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Review. Neuropathic Pain and Dry Eye

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Abstract

Dry eye is a common, multifactorial disease currently diagnosed by a combination of symptoms and signs. Its epidemiology and clinical presentation have many similarities with neuropathic pain outside the eye. This review highlights the similarities between dry eye and neuropathic pain, focusing on clinical features, somatosensory function, and underlying pathophysiology. Implications of these similarities on the diagnosis and treatment of dry eye are discussed.

Keywords

Dry eye; Genetics; Inflammation; Nerve sensitization; Neuropathic pain; Treatment

1. Introduction

Dry eye (DE) is a diagnosis that encompasses a wide variety of clinical manifestations that include ocular sensations of dryness, discomfort, pain, and ocular surface disturbances such

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as decreased tear production and increased tear evaporation.[1, 2] Other symptoms that frequently accompany dryness include fluctuating and/or blurry vision and ocular dysesthesias, often described as "burning," "tender," and "aching."[3, 4] Prior to 1990, DE was mostly discussed in the context of Sjögren's syndrome (SS) and other autoimmune diseases. This changed after population-based studies in various countries, including the US,[5, 6] Australia,[7] Japan,[8] Indonesia,[9] and China,[10] found that DE symptoms were a frequent finding in the general population. Although some studies showed that ocular surface abnormalities, such as fast tear film breakup time, low Schirmer score, and meibomian gland abnormalities, often accompanied DE symptoms,[10] subsequent studies demonstrated that for many patients, DE symptoms were not related to these DE signs.[11, 12]

Putting this information in context, it becomes apparent that DE is a complex, multifactorial, and heterogeneous disease that may be better understood and treated if grouped into various sub-types. For example, the presentation and underlying pathophysiology of SS and graft-versus-host-associated DE is very different from that in patients whose DE symptoms exist with minimal signs of ocular surface disease. In fact, the latter sub-type of DE has much in common with neuropathic pain (NP) conditions outside the eye (Table 1). This review highlights the similarities between NP outside the eye with some forms of DE and focus on implications with regards to the further diagnosis and treatment of these DE subtypes.

2. Overview of dry eye

2.1. Epidemiology

DE symptoms are common complaints in the general population. They are more frequently found in women than in men,[5] and with increasing age.[13] In the US, a population-based study out of Beaver Dam, Wisconsin, found that 14.4% of individuals between the ages of 48 and 91 years reported DE symptoms.[5] A similar frequency of symptoms was found in Salisbury, Maryland, with 14.6% of the population reporting one or more DE symptom often or all the time.[6] These numbers were even higher in Asia, where 34% of participants in a Taiwanese study[10] and 28% of participants in an Indonesian study[9] reported one or more DE symptoms often or all of the time. Ocular surface abnormalities are also common in the general population. In Melbourne, Australia, 11% of individuals had rose bengal staining scores greater than 3, 16% had Schirmer scores less than 8 mm, and 9% had tear film breakup times less than 8 seconds.[7]

Hospital-based studies have found even higher frequencies of both DE symptoms and signs.[12, 14] In one study of an older (mean age: 69), predominantly male veteran population, 91% of individuals had at least one ocular surface abnormality on standardized testing.[11] Overall, evaporative DE is more common than aqueous tear-deficient DE.[11, 15] In fact, in Asia, over 60% of the population had at least one eyelid margin abnormality, including abnormal vascularity, plugging, collarettes, gland dropout, and/or abnormal meibum quality.[16, 17] Beyond meibomian gland health, anatomic abnormalities such as eyelid laxity and conjuctivochalasis are commonly seen in older individuals and have been found to be associated with DE symptoms.[18–22]

2.2. Clinical manifestations

DE symptoms are varied and include complaints of dysesthesias (unpleasant abnormal sensations) which can be described as “dryness,” “burning,” “aching,” “tenderness,” “soreness,” etc.[4] These sensations can occur spontaneously or can be evoked by wind, cold, light, air pollution, and low humidity.[4, 23] DE symptoms also include visual complaints, often described as blurry vision, poor visual quality, or fluctuating vision. Some patients also report tearing. These constellations of symptoms have been found to impact quality of life, reducing both physical and mental functioning.[24] In fact, utility assessment has estimated that severe DE symptoms are as debilitating as severe angina.[25] Ocular signs of DE are also varied, and, therefore, a comprehensive assessment of the ocular surface is typically performed when evaluating a patient with DE symptoms. This includes assessments of eyelid function and anatomy (apposition, laxity, vascularity), meibomian gland parameters (atrophy, meibum quality), tear metrics (production, evaporation), and ocular surface disruption (with the use of various stains such as fluorescein, rose bengal, or lissamine green). More recently, point-of-care tests can measure tear osmolarity (TearLab, San Diego, CA), tear lactoferrin (Advanced Tear Diagnostics, Birmingham, AL), and ocular surface matrix metalloproteinase 9 (Inflammadry, RPS, Tampa, FL). Interestingly, just as with traditional DE signs, these newer diagnostics also often correlate poorly with patient complaints suggesting multiple subtypes of DE.[26, 27]

3. Overview of chronic neuropathic pain (NP) outside the eye

3.1. Definition

Pain, as defined by the International Association for the Study of Pain (IASP), is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”[28] Pain disorders are broadly categorized into two groups: nociceptive pain and neuropathic pain. Nociceptive pain is defined as a pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.[28] It is usually transient in nature. Outside the eye, examples of nociceptive pain are pain in the setting of acute trauma or surgery, or tissue inflammation.

NP is defined as pain caused by a lesion or disease of the somatosensory nervous system.[28] Several chronic pain entities are considered to be neuropathic in nature. Some of these have a known underlying pathology, such as diabetic neuropathy, post-herpetic neuralgia, and some cases of chronic post-operative pain that involve injury or trauma to nerves. Others have set clinical criteria, but evidence for an underlying pathophysiology is lacking. These include syndromes such as atypical facial pain (including some cases of temporomandibular joint disorders), chronic fatigue, irritable bowel, interstitial cystitis, vulvodynia, burning mouth, and fibromyalgia.[29, 30] Interestingly, even though these disorders manifest in different parts of the body, they are often found to co-exist and are likely tied to each other by a unifying pathophysiology linked to neuropathic mechanisms, i.e., peripheral and/or central sensitization.

