimal dysfunction [307,309]. In ptosis procedures via conjunctival incisions, damage to goblet cells and accessory lacrimal glands may affect tear quality or quantity; other mechanisms in ptosis surgery via the skin include kinking of lacrimal ductules, especially those originating from the palpebral lobe [280,285].

4.4.3.3. Recommendations for management.
Any signs of ocular surface problems, such as DED and blepharitis should be treated preoperatively [269,310]; after surgery, a curative treatment comprises two steps: the first conservative step involves medical treatment and the second step includes surgery.

Medical management of DED following lid surgery utilizes artificial tears and lubrication during the night [268,270,272,297,311]. Unpreserved products are recommended [269]. Medical options also include topical steroids and cyclosporine A [268,272,310]. Punctal occlusion could be considered in case of treatment failure [272]. A perioperative intravenous dose of systemic corticosteroids may also curtail the inflammatory response after surgery [268,288]. Chemosis can be treated with cold compresses, head elevation, massage, extra lubrication and eye patching [296,312]. A prolonged chemosis requires the prescription of steroid eye drops, topical phenylephrine and a tapering dose of systemic corticosteroids [288,290,311,312]. Conservative treatment of lagophthalmos and mild lower eyelid retraction involves massage with a topical steroid ointment as well as vertical eyelid traction, muscular re-education and taping [269,272,296,313].

More persistent symptoms may require surgical intervention such as tarsorrhaphy and lower lid repositioning including firm canthal tendon anchoring and lateral canthal reconstruction [268,269,295,309,312]. Surgical treatment also includes eyelid scar release and interpositional skin grafting [269,296,297,313].

4.4.4. Other surgeries

4.4.4.1. Specific surgeries.
Other ocular surgeries can induce dry eye.

4.4.4.1.1. Keratoplasty.
Corneal epithelial abnormalities are common in the early postoperative period; superficial punctate keratitis (SPK), epithelial defects, and filamentary keratopathy were observed in 63%, 75%, and 14%, respectively, of patients in a small study [314]. Pre-existing dry eye and blepharitis are known recipient-related risk factors for epithelial complications following keratoplasty [314,315].

Following penetrating keratoplasty on 20 patients, central corneal sensitivity decreased and returned to near normal levels after 12 months, but no sub-basal nerves were detected [316]. TBUT was observed to be significantly shorter at 3 and 12 months after keratoplasty, but there were no significant differences in the phenol red thread test results before and after surgery. In 151 patients after penetrating keratoplasty, 34 presented with Meibomian gland dysfunction (MGD), 16 with a combination of MGD and aqueous deficiency dry eye and 23 with aqueous tear deficiency alone [317]. However, large epidemiological studies have not been conducted. Huang et al. analyzed the tear film of 13 patients (13 eyes) aged 18–32 years, after lamellar keratoplasty for keratoconus [318]. Postoperatively, the Schirmer I test value was observed to increase for 2 months with a decrease afterwards, while TBUT remained decreased by 50% with increased corneal staining. Postoperative medicaments including BAK preservative, epitheliopathy and ocular inflammation were identified as possible etiologies for reduced corneal epithelial hydrated mucoprotein, decreased Schirmer I test and TBUT values, and increased corneal staining. The authors suggest that the observed initial increase in Schirmer I values could be attributed to the reflex lacrimal gland secretion secondary to irritation by sutures and corneal wound healing.

4.4.4.1.2. Conjunctival surgery.
Conjunctival tissue forms a significant part of the ocular surface and plays a critical role in the maintenance of pre-ocular tear film. Normal conjunctiva is important for smooth functioning of pre-ocular tear film and contributes to its formation. Conjunctival surgery, especially removal of a large part of conjunctiva such as excision of large ocular surface tumors, could lead to iatrogenic DED. Similarly, in ocular surface stem cell transplantation, a significant part of the surface epithelium is removed and regenerated using limbal explants, cultivated conjunctival or limbal epithelium, termed Cultivated Oral Mucosal Epithelial Transplantation (COMET) or more recently Simple Limbal Epithelial Transplantation (SLET) [319]. However, there are no studies documenting the impact of such procedures on pre-ocular tear film.

Several studies have investigated the relationship between pterygium and changes in tear film function [320,321]. A more recent study confirmed that tear hyperosmolarity and abnormal tear film function are associated with pterygium [320]. Excision of pterygium improved tear osmolarity and tear film function; however, tear osmolarity deteriorated with recurrence of pterygium [320]. Another study concluded that pterygium has a close

relationship with DED, although it still remains unclear which disorder is causative [322]. The surgery for conjunctivochalasis improved DED signs and symptoms in patients for whom topical tear replacement therapy was ineffective [323].

