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REVIEW ARTICLE

A Review of Management Strategies for Nociceptive and Neuropathic Ocular Surface Pain

Harrison Dermer[1] · Daniella Lent-Schochet[2] · Despoina Theotoka[1] · Christian Paba[3] · Abdullah A. Cheema[4] · Ryan S. Kim[5] · Anat Galor[6]

Abstract
Despite being a common presenting symptom to eye-care clinics, many ophthalmologists have difficulty diagnosing and managing ocular surface pain. The purpose of this review is to discuss potential causes of ocular surface pain, focusing on both nociceptive and neuropathic aetiologies. Specifically, we outline an approach to the diagnosis of ocular surface pain and focus on various management strategies, providing supporting evidence on the efficacy of various treatments.

Key Points

Pain arising from the ocular surface may be due to abnormalities in the environment (nociceptive pain), in the nerves (neuropathic pain), or in both. Various topical, systemic, and adjuvant therapies have benefit in treating ocular surface pain and its underlying contributors.

1 Introduction

The designation of pain as the "fifth vital sign" underscores the importance of a thorough pain assessment during the clinical examination. Ocular surface pain is a frequent presenting complaint to the eye clinic. Yet, eye-care providers may not recognise this entity or have a step-ladder approach to its diagnosis and treatment. Successful pain management requires a comprehensive evaluation of biopsychosocial contributors, and there is a need for increased training and education across all specialties to better approach an individual with pain [1]. The purpose of this review is to provide a framework that will improve understanding and treatment of ocular surface pain, including both nociceptive and neuropathic causes. Aetiologies are reviewed in terms of their pathogenesis, presentation, and diagnosis, but with a focus on management. Of note, in this review we focus only on ocular surface pain. It is important to recognise that abnormalities in any part of the eye can cause pain, including infectious keratitis, scleritis, uveitis, and intraocular pressure abnormalities, to name a few. These entities are beyond the scope of the current review, which focuses on pain that arises from the ocular surface, or from the nerves that connect the ocular surface to the brain. The contents of this review were compiled from articles accessed from the National Library of Medicine (NLM) MEDLINE database by searching PubMed for "ocular surface pain".

2 How Does Ocular Surface Pain Present?

Individuals often present to the eye clinic with complaints of "dryness", "burning", "aching", and "tenderness", to name a few descriptors [2]. These symptoms can occur acutely or be present chronically and they can occur spontaneously, or be evoked by triggers such as wind and light.

✉ Anat Galor
agalor@med.miami.edu

1 University of Miami Miller School of Medicine, 1600 NW 10th Ave, Miami, FL 33136, USA

2 California Northstate University College of Medicine, 9700 W Taron Drive, Elk Grove, CA 95757, USA

3 Universidad El Bosque, NO 131 A AK. 9 #131a2, Bogota D.C., Colombia

4 Imperial College London, School of Medicine, Kensington, London SW7 2DD, UK

5 McGovern Medical School, University of Texas Health Science Center At Houston, Houston, TX, USA

6 Bascom Palmer Eye Institute, 900 NW 17th Street, Miami, FL 33136, USA

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Initially, symptoms were attributed to tear film abnormalities or "dry eye". However, many groups have found that symptoms occur independently of measured ocular surface parameters [3, 4]. Thus, a better paradigm is to break down ocular surface pain into nociceptive, neuropathic, or mixed aetiologies, as is commonly done for pain in other parts of the body [5] (Table 1).

3 Nociceptive Causes of Ocular Surface Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [5]. Nociceptive pain "is due to the activation of nociceptors and arises from actual or threatened damage to non-neural tissue" [5]. This definition implies an intact somatosensory nervous system, as opposed to neuropathic pain, which is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [5], and as such is driven by abnormal nervous system function in the absence of other tissue injury. However, these entities are not mutually exclusive and can co-exist [6].

Nociceptive ocular pain can occur acutely after surgery or a traumatic injury, or chronically in the setting of anatomic abnormalities or tear film disruptions. While the cause can often be elicited by history alone, the elimination of symptoms with the application of a topical anaesthetic points to either a nociceptive aetiology or peripheral neuropathic pain [7]. The key to the treatment of nociceptive pain is to identify and target the underlying cause. In the acute setting, such as after surgery or injury, pain can be addressed via protection of the ocular surface with artificial tears (AT) or a bandage contact lens (BCL) [7]. Topical non-steroidal anti-inflammatory agents (NSAIDS) can also be used [8], typically in addition to prophylactic antibiotics. Ocular surface pain in the setting of infection is treated with appropriate anti-microbial agents. Specific guidelines for the management of nociceptive pain due to injury or infection are beyond the scope of this review. Herein, we outline the diagnosis and treatment of nociceptive ocular pain presentations related to chronic diseases of the eyelids and ocular surface. We then discuss the diagnosis and management of neuropathic ocular pain (NOP). In the Tear Film and Ocular Surface Dry Eye Workshop (TFOS DEWS II) [9], dry eye and NOP are listed as distinct entities; however, as in pain outside the eye, overlap of the two conditions is possible [10].

3.1 Eyelid Sources of Ocular Surface Pain

3.1.1 Ectropion and Entropion Pathophysiology

Ectropion is characterised by outward rotational displacement of the eyelid. It is commonly encountered in the lower eyelid due to the contribution of gravity. It may be acquired or congenital [11]. Congenital ectropion is rare and defined by developmental vertical shortening of anterior lamellar tissue or atrophy of the tarsal plate [11]. It is associated with genetic diseases such as Down's syndrome and blepharophimosis, ptosis, epicanthus inversus syndrome (BPES) [11, 12]. Involutional ectropion is the most common subtype of acquired ectropion [11]. It is due to attenuation or dehiscence of the lower eyelid retractors (LER), commonly in the context of age-related tissue atrophy [11]. Elongation of the tarsus, inferior displacement of pretarsal orbicularis oculi, or increased laxity of canthal tendons are other potential contributing factors. Cicatricial ectropion may occur secondary to vertical shortening of the lower eyelid anterior lamella, and is often preceded by surgery, trauma, chemical burns, or infiltrative conditions [11]. Paralytic ectropion manifests secondary to facial nerve palsy and subsequent orbicularis oculi hypotony [13]. Finally, mechanical ectropion may result from mass effect by surrounding tumours, cysts, or chemosis [11].

Entropion is inward deviation of the eyelid margin towards the globe, such that the pilosebaceous unit and mucocutaneous junction are directed inwards [14]. It may also be congenital or acquired. Acquired forms are subtyped as involutional, cicatricial, and acute spastic [15]. Overall, entropion more commonly occurs at the lower eyelid, but cicatricial changes of the upper eyelid may also lead to entropion [15]. Similar to ectropion, involutional entropion is thought to result from age-related decreases in collagen tensile strength, horizontal laxity of the tarsus and canthal tendons, disinsertion of the LER, or an overriding preseptal orbicularis oculi muscle [15]. Cicatricial entropion is due to tarsoconjunctival contraction secondary to fibrosis [15]. It may be associated with a history of surgical trauma, chemical burns, trachoma, mucous membrane pemphigoid (MMP), or Stevens–Johnson syndrome (SJS). Spastic entropion occurs in response to irritation of the ocular surface, often secondary to involutional changes. It is characterised by sustained contraction of the orbicularis oculi, which overwhelms oppositional action of LER to cause in-turning of the eyelid margin [15].

Presentation and Diagnosis Ectropion commonly presents with ocular surface pain secondary to exposure keratopathy or impairment of the lacrimal drainage system. Associated ocular symptoms include epiphora and discomfort of

Table 1 Management of nociceptive and neuropathic ocular surface pain

	Ocular surface pain management	Level of evidence[a]
Nociceptive pain		
Eyelid sources		
Ectropion and entropion	Conservative	
	Artificial tears [20]	5
	Injections	
	Hyaluronic acid injections [21, 22]	4
	Subcutaneous BoNT injection (spastic or involutional entropion) [23]	4
	Surgical	
	Lateral tarsal strip (LTS) [25]	3
	Everting suture (ES) approach (entropion) [26]	1
	Combination of LTS and ES [26]	1
	Other	
	Octyl-2-cyanoacrylate liquid bandage (entropion) [24]	4
Lagophthalmos		
	Conservative	
	Scleral contact lens [33]	5
	Moist chamber goggles [33]	5
	Taping eyelids while sleeping [33]	5
	Invasive	
	Narrowing interpalpebral fissure (cyanoacrylate glue, BoNT, or sutures) [35] [36]	3
	Surgical	
	Medial tarsorrhaphy [37]	3
	Other	
	Upper eyelid loading (paralytic lagophthalmos) [34]	4
Ocular rosacea		
	Conservative	
	Lid hygiene, lubrication, warm compresses [48]	2
	Meibomian gland expression [49]	4
	Thermal pulsation system (when Meibomian gland dysfunction is present) [50]	2
	Microblepharoexfoliation (when blepharitis is present) [51]	1
	Drugs	
	Topical cyclosporine A [52]	1
	Oral doxycycline (20 mg daily to 100 mg twice daily) or azithromycin (500 to 1000 mg daily) [54] [59]	1
	Non-invasive	
	Intense pulsed light therapy [60]	4
Ocular demodicosis		
	Conservative	
	Tea tree oil [75]	3
	Lid scrubs containing Octanediol [51]	1
Conjunctival sources		
Conjunctivochalasis	Conservative	
	Lubrication and artificial tears [86]	4
	Non-invasive	
	Thermoplasty [86]	4
	Surgical	
	Conjunctival excision or electrocoagulation [87]	4
Pterygium	Drugs	
	Topical NSAIDS, indomethacin (0.1%) or dexamethasone (0.1%) [93]	1

Table 1 (continued)

	Ocular surface pain management	Level of evidence[a]
	Surgical	
	Pterygium excision [95]	1
Superior limbic keratoconjunctivitis	Conservative	
	Autologous serum tears [102]	4
	Invasive	
	Supra-tarsal triamcinolone injection [104]	4
	Surgical	
	Resection of superior bulbar conjunctiva and Tenon layer [105]	2
Tear film sources		
Aqueous tear deficiency	Conservative	
	Preservative free artificial tears [116]	2
	Drugs	
	Cyclosporine A (0.05% twice daily) [120]	1
	Lifitegrast (5%) [125]	1
	Autologous serum tears [130]	3
	Low dose glucocorticoids (fluorometholone or preservative free 0.5% prednisolone) [134]	3
Evaporative tear deficiency	Conservative	
	Goggles [147] and avoid triggers	4
Chronic glaucoma medication use	Preservative free glaucoma medications [152]	2
Neuropathic pain		
Peripheral sensitisation	Preservative free artificial tears [10]	1
	Anti-inflammatory agents (corticosteroids, cyclosporine, lifitegrast, and tacrolimus) [10, 171]	1
	Autologous serum tears [10]	3
	Amniotic membrane transplant [173]	3
	Bandage contact lens [174]	2
Central and/or peripheral sensitisation	Gabapentinoids (gabapentin 300–900 mg and pregabalin 75–150 mg) with or without SNRIs (duloxetine or venlafaxine) [181, 185]	1
	Tricyclic antidepressants (amitriptyline 25–250 mg) [10]	1
Non-invasive adjuvant therapies	Transcutaneous electrical nerve stimulation [195, 196]	1
Invasive adjuvant therapies	Periocular Botulinum toxin [204]	3
	Periocular nerve blocks [184]	3
	Trigeminal nerve stimulation [208, 209]	5
	Intrathecal pain pump [208, 209]	5
Non-pharmacological	Cognitive behavioural therapy [171]	1

