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Always seek the advice of a doctor before changing your treatment plan.

Document Guide

Neuropathic pain is one of the most severe complications of refractive surgery. During this surgery a massive amputation of sensory nerve endings takes place. When these amputated nerves fail to grow back normally neuropathic pain can evolve. The neuropathic pain can appear immediately after surgery or after a delay of months or even years. Neuropathic pain can be continuous or be evoked by certain triggers like dryness, wind, touch or light. Pain triggered by light is also referred to as photoallodynia. The hallmarks of neuropathic pain after refractive surgery are pain (aching, stabbing, electrical, pins and needles, burning) and light sensitivity/ photoallodynia. Dry eye feeling may or may not be apparent at the same time. Neuropathic pain tends to be chronic and is hard to treat, can be very intense and may lead to despair.

This document is developed to detail the current known treatments that are being successfully used for neuropathic corneal pain.

Part 1 is advice by Michael Brouwer, a physician from The Netherlands who has experienced ocular neuropathic pain following refractive surgery.

Part 2 are extracts from studies that discuss neuropathic corneal pain.

Part 1

First choice for ocular treatment of neuropathic corneal pain are neuroregenerative therapies such as autologous serum tears (AST) and plasma rich in platelets (PRP). These blood-derived agents contain growth factors, promoting recovery of damaged nerve tissue. It may take up to nine months before effects can be noted. Meanwhile the intense pain often needs treatment with medication against neuropathic pain.

For some people scleral lenses may help. These lenses protect the cornea against dryness, which could be one of the triggers for pain. Scleral lenses are large contact lenses that rest on the sclera and create a tear-filled vault over the cornea. However, for many patients with neuropathic corneal pain scleral lenses fail to be effective because the ocular surface can be easily triggered by the soft touch of the lens margins. When ocular solutions do not work or have not worked yet, oral medication against neuropathic pain may be used to dull the often intense pain. For all medications against

neuropathic pain patients need to be prepared that it may take up to several weeks before the effects on pain can be evaluated. Meanwhile it is likely that someone will have to face side effects. Slowly increasing of the dose may prevent frustration from side effects.

First line medications against neuropathic pain are tricyclic antidepressants such as amitriptyline and nortriptyline. Alternatively anticonvulsants such as pregabaline and gabapentine can be tried. Alternatives for these first line options are the SNRI antidepressants (duloxetine or efexor) and other anticonvulsants (for example, topiramate or carbamazepine). When pain is acute or intense, opioid pain medication may be necessary. The NMDA antagonizing opioid methadone may be more effective against neuropathic pain than commonly used opioids. Different therapies may be combined, for example, the treatment can be a combination of amitriptyline, pregabalin and methadone all together. For every prescription the prescribing doctor needs to know about your present medication, allergies and contra indications.

A relatively light treatment could be low-dose naltrexone (LDN). Please note that LDN cannot be combined with opioids.

In my own situation autologous serum tears (AST) were the key factor for my recovery. Their mechanism is to restore damaged nerves and studies indeed show nerve growth after AST treatment and most importantly, of course, recovery from pain. My pain used to be 12 out of 10, sky high. After four months of use I could feel the first improvements. Nowadays after 3 years of use, I am often without pain or just a slight irritation.

Part 2

Table 1. Topical Treatments for Neuropathic Corneal Pain

Topical Agent	Mechanism of Action	Pathology	Efficacy, Level of Evidence
Autologous serum tears (AST) 20%	Neurotrophic factors: nerve growth factor, substance P, insulin-like growth factor-1	Injured nerves and epithelial cells	Medium level of evidence, Level 3 and 4
Corticosteroids (e.g., loteprednol 0.5%)	• Anti-inflammatory • Inhibit leukocyte migration • Inhibit cytokines, prostaglandin, and leukotriene synthesis	Ocular surface inflammation	High level of evidence, Level 1
Cryopreserved amniotic membrane	• Anti-inflammatory • Neurotrophic factors	Ocular surface inflammation	Medium level of evidence, Level 3
Bandage contact lens, scleral lens	• Protective effect against the environmental triggers	Ocular surface injury	Medium level of evidence, Level 2
Artificial tears (preservative-free, emulsion-based)	Decrease tear osmolality — dilution Protective mechanism in evaporative dry eye	Ocular surface disease	High level of evidence, Level 1

Reference for

Table 1 and Table 2 - Dieckmann, G., Goyal, S. and Hamrah, P., 2017. Neuropathic Corneal Pain: Approaches for Management. *Ophthalmology*, *124*(11), pp.S34-S47.