4.4.4.1.3. Glaucoma surgery. Glaucoma surgery, especially with use of MMC, has been associated with an increased risk of OSD [324]. Bleb size and location of the flap (limbal-based vs. fornix based) did not correlate with the presence of dry eye [325,326]. Trabeculectomy is an important surgical treatment in managing eyes that are sub-optimally controlled with topical anti-glaucoma medications alone. However, its effects on the ocular surface are multi-factorial and complex [324,327]. Although the success rate of trabeculectomy has significantly improved with the adjunctive use of anti-metabolites, such as MMC and 5-fluorouracil (5-FU), for scar prevention, they frequently result in tear film abnormalities, ocular surface complications, iatrogenic limbal stem cell deficiency and endothelial cell damage [328–337]. Lam et al.'s investigation on 15 eyes of 12 patients that underwent trabeculectomy with MMC or 5-FU demonstrated that all patients developed dry eye symptoms, with a median interval to symptom onset of 13.5 months; furthermore, once dry eye therapy was implemented, 46.7% of eyes were noted to have visual acuity improvement [324].

In glaucoma patients, these intra-operative OSD risk factors are further compounded by ongoing exposure to topical glaucoma medications and added preservatives that significantly reduce the percentage of live conjunctival and corneal epithelial cells (see section 4.2) [338–345].

4.4.4.1.4. Vitreoretinal surgery. Only a few studies have documented DED after posterior segment surgery, although corneal complications are observed quite often in clinical practice [346,347]. However, dry eye symptoms are commonly recognized after vitreoretinal surgery. Of 140 patients who underwent vitreoretinal surgery, brachytherapy or proton beam irradiation, 63% complained of symptoms of dry eye, presenting significantly decreased TBUT, but a similar tear volume, in comparison to controls [347]. Notable findings in the ocular surface included an increase in conjunctival epithelial stratification, a decrease in PAS- and MUC5AC-positive goblet cells, and a distributional change in MUC1, syndecan-1 and TN-C expression in conjunctival epithelium and stroma [347].

During pars-plana vitrectomy, conjunctival and scleral structures are damaged with the peritomy, similar to trabeculectomy, as well as the additional use of intravitreal injections, trocars and/or radiation therapy [347,348]. Furthermore, DED is a well-known complication in diabetes patients, with a frequency as high as 50–60% [8,16,349–351]. Thus, intra-operative corneal epithelial edema, delayed corneal and conjunctival wound healing, endothelial cell damage and even late corneal decompensation are often observed following diabetic vitrectomy [346,352–356], which are further complicated by exposure to ocular toxic povidone-iodine prep [357] and epithelial debridement [358–360].

Patients with non-healing cystoid macular edema (CME) requiring vitrectomy are often exposed to chronic use of topical NSAIDS as the initial mainstay of medical management, with ocular toxic side effects ranging from conjunctival hyperemia, corneal anesthesia, keratitis and rarely, corneal ulceration and full-thickness corneal melts (see section 4.2) [361–363].

4.4.4.1.5. Strabismus surgery. In strabismus surgery, the additional complications of scleral dehydration, necrosis and scleral dellen formation post-strabismus surgery lead to DED and OSD [364]. Li et al. studied the ocular surface in 60 patients undergoing a limbal incisional approach versus 60 undergoing a fornix incisional approach to strabismus surgery for the treatment of exotropia [363]. The limbal incisional approach group exhibited increased OSDI scores and decreased TBUT at post-operative weeks 1, 2 and 4

as compared to similar changes at post-operative weeks 1 and 2 alone with the fornix incisional approach. Statistically significant changes in corneal fluorescein staining were noted in both groups at post-operative weeks 1 and 2. There were no changes in corneal sensitivity or Schirmer scores in either group. Contributing factors with limbal incisions include corneal denervation, especially in the nasal and temporal quadrants, surgical manipulation of the ocular surface, increased tear film inflammatory factors, and the use of topical anesthesia, eye drops and preservatives [365]. If there is underlying ocular or orbital trauma causing the strabismus, there may also be concomitant cranial nerve dysfunction and/or associated conjunctival damage due to mechanical forces [366]. Antimetabolite adjuvants, despite their numerous ocular surface toxicities [328–337], have also been used to reduce the development of hypertrophic conjunctival scars over the operated-on muscles and postoperative adhesions as well as granuloma formation following strabismus surgery [367].

4.4.4.1.6. Intrastromal corneal ring segments. Intrastromal corneal ring surgery involves the implantation of polymethyl methacrylate (PMMA) ring segments into the peripheral stroma and is used for the treatment of low myopia, keratoconus and post-LASIK ectasia [368–370]. The advantages over commonly used refractive procedures include sparing of the visual axis, minimal risk of central corneal haze or scarring, and no removal of corneal tissue. Kessler et al. demonstrated only transient dry eye with restoration of the tear film within 1 week after surgery for patients after ICRS placements [371].