[a]Levels of evidence = 1: Randomised controlled trial (RCT) or meta-analysis of RCTs with homogenous results; 2: Prospective cohort study or meta-analysis of level 1 or 2 studies with inconsistent results; 3: Retrospective cohort or case–control study or meta-analysis of level 3 studies; 4: case series; 5: Case report or expert opinion

the lid margins [16]. Diagnosis of ectropion is clinical and may be confirmed if any of the following signs are present on physical examination: punctal malposition away from the globe, horizontal tarsal laxity evidenced by more than 1 cm of separation between the central eyelid and the globe, medial canthal tendon laxity evidenced by loss of apposition between the inferior and superior puncta on blink closure, or vertical tightness of eyelid skin and orbicularis oculi paresis on maximal forced closure examination [17]. It is important to note that while these anatomical findings indicate overt ectropion, patients with less obvious deformity may also be symptomatic.

Entropion generally presents with trichiasis and resultant irritation of the ocular surface. Symptoms include a foreign body sensation, epiphora, or blurry vision. In severe cases, corneal abrasions or infections may occur. The diagnosis is again made clinically and is confirmed by physical examination. Horizontal laxity is likely with ≥ 8 mm of distraction when the lower eyelid is pulled away from the globe ("pinch test") [18]. Horizontal laxity is also confirmed if the

lower punctum moves beyond the lacrimal caruncle when pulled medially or beyond the midpoint between the plica and corneal limbus when pulled laterally [18]. Vertical laxity secondary to LER dysfunction is likely if forniceal fat prolapses when pulling the lower eyelid down to the orbital rim [19]. Spastic entropion should be evaluated for by asking the patient to squeeze forcefully a few times. Spastic entropion may only become obvious after this dynamic test and is thus often missed as a cause of ocular pain and corneal staining.

Management Ectropion and entropion are treated according to aetiology. A conservative approach for pain secondary to ocular surface disease related to ectropion induced exposure includes lubrication with AT with or without taping of the inferolateral canthal skin. Hyaluronic acid (HA) injections may benefit involutional, cicatricial, and congenital ectropion by mechanically stretching the dermis to stimulate collagen synthesis by fibroblasts [20]. Assessments of HA injection for ectropion at various periocular sites demonstrated mixed results, with full resolution occurring in 27.3% [21] to 73.3% [22] of cases. More studies are necessary to identify the efficacy, optimal technique, and possible adverse effects of periocular HA injection for ectropion. For entropion, lash removal can provide temporary relief from trichiasis associated pain. Subcutaneous injection of botulinum toxin (BoNT) may be used for spastic or involutional entropion [23], by acting as a neuromuscular blocking agent at the pretarsal orbicularis muscle. Relief is often experienced 3–4 days post-injection and the effects and can last up to 16 weeks [23]. An additional non-surgical option for entropion treatment is repositioning of the lid using an octyl-2-cyanoacrylate liquid bandage [24]. These lower risk non-surgical options generally provide temporary relief of ocular surface disease and associated pain secondary to ectropion or entropion.

Anatomical restoration is beneficial for more definitive resolution of ocular surface disease and associated pain secondary to ectropion or entropion. A surgical approach is typically applied for definitive treatment of involutional ectropion and ectropion. Procedures such as lateral tarsal strip (LTS) have a high success rate, even in isolation. LTS is often combined with internal retractor reattachment. This combined technique has been reported to achieve up to 95% of anatomical success, 4.9% recurrence rate within 1.5 years, and minimal reports of severe complications in the setting of ectropion [25]. For entropion, a quicker but less definitive option is placing double armed full thickness everting sutures (*Quickert)* to rotate the margin anteriorly [26]. This technique is advantageous as it can be performed at the bedside under local anaesthesia and has minimal complication risk. However, the use of everting sutures is associated with entropion recurrence [27] when compared with the addition of a LTS procedure [26]. Reported complications of the combined LTS and quickert suture approach include haematoma and granuloma formation [28].

3.2 Lagophthalmos

Pathophysiology Lagophthalmos is incomplete eyelid closure. Resultant chronic exposure of the ocular surface promotes aqueous evaporation and tear film disruption, leading to pain and discomfort [29]. Paralytic lagophthalmos is due to orbicularis oculi hypofunction secondary to facial nerve deficits or trauma [29]. Postoperative lagophthalmos has been described following procedures that impact the eyelids, such as blepharoplasty [30]. Lagophthalmos may also be cicatricial secondary to postoperative scarring or fibrogenic diseases such as SJS. In addition, lagophthalmos may be due to exophthalmos, as in thyroid eye disease (TED) or orbital mass effect. Physiologic lagophthalmos usually occurs nocturnally and may be encountered in those without other obvious features of eyelid dysfunction [31].

Presentation and Diagnosis Presenting signs and symptoms are proportional to the degree of ocular surface exposure. Ocular discomfort and blurry vision upon awakening are common complaints, especially in nocturnal lagophthalmos. Diagnosis is by history and physical exam. For example, reports of acoustic neuroma resection or surgery involving the parotid gland may point to iatrogenic facial nerve damage in cases of paralytic lagophthalmos. A history of obstructive sleep apnoea is commonly endorsed in those with lagophthalmos due to floppy eyelid syndrome [32]. On gross examination, resting scleral show and inadequate lid closure are diagnostic. Punctate epithelial erosions in the inferior third of the fluorescein stained cornea are commonly observed in cases of lower lid lagophthalmos.

Management Individuals with lagophthalmos present with ocular surface pain secondary to exposure keratopathy. Protective scleral contact lenses (CL), moisture chamber goggles, and taping the eyelids closed during sleep all combat symptoms of corneal exposure in lagophthalmos [33]. Orbital decompression should resolve symptoms in cases that are related to proptosis. Paralytic lagophthalmos of the upper eyelid is treated by loading the lid with an implanted gold weight to enhance gravity-assisted closure [34]. Potential side effects include extrusion of the implant or an allergic reaction to it, in which case platinum chains are an acceptable alternative [34]. In paralytic lagophthalmos, patching of the eye is not advised as unopposed levator muscle action may result in the lids opening under the patch and putting the cornea at risk of abrasion [33]. Narrowing of the interpalpebral fissure is also beneficial to aid corneal healing and limit exposure-related ocular surface pain. This may be achieved temporarily using cyanoacrylate glue [35],

BoNT, or sutures (drawstring technique), or permanently via sutures and debridement to promote the formation of adhesions [36]. Permanent medial tarsorrhaphy performed on 30 eyelids with exposure keratopathy (80% of total) secondary to lagophthalmos (57% of total), facial nerve palsy (47% of total), and TED (13% of total) resulted in significant reductions in palpebral fissure and inferior scleral show distance [37]. Lagophthalmos improved in 60% of cases with a mean decrease from preoperative baseline of 0.4 mm ($p = 0.27$) after a 13-month mean duration of follow up [37]. Furthermore, corneal exposure index scores indicative of superficial punctate keratopathy, which is a sign of corneal epithelial disruption often associated with pain, improved by 61% ($p = 0.009$) [37]. Successful anatomic restoration generally results in resolution of ocular surface pain secondary to lagophthalmos associated exposure.

3.2.1 Ocular Rosacea

Pathophysiology Rosacea is characterised by chronic central facial cutaneous inflammation [38]. It is believed to be due to alterations in the production of vasoactive antimicrobial cathelicidin peptides that are induced by innate immune response pathways in the epidermis [39]. In this manner, stimulation by foreign microbial antigens may provoke the exaggerated inflammatory response characteristic of rosacea [39]. For example, eyelash infestation with the parasitic arthropod, *Demodex folliculorum*, has been associated with ocular rosacea [40]. Bacterial species such as *Helicobacter pylori* and *Staphylococcus epidermidis* have also been implicated [41].

Presentation and Diagnosis Individuals with rosacea typically present with cutaneous erythema and/or telangiectasias, pustules, papules, or less commonly, rhinophymatous changes [38]. As such, an eye exam begins with examination of the facial skin. Rosacea also affects the lid margin in up to 72% of patients, with 20% demonstrating ocular signs even before facial manifestations [38, 42]. However, more typically, ocular rosacea follows the development of facial findings in 50% of individuals and occurs concurrently in 30% [43, 44].

Ocular rosacea is diagnosed clinically [38]. Patients may be asymptomatic or may report painful ocular surface symptoms including burning, stinging, foreign body sensation, dryness, or itching [45–47]. Ocular symptom severity if often not related to the severity of facial manifestations [46]. Ocular examination findings include periocular erythema, lid margin irregularities and telangiectasias, inspissated meibomian gland orifices, and/or poor meibum quality. These may be accompanied by a variable amount of bulbar injection, tear film instability, and corneal staining [44, 45]. Recurrent chalazia may also be encountered [45, 47]. The National Rosacea Society categorises ocular rosacea as mild (lid findings only), mild-to-moderate (lid findings with conjunctival injection), moderate-to-severe (lid findings with corneal changes including staining, infiltrate, or neovascularisation), and severe (scleritis or severe keratitis) [45].

Management When ocular surface pain is thought to be driven by ocular rosacea, we utilise a step ladder approach, titrated to the severity of disease. Mild ocular rosacea is typically addressed with lid hygiene, lubrication, and warm compresses on the eyelids [48]. In office treatments that target obstructive Meibomian gland dysfunction (MGD) secondary to ocular rosacea can supplement in home therapies. Therapeutic Meibomian gland expression (MGX) may be performed manually [49] or with the application of heat via a thermal pulsation system (*Lipiflow*, TearScience, Morrisville, NC) [50]. Co-existence of anterior blepharitis (e.g. collarettes, lash debris) can be treated with antibiotic ointment or micro-blepharoexfoliation (*BlephEx*, Scope Ophthalmics, London) [51]. Topical cyclosporine A (CsA) can combat ocular surface inflammation in ocular rosacea and has been shown to alleviate discomfort in this group [52]. A randomised trial of topical CsA emulsion administered twice daily for 3 months for ocular rosacea reported a 52.6% decrease in the number of patients ($N = 19$) endorsing "pain" from baseline (57.9%) to 3 months post-treatment (5.3%) [52]. This effect was greater than a contemporary group that received 100 mg oral doxycycline twice daily for the first month and once daily for the subsequent 2 months ($N = 19$, 36.8% to 21.1%) [52]. Both treatment arms resulted in significant decreases in mean symptom score (the presence or absence of 9 symptoms including burning, stinging, itching, and pain, 0–9 scale). Specifically, mean scores in the CsA group decreased from 7.16 ± 1.21 at baseline to 1.79 ± 0.98 after 3 months versus 6.79 ± 1.08 to 3.32 ± 1.41 in the doxycycline group ($p < 0.01$ for both) [52]. The CsA arm also demonstrated a significantly greater decrease in mean Ocular Surface Disease Index (OSDI) scores (-20.04 ± 8.06) compared to the doxycycline arm (-11.22 ± 9.20) ($p < 0.05$) [52].