3.2. Epidemiology

Chronic pain is a common complaint in the United States, with over 100 million Americans affected at a cost of over $500 billion in health care and lost productivity.[29] Chronic pain is estimated to affect 11.2% or 25.3 million adults within the United States, as defined by the National Health Interview Survey as daily pain experienced over the past 3 months.[31] Within pain, the American Academy of Pain Management reports that back pain is most common (27%), followed by severe headache or migraine pain (15%), neck pain (15%), and facial ache or pain (4%).[32, 33]

3.3. Clinical manifestations

The diagnosis of NP is often associated with a demonstrable lesion (by history, on imaging, biopsy, or neurophysiology [nerve conduction]); or a disease that satisfies established neurological criteria (stroke, diabetes, genetic abnormality).[28] In many cases, however, the term NP is used as a clinical description. Several clinical features are more common in patients with a diagnosis of neuropathic as opposed to nociceptive pain.[34] These include using specific terms to describe the quality of pain, such as “burning,” “shooting,” “pins and needles,” and “itching.” The pain is typically spontaneous (no obvious inciting event) and may be continuous or episodic (the latter often being described as “stabbing,” “shooting,” or “electric shock”). Evoked pain is also a common feature in patients with neuropathic pain,[34] both over the initial site of injury and also in the surrounding areas, especially with expansion of the receptive field believed to be due to central sensitization. Pain can be evoked by a stimulus (such as light touch) that normally does not cause pain (i.e., allodynia), or exaggerated pain can be evoked by a stimulus (such as noxious pin prick) that is in the painful range but is reported at a higher intensity than is normally expected (i.e., hyperalgesia). These symptoms and signs may occur in the setting of an otherwise normal clinical examination.[35]

4. Similarities between some subtypes of dry eye and neuropathic pain

Many patients report that their ocular dysesthesias are painful.[4] Others do not consider sensations of dryness to be painful, but use words describing “discomfort.” Irrespective, many similarities exist between DE symptoms and NP outside the eye with respect to clinical characteristics, findings on somatosensory testing, and underlying biologic mechanisms.

4.1. Clinical similarities

4.1.1. Similar descriptors are used in dry eye and neuropathic pain—Most DE questionnaires combine questions about pain with other DE symptoms to arrive at a total symptom score.[36] Therefore, it is often difficult to parse out the frequency of ocular pain in those with symptoms of dryness. However, several studies have focused specifically on this point. For example, we asked veterans to rate the intensity of their average and worst eye pain over a 1-week recall period using a numerical rating scale (NRS) anchored at “0” for “no pain sensation” and at “10” for “the most intense eye pain imaginable.” This type of 0–10 NRS has been validated as a measure of pain intensity across multiple populations[37–41] and has been recommended for use as the primary outcome metric in clinical trials for

chronic pain.[42] In a cohort of 154 veterans with mild or greater DE symptoms (dry eye questionnaire 5 [DEQ5] score ≥6), and based on previously defined cut-offs in diabetic peripheral neuropathy[43], 11% (n = 17) of subjects reported no pain (NRS = 0) on average over a 1-week recall period, 36% (n = 56) reported mild pain (NRS 1 – 3), 34% (n = 52) reported moderate pain (NRS 4 – 6), and 19% (n = 29) reported severe pain (NRS 7 – 10).[4] A similar pattern was seen for worst pain over a 1-week recall period. In a different population, Vehof et al. evaluated ocular pain in white female volunteers from the Twins UK Adult Registry at St Thomas' Hospital, London. The group used the sum of the first three questions of the ocular surface disease index (OSDI) to investigate ocular pain (i.e., 1: eyes that are sensitive to light, 2: eyes that feel gritty, and 3: painful or sore eyes). A sum score of 3 or higher was regarded as having DE pain symptoms. Of 689 women who filled out the OSDI, 118 (17.1%) had DE pain symptoms.[44]

Other studies have focused on ocular pain symptoms in general (non-hospital based) populations. For example, as part of the Salisbury Eye Evaluation, a questionnaire was administered to residents of Salisbury, Maryland, that asked about the frequency (rarely, sometimes, often, or all the time) of six symptoms (dry, gritty or sandy, burn, red, crust, stick shut).[6] Of 2482 volunteers, approximately 33% reported grittiness and 25% reported burning sometimes, often, or all the time. In the Blue Mountains Eye Study, Australian participants answered questions about the severity of dryness, grittiness, itchiness, and discomfort over a 12-month recall period.[45] Of 1172 volunteers, mild, moderate, or severe grittiness was reported by approximately 25% and discomfort by approximately 30%. Similar to DE symptoms in general, ocular pain symptoms were more severe in women than in men.[45] In another Australian study from Melborne, mild, moderate, or severe ocular discomfort was reported by 25%, and photophobia by 50%, of the approximately 890 participants.[7]

We have also used validated pain questionnaires to further characterize the quality and severity of the ocular pain reported by individuals with other DE symptoms. For example, the short-form McGill Pain Questionnaire (sf-MPQ)[46] characterizes the severity (mild, moderate, severe) and quality of pain using 15 descriptors (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting, tiring-exhausting, sickening, fearful, and/or punishing-cruel). We found that 82% of individuals with DE symptoms endorsed one or more of these qualities when describing their eye symptoms.[4] Descriptors that were most common included "tiring-exhausting" (56%), "aching" (56%), and "hot burning" (53%).[4] In fact, the distribution and frequency of ocular pain descriptors used by our population with DE symptoms was similar to that of a population with central NP.[47] We also applied a modified version of the Neuropathic Pain Symptom Inventory[34], which we termed NPSI-Eye, to the study of ocular pain.[4] The NPSI has been used in a number of pain patient populations to assess the severity of NP-related complaints, including the quality of spontaneous pain and the severity of evoked pain.[34, 48] In our modified version, the spontaneous pain qualities were kept the same, but the pain-evoking stimuli were changed from brushing, pressure, or contact with cold on the skin to light, change in temperature, or wind on the eye. These environmental elements were selected because they are well-known triggers of ocular dysesthesias, appearing in other DE questionnaires, such as the OSDI.[36] Spontaneous burning pain was a frequent complaint in our cohort with DE symptoms,[4] as it was in individuals with chronic NP conditions.[49] Similar to other

studies[7, 44], a subset of our patients also reported evoked pain to wind and light[50], consistent with a subtype of DE with NP. Ocular pain assessment survey (OPAS) is another validated eye pain questionnaire that has been used in the clinic to detect and follow patients with neuropathic ocular pain (NOP).[51] Table 2 summarizes features that suggest a neuropathic component to DE symptoms.

