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# Neuropathic Corneal Pain

## *Approaches for Management*

*Gabriela Dieckmann, MD,*[1,2] *Sunali Goyal, MD,*[3] *Pedram Hamrah, MD, FACS*[1,2]

Neuropathic pain is caused by a primary lesion or dysfunction of the nervous system and can occur in the cornea. However, neuropathic corneal pain (NCP) is currently an ill-defined disease. Patients with NCP are extremely challenging to manage, and evidence-based clinical recommendations for the management of patients with NCP are scarce. The objectives of this review are to provide guidelines for diagnosis and treatment of patients with NCP and to summarize current evidence-based literature in this area. We performed a systematic literature search of all relevant publications between 1966 and 2017. Treatment recommendations are, in part, based on methodologically sound randomized controlled trials (RCTs), demonstrating superiority to placebo or relevant control treatments, and on the consistency of evidence, degree of efficacy, and safety. In addition, the recommendations include our own extensive experience in the management of these patients over the past decade. A comprehensive algorithm, based on clinical evaluation and complementary tests, is presented for diagnosis and subcategorization of patients with NCP. Recommended first-line topical treatments include neuroregenerative and anti-inflammatory agents, and first-line systemic pharmacotherapy includes tricyclic antidepressants and an anticonvulsant. Second-line oral treatments recommended include an opioid-antagonist and opiate analgesics. Complementary and alternative treatments, such as cardiovascular exercise, acupuncture, omega-3 fatty acid supplementation, and gluten-free diet, may have additional benefits, as do potential noninvasive and invasive procedures in recalcitrant cases. Medication selection should be tailored on an individual basis, considering side effects, comorbidities, and levels of peripheral and centralized pain. Nevertheless, there is an urgent need for long-term studies and RCTs assessing the efficacy of treatments for NCP. *Ophthalmology 2017;124:S34-S47 © 2017 by the American Academy of Ophthalmology*

The International Association for the Study of Pain defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction of the nervous system."[1] The diagnosis of neuropathic pain requires confirmation of injury or disease affecting somatosensory pathways of the peripheral and/or central nervous systems (CNS).[2] Neuropathic pain can also occur in the cornea,[3–7] the most richly innervated tissue in the body.[8] Neuropathic corneal pain (NCP) remains an ill-defined entity (also termed corneal neuralgia, keratoneuralgia, corneal allodynia, or corneal neuropathy)[3–7] and can be perceived as pain,[9] discomfort,[10] aching,[11] photoallodynia,[6] burning,[10] irritation,[10] dryness,[11] and grittiness,[11] symptoms that may overlap with diseases such as dry eye disease (DED).[12] NCP can result from both peripheral nerve injury[5–7,9] and systemic etiologies,[4,9,10,13] and owes much of its understanding to advances in the pathophysiology and neurobiology of systemic neuropathic pain. Although recent articles have attempted to elucidate the pathophysiology behind NCP, very limited literature exists on the management of NCP.[6,13] This review article provides an evidence-based approach on management strategies for NCP and further reflects our own extensive clinical experience on a large cohort of NCP patients. We have been treating NCP patients since late 2008. Our recent medical records review has shown that we are currently treating around 100 new NCP patients per year. We estimate that we have treated well over 700 patients over the past 9 years.

## Methods

We performed a systematic search of all relevant publications between 1966 and 2017, from MEDLINE (National Library of Medicine), PubMed, PubMed Central, Embase, OVID, and Cochrane Database. Search terms included the following: pain, neuropathic pain, somatosensory pain, central pain, peripheral pain, dry eye, ocular discomfort, contact lens (CL) discomfort, ocular surface disease, corneal pain, corneal neuralgia, keratoneuralgia, allodynia, photoallodynia, corneal neuropathy, confocal microscopy, trigeminal neuralgia (TGN), and postherpetic neuralgia (PHN). We considered all systematic reviews, meta-analyses, randomized controlled trials (RCTs), retrospective studies, case series, and case reports. Studies were evaluated according to the Oxford Centre for Evidence-Based Medicine levels of evidence.[14]

## Pathophysiology of Neuropathic Corneal Pain

The sensory nervous system consists of sensory neurons, neural pathways, and the sensory cortex. Nociceptors are receptors necessary for pain perception,[15] and they may generate action potentials to thermal, mechanical, chemical, or polymodal (more than 1) stimuli.[16] They are