Regardless of the study results, systemic therapy is often used in individuals with moderate-to-severe ocular rosacea [53]. Oral doxycycline is believed to exert its effect due to anti-inflammatory properties [54]. Specifically, by antagonising pro-inflammatory proteinases including matrix metalloproteinases (MMP) 8 and 9 that are elevated in the tears of ocular rosacea patients [55, 56]. Various dosing strategies are used ranging from 20 mg daily to 100 mg twice daily, typically for at least one month. Data suggest that the lower dose is as effective as higher doses [57, 58]. Gastrointestinal intolerance and sunlight sensitivity are the most frequent side effects of doxycycline [58]. Three-weekly doses of oral azithromycin (500 mg to 1000 mg daily) can be used as an alternative in patients with gastrointestinal side effects or for

paediatric or pregnant patients for whom tetracyclines are contraindicated [59].

Another option for the treatment of ocular surface pain associated with ocular rosacea is Intense Pulsed Light (IPL). IPL reduces facial erythema and telangiectasias, with results lasting at least 6 months after four treatments at 3-week intervals [60]. IPL works via selective photothermolysis, a process where polychromatic light is emitted at specific wavelengths known to be preferentially absorbed by targeted tissue types in order to facilitate its conversion to thermal energy [61]. Doing so, allows for the selective ablation of superficial telangiectatic vessels. One hypothesis on the effect of IPL in ocular rosacea is restoration of a beneficial hypoxic environment around meibocytes after treatment [62]. Other potential mechanisms of action of IPL are reduced access of inflammatory compounds to Meibomian glands, heating of glands with improved expressibility and anti-microbial effects [61]. IPL is postulated to damage certain organisms with a specific chromophore content that renders them susceptible to the wavelengths of light that are emitted. For example, IPL led to coagulative necrosis of demodex organisms at the pilosebaceous follicles [63].

IPL has been found to be efficacious in the treatment of ocular pain from rosacea-associated MGD in a number of studies. A prospective case series of subjects with moderate-to-severe rosacea-associated MGD ($N=17$) who underwent 4 IPL treatments at 3-week intervals demonstrated significant improvement in OSDI scores from baseline at each assessment time point up to 1 year post-IPL ($p<0.001$) [64]. In a randomised trial that compared combined IPL with MGX ($N=45$) versus MGX alone ($N=45$) in eyes with refractory MGD, the IPL-MGX group showed significant improvements in Standardised Patient Evaluation of Eye Dryness (SPEED) scores at 32 weeks ($p=0.044$) compared to the MGX control group [65]. The SPEED questionnaire specifically asks about eye soreness, irritation, and burning. Potential adverse effects of IPL include self-limiting hyper- or hypopigmentation, blistering, and scarring [66].

3.2.2 Ocular Demodicosis

Demodex are parasitic arthropods commonly referred to as "dust mites". Two species, *D. folliculorum* and *D. brevis*, may be found on human facial skin adnexa. *D. folliculorum* is commonly observed in patients with blepharitis as it has a predilection for hair follicles, opposed to sebaceous glands [67]. *D. brevis* is appropriately named for its relatively smaller length (0.2–0.3 mm) compared to *D. folliculorum* (0.3–0.4 mm) [68].

Pathophysiology The pathogenic mechanism of symptomatic ocular demodicosis has not been fully elucidated and is likely multifactorial. Symptoms, such as pain or itching [69], may occur secondary to an immune response to exoskeleton components or bacteria found on the surface of the mite [67]. However, demodex are also often found in asymptomatic individuals so their contribution to ocular surface pain is unclear [70]. Elevation in the pro-inflammatory cytokine interleukin (IL) 17 was noted in the tears of individuals with demodex blepharitis (95.1 pg/mL) compared to those with blepharitis but no demodex infestation (84.9 pg/mL) and controls (79.7 pg/mL) ($p<0.05$) [71]. As such, potential causes of ocular surface pain in the setting of demodex include inflammation in addition to MGD secondary to mechanical blockage of Meibomian gland orifices by mites or their excretory products [72]. The characteristic lash deposits encountered in demodex blepharitis that are composed of epithelial cells, keratin, and eggs or materials regurgitated by the mites are reported to contain proteases and lipases implicated in ocular irritation [73].

Presentation and Diagnosis Demodex is a ubiquitous parasite and is often found in asymptomatic healthy individuals. This suggests variable host susceptibility to ocular symptoms secondary to isolated demodicosis. Overall, studies have found a higher frequency of Demodex in individuals with blepharitis compared to controls. Sixty-two percent of blepharitis patients ($N=544$), diagnosed by the presence of lid margin telangiectasias or crusting or cylindrical dandruff at the eyelash bases on slit lamp examination, were found to be infested compared with 24% of healthy controls ($N=100$) who did not exhibit symptoms or signs of blepharitis [74]. Furthermore, Demodex infestation correlates with symptoms of ocular surface discomfort. In the same case–control study, individuals with Demodex reported itching as the most frequent symptom (OR = 0.53, $p<0.0001$), and the degree of organism burden demonstrated a significant positive correlation with ocular itch (r = not reported, $p<0.05$) [74].

Most studies found increasing frequency of demodex infestation with increasing age, especially in individuals aged > 50 years [74]. Demodex blepharitis has rarely been documented in paediatric patients [67].

Demodicosis is diagnosed via lash sampling followed by microscopic examination. Specifically, nasal and temporal lashes are pulled using a jeweller's forceps from the upper and lower lid of each eye (8 in total). The sampled lashes are placed on a slide and fluorescein dye is used to aid in microscopic visualisation of organisms (Fig. 1).

Management Asymptomatic demodex infestation does not necessitate treatment. Symptomatic patients may benefit from administration of topical formulations containing dilute tea-tree oil (TTO) to the eyelids [75]. TTO is thought to have anti-inflammatory properties by promoting superoxide production and the suppression of cytokines. It is also

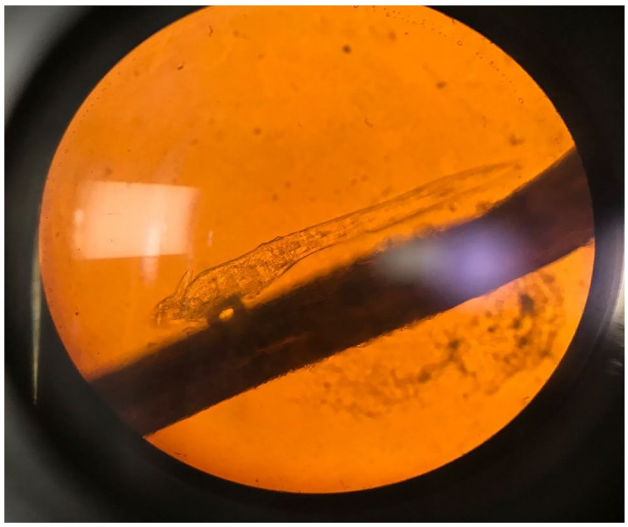

Fig. 1 Optical microscopy demonstrating demodex follicularum on the eyelash follicle

proposed to have antibacterial properties via disruption of the cytoplasmic membrane of certain microorganisms. In one study, 4 weeks use of a weekly lid scrub containing 50% TTO in addition to daily lid hygiene with tea-tree shampoo led to relief of irritating ocular surface symptoms measured by subjective reporting of percent improvement in 10 of the 11 patients [75]. Of note, three patients reported periocular irritation as a side effect to the treatment itself [75]. Another study of 106 demodex blepharitis patients who reported symptoms including ocular surface pain demonstrated a significant reduction in mean OSDI scores (34.5 to 24.1, $p = 0.004$) after completing 1 month of treatment with 50% TTO lid scrubs [76]. As an alternative, 1% topical formulations of the active ingredient in TTO, Terpinen-4-ol (T4O), have been utilised [75]. Other treatments for demodex blepharitis include exfoliation (*BlephEx*, Scope Ophthalmics, London) and lid scrubs containing 1–2 Octanediol (*OcuSoft*, OCuSOFT, Houston). In a randomised controlled trial, four weeks of nightly lid hygiene with TTO, Ocusoft, and Blephex resulted in similar significant reduction in debilitating ocular surface pain and discomfort as measured by OSDI scores [51]. Each treatment modality also resulted in similar and significant reductions in *D. follicularum* counts [51]. A systematic review of the efficacy of various treatments for Demodex blepharitis reported symptomatic improvement with an effect size > 0.8 on stratified meta-analysis for 50% and 5% formulations of TTO, T4O, and Ocusoft lid scrubs [77]. They report no significant differences in efficacy between topical and systemic treatments and argue that topical formulations are preferred due to their more favourable side effect profiles [77].

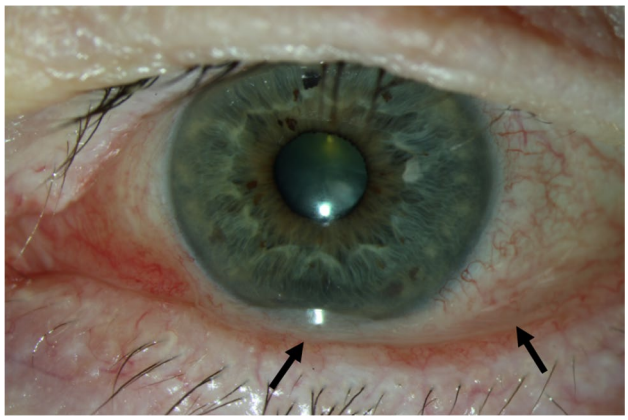

Fig. 2 Conjunctivochalasis at the middle and temporal aspects (arrows) of the inferior bulbar conjunctiva

3.3 Conjunctival Sources of Ocular Pain

3.3.1 Conjunctivochalasis

Pathophysiology Conjunctivochalasis (Cch) is characterised by the presence of loose and redundant conjunctival folds in the absence of oedema or chemosis (Fig. 2). The presence of Cch is hypothesised to be due to degradation of elastic tissue components and tenon's capsule. This is supported by observations of increased MMP 1, 3 and 9 expression in fibroblasts isolated from Cch tissue compared to normal conjunctival fibroblasts [78]. Increased proteolytic activity degrades the extracellular matrix (ECM) and is promoted by pro-inflammatory cytokines at the ocular surface [79]. Mechanical friction between conjunctival components that occurs during blinking may contribute to inflammation and perpetuate a positive feedback cycle that promotes further Cch development [80]. Repeated frictional insult may also play a role in breakdown of conjunctival connective tissue and the development of lid-parallel conjunctival folds (LIPCOF) [81]. LIPCOF are believed to displace tears and destabilise the ocular surface as evidenced by their impact on tear meniscus height [82].