4.1.2. The natural history of dry eye and neuropathic pain are similar—NP tends to be chronic and disconnected in time from peripheral tissue abnormalities, as maladaptive changes in peripheral and central somatosensory nerves can persist after the precipitating injury (e.g., surgery, viral infection, trauma, metabolic disease) has resolved.[35] Similarly, discordance between ocular symptoms and signs is frequently seen in DE.[52] For example, similar to observations on persistent post-surgical pain, chronic DE symptoms in the setting of corneal nerve injury despite a normal ocular surface exam are common after refractive surgery, particularly after laser-assisted in situ keratomileusis (LASIK).[53] Like post-viral pain, chronic ocular pain and headache are common in patients with a history of herpes zoster ophthalmicus long after the eye findings have resolved.[54] We found that patients with idiopathic DE symptoms who also report NOP complaints, including burning and evoked pain to wind and light, have a more severe and chronic DE symptom course[52,55] and respond less well to topical therapy with artificial tears.[56]

4.1.3. DE symptoms are co-morbid with other chronic neuropathic pain conditions—DE symptoms are often found in those with other chronic pain conditions, both in male[57] and female[58] populations. DE symptoms were more severe in those with DE and at least one chronic non-ocular pain condition (mean OSDI score 46) compared to those with DE and no other chronic pain conditions (mean OSDI score 34; P-value<0.0005).[59] Interestingly, ocular signs were similar or less severe in those with one or more co-morbid chronic pain condition compared to those without this association. In fact, the presence of a chronic non-ocular pain condition was the most significant predictor of discordance between DE symptoms and signs, with symptoms greatly outnumbering signs.[52] This is similar to what is seen in NP outside the eye where pain complaints frequently present without peripheral tissue abnormalities.[35]

4.1.4. Dry eye and neuropathic pain symptoms are co-morbid with other conditions impacting pain amplification and psychological distress (e.g., depression, anxiety, fatigue and sleep disturbance)—As is common in other chronic NP conditions, several groups have found that depression and anxiety are frequently co-morbid in individuals with DE symptoms but not with DE signs.[60–63] In fact, depression was more closely associated with DE symptoms in those with normal tear production.[62] In a Veterans Affairs cohort, we found that DE symptoms (measured by the DEQ5 and OSDI) aligned more closely with non-ocular pain and post-traumatic stress disorder (PTSD) scores than DE signs, accounting for 36% and 40% of variability in questionnaire scores, respectively.[64] In fact, this relationship was strongest in individuals with NOP complaints.[65] In a similar manner, insomnia has been found to be co-morbid with both DE symptoms and NP.[66,67]

4.2. Similarities in somatosensory abnormalities observed for dry eye and neuropathic pain

An important feature of NP is altered somatosensory function within the area of spontaneous pain reported. Evidence of hypoesthesia (i.e., reduced sensitivity to mechanical or thermal stimuli) in a neuroanatomically plausible area based on the location of suspected neural lesion or disease, is necessary for "probable" or "definite" NP [68] and hyperalgesia (i.e., increased pain from a stimulus that normally provokes pain) is also often reported. This scenario is commonly seen in diabetes, where patients report spontaneous painful sensations in the lower extremities but have reduced sensation on exam. An analogous situation is seen in the eye after LASIK-associated nerve injury where hypoesthesia and DE symptoms are common findings after the procedure.[69]

Another salient feature of NP can be secondary hyperalgesia (expansion of the receptive field believed to be due to central sensitization), which is an increase in evoked pain sensitivity in the uninjured region surrounding the site of direct injury.[70] In the eye, a comparable scenario may be seen by the co-existence of DE, migraines, and other pain conditions in the face or head.[58,71,72]

4.2.1. Patients with dry eye and neuropathic pain both have altered nerve anatomy—In vivo confocal microscopy (IVCM) allows the visualization of sub-basal corneal nerves. Morphological differences in sub-basal corneal nerves have been found in individuals with SS and non-SS-associated DE compared to controls. While most studies reported that patients with DE had reduced nerve densities[73–76] compared to controls, others found no differences[77–79] or increased nerve densities.[80] Overall, most studies found lower nerve density in SS patients compared to non-SS DE patients and controls.[81] Other morphologic abnormalities have also been described in DE, including nerve spouting and nerve growth cone-like structures,[78,79] increased thickness,[79] tortuosity,[80,82–84] and beading.[82,83] Interestingly, while some studies reported a positive correlation between nerve density and corneal sensitivity,[73,82] others did not find a relationship between corneal nerve structure and function.[77,79] As in NP, such discrepancies are not uncommon. In fact, diagnostic testing often yields varying, inconclusive, and even inconsistent data when patients suspected of having pain due to a neuropathic etiology are evaluated.[28] More recently, IVCM technology was applied in individuals with suspected NOP. Sub-basal nerve parameters were found to be decreased in 6 patients with corneal allodynia associated with a number of conditions (dry eye, recurrent corneal erosion syndrome, exposure to ultraviolet radiation, and Accutane use) compared to 15 healthy controls.[85]

Individuals with other types of chronic pain thought to be neuropathic in origin also have structural abnormalities on corneal confocal microscopy examination. For example, individuals with fibromyalgia were found to have significantly decreased nerve fiber length, density and thickness, and branching of corneal nerves as compared to age- and gender-matched controls.[86,87] Corneal nerve fiber density was also significantly lower in patients with migraine headache compared to controls.[88] A point to consider when interpreting these data, however, is that patients with migraine and fibromyalgia frequently report DE symptoms that have neuropathic features (discordance between symptoms and signs of dry

eye, non-response to therapies that target the ocular surface, descriptors of spontaneous burning pain, sensitivity to light and wind).[88]

Another example of nerve abnormalities seen in individuals with NP comes from brain magnetic resonance imaging (MRI) studies. In humans with painful trigeminal neuropathy, imaging revealed discrete alterations in the anatomy of primary synapses in the spinal trigeminal subnucleus caudalis and decreases in regional and higher brain center (thalamus, insula and cortex) gray matter volume.[89,91] The same authors found that, in contrast to the anatomical changes at the level of the synapses, at the spinal trigeminal subnucleus the anatomy of primary afferents and efferent fibers was unaffected,[89] except for changes in trigeminal nerve volume (decreased in neuralgia, increased in neuropathy). In comparison, no changes in trigeminal nerve volume were found in patients with non-NP in the face.[91]

4.2.2. Patients with dry eye and neuropathic pain both have abnormalities on quantitative sensory testing—Individuals with NP often have lower pain thresholds and experience pain at a greater intensity than those without NP.[92,93] These alterations in pain perception are usually widespread and not limited to a specific area of the body,[29] indicating a centralized somatosensory processing disorder. Patients with DE have likewise been found to have local (corneal) and systemic (forearm) sensory alterations.[44,94,95] The Belmonte aesthesiometer has been used to evaluate corneal sensitivity to mechanical, chemical and thermal stimuli.[96] Some studies found reduced corneal sensitivity to mechanical, chemical, and thermal stimuli in those with DE compared to controls,[73,97] while others found increased sensitivity to mechanical stimuli.[79,94,98,99] As above, such discrepancies are common when patients with NP are evaluated, as both hypoesthesia and hyperesthesia can be clinical features of the disease.