4.4.4.2. Mechanism. Mechanistic causes of dry eye from ocular surgery include: disruption to the normal architecture or functions of the conjunctiva, eyelids and cornea - surgical disruption of the normal ocular architecture and micro-traumatic insult to the limbus results in surface irregularity of the conjunctiva, bleb dysesthesia due to large bleb formation, dellen formation from trabeculectomy [324,327], intravitreal injection use, trocar placement, epithelial debridement, radiation therapy from vitreoretinal surgical intervention [348,358–360] and scleral dehydration, necrosis and scleral dellen formation from strabismus surgery [364]; surgical manipulation of the ocular surface resulting in goblet cell deficiency as well as loss of normal homeostasis of the corneal epithelial surface and corneo-scleral limbus, limbal stem cell deficiency and proper anatomic orientation of the eyelids from prolonged and frequent speculum use [324,331,372–374]; denervation of the cornea [375] as a result of surgical manipulation, upregulation of MMP expression and diabetes [376–379], in particular with the use of limbal incisions in the nasal and temporal quadrants [365]; use of topical antimetabolites such as MMC and 5-FU which both target the active replication of corneoscleral limbal cells and thus prevent adequate replacement of the corneal epithelium [330–334]; proinflammatory conjunctival responses (such as subepithelial macrophages, lymphocytes, mast cells and fibroblasts) that occurs due to a combination of surgical manipulation of the conjunctiva, exposure to anti-fibrotic adjuncts and exposure to ocularly toxic medications, such as topical anesthesia, topical NSAIDs, glaucoma medications and povidone-iodine prep [324,327,380]; reduction in epithelial thickness resulting from corneal denervation, chronic use of ocular toxic medications and application of anti-fibrotic adjuncts [381–383]; and toxicity to conjunctival epithelial/goblet cells from chronic exposure to pre- and post-operative topical glaucoma medications, preservatives and topical NSAIDs causing conjunctival epithelial and goblet cell damage (see section 4.2) [114,324,327,342–345,361–363,384–386]. The combination of all these factors add to a patient's baseline pre-existing OSD and DED status [2,8,16], hence the pre- and post-operative

health of the ocular surface is critical to the eventual surgical outcome.

4.4.4.3. Recommendations for management. The importance of pre-op dry eye screening and management is critical, as is pre- and post-operative planning [387–389]. In susceptible eyes, strict implementation of pre-operative aggressive topical lubrication, oral and topical anti-inflammatories and punctual plugs can be utilized. For more severe DED states, autologous serum tears and disease-modifying procedures, such as thermal pulsation (Lipi-flow®; TearScience) [390] and intense pulsed-light therapy (off-label use of an FDA-approved device) should be considered [391].

Intra-operative strategies to minimize ocular surface damage include gentle manipulation, preservation of the conjunctival architecture post-peritomy, secure wound closure, minimized thermal cautery use [364], reduced surgical time to avoid prolonged corneal exposure, use of a corneal light shield, and frequent instillation of balanced salt solution.

For glaucoma patients with pre-existing OSD, the possibility of earlier and more aggressive use of laser trabeculoplasty should be considered for the purpose of minimizing the chronic, ongoing exposure to topical IOP-lowering agents. If needed, preservative-free or preservative alternatives should be selected. Concurrent use of agents known to adversely affect the ocular surface should be approached with caution [342–345,392].

For pars-plana vitrectomy, use of a 25-gauge and potentially 27-gauge transconjunctival sutures sclerotomies, would be less invasive, not require sutures for wound closure, result in less of a cytokine-induced inflammatory response, have the potential for faster wound healing and thus be preferred over convention 20-gauge and 23-gauge sutures. A non-contact rather than a contact binocular indirect ophthalmoscope system should be used to decrease the rate of epithelial debridement [358–360]. Additionally, it is advisable that all instrument shafts pass through the sleeve of the cannula in a manner that minimizes tissue manipulation from repeated insertion and removal of instruments [348,393–395].

For diabetes patients, strict glucose control should be optimized pre-operatively and epithelial debridement should be avoided when possible. If an epithelial debridement is performed, use of a bandage contact lens post-operation will aid in epithelial healing [396].

It is important to minimize exposure to anti-metabolite adjuvants, and when necessary to use, avoid contact with limbal stem cells. Future research directions include the development of biodegradable drug delivery devices [397–400] and safer alternatives to prevent scarring. Amniotic membrane [401–403], daunorubicin [404–406], mitoxantrone [407], MMP inhibitors [408,409] and other small molecule inhibitors such as dendrimers and proteoglycans, and Rho-associated protein kinase (ROCK) inhibitors have shown promise in this regard [410,411].

Additional innovations in the pipeline include the potential use of eye platelet-rich plasma (E-PRP) for dry eye [410] and combination drops of substance P and insulin-like growth factor-1, which for the treatment of neurotrophic keratitis topical rebamipide have been shown to increase the number of goblet cells after vitrectomy [412,413], as well as aldose reductase inhibitors [414] and MMP-10 inhibitors [413] to expedite corneal wound healing.