Table 2. Systemic Pharmacotherapy for Neuropathic Corneal Pain

Medication (Class)	Mechanism of Action	Starting Dosage	Maximum Dosage	Side Effects	Precautions and Contraindications
First-line agents					
Nortriptyline, desipramine (Tricyclic antidepressants) Use a tertiary amine TCA only if a secondary is not available Nortriptyline/desipramine are FDA-approved for treatment of symptoms of depression	Monoamine reuptake inhibition, sodium channel blockade, and anticholinergic effects	10 - 25 mg at bedtime	100 mg at bedtime	Dry mouth, constipation, somnolence, anticholinergic effects, weight gain	Cardiac disease, prostatic adenoma, and seizure disorder High doses should be avoided in adults >65 years of age
Carbamazepine (anticonvulsant) FDA-approved for epilepsy, trigeminal neuralgia, and manic and mixed episodes of bipolar disorder	Sodium channel blocker	200 mg daily	400—800 mg/day. divided in 2—3 doses	Hyponatremia, drowsiness, headache, dizziness, rash, and nausea	Concomitant use of MAO inhibitors, Cardiac or hepatic disease, Renal failure, Prostatic hyperplasia
Second-line agents					
Low-dose naltrexone (opioid antagonist) FDA-approved at higher doses (50-300 mg) for treatment of drug and alcohol addiction	At low doses has an anti-inflammatory effect, reducing the proinflammatory cytokines Modulating microglial activity Opioid antagonist - : μ-opioid and κ-opioid receptors	1.5 mg at bedtime	4.5 mg at bedtime	Headache, vivid dreams, nightmares, tachycardia, and anxiety	Past organ transplant and use of immunosuppressive drugs
Tramadol (opioid agonist) FDA-approved for treatment of moderate to moderately severe pain	μ-Receptor agonist and monoamine reuptake inhibitor	50 mg/day	100 mg/day in divided doses every 3-7 days as tolerated	Nausea, vomiting, constipation, dizziness, and somnolence	History of substance abuse, suicide risk, and antidepressant use in elderly patients
Third-line agents					
Calcium channel α2δ ligands Gabapentin (anticonvulsants) FDA-approved for treatment of postherpetic neuralgia Pregabalin (anticonvulsant) FDA-approved for treatment of neuropathic pain and fibromyalgia	Act on the α2δ subunit of voltage-gated calcium channels, which decrease central sensitization	100 - 300 mg 3 times per day 50 mg 3 times per day or 75 mg twice daily	2400 mg/day 300 mg/day	Sedation, dizziness, peripheral edema	Reduced dose in renal insufficiency
(Serotonin-noradrenaline reuptake inhibitors) Duloxetine FDA-approved for treatment of diabetic peripheral neuropathic pain and fibromyalgia	Serotonin-noradrenaline reuptake inhibitors	30 mg/day	60 mg twice per day	Nausea, abdominal pain, constipation	Hepatic disorders, Use of tramadol, Hypertension
Mexiletine (sodium channel blocker) FDA approved for treatment of cardiac arrhythmia	Voltage-gated sodium channel blocker Lidocaine analogue Class IB antiarrhythmic	225-675 mg/day	675 mg/day	Nausea, headache, sleep disturbances, tiredness Gastritis is the most common side effect	Hepatic impairment, Severe heart failure, Sinus node dysfunction or intraventricular conduction defect

FDA = United States Food and Drug Administration; MAO = monoamine oxidase; TCA = tricyclic antidepressant

Table 3. Consider these alternatives for neuropathic pain

Intervention	Dose	Adverse effects/special considerations
Acetyl-L-carnitine	2,000-3,000 mg/day	Nausea, vomiting; Urine, breath, and sweat may have fishy odour Avoid use in patients taking warfarin
Alpha lipoic acid	600 mg/d	Nausea, vomiting, skin rash Possible injection site reaction with IV administration
Alpha lipoic acid/Rx combination	Alpha lipoic acid 100 mg bid + pregabalin 75 mg bid + methylcobalamin 750 mcg bid	Nausea, vomiting
B Vitamins	Benfotiamine 100 mg qid OR B1 25 mg OR benfotiamine 320 mg + B6 50-720 mg + B12 1,000 mcg/d OR L-methylfolate 3 mg + pyridoxal S-phosphate 35 mg + methylcobalamin 2 mg bid	Nausea, vomiting
Gamma linolenic acid	360-480 *mg/d*	Nausea, vomiting
Magnesium	Magnesium gluconate 300 mg/d	Gastrointestinal irritation, nausea, vomiting, diarrhoea Monitor for hypermagnesemia and drug-drug interactions Avoid in patients with elevated Magnesium. renal dysfunction, or cardiac abnormalities

Reference for Table 3. Onysko, M., Legerski, P., Potthoff, J. and Erlandson, M., 2015. Targeting neuropathic pain: consider these alternatives: when patients with painful peripheral neuropathy fail to respond to--or are unable to tolerate--standard therapies, consider these lesser-known treatments. Journal of Family Practice, 64(8), pp.470-476.