Individuals with DE have also been found to have increased pain sensitivity outside the eye. In a study in British women, subjects with eye pain had decreased heat pain tolerance over the forearm compared to those without eye pain.[44] In a primarily male veteran population, several pain sensitivity metrics, including cold pain thresholds, ratings of pain intensity to threshold and suprathreshold thermal noxious stimuli, and temporal summation of noxious heat, correlated with measures of both ocular pain and severity of DE symptoms.[95] In addition, using the Pain Sensitivity Questionnaire, Li et al. demonstrated that higher pain sensitivity scores significantly associated with increased ocular dryness and discomfort scores (quantified with the OSDI).[100] Taken together, this suggests that “dry eye” is likely not a disorder limited only to the ocular surface but can also include both local and widespread somatosensory dysfunction.

5. Similarities underlying mechanisms in dry eye and neuropathic pain

5.1. Inflammation and neurogenic inflammation (interactions between somatosensory neurons and supporting cells)

5.1.1. Supporting cells—Nociceptors are in constant contact and interaction with supporting cells, which in the periphery include Schwann cells and keratinocytes. These supporting cells respond to their environment and, after injury, release a variety of molecules, including adenosine 5′-triphosphate (ATP), nerve growth factor (NGF),

prostaglandin (PG) E_2, and matrix metalloproteinase (MMP) 9.[101] Centrally, glial cells, such as microglia, astrocytes, and oligodendrocytes, interact with and modulate central neurons. As in the periphery, microglia rapidly respond to peripheral nerve injury[101] and produce a variety of pro- inflammatory molecules such as tumor necrosis factor (TNF)α, interleukin (IL)1β, and PGE_2.[35] Astrocytes too activate after nerve injury, with a subsequent loss in the ability to regulate levels of extracellular potassium and glutamate (an excitatory neurotransmitter) with resulting neuronal hyperexcitability.[101] In the eye, corneal epithelium plays a similar role to Schwann cells and keratinocytes.[102] For example, corneal epithelial cells are important in recycling nerve endings under normal conditions. As such, it is likely that injured or altered corneal epithelium may contribute to pathophysiologic changes in nerves in DE, in a fashion analogous to supporting cell alterations in non-ocular NP.

5.1.2. Inflammation—Neurogenic inflammation arises from the local release of inflammatory mediators from damaged epithelial cells (ATP, histamine, prostaglandins, bradykinin) and peripheral neurons (Substance P [SP], calcitonin gene-related peptide [CGRP], neurokinin A) as a result of injury.[103] These mediators recruit inflammatory cells, which add to the pro-inflammatory environment by secreting TNFα and IL1β. Peripheral neuron terminals contain receptors for these mediators, and through protein kinase pathways, ion channels become phosphorylated, enhancing their function, and new ion channels are made via transcription and translation (Fig. 1). Electrophysiologically, these changes manifest as increased responsiveness to normal input and/or recruitment of a response to normally subthreshold inputs, both hallmarks of sensitization.[28]

With regard to DE, many mediators involved in neurogenic inflammation, such as TNFα, IL1, IL6,[104,105] PGE_2,[106,107] MMP-9,[108] and NGF,[109] are elevated in tears of patients with DE. Furthermore, T cells are detected in the conjunctivae of DE patients.[110] A pro-inflammatory environment has been found to sensitize peripheral corneal nociceptors in a fashion similar to that seen elsewhere in the body.[111]

5.2. Evidence of peripheral sensitization

The cornea is innervated by the primary sensory neurons coming off the ophthalmic branch of the trigeminal nerve. Corneal nociceptors are predominantly unmyelinated C fibers, with myelinated Aδ fibers also present to a lesser extent.[112] Polymodal nociceptors are the most frequent sub-type (~70%) and sense chemical, thermal, and endogenous inflammatory mediators through interactions with transient receptor potential cation channel subfamily V member 1 (TRPV1, a non-specific cation channel) on their terminal membranes.[111]

Aδ mechanoreceptors (~20%) sense mechanical stimuli, while C-fiber cold thermoreceptors (~10%) sense temperature changes through another non-specific cation channel, TRPM8.[111,113] Corneal nociceptors' terminal nerve endings interact with the tear film and are thus susceptible to repeated damage under conditions of inflammation or repetitive environmental injury. Recurrent injury is hypothesized to lead to maladaptive neuronal plasticity and the development of NOP. Prolonged and intense inflammation and ongoing input of nociception may lead to sensitization of the peripheral and central somatosensory pathways.

Several changes occur with peripheral sensitization, including modifications in gene expression due to alterations in translation, or post-translational modification of signaling molecules, including kinases and ion channels onto the nerve membrane.[114] On a molecular level, modifications to TRPV1 lead to reduced firing threshold and enhance neuronal excitability. Neuroplastic changes include the emergence of ectopic firing of nerve fibers, spontaneous generation of action potentials, aberrantly enhanced conduction of signals, increased excitatory neurotransmitter release at presynaptic terminals, as well as nerve sprouting and rewiring, and conversion of non-nociceptive sensory afferent into fibers exhibiting nociceptive phenotype. Similar correlates have been found in the cornea. For example, corneal polymodal nociceptors were found to sensitize, with increased transduction and conduction, after injury and when exposed to an inflammatory milieu.[111,115] In a similar manner, lacrimal gland transection was found to sensitize cold thermal receptors with a shift in the cooling threshold to warmer values, and with an increased peak frequency of discharge to cooling.[116] Fig. 1 depicts potential peripheral mechanisms that drive chronic DE symptoms and ocular pain.