4.5. Procedures

4.5.1. Botulinum toxin

Botulinum toxin (BTX) is produced by *Clostridium botulinum*, an anaerobic, gram-positive bacterium, which blocks acetylcholine release at the cholinergic nerve terminals of the neuromuscular

synapses [431] and autonomic cholinergic nerve fibers of the sweat [432], lacrimal [433] and salivary [434] glands. Various BTX serotypes (A-G) exist of which types A and B are commercially available for clinical use [435]. Periocular BTX injection has become the first-line treatment for patients with blepharospasm and hemifacial spasm [435–441]. Further ophthalmological indications include persistent epithelial defects or ulcers in which protective ptosis is induced [442,443], lid retraction in thyroid eye disease [444], entropion [445,446], strabismus, abducens paralysis [447], nystagmus, gustatory tearing [433,448], superior limbic keratoconjunctivitis [449], refractory filamentary keratitis [450] and dry eye [451–455]. Periocular BTX injections are also currently widely used in facial rejuvenation to reduce lateral periocular wrinkles (crow's feet), medial nose-bunny lines and glabellar rhytids [456,457].

A randomized, placebo-controlled, double-blind, single-dose trial in 109 blepharospasm patients reported dry eye symptoms in 18.9% of patients after injection of highly purified botulinum neurotoxin A [458]. In retrospective studies, symptomatic dry eye was found in 0.5–7.5% of blepharospasm patients after BTX injection [438,459]. Injection of BTX-A into the lateral canthal region for aesthetic correction of crow's feet can trigger dry eye of varying severity [460,461] as reported in 1–5% of recipients [104].

The possible mechanisms responsible for the development of dry eye after BTX treatment are weakness of the orbicularis oculi muscle, causing reduced tone, blink strength and delayed tear clearance, and direct diffusion of toxin into the lacrimal and meibomian glands, decreasing secretory function [461]. Orbicularis muscle weakness [437,438,462] leading to poor blink function and incomplete eye closure (lagophthalmos) has been observed in up to 64% of toxin-treated blepharospasm patients [441,463]; impaired blinking lead to corneal exposure and desiccation, often associated with superficial keratopathy, photophobia, and epiphora [435,437,438,441]. BTX-induced paralysis of the medial pretarsal fibers of the orbicularis muscle causes absence of contractive forces around the walls of the lacrimal drainage pathway and weakness of the punctal apposition during blinking, which leads to reduced tear outflow [437,451,460]; consequently, the delayed tear clearance after BTX injections with a stagnant tear meniscus [464] may provide an environment favorable to microorganism growth and allow for inflammatory products to accumulate, leading to conjunctivitis and dry eye [302,465,466]. Alternatively, medial canthal injection may lessen the blink output of tears and extend lacrimal lubrication of the ocular surface [451,452]; this aids in the treatment of DED [103,104,451–454,467], with observed improvements in Schirmer test scores or TBUT measurements [453,454,464,468] and improvement of dry eye symptoms [451,452,464,468]. BTX injection also impairs autonomic cholinergic transmission and inhibits lacrimal gland secretory function [448,469]; thus, it is still used to treat disorders related to pathologic tearing [433,468,470,471].

BTX chemodenervation paralyzes the orbicularis oculi and Riolan muscles and decreases the driving force for delivery of meibomian secretion [461]. BTX may also diffuse to nearby meibomian glands. Since parasympathetic innervation of the meibomian glands was observed [472], it has become obvious that meibum secretion can be blocked, contributing to lipid deficiency and an unstable tear film after injection [461].

The literature is inconclusive regarding tear volume measured by Schirmer test after BTX-A injections to periocular tissues; some studies report increased tear volume [453].whereas others report decreased tear volume [103,460,461] and still others report no change [455,468,473–475]. Differential changes in tear function parameters may result from the diverse techniques used for BTX injection, such as the number and position of injection sites (pre-

septal, pre-tarsal, medial, lateral, intra-subcutaneous, intramuscular) and differing dosages and dilutions of BTX [103,439,476,477].

Patients scheduled to receive BTX treatment, especially for cosmetic reasons like lateral canthal rhytids, should be informed of the possible complication of dry eye [461,475]. Since blepharospasm patients often have dry eyes [463,473], and symptomatic dry eye is one of the most common side effects [438], it may be necessary to use artificial tears as a supplement to BTX treatment. In a mouse model of dry eye secondary to BTX, treatment with topical immunomodulators, such as cyclosporine A and tacrolimus ophthalmic solutions, has demonstrated some effectiveness [478,479]. Snap-test and distraction tests are recommended before any periocular BTX injection to test for poor tone and contractility of the orbicularis oculi muscles and for lid laxity resulting from the stretching of canthal ligaments [104]. Keeping the toxin volume low helps to reduce uncontrolled diffusion from the injection site [435,480]. Persistent complications of dry eye unresponsive to 12 months of medical treatment may necessitate surgical management, such as lateral musculoplasty [104].

4.5.2. Corneal crosslinking

Corneal collagen crosslinking (CXL) is a treatment based on ultraviolet A (UVA) light and riboflavin as a photosensitizer that strengthens chemical bonds in the cornea. It has been reported to slow or halt corneal ectasia, as observed in keratoconus eyes [481,482]. Off label indications for CXL include treatment of infectious keratitis, corneal edema and corneal melting. Ashwin and McDonnell, 2010) The classic CXL technique (Dresden protocol) consists in epithelial removal, application of 0.1% riboflavin solution for 30 min followed by 30 min of UVA irradiation with a wavelength of 370 nm and power of 3 mW/cm^2 (5.4 J/cm^2) [481]. More recently, ultrafast CXL devices have allowed ophthalmologists to apply treatment in a shorter time with similar efficacy compared with the Dresden protocol [483,484]. Alternatively, CXL can also be applied without corneal epithelial debridement, in a procedure called the epi-on technique. Confocal imaging reveals that epi-on techniques induce almost one-third less apoptosis than standard protocols [485]. Nonetheless, the effectiveness of this technique is also lower than that of the standard procedure [486–494].