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connected centrally to higher-order somatosensory pain pathways and the thalamus, where pain is perceived. During homeostasis, sensory neurons detect various stimuli to generate physiological pain responses, protecting tissues from acute injuries.[17] However, tissue damage and inflammation of the ocular surface can result in peripheral axonal injuries and the release of proinflammatory mediators,[18,19] potentially resulting in increased sensitivity of peripheral nerves, thus intensifying peripheral pain signaling (peripheral sensitization). Over time, this can result in central sensitization, with central neurons becoming highly responsive to similar magnitudes of pain and heightened pain awareness.[20] The hallmark of central sensitization is pain that is disconnected from ongoing peripheral signs. Sensitization may result in allodynia,[7] photoallodynia (pain owing to non-noxious stimuli or light),[6] or hyperalgesia[11] (enhanced pain response to infrathreshold noxious stimuli), causing unpleasant sensations. NCP may have a peripheral origin (e.g., ocular surgery[9,21] or herpes zoster ophthalmicus[22]) or a systemic origin (e.g., small-fiber polyneuropathy or fibromyalgia).[4,13] Additional underlying causes include DED, infectious keratitis, recurrent erosions, radiation keratopathy, CL wear, among others, as summarized in Table 1. Important comorbid conditions include anxiety,[23,24] depression,[23–25] and posttraumatic stress disorders.[23,24]

Table 1. Etiology of Neuropathic Corneal Pain

1. Ocular Diseases
   - Dry eye disease[4–6,12]
   - Infectious keratitis[13]
   - Herpetic keratitis[23,38]
   - Recurrent erosion syndrome[13]
   - Radiation keratopathy[13]
   - Trauma[4]
2. Postsurgical
   - Refractive surgery[6,9]
   - Cataract surgery[5]
3. Systemic diseases
   - Small-fiber polyneuropathy[4,6]
   - Fibromyalgia[4,6]
   - Trigeminal neuralgia[5]
   - Medication-induced neuropathy (chemotherapy)
   - Autoimmune conditions (Sjögren's syndome, lupus, sarcoidosis, inflammatory bowel disease, celiac disease)[4]
   - Diabetes[4,14]
   - Oculofacial pain[5]
4. Comorbidities
   - Anxiety[12]
   - Depression[12,69]
   - Posttraumatic stress disorders[12]

## Management of Patients with Neuropathic Corneal Pain

### Diagnosing Neuropathic Corneal Pain

Diagnosing NCP has been challenging for vision care providers, partly because of the lack of understanding of this disease, as well as owing to minimal or absent clinical signs, thus masking the underlying condition.[5,6,11] NCP is typically diagnosed based on clinical history, symptoms, ophthalmologic examination, and evidence of nerve injury (by in vivo confocal microscopy [IVCM]) and/or nerve dysfunction (nerve function tests) (Fig 1). Patients typically complain of prolonged dry eye treatment, experience multiple treatment failures, note an inciting event (e.g., infection or surgery), and may complain about nonocular pain, neurologic, or psychiatric conditions upon questioning.

**Ocular Pain Questionnaires to Assess Symptoms.** Validated pain questionnaires enable clinicians to evaluate patients' symptoms and quality-of-life (QoL) changes. However, most validated questionnaires to date were designed to address DED symptoms, including the Ocular Surface Disease Index (OSDI),[26] McMonnies Dry Eye Questionnaire,[27] Standardized Patient Evaluation for Eye Dryness,[28] National Eye Institute Vision Function Questionnaire,[29,30] and Symptom Assessment in Dry Eye.[31,32] In contrast, the recently validated Ocular Pain Assessment Survey (OPAS)[33] is a quantitative, multidimensional questionnaire, specifically designed for assessment of corneal and ocular surface pain and related QoL changes. The Ocular Pain Assessment Survey assesses pain intensity, frequency of eye and noneye pain, QoL changes, aggravating factors, associated factors, and symptomatic relief quantitatively, allowing for monitoring of treatment responses.[33] Other questionnaires, including the Neuropathic Pain Symptom Questionnaire (modified for the eye), have been used, although they have not been formally validated yet for the eye.[34]

**Functional Somatosensory Testing.**

***The Proparacaine Challenge Test.*** Establishing the origin of pain, whether central or peripheral, is important for selecting appropriate treatment measures. Topical 0.5% proparacaine hydrochloride (Alcaine, Alcon, Fort Worth, TX) allows for differentiation of central from peripheral sources of pain.[13] Although proparacaine abolishes peripheral pain, it has no effect on pain from central sensitization. Thus, patients experiencing complete or partial relief with proparacaine challenge likely suffer from peripheral or mixed combined NCP. In contrast, patients not responding to proparacaine suffer, at least in part, from central NCP (Fig 2). It has been our clinical experience that many patients achieve only partial relief from topical proparacaine, suggesting that both peripheral and central sensitization are at play, albeit in different proportions, depending on etiology and disease duration. Additional measures, including bandage CLs and moisture goggles, may decrease evaporation-induced symptoms. It is however important to highlight that the proparacaine challenge test cannot distinguish between patients with pathologic dry eye symptoms and patients with peripheral symptoms of neuropathic origin. We believe that patients with signs of DED may also present with symptoms of NCP. However, no tests are currently available to distinguish between these entities.

***Corneal Esthesiometry.*** Direct somatosensory measurement using esthesiometers, such as the Cochet-Bonnet contact esthesiometer, allows for evaluation of