5.3. Evidence of central sensitization

The central neuronal changes that manifest in enhanced synaptic transmission of pain signals via reduced post-synaptic activation thresholds and increased post-synaptic excitability generate further abnormal signal amplification (or even spontaneous pain), and are similar to those seen in peripheral sensitization. These changes also include altered gene expression and post-translational modifications of signaling cascades (such as those mediated via cytosolic calcium and the protein kinase C), modifications in the opening of ion channels, generation of inflammatory mediators (prostaglandins, nitric oxide) and anatomic reorganization in the dorsal horns of the spinal cord or higher centers.[114,117]

Overstimulation and enhanced opening of N-methyl-D-aspartate (NMDA) glutamate receptor, driven by the prolonged and intense input of nociceptive signals and release of excitatory neurotransmitters such as glutamate and SP, play an important role in the generation and maintenance of central sensitization. Microglia may further activate the NMDA receptor by producing quinolinic acid (QA) and releasing pro-inflammatory cytokines. Beyond its effect on the NMDA receptor, QA also inhibits the function of astrocytes, which would normally take up excess glutamate, leading to a build-up of this excitatory mediator.

The ascending pathways that convey pain are modulated by descending pathways that can mediate analgesia when inhibitory, creating a negative feedback loop. Attenuation of descending inhibitory pathways may further enhance central sensitization and pain perception. Normally, interneurons within the central nervous system release neurotransmitters including gamma amino butyric acid (GABA) and glycine, which inhibit nociceptive signaling.[118] After a noxious insult, GABA has less of an inhibitory influence on ascending pathways[119] partially due to changes in chloride currents. This lack of inhibition leads to increased ascending pain pathway signals and helps maintain the chronic pain state.[120,121]

Various correlates to these pathophysiological findings have been found in DE. For example, lacrimal gland removal in rats led to enlarged, convergent periorbital sensory receptive fields, a finding consistent with central sensitization.[122] GABA receptor activation inhibited nociceptive neuronal activity in spinal trigeminal Vi/Vc and Vc/C_1 nuclei as a response to CO_2 exposure on the ocular surface.[123] Conversely, a loss of the inhibitory GABA-mediated chloride currents led to an upregulation of ascending pain signals and heightened painful responses.

When changes occur at the level of the central nervous system, the perception of pain is disproportional to the initial peripheral stimulus and may persist after the initial peripheral pathology has resolved. Discordant DE (discrepancies between severity of signs and symptoms) is common and is associated with specific systemic profiles such as chronic pain, depression, and anxiety.[52] Many affected patients have clinical correlates of sensitization, including spontaneous eye pain, hyperalgesia (evoked pain with wind), cold induced pain (cold allodynia) and photo-allodynia (evoked pain with light).[124] Fig. 2 depicts potential central mechanisms that drive chronic DE symptoms and ocular pain after exposure to a non-noxious stimuli (light or wind).

5.4. Heritability – shared genetic factors

Genetic polymorphisms underlie individual differences in somatosensory processing, pain perception, and the development of persistent pain syndromes.[125–128] Thus, many forms of chronic NP are heritable. Relevant to DE, polymorphisms in TRPM8, IL1, and IL6R have been implicated in both pain perception and DE.[113,129–136] A large twin study utilizing the Twins UK database identified shared genetic factors common to DE, irritable bowel syndrome, fibromyalgia (chronic widespread pain), and vulvodynia. The study results show that DE and these other disorders share two latent genetic factors with an estimated overall heritability of 66%.[137] There is biologic plausibility that functional alterations in inflammatory and other genes would affect the function of peripheral and central neurons common to these co-morbid conditions.[138–141]

6. Novel approaches in the diagnosis and treatment of neuropathic ocular pain-subtype of dry eye based on these similarities

A better understanding of the neurobiology underlying DE can improve our diagnosis and treatment algorithms. A necessary first step is the evaluation of ocular symptoms and signs for discordance suggesting an underlying NP etiology. This observation would then be followed by an assessment of somatosensory function in patients with NP subtype of DE symptoms.

6. 1. Assessing ocular pain

Pain questionnaires that are specific for eye pain can be immediately incorporated into clinical practice to help clinicians gauge the contribution of nerve activation to the DE phenotype. Pain questionnaires are commonly used by pain specialists to assess features of NP in non-ocular pain conditions. We and others have demonstrated that such questionnaires can be easily adapted to assess ocular pain.[4,51] Specifically, descriptors suggestive of a

neuropathic component to the pain, such as burning ocular pain and sensitivity to wind and light, have been found to correlate with other metrics of somatosensory alterations (aesthesiometry[94,95], persistent pain after proparicaine[124]), providing criterion validity of their use.[142]

6.2. Assessing somatosensory function in the clinic (cursory)

A cost-effective and quick test that can be performed in the clinic to assess somatosensory function is evaluation of corneal sensation with a cotton tip or dental floss. While this is a qualitative test, the report of no sensation or the report of extreme sensitivity to light touch (tactile allodynia) points to somatosensory pathway dysfunction, such as that seen in various peripheral and central neuropathic states.[68,93] Persistent pain after placement of topical anesthetic onto the eye surface also points to a central etiology,[143] as peripheral topical anesthetics quiet the firing of peripheral nociceptors. Other features suggestive of somatosensory dysfunction include a disconnect between symptoms and signs of DE (more symptoms than signs)[52] and a lack of symptom improvement with topical therapy.[56] While none of these metrics are pathognomonic of NP (which would require advanced imaging or electrophysiological testing), they can suggest its presence.

6.3. Assessing somatosensory function in a research setting (comprehensive)

6.3.1. Afferent (sensory) arc—The Cochet-Bonnet and Belmonte aesthesiometers have been used to evaluate corneal sensation, mostly in research settings. The Cochet-Bonnet is a hand-held device that contains an adjustable fiber. The clinician touches the cornea with the fiber fully extended (6 mm) and reduces its length until the patient reports feeling a sensation. The lower the length required to elicit sensation, the lower the corneal sensitivity. A limitation of this device is that it requires contact with the patient, and it is not possible to fully sterilize the fiber between patients. Patients with DE who were tested with this device were found to have reduced mechanical sensitivity,[75,144,145] implying impaired somatosensory function.