CCh itself can interfere with tear film formation and dispersion. It may also result in mechanical occlusion of the punctum leading to delayed tear clearance and subsequent epiphora [83]. When severe, CCh can prevent adequate lid closure and result in exposure related pathologies [80]. As such, patients may present with dryness and/or excessive tearing. The loss of tear film homeostasis further promotes a state of chronic inflammation that can ultimately worsen CCh.

Presentation and Diagnosis Cch is a common finding in older individuals [84] and may not be associated with symptoms. However, frequent complaints include both tearing

and pain-related complaints (irritation, burning, dryness, or a foreign body sensation) [85]. Cch is diagnosed at the slit lamp by disruption of the normal tear lake with redundant tissue. Its presence is often highlighted by the use of fluorescein dye. One grading system defines Grade 1 Cch as the presence of a single small fold, Grade 2 as more than two-fold no higher than the tear meniscus, Grade 3 as multiple folds higher than the tear meniscus, and Grade 4 as folds with punctal occlusion [80].

Management Asymptomatic Cch requires no management beyond observation. Symptoms of ocular surface pain related to Cch may be addressed by lubrication with AT and/or combating inflammation. However, surgical treatment is often needed when medical therapy is unsuccessful. The two most common procedures are thermoplasty via electrocautery and conjunctival excision. Thermoplasty of the inferior bulbar conjunctiva with low temperature cautery demonstrated complete resolution of symptoms in 36 of 39 (92.3%) eyes that had previously failed medical management [86]. It is common for patients to experience postoperative injection and discomfort from the procedure, and scarring may also occur. Conjunctival excision involves resection of bulbar conjunctiva from 5 mm below the limbus to the inferior fornix. Amniotic Membrane Transplant (AMT) may be secured to the sclera using fibrin glue to replace the excised conjunctiva. Another option for CCh is electrocoagulation, which utilises high frequency radio-waves to shrink conjunctival tissue. It has comparable efficacy in decreasing symptoms when compared to surgical excision, and generally results in less postoperative discomfort [87].

3.3.2 Pterygium

Pathophysiology Pterygia are benign degenerative fibrovascular subepithelial proliferations of perilimbal bulbar conjunctiva that occur within the palpebral fissure and may involve the cornea [88]. They are commonly encountered in individuals living in regions of the globe where ample sunlight exposure occurs [89]. Their formation is associated with exposure to type B ultraviolet radiation (UVB), and the pathogenesis is believed to involve alterations in expression of tumour protein 53 secondary to radiation-induced genetic damage [90]. These lesions may destabilise the ocular surface and result in the sensation of pain [91].

Presentation and Diagnosis While the diagnosis is confirmed by physical exam, patients usually endorse a history of recreation or occupation involving increased sun exposure [89]. On slit lamp examination, pterygia are well demarcated and wedge-shaped (Fig. 3). Intralesional vessels are generally deep, go to the edge, and lack hair-pin loops. It is important to keep in mind that ocular surface squamous neoplasm (OSSN) may masquerade as pterygia and the two pathologies are known to coexist [92]. Anterior segment optical coherence tomography (ASOCT) or incisional biopsy are necessary to rule out OSSN before considering management options for isolated pterygium.

Management Asymptomatic pterygia not affecting the visual axis should be monitored for progression. Ocular surface pain and discomfort is more often encountered in cases of inflamed pterygia, and topical NSAIDS or steroids can be beneficial for relief in these cases. A randomised controlled trial of a two-week course of either 0.1% topical indomethacin ($N=10$) or 0.1% topical dexamethasone ($N=7$) for inflamed pterygium found significant improvement in total symptom scores, measured by subjective reporting on a scale of 0 = no pain or discomfort symptoms to 3 = severe symptoms, for both treatment groups ($p=0.001$) [93]. No significant differences in symptomatic relief were observed between the NSAID and steroid groups [93]. Of note, a case report describing the effect of limbal subconjunctival bevacizumab (1.25 mg/0.05 mL) injection for primary pterygium reported resolution of ocular surface irritation at one week post-injection, but this effect was transient [94].

Surgical excision is recommended when ocular surface pain is refractory to medical management or when there is occlusion of the visual axis. We do not recommend excision for cosmesis alone as postoperative scarring and recurrence may occur. However, a recent survey of 199 cornea specialists who perform complete lesion resection with subsequent autologous or limbal-conjunctival graft placement found that cosmesis was reported as an indication in 41.7%, and recurrence rates among most respondents was less than 5% [91]. Resection of primary pterygium in 98 eyes was reported to result in significant decreases in dry eye symptom scores (specific values not provided) measured by

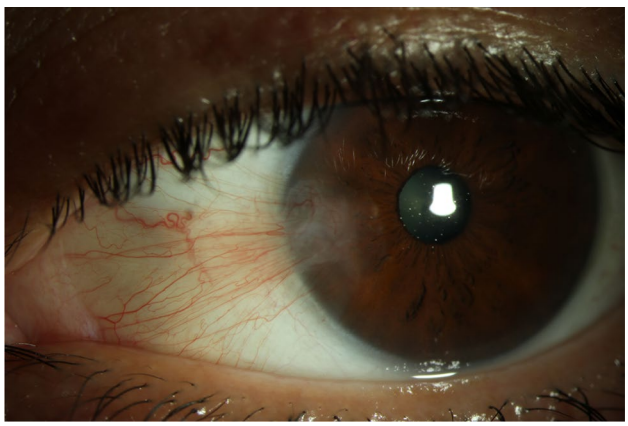

Fig. 3 Nasal pteryigium

subjective questionnaire after 2 postoperative weeks, regardless of whether postoperative intradermal needling was utilised ($p < 0.05$) [95].

3.3.3 Superior Limbic Keratoconjunctivitis

Pathophysiology Superior limbic keratoconjunctivitis (SLK) is a relatively uncommon condition characterised by chronic inflammation at superior aspects of the bulbar conjunctiva, limbus, and cornea [96]. It is believed to be triggered by recurrent blink-related frictional microtrauma between the upper lid and affected area of the ocular surface [97]. This pathogenic mechanism is evidenced by the histologic finding of squamous metaplasia in affected areas [98]. It is also supported by the fact that SLK associates with upper bulbar Cch [99] and endocrine exophthalmos, both of which may contribute to friction at the upper palpebral-bulbar conjunctival interface via tissue redundancy or pressure from the bulging globe, respectively [96]. It is plausible that ill-fitting contact lens wear also contributes to the development of SLK in some cases.

Presentation and Diagnosis SLK presents with irritating ocular discomfort and pain [100]. A case series of 45 individuals with clinically diagnosed SLK found the most frequently reported symptoms to be foreign body (71.1%) or burning sensation (68.9%), followed by ocular pruritis (46.6%) and dryness (31.1%) [101]. Diagnosis of SLK is by clinical examination. A papillary reaction at the superior palpebral conjunctiva and/or superior bulbar conjunctival injection are generally observed [98]. Lissamine green staining can be used to identify disruption of superior bulbar conjunctival epithelium in the pathognomonic location [96]. It is also important to assess autoantibody status if comorbid TED is suspected.

Management Potential contributors like TED and Cch should be addressed appropriately. There is no consensus or gold standard for managing ocular pain secondary to SLK, and many modalities have been explored. Topical application of 0.5%–1% silver nitrate, *N*-acetylcysteine, corticosteroids, cromolyn sodium, lodoxamide tromethamine, and vitamin A have all been proposed as options for relief of ocular surface pain due to SLK [96]. Of topical modalities, autologous serum tears (AST) show promise for pain secondary to SLK, likely due to their lubricating and anti-inflammatory effect. Details regarding AST are described further in Sect. 3.3.1. In 22 eyes with SLK, the administration of 20% AST resulted in a significant improvement in ocular surface pain with mean face scores decreasing from 8.7 ± 0.65 at baseline to 6.9 ± 1.5 after 4 weeks of treatment ($p < 0.01$) [102]. This validated face score, where patients select a representative face image that matches their comfort level (1 = no discomfort to 9 = severe discomfort), has also been used to evaluate other treatment modalities [103].

If ocular pain in SLK is refractory to topical management, more invasive measures may be of use. Supra-tarsal triamcinolone injection in 40 eyes with SLK refractory to AT and topical corticosteroids found symptomatic improvement with face scores significantly decreasing from 8.0 ± 0.99 at baseline to 2.2 ± 0.97 after a mean follow-up period of 11.6 months ($p < 0.001$) [104].

If refractory to anti-inflammatory modalities, surgical removal of the affected superior conjunctivae should be considered. Resection of the superior bulbar conjunctiva and Tenon layer was performed in a retrospective study of 40 individuals with medically unresponsive SLK (previous topical steroid, mast cell stabiliser, and AT use in all, punctal plugs in an unspecified proportion with DE) [105]. They assessed ocular irritation scores (defined as burning, stinging, or foreign body sensation subjectively reported on a scale of 0 = absent, 1 = mild, 2 = moderate, 3 = severe) before and after resection [105]. Mean irritation scores significantly decreased from 2.3 (SD not provided) at baseline to ~ 0.4 (SD not provided, $p < 0.05$) 3 months post-procedure [105]. Of note, topical 0.1% fluorometholone was administered four times daily for the first two post-procedure weeks in this cohort [105].

3.4 Tear Film Causes of Ocular Surface Pain

3.4.1 Aqueous Tear Deficiency

Pathophysiology Aqueous tear deficiency (ATD) is a subtype of dry eye (DE) in which tear production is deficient. ATD is often seen in individuals with a systemic autoimmune disorder, including Sjögren's syndrome (SS), rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE) [96]. The pathophysiology of SS associated ATD is lymphocytic infiltration into the lacrimal glands [106]. ATD may also occur outside the purview of SS due to a variety of aetiologies. Glandular deficiency, for example, may present secondary to congenital agenesis, damage from trauma or radiation, infiltration by lymphoma, or due to age-related hypofunction [96]. Obstruction of lacrimal gland output may occur in cases of graft versus host disease (GVHD) or cicatrising states like mucus membrane pemphigoid and SJS [96]. Disruption of the sensory tear secretion reflex pathway due to trigeminal nerve injury, chronic contact lens wear, or refractive surgery is another potential cause of ATD [96]. Regardless of underlying aetiology, ocular surface damage in ATD leads to an inflammatory response that perpetuates further damage in a positive feedback loop ("vicious circle") [96]. This cycle of tear film derangement and ocular surface inflammation activates corneal nerve fibres, which leads to a sensation of pain. Burning and stinging sensations have

been attributed to corneal polymodal nociceptor activation by inflammatory mediators, while sensations of dryness have been attributed to corneal cold thermoreceptor activation by tear evaporation [107].