Keratoconic corneas present several changes in central stromal nerves, subbasal nerves and terminal bulbs [495], resulting in a decrease in corneal innervation, sensation, and basal epithelial density [496]. CXL has been reported to affect the corneal stroma, as well as the corneal epithelial nerves [497–504]. Clinical studies have suggested that corneal stroma morphology remains stable for at least 4–5 years after CXL [505–509]. Subbasal nerve regeneration after CXL has been shown to occur during the first postoperative year [497,498,502–504]. However, after this period, no studies have demonstrated whether corneal innervation reaches equilibrium or continues to regenerate, or if nerve density is improved in the long-term after CXL [496,510–513]. However, studies following patients who had had CXL for up to 24 months have found no clinical changes in the tear film [502,514], changes in the levels of several proteins, including cytokines, chemokines, metalloproteinases and their inhibitors, and growth factors have been reported [515].

4.5.3. Cosmetic procedures

The desire to enhance "eye beauty" and reverse signs of aging has led to the ongoing development of a number of ocular cosmetic procedures [516]. An ever-growing body of evidence regarding their complications is now available, given their increasingly widespread use.

4.5.3.1. Eye makeup. Some pigmented cosmetic products, such as powder eye shadow, pencil eyeliner and mascara, may accumulate within the lacrimal system and conjunctivae over many years of use, but reports of immediate eye discomfort after application are most common. Changes to the tear film and its stability may occur shortly after application. Additionally, creams used in the prevention of skin aging are often applied around the eyes, and retinoids present in these formulations can have negative effects on meibomian gland function and may be a contributing factor for dry eye [517]. In a group of 1360 female respondents, 83% reported using eye cosmetics regularly ($\geq$3 times per week) with mascara being most commonly used. Fifty-three percent used at least three different eye cosmetics products regularly. The OSDI scores of cosmetics users were similar to those of non-users, but perceived comfort was greater when cosmetics were not used [518]. Goto et al. [519] simulated the use of eye makeup with equal volumes of hydroxyethylcellulose gel and 10% fluorescein in a group of 75 women; the rate of migration to the ocular surface, as well as the intensity of fluorescence, was higher when the product was applied on the inner eyelash line (96%) in comparison to the eyelash line (20%) and outer eyelash line (12%). Formulation considerations are of great importance when applying products to the eyelids and eyelashes. The desire to create fashionable eye cosmetics must be balanced with safety considerations and standards [104]. Should side effects develop, products or additional ocular procedures should be discontinued and appropriate therapies should be implemented [520].

4.5.3.2. Eyelash growth. Eyelashes, in addition to their protective function [521], also have become a source of cosmetic attraction [522]. However, the complications resulting from eyelash cosmetic procedures have resulted in increasing number of ophthalmic consultations [520,523]. Bimatoprost, a synthetic prostaglandin structural analog, originally approved by the US Food and Drug Administration (FDA) in 2001 as Lumigan® (Allergan Inc. Irvine, CA) [524], for the treatment of glaucoma, was thereafter approved in 2008 as Latisse® (Allergan Inc. Irvine, CA) [525], for increasing eyelash length, thickness and darkness in patients with hypotrichosis [526–530]. Increasing applications of the product in recent years include use for chemotherapy-induced hypotrichosis and scalp alopecia [531,532]. Potential side effects include dry eye, ocular irritation and pruritis [523], conjunctival hyperemia [533], periocular skin hyperpigmentation [534], herpes simplex virus keratitis [528,535] and uveitis [536–538]. Additional eyelash cosmetic procedures commonly resulting in allergic blepharoconjunctivitis and dermatitis include the application of eyelash extensions [520], eyelash transplantation [539], and the use of dyes [540–542] and curlers [543–545]. Topical bimaprost use for eyelash growth should be avoided in high risk, susceptible eyes with severe dry eye or a prior history of uveitis or herpes simplex virus [536–538].

4.5.3.3. Fillers. The development of symptoms and signs of dry eye have been far less reported with the use of facial fillers than with botulinum toxin, with only rare cases of facial nerve palsy, indirectly leading to corneal exposure [546,547]. On the contrary, fillers have been utilized for the treatment of eyelid misalignment, eyelid retraction and cicatricial ectropion, reducing tear film instability and leading to dry eye [548–550].