The Belmonte aesthesiometer can be used to evaluate corneal sensation in response to mechanical, chemical, and thermal stimuli. It is relatively large and requires in-house manufacturing and maintenance, as it is not commercially available. There are approximately five such devices available world-wide. With the Belmonte aesthesiometer, both increased and decreased corneal sensation have been reported in DE versus control patients.[79,97,98]

The confocal microscope can be used to study corneal nerve architecture in vivo.[146] Commercially available confocal microscopes are produced by Heidelberg Engineering GmBH, Germany and Nidek Technologies SRL, Italy. In the Confoscan 4 (Nidek), the lens (40x) does not contact the eye directly but uses a gel interphase (such as Genteal, Novartis). In the Heidelberg Retinal Tomograph (HRT) III/Rostock Cornea Module, a disposable plastic cap (TomoCap), placed on top of the lens (63x), comes in contact with the eye. Gel is placed in between the plastic cap and lens and over the cap. The Confoscan 4 uses a bright light source to image corneal nerves, which some patients find uncomfortable, while the HRTIII uses laser technology. Both technologies require trained operators to make the

imaging process easier for the patients and to acquire scans of good quality. Furthermore, there is no validated software available to automatically quantitate corneal nerve density and structural parameters, such as beading, tortuosity, and micro-neuromas. Therefore, different studies have used different tools to analyze images.[147–149] In order to better apply the IVCM to evaluate patients with corneal nerve damage and NOP, commercially available software programs are needed to quickly, easily, and quantitatively assess corneal nerves. It is noteworthy that IVCM does not provide any functional assessment of corneal nerves and decreased corneal nerve density is not always equal to decreased corneal sensitivity.

6.3.2. Efferent (response) arc—Researchers have measured tear production, blink rate, and conjunctival blood flow as surrogate measures of efferent neural responses elicited by pain signaling.[150–152] It is important to consider, however, that these metrics can be affected by other variables, beyond neural function, and thus represent surrogate measures of efferent function.

6.4. Therapeutics targeting somatosensory dysfunction

6.4.1. Topical therapies - treating peripheral sensitization

6.4.1.1. Anti-inflammatories: Anti-inflammatory medications are often used in the treatment of chronic pain,[153] given the close relationship between inflammation and pain amplification by nerve sensitization. Several anti-inflammatories have been used in DE, including short courses of topical corticosteroids, cyclosporine, and lifitegrast.[154,155] Of these, the latter two have Food and Drug Administration (FDA) approval for DE. However, not all patients with chronic pain respond to anti-inflammatories, and this is also the case for patients with DE.[154] Interestingly, in one study, response to anti-inflammatories was dependent on corneal nerve status. In patients treated with loteprednol 0.5% twice daily for 4 weeks, those with low baseline corneal nerve fiber lengths did not experience improvement in DE metrics, while those with near-normal baseline lengths noted improvement in symptoms and corneal staining.[156]

6.4.1.2. Trophic factors: Autologous serum tears have been used off-label to treat various components of DE (symptoms and signs),[157–159] and their effect is believed to be in part mediated by NGF. NGF is a neurotrophin that regulates the survival and differentiation of neurons in all vertebrate species, by activation of the tyrosine kinase A (TrkA) receptor.[160] NGF may promote health and regeneration of the corneal stroma and epithelium, as well as sensory nerves, and has been shown to be therapeutic in neurotrophic keratitis and corneal ulcers, but may also result in ocular and periocular pain.[161–163] Autologous serum tears, however, also contain other trophic factors, such as epidermal growth factor, platelet derived growth factor, and transforming growth factor, and their effect may be more complex.[164]

A concentration of 20% is most commonly used, but reported concentrations have ranged from 20% to 100%.[165] The more concentrated the serum, the more blood needs to be harvested from the patient. Interestingly, in a retrospective study of 16 patients with sensitivity to light and no ocular surface disease (hallmarks of NOP), autologous serum tears led to improvements in DE symptoms and corneal nerve parameters.[166] Limitations to the use of autologous serum tears include the need to harvest blood for their production, limited

availability, lack of insurance coverage, and the need for storage in a freezer. Given these limitations, the effects of NGF mimetics, such as MIM-D3 (a TrkA receptor partial agonist) have been studied in patients with DE, and have demonstrated favorable responses.[160,167] However, taking into consideration the controversial effects of NGF regarding pain, it is still not clear if NGF agonists will be good options for patients with NP subtype of DE. In fact, based on its pathologic role in nerve sprouting, anti-NGF therapies are currently under development to treat chronic pain.[168]

6.4.2. Oral medications - treating peripheral and/or central sensitization

6.4.2.1. Calcium channel alpha 2 delta ligands: Gabapentin and pregabalin are first-line therapies for the treatment of NP.[169] While their mechanism of action is not entirely clear, they influence central nerve function through interactions with voltage-sensitive Ca^{2+} channels and inhibition of voltage gated calcium currents that mediate excitatory neurotransmitter release.[170] The most recent Cochrane systematic review found that 1800 mg to 3600 mg daily gabapentin could decrease pain intensity by more than 50% in patients with diabetic neuropathy and postherpetic neuralgia.[171]

We have anecdotally used gabapentin as an off-label treatment for the NP subtype of DE with success in some patients. In our experience treating approximately 25 patients a year with this therapy, improvement in symptoms occurs at relatively high doses, i.e. 900 mg, or higher, three times a day. The main side effect of gabapentinoids is central nervous system depression, which can manifest as drowsiness, dizziness, headache, and/or loss of balance. In most patients, side effects are absent or subside with time. Formal studies are lacking, however, on the efficacy of alpha 2 delta ligands and other such medications in treating ocular pain and dry eye symptoms.

6.4.2.2. Anti-depressants: Anti-depressants are also used in the treatment of NP and are frequently combined with calcium channel alpha 2 delta ligands.[169] In particular, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine (Cymbalta) and venlafaxine (Effexor) are used due to their mild side effect profile, which can include nausea, dizziness, and sweating. For example, seven randomized controlled trials (RCT) using duloxetine and two using venlafaxine found that both were superior to placebo in treating peripheral NP in patients with diabetes. Given their more severe side effects, tri-cyclic anti-depressants, such as amitriptyline, are generally reserved for patients who have failed newer agents given.[172] Furthermore, there are less data supporting their use, as amitriptyline did not show superiority over placebo in patients with cancer-related or HIV-related NP. However, amitriptyline was more effective than placebo in patients with mixed NP, post-stroke pain, and postherpetic neuralgia.[173] No data are available on their off-label use in DE.