Presentation and Diagnosis In addition to sensations of burning, stinging, and dryness, individuals with ATD endorse a variety of unpleasant sensations (e.g. aching, tenderness, itching) and may or may not present with compensatory tearing. Other commonly encountered features include photosensitivity and blurry or fluctuating vision [108].

In diagnosing ATD we recommend first stratifying individuals by the presence or absence of a systemic immune disorder, specifically SS. The American College of Rheumatology diagnostic criteria for SS requires a total score of ≥ 4 with regard to the following criteria: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥ 1 foci/4 mm^2, each scoring 3; an abnormal ocular staining score ≥ 5 (or van Bijsterveld score of ≥ 4), a Schirmer's test result of ≤ 5 mm/5 min and an unstimulated salivary flow rate of ≤ 0.1 mL/min, each scoring 1 [109]. A problem with the current definition is that currently utilised serologies for SS appear late in the disease course, if at all [110]. Early markers of SS are now available [anti-salivary protein-1 (SP1), anti-parotid secretory protein (PSP), and anti-carbonic anhydrase VI (CA6) immunoglobulins, abnormal value > 20 EU/mL] [111]. However, these early markers are not part of the current definition and it is unknown what percent of individuals with early markers will eventually meet full SS criteria.

After assessment of systemic status, ATD is evaluated with clinical and point-of-care testing. Basal tear production can be assessed via Schirmer test under topical anaesthesia. Less than 8 mm of wetting length after 5-min strip placement is suggestive for ATD [112]. The phenol red thread test is a faster and less invasive alternative method for quantification of tear volume. A cotton thread impregnated with pH sensitive phenol turns red when exposed to tears due to their alkalinity [112]. Less than 9 mm of red area after 15 s points to low tear volume [112]. Tear meniscus, height less than 0.2 mm, assessed via slit lamp examination, is also suggestive of ATD, but this measure is not reliable after instillation of drops [113].

Ocular surface inflammation typically accompanies ATD and should be evaluated as well. Bulbar conjunctival injection is a suggestive clinical sign, and point-of-care and imaging tests are useful to confirm the presence of inflammatory mediators. The *Inflammadry* (Quidel, San Diego) swab detects the presence of MMP-9 on the inferior palpebral conjunctiva [114]. Although the result is binary, the saturation of the pink stripe indicating positivity may be used to qualitatively assess the amount of ocular surface inflammation (0 = below limits of detection, 1 = mild, 2 = moderate, 3 = severe). In vivo confocal microscopy (IVCM) is another modality used to assess inflammation, as assessed by the presence and morphology of dendritic cells found at the level of the sub-basal nerve plexus [115] (Fig. 4a).

Management ATD is multifactorial and many aetiology-specific management options are beyond the scope of this review. Herein, we review lubricating and anti-inflammatory modalities with known benefit in relieving inflammatory-mediated ocular pain secondary to ATD.

First-line conservative treatment of ATD is tear supplementation with AT. Components of AT can include cellulose to maintain viscosity, polyethylene glycol or polyvinyl alcohol to prevent evaporation, and a preservative to prevent contamination. Preservative free forms (PFAT) are recommended for patients with inflammatory reactions to preservatives and are available in single-use vials [116]. AT should be administered at regular intervals to ensure adequate lubrication, and many patients use them on an as-needed basis to provide short-term relief. Beyond AT, several anti-inflammatory and regenerative therapies are commonly prescribed in ATD.

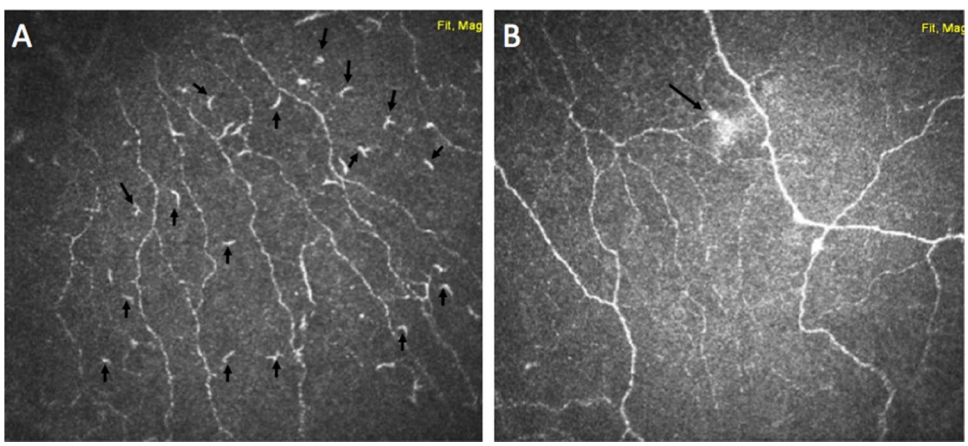

Fig. 4 Dendritic cells (**a**, arrows) and microneuroma (**b**, arrow) seen on In Vivo Confocal Microscopy (IVCM) at the level of the corneal sub-basal nerve plexus

Cyclosporine A (CsA) is an anti-inflammatory agent that binds to cyclophilins and halts T-cell activation by inhibiting IL-2. The reduction in conjunctival and lacrimal gland inflammation is thought to underlie improvements in tear production and goblet cell density and decreases in epithelial cell apoptosis [117]. Some patients report worsening of their burning sensation with initial use, and as such, concomitant use of a topical corticosteroid for the first two weeks can increase long-term compliance [118]. Although systemic use is associated with a risk of renal toxicity, topical application is not [119]. Results from trials of topical CsA vary by dose, but a concentration of 0.05% (0.5 mg/mL) applied twice daily is most often used [120]. One randomised controlled trial of individuals with ATD [Schirmer test (without anaesthesia) score ≤ 7 mm/5 min in at least one eye; 32.2% SS-related] and associated ocular discomfort (one or more moderate symptoms including burning, soreness and pain) assessed the symptom response to twice daily topical CsA [0.05% ($N=17$), 0.1% ($N=18$), 0.2% ($N=20$), 0.4%, ($N=17$)] compared to vehicle alone ($N=16$) [121]. They found that a 12-week course of 0.1% or 0.2% formulations significantly reduced mean OSDI scores from baseline (data not provided, $p \leq 0.008$), while vehicle alone did not [121]. Interestingly, there was a more robust improvement observed in the 0.1% group compared to those who received 0.05% or 0.2% formulations ($p \leq 0.043$) [121]. After a 4-week post-treatment period, however, mean OSDI scores were reported to significantly improve in those who also received 0.2% CsA [121].

Another randomised trial compared twice-daily application of 0.05% CsA ($N=53$) to 0.05% ($N=51$) or 0.1% ($N=51$) water-free formulations (*CyclASol*) and vehicle alone ($N=52$) [122]. They assessed relief of ocular discomfort as measured by changes in Visual Analog Scale (VAS) in addition to OSDI scores in patients with ATD (Schirmer test scores ≥ 2 mm and ≤ 8 mm wetting/5 min) [122]. After 16 weeks of treatment, VAS scores improved across all treatment arms with no significant differences between the groups, while the improvement in OSDI scores was greatest in those who received 0.05% CsA [122]. A larger ($N=323$) prospective study assessed the frequency of ocular pain or soreness (scale of 0 = no symptoms to 4 = constant symptoms) in relation to twice-daily 0.05% CsA use in individuals with ATD (mean baseline Schirmer score < 8 mm wetting length/5 min) [123]. They found that mean pain or soreness frequency scores significantly decreased from 2.0 ± 1.3 at baseline to 0.9 ± 1.0 after a 3-month course ($p < 0.0001$) [123]. Tacrolimus is another topical anti-inflammatory agent that has a similar mechanism and effect as CsA. It inhibits T- and B-cell lymphocytes when bound to immunophilin, thus reducing IL-2 synthesis and the inflammatory response. It is used systemically in DE associated with GVHD. Tacrolimus is also available in 0.03% and 0.1% ointments and can be compounded as an eye drop, but is not frequently used in the treatment of ATD [124].

Lifitegrast 5% (50 mg/mL) is another topical anti-inflammatory agent that has been approved for ocular surface pain secondary to ATD. It acts as an antagonist to lymphocyte function-associated antigen-1 on the T-cell surface by blocking binding to intercellular adhesion molecule-1 (ICAM-1) [125]. This ultimately inhibits T-cell recruitment, activation, and the release of pro-inflammatory cytokines that contribute to inflammatory-mediated ocular pain in ATD [125]. In a Phase III randomised controlled trial (*OPUS-3*) of adults with ATD (Schirmer test scores ≤ 10 mm wetting/5 min), baseline eye dryness scores (EDS) ≥ 40, and a history of AT use within 30 days of study entry, 84 days of twice-daily treatment with 5% topical lifitegrast ($N=355$) resulted in significantly greater improvement in EDS when compared with those using the isolated vehicle ($N=356$) [Treatment Effect (TE) = 7.16; 95% CI 3.04–11.28; $p=0.007$] [125]. Individuals treated with lifitegrast found significantly greater improvements in ocular itch [TE, 4.17 (1.940); nominal $p=0.0318$] and eye discomfort [TE, 5.86 (2.071); $p=0.0048$] compared to controls [125]. The most commonly reported side effects with topical lifitegrast use included irritation at the instillation site (18.2%), and dysgeusia (12.9%) [125].

Autologous serum tears (ASTs) produced from the patient's blood have also been shown to improve painful and irritating ATD symptoms. They act on the ocular surface by providing lubrication and inhibiting the inflammatory cascade. This anti-inflammatory effect is due to the presence of factors in serum that inhibit MMPs, IL-1, and tumour necrosis factor (TNF) [117]. Furthermore, epidermal growth factor (EGF), nerve growth factor (NGF), and insulin-like growth factor 1 (IGF-1), which are all components of AST [126], likely play a role in improving epithelial cell and nerve health [127]. Specifically, NGF promotes the survival and maturation of nerve fibres while IGF-1 aids in epithelial cell adhesion [127]. ASTs also harbour additional components of natural tears such as fibronectin and vitamin A [128].