4.5.3.4. Conjunctival whitening. Cosmetic eye-whitening procedures for the treatment of conjunctival hyperemia, the regional conjunctivectomy, originating in South Korea in 2013, and along with a similar procedure in the United States, I-BRITE® (Boxer Wachler Vision Institute, Beverly Hills, CA, USA), have been the topic of great controversy, given the severity and rate of

complication, reported to be as high as 82.9% [551–554]. Post-operative complications include chronic dysfunctional tear syndrome, conjunctival epithelial defects, ocular hyperemia, fibrovascular proliferation, calcium deposition, and more seriously, glaucoma, keratitis, limbal stem cell deficiency and necrotizing scleritis [551–554]. For conjunctival whitening procedures, definitive exclusion of autoimmune and infectious etiologies must be carried out prior to instituting appropriate therapy [551–555].

4.5.3.5. Tattooing. Eyelid tattooing has been found to shorten TBUT, increase fluorescein staining, and induce meibomian gland loss as well as other acute and chronic conjunctival inflammatory reactions [556,557]. Ocular tattoos of the conjunctiva, sclera and cornea can lead to far worse ocular reactions and dry eye states than eyelid tattooing [558–560]. It should be noted that methods similar to those used to remove undesired tattoos from the skin, when used on the conjunctiva or sclera, are likely to cause more harm than benefit and must be carried out with great caution [555,561,562].

4.5.3.6. Jewelry/piercings. Piercing has been a long-standing popular method for self-expression. In cases of eyebrow and eyelid piercings, complications include allergic dermatitis, necrosis and pre-septal and orbital cellulitis. JewelEye, a form of extraocular implant, involves the implantation of a small piece of platinum jewelry in the superficial interpalpebral conjunctiva of the eye that poses theoretical ocular surface complications, though none have been reported to date [563–565].

4.5.4. Indirect procedures

4.5.4.1. Positive pressure non-invasive ventilation. Noninvasive ventilation can be defined as a ventilation modality that supports breathing without the need for intubation or surgical airway. Noninvasive ventilation has been used for the management of pediatric and adult respiratory conditions in both the emergency department and the intensive care unit, and it has gained increasing popularity in the treatment for moderate-to-severe obstructive sleep apnea hypopnea syndrome (OSAHS) [566]. Positive pressure noninvasive ventilation includes continuous positive airway pressure (CPAP) and bilevel positive airway pressure. The masks are held in place by straps around the head, and patients often complain that the masks leak air into the eyes and irritate the surrounding skin [566]. There are a few studies reporting a negative effect of the short term CPAP treatment on the ocular surface of patients with OSAHS. Hayirci et al. [567] found elevated Schirmer and lower TBUT values after the CPAP therapy which was explained by its irritative properties. On the other hand, Kadyan et al. [568] reported increased TBUT values in patients with OSAHS after the application of CPAP treatment. Similar results were found by Acar et al. [569] in patients with OSAHS and floppy eye syndrome who underwent an appropriate, 18 months CPAP therapy. The authors also reported a significant decline in the corneal staining scores and a decrease of the OSDI in these patients, which can be explained by the increasing of ocular surface stability as part of the improvement of the clinical situation of floppy eye syndrome. CPAP therapy warrants awareness by physicians of the associated ocular surface problems [567]. For patients with preexisting OSD, more sophisticated CPAP devices or alternative treatment modalities should be considered, in addition to the use of topical lubricants [567].

4.5.4.2. Radiation treatment (RTx). DED has been associated with radiation treatment (RTx) for head and neck cancer [570,571], and Graves' ophthalmopathy [572,573]. The incidence varies depending on the type, location and dose of the RTx [571]. According to Bhandare et al., a logistic normal tissue complication probability at

a dose of 34 and 38 gray units of RTx directed to primary extracranial head-and-neck tumors corresponded to a 5% and 10% incidence of DED respectively [571].

One of the mechanisms of therapeutic action of RTx involves oxidative stress [574], which is also an important factor in the pathophysiology of dry eye found in inflammatory and endocrine diseases [575]. In 2013, Rocha et al. reported ocular surface changes and tear production decrease in a mice experimental model of RTx-induced salivary and tear dysfunction [576]; this model develops both DED and dry mouth, with a 50% reduction in tear secretion. Moreover, they observed that neither the body nor the lacrimal gland weight recovered to control levels in the RTx groups after 50 days.

Treatment for RTx-induced dry eye includes the use of topical artificial tears, autologous serum and immunomodulators [577]. Hoehn et al. found that treatment with topical cyclosporine 0.05% emulsion twice daily improved only 27% of children with radiation-associated dry eye [577]. Other possibilities include new therapeutic strategies, such as the use of therapeutic contact lens and surgical approaches as tarsorraphy [577]. Rocha et al. found that pre-RTx gene therapy with erythropoietin, which has an antioxidative stress action, protected corneal epithelia and resulted in some recovery of lacrimal gland function, supporting the need for further studies using this type of therapeutic approach for this condition [576].