6.4.2.3. Omega-3 fatty acids: Omega-3 fatty acids are used in the treatment of NP based on the biology that lipid mediators derived from omega-3, such as resolvins and protectins have anti-inflammatory effects. High doses of omega-3 demonstrated significant pain reduction in five patients with variable sources of NP, including cervical radiculopathy, thoracic outlet syndrome, fibromyalgia, carpal tunnel syndrome, and burn injury.[174]

In the eye, dietary supplementation with omega-3 decreased inflammation on the ocular surface, as demonstrated by reduced HLA-DR expression.[175] In addition, the tear film of individuals taking omega-3 supplements contain a higher amount of anti-inflammatory lipids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) as compared to pro-inflammatory (arachidonic acid) mediators.[107] This indicates that oral ingestion of essential fatty acids has an effect on the tear film and ocular surface. However, no formulation has been specifically approved for use in DE.

6.4.2.4. Other medications: Several other medications are used in the treatment of NP, including traditional and atypical opioids (tramadol), anticonvulsants (carbamazepine, oxcarbazepine, topiramate, lamotrigine),[176,177] capsicin and lidocaine patches[171], potassium channel openers,[178,179] and sodium channel blockers. In fact, topical tetrodotoxin (a sodium channel blocker) suppressed corneal pain after laser keratectomy.[181] However, none of the medications discussed above has been studied in ocular pain and it is not known which, if any, will help the subset of patients with DE symptoms and NOP. Furthermore, these oral medications are not routinely prescribed by ophthalmologists, so consultation with a psychiatrist or primary care physician is advised, as these medications can cause side effects that need to be monitored.

6.4.3. Ancillary therapies—Non-pharmacological approaches are important adjuvants in the treatment of NP. They may also be used as primary treatments for those whose NP is especially refractive to pharmacologic interventions. These include therapies such as exercise, massage, acupuncture, and peripheral and central stimulation.[181] In particular, cognitive behavioral therapy (CBT) is an important component in treating patients with chronic pain.[182] Such therapy can help decrease dysfunctional and maladaptive thoughts and behaviors, reduce anxiety and stress associated with chronic pain, and help improve coping mechanisms.

6.4.4. Nerve blocks—Injections, such as nerve blocks, are another form of therapy used to treat chronic pain. The area adjacent to a sensory nerve can be injected, typically with a combination of a sodium channel inhibitor, such as lidocaine (or other local anesthetic) and a corticosteroid, when pain arises from a defined nerve (i.e., neuralgia). Repeated neural blockade may have an effect by reducing dynamic maintenance of peripheral or central sensitization and attenuate pain.[116] Blockade of nerves adjacent to the eye has been found helpful in a small case series of individuals with pain involving the periocular tissues.[183,184]

In patients with parasympathetically (or sympathetically) mediated pain, sphenopalatine (or superior cervical ganglion) blocks and/or stimulations have been used with some success, based on the clinical scenario.[185,186] Raised parasympathetic hyperactivity via the sphenopalatine ganglion has been described in other neuropathic facial pain conditions, such as cluster headache syndromes. While not common, severe ocular pain not responsive to traditional therapies may need more aggressive treatment. In one case report, a woman with severe post-refractive surgery-associated pain was treated with a trigeminal nerve stimulator followed by intrathecal catheter placement for delivery of bupivacaine and low dose fentanyl.[187]

7. Limitations of the current review

Several limitations of this review should be considered. Ocular pain as a feature of DE has only recently been investigated, and many questions remain as to its epidemiology, clinical manifestations, and optimal treatments. While two groups have found similarities with regard to the epidemiology of ocular pain and somatosensory function in disparate populations (white British women[44,58,59] versus predominantly male South Florida veterans[57,95]), the findings in these series may not be generalizable to other populations. Furthermore, only two studies have reported on genetic susceptibility in DE,[129,137] and validation studies in different populations are needed to corroborate these findings. In addition, questionnaires such as NPSI-Eye have not been validated against other questionnaires for eye pain. However, their correlation with other metrics of somatosensory dysfunction provide criterion validity for their use.[142] Finally, agents used to treat NP have not yet been formally evaluated in well powered controlled trials as treatments of ocular pain and dry eye symptoms, and, therefore, it is not possible to discuss which strategies, if any, would be most beneficial.

8. Conclusions

While DE was initially thought to be a “simple” disorder of tear production, a deeper understanding of the disease has revealed its complex and heterogeneous nature with diverse neuro-pathologic mechanisms.[188] While ocular surface findings, including tear film status and inflammation, are important components of the disease, it is clear that somatosensory dysfunction, in a manner that resembles NP, is also involved. Developing better diagnostic techniques to evaluate nerve structure and function in DE will allow for more specific tailoring of therapy that can improve the quality of life of millions of Americans.

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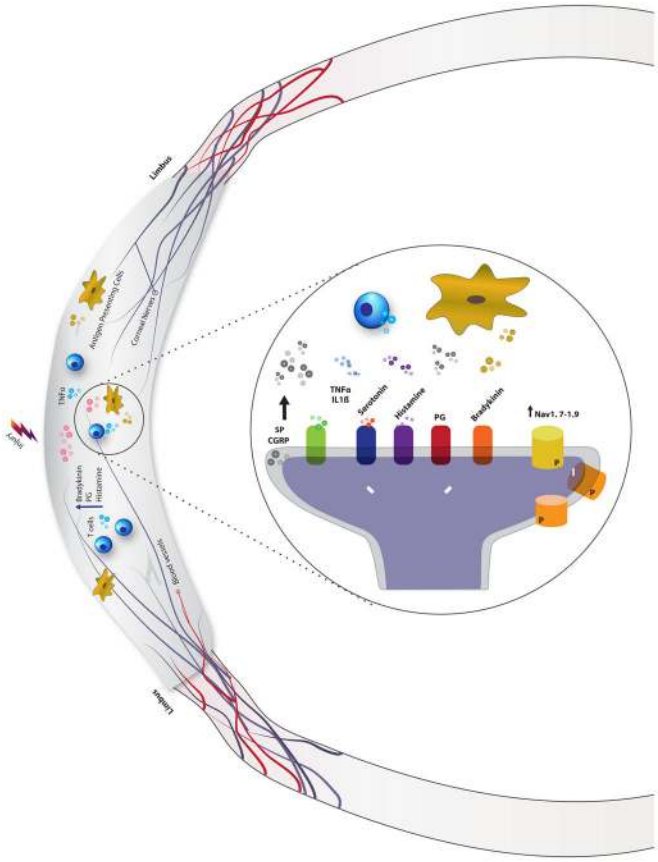

Fig. 1.