ASTs are prepared by diluting serum in sterile normal saline. We recommend four-times daily administration starting at a concentration of 20% and titrating up by 10% increments as needed. It is important to advise the patient that the AST must be refrigerated between daily uses and unopened vials should be stored frozen. While it seems plausible that individuals with elevated levels of pro-inflammatory components in their serum due to systemic disease would preclude the use of AST, this does not seem to be the case. The safety and efficacy of AST use in individuals with ATD and comorbid autoimmune disease (GVHD, SS, RA, MMP, or SLE) has been documented [129]. In a retrospective study of 123 individuals with ATD (mean Schirmer test score

6.6 ± 6.5 mm wetting length/5 min) that received 50% AST over a 12-month period, mean OSDI scores significantly improved from baseline (54.1 ± 22.3) at 3- to 6-month (49.5 ± 8.2; $p = 0.029$) and 6- to < 12-month follow-up periods (39.3 ± 21.4; $p = 0.003$) [130]. A randomised prospective assessment of 37 eyes with severe ATD (54% SS related) found that six-times daily administration of 20% AST resulted in significantly lower ocular pain symptom scores measured by VAS after two weeks (52 ± 24) compared to as-needed PFAT administration during the same period (70 ± 20; $p < 0.05$) [131]. This symptomatic relief was also noted in a retrospective study of 83 eyes with severe ATD (19% SS related) that found significant decreases in OSDI scores with a 1- to 3-month (− 19.34 ± 29.37; $p < 0.05$) and > 24-month (− 23.06 ± 18.41; $p < 0.05$) course of AST (dose unspecified) [132]. In another study, subjective ocular discomfort was assessed via face score, where patients selected a representative face image that matched their comfort level from 1 to 9 as described above [103]. They found that mean face scores significantly improved from 7.9 at baseline to 5.2 after a 4-week course of 20% AST in 12 individuals with SS-related ATD (Schirmer test scores < 10 mm wetting/5 min; $p < 0.05$) [103].

Low-dose topical glucocorticoids, including fluorometholone (FML) or preservative-free 0.5% prednisolone, may be considered for short-term symptom management in ATD. Corticosteroids suppress cellular infiltration, capillary dilation, fibroblast proliferation, and collagen deposition [133]. They also block phospholipase A_2, which is crucial for progression of the inflammatory cascade, and inhibit NF-κβ, which regulates the synthesis of pro-inflammatory molecules [133]. A retrospective assessment showed that a 2-week course of 3- to 4-times daily topical 1% non-preserved methylprednisolone resulted in moderate (43% of patients) to complete (57% of patients) relief of symptoms in individuals with SS-related ATD ($N = 21$) [134]. When continuously used, topical steroids may induce cataract and increase intraocular pressure, so careful supervision is crucial.

Additional treatment options are diquafosol and rebamipide, which are products approved in Asia but not available in the USA. Diquafosol is a $P2Y_2$ receptor agonist that stimulates mucin and water secretion, while rebamipide is a quinolone derivative known to increase the density of goblet cells and expression of mucin production genes [135]. These tear-film oriented therapies may be considered for supplementary optimisation of the ocular surface in individuals with discomfort, where available.

3.4.2 Evaporative Tear Deficiency

Pathophysiology Evaporative dry eye (EDE) is another DE sub-type that can manifest with ocular surface disruption and resultant nociceptive pain. While it may coexist with ATD, EDE is most commonly associated with MGD. In this context, inadequate barrier function of the dysfunctional non-polar component of the tear film lipid layer allows for increased aqueous evaporation [136]. EDE may also manifest in response to environmental conditions and exposures (e.g. low humidity, air pollution) that contribute to the cascade of ocular surface inflammation and associated ocular pain. Corneal nerve bundles just deep to the epithelium are vulnerable to repetitive damage from the environment when lacking protection from a stable tear film. For example, ocular discomfort has been described in relation to poor indoor air quality [137], low humidity [138], extremes of ambient temperatures [139], and exposure to common air pollutants like ozone [140]. Low humidity environments have also been shown to increase aqueous tear evaporation [141] and low ambient temperatures to negatively impact Meibum quality and tear-film stability [142].

Presentation, and Diagnosis Tear-film stability is assessed clinically by measuring tear break up time (TBUT), which is defined as the time it takes for the first black spot to appear on the fluorescein stained tear film after blinking. A TBUT < 10 s suggests instability, and patterns in TBUT may be of use in tear-film oriented diagnosis. MGD often accompanies EDE and thus it is important to look for signs of MGD, which can include thickening, vascularisation and keratinisation of the eyelid margin and inspissation ("plugging") of gland orifices [143]. In addition, it is important to apply pressure on the eyelid and qualitatively assess the composition of extracted meibum. Meibum that is white and thick (e.g. toothpaste like) is seen in MGD. Imaging the Meibomian glands via Meibography can be performed to quantify gland atrophy ("drop out") [143]. Evaporimetry is a formal tool for EDE confirmation, but is generally reserved for research use and is not available in most ophthalmology clinics [144].

As environmental factors can also influence EDE, it is important to obtain an occupational and exposure history. For example, a temporal relationship between frequent air travel and ocular discomfort may point to low in-flight humidity and poor cabin air quality as contributors. Excessive screen time is another commonly encountered historical feature that can be combated by set breaks and blinking exercises. Nocturnal leakage from an ill-fitting CPAP mask is another potential culprit that may be addressed by CPAP fitting [145]. Finally, allergy is often co-morbid with EDE and it is important to assess and manage potential allergenic exposures [146].

Management MGD-specific management options are described in Sect. 3.1.3. Tailored exposure and lifestyle modification are often beneficial in EDE with a known

environmental contributor. For example, wrap-around goggles designed to increase periocular humidity have been shown to reduce symptoms of ocular discomfort in EDE. 125 non-contact lens wearers with ocular discomfort due to EDE (TBUT < 10 s and evidence of MGD) were randomly assigned to wear either intact goggles ($N = 100$) or frames with the central lens removed (control, $N = 25$) for 20 min in a room maintained at 40%–50% relative humidity and constant temperature [147]. Subjects ranked their ocular discomfort on a five-point scale (0 = no discomfort to 4 = intolerably uncomfortable) at baseline, after 20 min of goggle wear, and 15 min after completion of the trial [147]. Ninety-nine percent of those who wore intact goggles had symptomatic improvement by at least one point, with 33.3% of those improving by 2 points, 32.3% by 3, and 10.1% by 4 points ($p < 0.0001$) [147]; 91.9% of those who had complete relief after 20 min of wear noted a return of discomfort within the next 15 min [147]; 76% of those who wore control goggles reported no improvement in symptoms, and although 24% improved, the result was not significant ($p = 0.89$) [147]. There are many additional potential strategies for exposure modification in cases of EDE with known environmental contributors, and these should be explored on a case-by-case basis. A full discussion of therapies for the management of the various DE subtypes can be found in the TFOS DEWSII Management and Therapy Report [148].

3.4.3 Ocular Surface Toxicity in the Setting of Chronic Glaucoma Medication Use

Pathophysiology Chronic use of topical glaucoma medications may cause and exacerbate ocular surface disease, with Benzalkonium chloride (BAK) being one main culprit [149]. BAK is a surfactant that disrupts the lipid layer of the tear film, contributing to increased aqueous layer evaporation and overall tear film instability [150]. Low-grade, persistent BAK cytotoxicity impairs corneal and conjunctival epithelial barrier function and contributes to inflammation at the ocular surface [150]. Chronic use of other topical medications, including antimetabolites such as 5-fluorouracil, may also adversely impact the ocular surface [151].

Presentation and Diagnosis Many reports link BAK to burning ocular discomfort [152]. One cross-sectional study of 62 glaucoma patients found that a greater percentage of those using three or more medications had symptoms of shooting ocular pain, dryness, and pruritis measured by Dry Eye Questionnaire-5 (DEQ5) scores > 6 (81.3%) compared to those on fewer than three medications (46.7%, $p = 0.004$) [153]. Medication reconciliation is necessary to confirm the contribution of chronic low-grade iatrogenic toxicity in ocular pain associated with tear-film disruption.

Management Converting to preservative-free glaucoma medications is an important strategy in these cases. A prospective survey of 4107 glaucoma patients found that individuals using preservative-containing drops reported significantly more dose-dependent ocular burning or stinging (40%), compared to those using preservative-free formulations (22%, $p < 0.001$) [152]. A significant reduction in symptoms was observed in the group of patients ($N = 349$) who switched from preservative-containing to preservative-free drops after their baseline visit (82.7% at baseline to 35.8% at follow up, $p < 0.001$) [152].

4 Neuropathic Causes of Ocular Pain

In individuals with persistent ocular surface pain, despite targeted management or in the absence of nociceptive aetiologies, a neuropathic component should be considered. Neuropathic pain (NP) is defined as pain caused by a lesion or a disease of the somatosensory nervous system [154]. Chronic tear film abnormalities, anatomic issues, and/or ocular surface inflammation (from any aetiology), as described above, may lead to the development of chronic changes in corneal nerve structure and function, with resulting NP.

Pathophysiology NP can be classified as peripheral and/or central, depending on the location of dysfunction [peripheral and/or central nervous system (CNS)] [154]. The underlying premise is that corneal nerve damage (from a variety of causes) results in neurogenic inflammation which leads to peripheral sensory nerve sensitisation. Constant peripheral nerve stimulation can then elicit a complex cascade of events in the nociceptive pathways, which through maladaptive neuroplasticity and down-regulation of inhibitory impulses, can lead to sensitisation of the CNS [155]. With central sensitisation, ocular surface pain is no longer coupled with peripheral stimuli. As a result, pain can be perceived spontaneously or inappropriately amplified even in the setting of a normal ocular surface [156].

Aetiologies Neuropathic ocular pain (NOP) can result from a variety of neurologic and inflammatory conditions, as well as a consequence of surgery (e.g. refractive surgery) [9, 157]. Ophthalmic aetiologies include chronic ATD and EDE, infectious keratitis (especially herpetic), and keratopathies due to radiation or trauma [10]. Systemic diseases that have been associated with NOP include diabetes mellitus and small-fibre peripheral neuropathies, trigeminal neuralgia, and inflammatory auto-immune conditions like SS and SLE [10]. In fact, individuals with SS have also been found to have peripheral nerve abnormalities outside of the eye [158]. Other associated conditions include migraine [159], traumatic brain injury [160], and fibromyalgia [161].

Furthermore, many individuals have comorbid depression, anxiety, or post-traumatic stress disorder [162].

Diagnosis NOP is a diagnosis of exclusion. It begins with a medical history, assessing for ocular diseases such as herpes keratitis and recurrent erosion syndrome, systemic diseases such as diabetes, SS, fibromyalgia, and migraine, and neuropathy-inducing medications such as chemotherapeutics [163]. It should be suspected in cases of ocular pain lasting greater than 3 months, and especially when the patient endorses neuropathic-specific features such as ocular surface burning and increased pain with stimuli such as wind and light [162, 164, 165]. Intense symptoms in the context of minimal observable ocular surface disease signs, or a disconnect between reported symptoms and signs are also features that suggest a neuropathic component [166].