4.6. Non-ophthalmic conditions

4.6.1. Graft versus host disease (GVHD)

Graft versus Host Disease (GVHD) is a common cause of morbidity after human leukocyte antigen (HLA)-matched, (related or unrelated) allogeneic hematopoietic stem cell transplantation. The latter is used as a treatment for both malignant and benign hematologic diseases. The challenge for clinicians is to maintain the graft versus leukemia effect while dampening the GVHD. GVHD is mediated by donor-derived T-cell recognition (CD4$^+$ and CD8$^+$) of host antigens (minor histocompatibility (MiHA) antigens) [415] and its incidence varies from 10 to 90% of patients [416]. The incidence varies depending on the source of the donor tissue, underlying etiology, age, degree of mismatch, female donors to male recipients, racial predilection, prior herpes exposure and antibiotic gut decontamination [417–420]. The main end organ targets for disease manifestations are the gastro-intestinal (GI) system, liver, lung skin, oral mucosa and eyes [416].

Ocular GVHD can occur in both acute and chronic GVHD and affects 40–60% of patients [421,422] undergoing transplantation, whereas ocular complications occur in 60–90% of transplant recipients [423]. Ocular GVHD primarily affects the ocular surface by secondary inflammation also involving the lacrimal/meibomian glands leading to glandular fibrosis [424].

In the acute stage, patients may present with conjunctival hyperemia, which may progress to a pseudomembranous conjunctivitis with corneal epithelial desquamation [423]. In the chronic form of ocular GVHD, patients present with dry eye symptoms, burning, excessive tearing, pain, redness and foreign-body sensation. Intraocular involvement may occur, leading to visual impairment [425]. Clinically, patients have signs of cicatricial conjunctival changes with consequent lid scarring and lid malposition (entropion, ectropion).

Dry eye is the most common ocular complication of GVHD, occurring in 69–77% of patients [423], especially the chronic form [426]. Risk factors include ocular toxicity of chemotherapeutic drugs, meibomian gland destruction secondary to total body irradiation and immunosuppressive therapy [426]. Mild-to-moderate DED can be present before hematopoietic stem cell

transplantation (HSCT). It was observed by Giannaccare et al. in 42.8% of their patients before HSCT, mostly associated with older age, female sex, advanced stage of hematological disease, and previous auto- or allo-HSCT [427]. Severe DED, however, is a common finding after HSCT and can significantly increase morbidity and decrease quality of life [428,429]. Reduced TBUT and Schirmer test results were reported to occur in 82% and 50% of 110 patients, respectively, and DED showed a worsening trend in the second half of the second year post HSCT [430].

5. Conclusion and areas for future research

Iatrogenic DED may be caused by topical or systemic medications, CL wear and different surgical and non-surgical procedures. Several large-scale epidemiologic studies have investigated the prevalence and incidence of DED as are discussed in the TFOS DEWS II epidemiology report [8,9,11,578–581]. Additional studies and epidemiological surveys are needed to evaluate iatrogenic dry eye. Appropriate evaluation at pre- and post-intervention and improved knowledge of diagnostic criteria for DED [157] will contribute to the elucidation of unmet medical needs in patients suffering from iatrogenic DED.

5.1. Areas of future research in drug-induced dry eye

Ophthalmic preservatives, such as BAK, are frequently used for their anti-bacterial effects and have been recognized as a risk factor for corneal and conjunctival inflammation [339,582–585]. Combined formulation to reduce the total amount of ophthalmic preservatives may help glaucoma patients who need multiple medications [586,587]. Preservative-free eye drops reduce iatrogenic dry eye [136,588–592]. There is a trend for the development of new multidose preservative-free systems, such as ABAK and COMOD bottles, that can improve patients' adherence [593,594]. The establishment of more preservative-free drugs and the development of novel combination products of anti-glaucoma eye drops and anti-inflammatory eye drops with long acting compounds are possible strategies to decrease the frequency of their instillation [383,587,595].

Oral medications, such as antihypertensive and antidepressant agents that have an anticholinergic effect, may decrease tear production via binding to receptors on the lacrimal glands and also meibomian glands [20,23,217]. Punctal keratitis is often observed in patients treated with anticancer agents, including tegafur gimeracil oteracil potassium (TS-1®) [596]. Improvements in preventing systemic action of drugs as a causative factor for dry eye will come from further research focused on the development of more highly engineered systemic drug molecules designed to avoid receptor targets that affect tear production or secretory gland function for a more tissue-specific effect and to develop topical antagonists that counter the activity of systemic medication. Technical advancements in the development of combination products and their dose-adjustment to minimize side effects of systemic medications are required as well as improvement of early identification of drug-induced dry eye by patients and physicians via drug labeling and education [19,79].

5.2. Areas of future research in Cl-induced dry eye

The literature describing CL-associated DED is largely reliant upon subjective reports of 'dryness', a symptom confounded by overlap with that of discomfort during CL wear [597] and for which the cause is multifactorial. Therefore, a fundamental consideration for researchers who intend to study DED in CL wearers is the need to validate their cohorts against the TFOS DEWS II diagnosis of dry eye [157], versus CLIDE/-CLADE, by verifying the existence of signs and symptoms of DED before and during CL wear.