Mechanisms of peripheral sensitization. Injury to epithelial cells results in the release of numerous inflammatory mediators such as bradykinin, prostaglandins (PG), serotonin, and histamine, to name a few. Peripheral nerve terminals have receptors that recognize these inflammatory molecules (5HT for serotonin, H1 for histamine, EP for PG, B2/B1 for bradykinin). Their activation triggers the release of substance P (SP) and calcitonin gene-related peptide (CGRP). These mediators co-activate resident antigen presenting cells and recruit additional immune system cells to the site of injury. T cells and macrophages then secrete additional inflammatory cytokines (tumor necrosis factor alpha (TNFα) and Interleukin 1 (IL1)) that changes the function of peripheral nociceptors via protein kinase cascades. Mechanistically, this is largely prompted by the changes in ion channel function (through phosphorylation) and expression of new channels. These include specific ion channels such as voltage gated sodium channels (Nav1.7–1.9) and non-specific cation channels (transient receptor potential cation channel subfamily V member 1 (TRPV1).

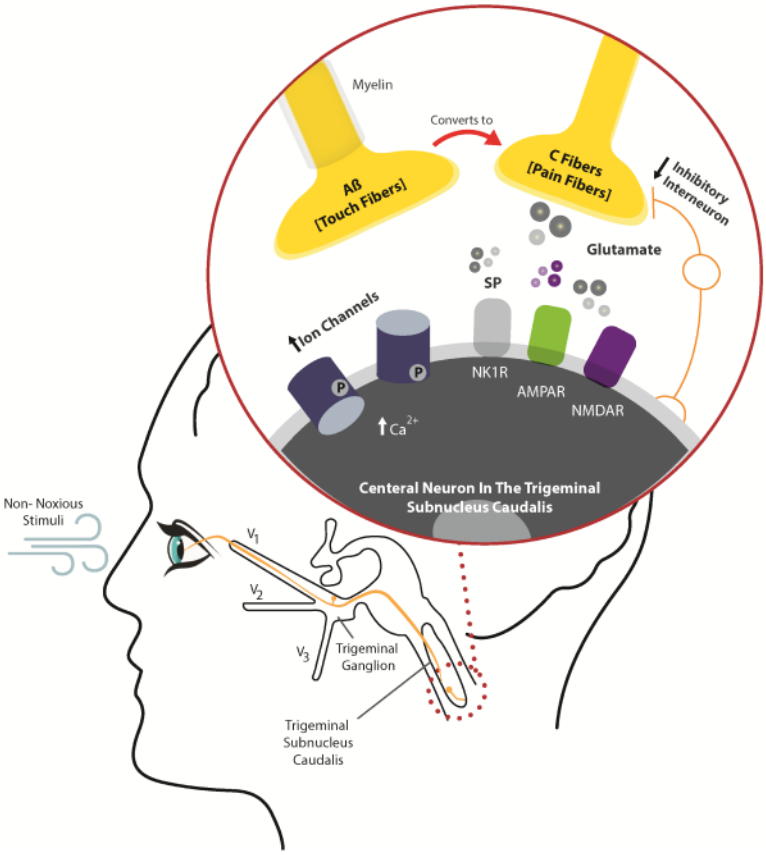

Fig. 2.

Mechanisms of central sensitization that lead to ocular pain following a non-noxious stimulus (e.g., light or wind). After leaving the cornea, peripheral corneal nerves synapse with second-order neurons in the Vi/Vc and Vc/C1 regions within the trigeminal subnucleus caudalis. Sensory (touch) neurons also synapse with central neurons in this area. Increased peripheral traffic leads to the release of substance P (SP) and glutamate at the synapse junction. Several receptors respond to these mediators including the N-methyl-D-aspartate receptor (NMDAR) (ion channel that responds to glutamate), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (ion channel that responds to glutamate), and the neurokinin 1 receptor (NK1R) (G protein coupled receptor that responds to substance P). In a similar manner to what occurs in the periphery, the co-activation of these receptors leads to increased calcium (Ca^{2+}) and phosphorylation of existing ion channels and production of more channels, leading to a more excitatory phenotype. Other mechanisms involved in central sensitization include decreased number and function of inhibitory interneurons (which results in pain amplification), activation of glial cells (with resulting central inflammation), and conversion of touch receptors into pain receptors. The latter has the effect of converting innocuous sensations to painful ones (hyperalgesia, allodynia). Of note, features of hyperalgesia and allodynia (in the form of sensitivity to wind and light) are often concomitant with dry eye symptoms.

Table 1

Common features between dry eye and neuropathic pain

Epidemiology	Both are common conditions, affecting a large proportion of the older population. More common in females than males.
Shared clinical features	Frequent disconnect between symptoms and signs; spontaneous dysesthesias and evoked pain common to both entities, even in the absence of ongoing nerve damage.
Shared co-morbidities	Dry eye and other chronic neuropathic pain conditions often co-exist, including co-morbid conditions associated with pain amplification and psychological distress (e.g., pain, fatigue, sleep disorders, depression, anxiety, etc.).
Abnormal somatosensory testing	Hypoesthesia, hypo- or hyperalgesia, or allodynia commonly seen on somatosensory testing. Dynamic testing has revealed increased wind up, a surrogate metric of central sensitization in both conditions.
Nerve injury implicated	Anatomical abnormalities observed in corneal nerves consistent with nerve injury (confocal microscopy), similar to neuropathic pain elsewhere in the body (magnetic resonance imaging)
Shared pathophysiology	Somatosensory nerve sensitization, inflammation and supporting cell abnormalities are common to both entities.
Heritability	Both conditions appear to be heritable and shared genetic factors have been demonstrated in large twin studies.
Overlapping therapeutic response	Nerve modulators, such as calcium channel alpha 2 delta ligands (e.g., gabapentinoids), improve symptoms in some individuals.

Table 2

Features suggestive of a neuropathic component to dry eye symptoms

Discordance between DE symptoms and signs, with symptoms outweighing signs[145]
Non-response to therapies that target the ocular surface and tears[57]
Presence of chronic overlapping pain conditions[58, 191], depression, anxiety[65]
Specific descriptors including spontaneous burning pain, sensitivity to wind and light[4, 66]
Persistent ocular pain after topical anesthesia (e.g. proparacaine)[125]

DE=dry eye