Ocular pain can be quantified using a number of validated questionnaires including the OSDI (a subset of questions that ask about various aspects of pain), Neuropathic Pain Symptom Inventory modified for the Eye (NPSI-Eye, questions are more specific for neuropathic pain) [167], or the Ocular Pain Assessment Survey (OPAS, evaluates several facets of pain) [168]. The evaluation of NOP necessitates a complete ocular surface evaluation as documented above. An additional test to consider is corneal aesthesiometry. This can be done in the clinical setting with the use of a cotton wisp or dental floss. Corneal sensation can be qualitatively assessed as none, reduced, normal, or increased. Individuals with NOP often have abnormal sensation, including both increased and decreased sensation from normal. The Cochet-Bonnet and Belmonte aesthesiometers have been used to quantify corneal sensation in the research setting [169].

The anaesthetic test is often used to identify individuals with a central component to pain. The presence or worsening of persistent ocular surface pain after a drop of topical anaesthetic is placed on the ocular surface suggests a central component to the pain [164]. Incomplete improvement in symptoms after topical anaesthetic challenge may indicate a mixed peripheral and central aetiology [10]. Of note, elimination of pain with topical anaesthetic cannot differentiate between nociceptive or peripheral neuropathic causes of pain.

In vivo confocal microscopy (IVCM) can be used to image the cornea, evaluate the sub-basal nerve plexus morphology, and assess for the presence of inflammatory cell infiltrate [163]. In one IVCM analysis, 16 individuals with NOP were found to have decreased sub-basal nerve plexus density compared to controls. Furthermore, micro-neuromas were found in 62.5% of patients with peripheral NOP [170]. Neuromas, which are defined as severed nerves that appear as abrupt fibre endings on IVCM [170], have been described as a specific finding of corneal NOP by one group; however future study is necessary to determine their relevance in this context [10] (Fig. 4b). However, no one finding definitively rules in or out the presence of NOP and thus the diagnosis remains a clinical one that requires holistic consideration of the presentation.

4.1 Treatment of Neuropathic Ocular Pain (NOP)

4.1.1 Topical Therapies to Address Peripheral Sensitisation

Ocular Surface Lubrication Conservative symptomatic treatment should be considered in all aetiologies causing NOP. ATs can decrease the hyperosmolarity of tears and dilute pro-inflammatory mediators, thus halting overstimulation of corneal receptors [10]. PFAT formulations are preferred in cases where frequent lubrication is needed. Decreasing tear evaporation through the use of emulsion-based tears, moisture chamber goggles, and management of concurrent MGD can also ameliorate tear film stability [10]. These first-line options are all generally well tolerated, and a trial-and-error approach is recommended.

Anti-inflammatories Inflammation induced by injury to peripheral nerves can lead to peripheral sensitisation and the amplification of NOP. Thus, anti-inflammatory topical corticosteroids may be considered for short-term treatment [171]. One reported regimen is with Loteprednol 0.5% suspension or gel with a taper of 4 times daily for 2 weeks, followed by two times daily for 2 weeks and then one time daily for 6–12 weeks [10]. Steroid-sparing anti-inflammatory therapies such as topical cyclosporine 0.5%, lifitegrast 5%, and tacrolimus 0.03% have been used as well, with variable efficacy [10, 171]. Details regarding these medications are outlined in Sect. 3.3.1.

Neuro-regenerative Therapy (AST) Regenerative therapy with neurotrophic factors has been studied in individuals with a suspected neuropathic component to pain. The recommended treatment regimen for NOP consists of 20% AST administered up to eight times daily until symptom relief is reported (3–4 months are usually required) followed by a very slow taper over a period of 9–12 months [10]. A retrospective study of 16 individuals with severe photo-allodynia, or painful sensitivity to light, in the context of NOP (aetiology unspecified, all had absence of signs of ocular surface disease on slit lamp examination) found that 8-times daily treatment with 20% AST (mean duration 3.6 ± 2.1 months) resulted in significantly decreased photo-allodynia as reported by a subjective 0–10 scale (mean 8.8 ± 1.1 at baseline to 1.6 ± 1.7; $p = 0.02$) [170]. The capacity of AST to facilitate corneal nerve regeneration was hypothesised to be responsible for the symptomatic improvement noted in those patients. Other products, such as platelet-rich growth factor (PRGF) and recombinant nerve growth factor, help restore

ocular surface health and may also have a potential role in NOP [126, 172].

Amniotic Membrane Transplant (AMT) Cryopreserved amniotic membrane (CAM) graft has also been evaluated in NOP [173]. Amniotic epithelial cells have a neuro-regenerative potential that aids neuronal development and survival through the release of various anti-inflammatory and anti-fibrotic factors. Prokera slim (PKS) and clear (PKC) (Bio-Tissue, Miami, FL) formulations contain a self-retained CAM situated between two polycarbonate rings that allow for sutureless application. The application of PKS/PKC (mean duration 6.4 ± 1.1 days) in ten eyes with peripheral (defined by proparacaine challenge) NOP [defined by corneal nerve damage on IVCM, aetiologies include DE ($N=6$), MGD ($N=3$), and post-refractive surgery ($N=1$)] improved pain severity as measured by VAS [scale 1 (no pain) to 10 (greatest pain)] from baseline (mean VAS 6.3 ± 0.8) to 1.9 ± 0.6 ($p=0.0003$) in one retrospective case series [173]. Patients with adverse effects such as ring dysesthesia (4/10) or premature implant disengagement (2/10) also saw significant improvement in pain severity from mean baseline VAS of 6.8 ± 1.0 to 2.4 ± 0.9 after a mean duration of 4.0 ± 0.7 days use ($p=0.009$) [173]. If the ring cannot be tolerated (ring dysesthesia), the CAM can be repositioned into a BCL [10]. One anecdotal case series reported that 78.5% (11/14) of NOP patients (aetiologies and diagnostic criteria unspecified) who did not tolerate PKS/PKC did tolerate subsequent CAM/BCL [10].

Contact Lenses (CL) The Prosthetic Replacement of the Ocular Surface Ecosystem (*PROSE*, Boston Foundation for Sight) has been studied in individuals with NOP [174]. PROSE is a fluid-filled "tailored oxygen permeable fluorosilicone-acrylate scleral lens designed to replicate the natural ocular surface" [175]. In doing so, it promotes corneal healing by protecting sensitised receptors from external stimuli [10]. For this reason, scleral CL are better suited for relief in those with peripheral, as opposed to centrally mediated NOP. Scleral CL have been reported to disrupt the pain cycle in cases of corneal neuralgia [176]. A case series of 49 individuals reporting photophobia and ocular discomfort in the context of chronic ocular surface disease (range of aetiologies including but not limited to SJS-TEN, OCP, and SS) by unspecified questionnaire found subjective improvement in 75% (photophobia) and 82% (ocular discomfort) with the use of gas permeable scleral CL (Boston Scleral Lens, mean wearing time 13.7 h per day with mean follow up of 33.6 months) [177]. Thirty-three percent of the participants had failed therapy with another type (soft, rigid, or polymethylmethacrylate scleral CL) before the trial. In an anecdotal case series of individuals with post-LASIK corneal neuralgia ($N=2$), NOP symptoms measured by OSDI were subjectively reported to improve with PROSE treatment [178]. It is important to keep in mind that prolonged CL wear may not be tolerated in patients with significant hyperalgesia [163] and it affords a potential infection risk.

4.1.2 Oral Therapies to Address Central and/or Peripheral Sensitisation

If chronic NOP is refractory to topical therapies, the addition of systemic medications should be considered, especially in individuals with a suspected central component or co-morbid pain outside the eye.

Gabapentinoids Gabapentin *(Neurontin)* and pregabalin (*Lyrica*) are commonly used first-line oral therapies for NP [179]. They act as ligands to the α2δ subunit of presynaptic voltage-gated calcium channels in the neuronal cell membrane to decrease calcium influx and subsequently reduce excitatory neurotransmission [180]. Gabapentin is initially administered at 300 mg daily and should be escalated up to 600–900 mg three times per day, as tolerated [181]. This slow titration is often necessary to allow patients to acclimate to the medication effect and increase compliance. An acceptable alternative to gabapentin is pregabalin 75–150 mg given once nightly or up to twice daily [181]. Common side effects of gabapentinoids include drowsiness, dizziness, nausea, blurry vision, or gastrointestinal discomfort. In 36 individuals with NOP secondary to DE (defined by scores > 18 on the painDETECT questionnaire which is validated for determination of a neuropathic component to chronic pain [182]), the addition of 1800–2400 mg daily oral gabapentin to a six-week course of AT and topical CsA treatment resulted in significantly fewer pain symptoms measured by mean OSDI scores (31) when compared to AT and CsA treatment alone (49, $p<0.001$) [183]. A retrospective case series of individuals with NOP secondary to DE defined by specific features including a discordance between symptoms and signs, spontaneous burning or sensitivity to wind and light, and/or persistent pain after the application of topical anaesthesia assessed symptom response to oral gabapentinoids (cumulative daily doses ranged from 900–3600 mg for gabapentin ($N=7$) and 300 mg for pregabalin ($N=1$)) [184]. They reported on overall qualitative relief of subjectively reported nonspecific ocular pain after a 3- to 36-month follow-up period, citing that two individuals had complete relief that persisted for 8 months, three had significant improvement in pain, and one had a slight improvement [184]. Interestingly, the two patients who endorsed complete pain relief also received concomitant oral duloxetine during the study period [184].

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) If relief with gabapentin or pregabalin is inadequate, adjunct

oral SNRIs such as duloxetine (*Cymbalta)* or venlafaxine (*Effexor)* should be considered for their synergistic effect [185]. They act by inhibiting reuptake of serotonin and norepinephrine and are useful adjuvants to treat severe anxiety in the setting of chronic pain [10, 186]. Doses of 20–120 mg/day are appropriate [10]. Their side-effect profile is usually mild, but nausea, headache, dry mouth, dizziness, decreased libido and somnolence or insomnia have been reported [186]. Duloxetine is not recommended for use in those with hepatic or severe renal impairment [186, 187]. An additional agent to consider in the setting of NOP is tramadol (*Ultram).* While its effectiveness has been reported for pain relief in post-herpetic neuralgia and diabetic peripheral neuropathy [188], a recent systematic review concluded that there are insufficient quality data to corroborate its effectiveness in generalised NP [189]. Tramadol also acts as a weak μ-opioid receptor agonist and thus has the potential for misuse [188]. Due to this property, tramadol should be considered in the setting of NOP only after first- and second-line treatment options fail. Doses of 50 mg once or twice daily with gradual increase to a daily maximum of 400 mg have been suggested [10]. Common side effects include nausea, vomiting, constipation, and confusion, especially in the elderly [190].