The concept of the lid wiper [171,178] has led researchers towards developing a greater understanding of the nature of the essential interface between the anterior CL and ocular surfaces [598]. However, equivocal reports of the association between the extent of lid wiper staining and the severity of dry eye in CL wearers, with reports prior to 2011 claiming to have demonstrated an association [159,169,178–181] and post-2011 papers failing to demonstrate an association [182–185], raising questions about the relevance of lid wiper epitheliopathy in assessing CLIDE [171]. Large scale, well executed, masked, randomized and statistically validated clinical trials are needed to elucidate the clinical utility of this recently-described ocular reaction and to determine its value as a surrogate marker for CLIDE.

Dumbleton et al. [599] reported that 23% of CL wearers in Canada ceased wearing lenses between 2008 and 2010. Such a large drop-out rate comes at considerable cost to the CL industry and eye care practitioners, in addition to the inconvenience and frustration of CL wearers who are unable to continue with their preferred mode of vision correction. As CLIDE is a major cause of drop-out from CL wear [597,599], more focused research into the cause of this condition should continue to identify an effective solution.

5.3. Areas of future in surgery-induced dry eye

Corneal hyposensitivity by corneal denervation during refractive surgery such as PRK and LASIK, which occurs by direct corneal nerve injury and following abnormal neuronal remodeling [600], has been recognized as a major risk factor for postoperative DED, although the pattern of nerve injury in the cornea differs with different types of surgery [601–604]. Recent advances in surgical procedures, including SMILE, have served to minimize corneal denervation during surgery and reduce the incidence of postoperative DED [208]. At the same time, discovery of topical medications that augment regeneration of corneal nerves after refractive surgeries to lessen the neurotrophic effects would be helpful [605–611]. Research is needed to determine whether refractive surgery can cause permanent worsening of dry eye in some patients, or whether the surgery only exacerbates underlying inflammatory dry eye, which returns to baseline when neurotrophic effects resolve with nerve regeneration [600]. Novel research is also needed into the detection of early dry eye prior to refractive surgery, so that patients with underlying dry eye are properly pre-treated for dry eye to improve the outcomes of refractive surgery [612].

Impaired corneal nerve sensation after PK can induce DED and persistent corneal epithelial defects, which can lead to a corneal ulcer and eventual graft failure [613]. To guide nerve growth to the graft after keratoplasty, the application of various of neurotrophic factors including substance P, insulin-like growth factor 1 (IGF-1) and semafpholin-3A inhibitor have shown promising outcomes [411,607,614]. A more ideal therapeutic approach to induce neuronal regeneration after keratoplasty using novel molecules should be pursued to realize functional restoration of corneal sensory nerves, without possible complications of neovascularization and hypersensitivity due to excess innervation, as well as the development of advanced surgical techniques to minimize nerve damage during procedures [607,615].

Although current cataract surgery with clear corneal microincisions has been recognized as one of the most promising surgical procedures, studies have reported that postoperative ocular discomfort exists in a majority of patients due to DED [242,247,252]. The changes in multiple ocular and systemic factors, including tear film dysfunction due to reduced corneal sensitivity

[254,616–618], and loss of conjunctival cells via topical medication with preservatives [125,241,242] and anesthetics [619], the increase in inflammatory factors [255,256], and the morphological changes in lids and meibomian glands, are all involved in the onset of cataract surgery-induced dry eye [246]. Efforts to establish appropriate therapeutic strategies taking into consideration the effect of these concomitant pathological changes may contribute to better clinical outcomes after cataract surgery in the future [591].

Oculoplastic surgery, including blepharoplasty, ptosis repair, lid tumor removal and aesthetic reconstruction of the lateral canthus, has been recognized as a risk factor for postoperative DED [265–269]. Investigation of the details of pathological alterations of eyelid movement before/after surgery and postoperative changes in peripheral ocular tissues, such as the conjunctiva, meibomian glands and lacrimal glands, will be required to better understand and diagnose lid surgery-induced dry eye [276,282,285,309,620]. Moreover, a multicentric large-scale epidemiological study with the participation of oculoplastic surgeons is needed to precisely determine its real prevalence, identify risk factors and define effective educational approaches for clinicians and patients.

5.4. Areas of future research in other procedures that can result in dry eye

It has been reported that BTX-A injection for treatment of blepharospasm, after periorbital surgery, and correction of crow's feet is a possible cause of dry eye [103,463,475,547], whereas this procedure also has been used as a therapy for DED by decreasing lacrimal drainage [451]. Identification of predictive factors for the onset of postoperative DED after BTX-A injection for early diagnosis will contribute to the establishment of therapeutic intervention strategies [104].

A host of elective and cosmetic ophthalmic procedures (such as eyelash growth, fillers, conjunctival whitening, eyelid/conjunctival tattooing, jewelry/piercings, and the use of adjunctive MMC and/or anti-VEGF agents) have emerged in the marketplace. Many of these procedures are performed by providers other than eye care specialists and have been associated with iatrogenic dry eye as well as other ophthalmic complications. As these procedures continue to evolve and increase in popularity, future directions in this space are unclear, but will probably not cease to interest the public. In light of the associated complications (with some of them being severe and sight-threatening), a greater effort to regulate and oversee these procedures needs to be considered.

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