Tricyclic Antidepressants (TCAs) TCAs (e.g. amitriptyline and its metabolite nortriptyline) may also be used as primary therapies or in conjunction with gabapentinoids. They act similarly to SNRIs by inhibiting the presynaptic reuptake of norepinephrine and serotonin, which reduces sensory perception between the brain and the spinal cord [191]. They also block cholinergic, histaminergic, and adrenergic signalling and sodium channels [192]. TCAs that are secondary amines are recommended as first-line treatment for generalised NP [163] at a dose of 25–150 mg per day [10]. In a randomised double-blind crossover study of 24 individuals with peri-ocular PHN, significant pain relief (measured by VAS, data not provided, $p \leq 0.001$) was noted in 67% of individuals after 3 weeks of amitriptyline (median dose 75 mg) [193]. This pain relief was significantly greater in terms of mean, best, and last week VAS scores when compared to those who had placebo (data not provided, $p \leq 0.0001$) [193]. A double-blind placebo-controlled study found that individuals with PHN (13% with presumed peri-ocular involvement as pain localised to the trigeminal dermatome) had significantly decreased pain symptoms measured by VAS after an 8-week course of amitriptyline (12.5 mg increased in 25 mg increments weekly to a maximum of 200 mg) [194]. Specifically, VAS scores in those who received amitriptyline ($N=11$) and those who received amitriptyline and fluphenazine ($N=12$) decreased from 55.9 ± 19.58 and 47.6 ± 13.43 to 26.6 ± 16.77 ($p < 0.0005$) and 35.41 ± 24.53 ($p=0.04$), while those who received fluphenazine alone ($N=13$) or placebo ($N=13$) had no significant decrease ($p=0.08$, $p=0.34$) [194]. TCAs should be used with caution in patients aged > 65 years due to their potential side effects. These include anticholinergic effects such as dry mouth and eyes, constipation and urinary retention, and the risk of precipitating cardiac abnormalities. Side effects can be minimised by starting with a low dose and slowly titrating up [192]. Nortriptyline may be preferred given its more favourable side-effect profile and comparable efficacy to amitriptyline [195].

4.1.3 Non-invasive Adjuvant Therapies

Transcutaneous Electrical Nerve Stimulation (TENS) Adjuvant treatments should be considered when NOP is refractory to topical and systemic intervention. One such modality is Transcutaneous Electrical Nerve Stimulation (TENS). TENS acts via neuromodulation by conveying electrical current to the peripheral nervous system (PNS) through cutaneous electrodes. It has demonstrated efficacy in alleviating NP in variable conditions [196, 197]. Some speculate that TENS is effective by application of the Gate Control Theory, which describes inhibition of presynaptic nociceptors and ascending pain signals. Others suggest that TENS works through inhibitory modulation of descending pain pathways [198, 199]. One TENS device is the RS-4i Plus Sequential Stimulator (*RS-4i,* RS Medical, Vancouver, WA*)*, which utilises an interferential current generated between electrodes that are set to slightly different frequencies [165]. It uses two pairs of electrodes (4 in total) that are placed bilaterally along the ocular midline above the brow and at the temple. Once applied the current (dose) should be titrated up as tolerated in sub-milliampere (mA) increments. One study of 14 individuals with chronic NOP (defined by specific features of burning, sensitivity to wind or light, and/or a discordance between symptoms and signs of DE) due to various aetiologies reported a significant reduction in mean ocular pain intensity as measured by the Defence and Veterans Pain Rating Scale (DVPRS, 0–10 scale) 5 min after the completion of treatment with RS-4i (30-min duration, beat frequency of 100 Hz to 5 K Hz sine wave mixed with 5.1 kHz sine wave, mean amplitude approximately 11 mA) in both eyes (right eye mean DVPRS score decreased from 4.54 ± 3.18 to 1.92 ± 2.5, $p=0.01$; left eye mean DVPRS score decreased from 4.46 ± 3.36 to 2 ± 2.38, $p=0.01$) [165]. No significant side effects were noted in this trial, although 2 of 14 patients reported epiphora and exacerbation of pain [165].

Another potentially useful TENS device for NOP is *Cefaly* (Cefaly US, Inc, Wilton CT). It is positioned in the central supraorbital region and acts by externally stimulating cutaneous branches of the ophthalmic division of the trigeminal nerve (V1) (Fig. 5). It has demonstrated efficacy in prevention and abortion of migraine and while it is plausible that use benefits migraine-associated NOP, future study is required to quantify its efficacy [200]. TENS is

Fig. 5 Cefaly TENS device applied to the central supraorbital region

contraindicated in pregnant patients and those with epilepsy or implanted devices like cardiac pacemakers and internal defibrillators [165].

4.1.4 Invasive Adjuvant Therapies

Periocular Botulinum Toxin and Subcutaneous Anti-calcitonin Gene-related Peptide Injections If pain is unresponsive to TENS or its use is contraindicated, other adjuvant measures may be taken. Botulinum toxin type A (BoNT-A) is approved for use in individuals with chronic migraine who have failed prophylactic medications. BoNT-A is speculated to modulate pain by inhibiting the release of inflammatory mediators such as calcitonin gene-related peptide (CGRP) [201]. BoNT-A (intramuscular injection of 155–195 units to at least 31 sites across 7 anterior and posterior head and neck muscles [202]) is typically administered at 3-month intervals. Of note, several drugs can interfere with the release of the toxin, so thorough medication reconciliation is recommended [203]. A retrospective review of individuals with chronic migraine who received BoNT-A injections found significant improvements, not only in migraine pain, but also in photophobia and symptoms of dryness [204]. Specifically, photophobia scores decreased by a mean of 2.64 ± 2.56 (95% CI -3.18 to -2.11, $p < 0.001$) and dryness scores by a mean of 0.716 ± 2.11 (95% CI -1.18 to -0.249, $p = 0.003$) over a mean 3- $\pm$ 2.4-year period [204]. The improvement in symptoms was independent of improvement in tear volume [205], suggesting that factors beyond tear health drove the effect. We have modified the BoNT-A protocol to treat individuals with suspected NOP but without chronic migraine. This modification for targeted periocular chemo-denervation consists of intramuscular injection of 35 U of BoNT-A delivered to seven sites (10 U to bilateral corrugators, 5 U to the procerus, 20 U to bilateral medial and lateral frontalis muscles). In a preliminary assessment of six patients with severe photophobia and NOP secondary to DE (all had frequent or constant discomfort related to dryness defined by DEQ5 questionnaire), this modified BoNT-A injection protocol resulted in significantly reduced ocular discomfort [206]. Specifically, mean scores for intensity of discomfort at the end of the day (0–5 scale) improved from 4.67 to 2.83 at 1-month post-injection ($p = 0.03$) [206]. Furthermore, mean scores (0–5 scale) documenting how often eyes felt discomfort in the past month decreased from 3.83 to 2.33 ($p = 0.05$) in the same time period [206]. The protocol was generally well tolerated with no significant adverse effects except for the development of post-injection brow ptosis in one individual [206].

Via similar mechanisms, recently approved anti-calcitonin gene-related peptide (CGRP) agents (e.g. erenumab, fremanezumab, and galcanezumab) may have a role in NOP but no data are available in this regard.

Periocular Nerve Blocks Periocular nerve blocks have also been used in the treatment of NP, especially in patients with pain confined to a specific anatomical area. Applied to NOP, these include blocking supraorbital, supratrochlear, infratrochlear and infraorbital nerves, targeting cutaneous areas overlying terminal branches of these four nerves [184]. Typically, a combination of anaesthetic and anti-inflammatory corticosteroid is used [184]. In our clinic, we use 4 mL of 0.5% bupivacaine mixed with 1 mL of 80 mg/mL methylprednisolone acetate. A review of outcomes in individuals with NOP (defined as above) refractory to traditional treatments reported that bupivacaine/methylprednisolone periocular nerve blocks provided immediate pain relief in 7 of 11 patients, with transient effect lasting from hours to months [184]. Similarly, a case report described the administration of periocular nerve blocks that provided substantial relief in a 66-year-old male suffering from chronic uncontrolled NOP (defined by hyperalgesia and allodynia in the absence of remarkable slit-lamp exam findings) [207]. The patient noted complete resolution of symptoms for 7 months after administration. No significant complications with periocular nerve blocks have been noted, although the all the risks associated with periocular injections and the medications utilised do apply [184, 207].

Trigeminal Nerve Stimulation—Intrathecal Pain Pump One final invasive adjuvant option for recalcitrant NOP is electrical stimulation of the trigeminal ganglion through an implantable electrode combined with a high cervical intrathecal pain pump (bupivacaine and low-dose fentanyl). The trigeminal nerve stimulator initially provides short-term pain relief while the intrathecal pain pump provides a long-term

pain relief. Potential complications include post-dural puncture headache after the insertion of the implant as well as caudad migration of the intrathecal catheter, which then requires catheter revision. This modality has been reported to have efficacy in the context of refractory NOP in post-LASIK patients [208, 209]. Due to the invasive application and addictive potential it should only be considered after other options have been exhausted.

4.1.5 Non-pharmacological Approaches

In addition to pharmacologic therapy, non-pharmacological approaches such as cognitive behavioural therapy (CBT), exercise, and acupuncture may all provide supplementary pain relief in individuals with NOP. In fact, individuals with ocular pain have been found to have maladaptive coping mechanisms [210] and as such, CBT may be particularly beneficial as it can enable the patient to better cope with the psychological sequelae of chronic pain [171]. While there is a need for randomised controlled trials of CBT specifically with regards to chronic ocular pain, the cognitive behavioural approach is a safe method to promote conceptualisation of neuropathic pain with the goals of regulating mood and increasing overall quality of life [211].

5 Conclusion

Ocular surface pain may be caused by a variety of infectious, inflammatory, anatomical, traumatic, and iatrogenic aetiologies. Nociceptive ocular surface pain often results from disease of the eyelids, conjunctivae, and tear film. Neuropathic pain can occur in the setting of any chronic ocular or systemic disease. It is critical to have a stepladder approach to diagnosis of ocular surface pain in order to optimise management. First, nociceptive causes need to be evaluated for and treated. In patients with ongoing ocular surface pain with the appropriate risk factors, clinical findings, and poor response to topical therapy, a neuropathic component must be considered. The treatment of neuropathic pain is multimodal and often includes topical, systemic, and adjuvant therapies. In addition, psychosocial factors contributing to pain must be considered and appropriately addressed. As such, an interdisciplinary approach to management characterised by the collaboration of the ophthalmologist with other medical specialties and the collective establishment of an individualised treatment plan is essential. Finally, it is critical for both the patient and the physician to set realistic treatment goals and manage expectations so the patient can achieve maximal quality of life. Further studies are needed to develop diagnostic techniques to differentiate between nociceptive and neuropathic sources of ocular surface pain and to test which therapies are most efficacious in treating NOP.

Compliance with Ethical Standards

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