PO084 Low-Dose Naltrexone is Effective and Well Tolerated in Patients with Neuropathic Corneal Pain

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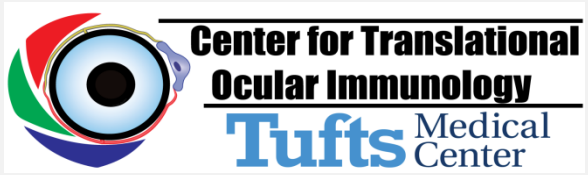

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Low-dose Naltrexone is Effective and Well-tolerated among Neuropathic Cornea Pain Patients

Introduction

- **Neuropathic Corneal Pain (NCP)** is a condition resulting from nerve damage, presenting with symptoms of pain or persistent unpleasant sensations, such as dryness, burning, aching, foreign body sensation, or light sensitivity, among others.[1;2;3;4] When symptoms do not resolve with topical anesthetics, this points to a non-ocular source of pain.[4]
- Nerve injury may lower the threshold necessary to activate corneal nociceptors, causing peripheral sensitization, which when persisting, can lead to chronic centralized pain.[5]
- **Low-dose naltrexone (LDN)** act as a neuromodulator with a neuroprotective effect via inhibition of microglial activation in the central nervous system.[6] Further, upregulation of endogenous opioid production is another mechanism of action of LDN.[7;8]
- Recent studies have explored the safety and efficacy of the off-label use of LDN for pain and inflammation in patients with auto-immune diseases.[9]

Purpose

- Assess the efficacy and tolerability of low-dose naltrexone among NCP with central component of pain.

Methods

- **Retrospective cohort study** (chart review) conducted at the Cornea Service, Tufts Medical Center, Boston, MA.
- **Inclusion criteria**: diagnosis of NCP (clinically and by IVCM), treatment with LDN (1.5-4.5 mg) for at least 4 weeks and Ocular Pain Assessment Survey (OPAS)[10]
- **Exclusion Criteria**: ocular pathology that may result in pain, complete resolution of symptoms after topical anesthetic.
- **Outcome measures**:

1. assessment of mean pain levels using VAS scale (0-10) in the office visit, past 24 hours and two weeks.
2. interference of pain in quality of life (QoL).

Figure 1- Percentage change in pain score based on OPAS #1

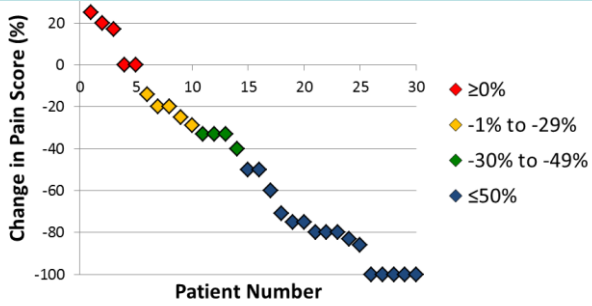
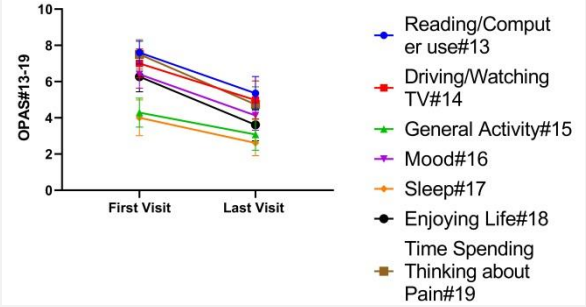


Figure 2- QoL score changes between the visits



Results

- 30 out of 70 patients were included in the final data-set based on inclusion/exclusion criteria.
- Mean age (years ± SD) was 45.60 (19.30) with a caucasian (80.00%) female (73.33%) predominance.
- Time between visits (duration of naltrexone use) was 14.87±11.25 months (range 1-36 months) and duration of NCP prior to treatment was 17.53±17.29 months (range 3-79 months)
- **Pre-treatment comorbidities were dry eye disease (66.67%), neuropsychiatric diseases (30.61%) and auto-immune diseases (10.20%).**
- All patients were on previous systemic medications (most common being Nortriptyline 26.7% and SSRI 16.7%).
- **The average percent improvement was -49.22%.** 16 patients (53.33%) had equal to or more than 50% improvement, 4 patients (13.33%) had 30-49% improvement, 5 patients (16.67%) had 1-29% improvement, and 5 patients (16.67%) did not improve **(Figure 1).**
- Mean Quality of life (QoL) score was 5.84±2.57 (range 1.14-9.00) at the first visit ($p<0.0001$) suggesting QoL of life was affected in these patients. **Mean QoL score improved** to 3.77±2.91 (range 0-8.86) at the last visit ($p=0.023$;**(Figure 2).**

Summary/ Conclusion

- 50% of NCP patients improved ≥50%.
- QoL significantly improved with LDN.
- LDN was effective and well tolerated as an adjunct therapy for NCP.

BACKGROUND/OBJECTIVE

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- Neuropathic Corneal Pain (NCP) is a condition presenting with symptoms and signs consistent with nerve damage resulting in pain and peripheral sensitization[1;2].
- The presence of injury may lower the threshold necessary to activate the corneal nociceptors resulting in peripheral sensitization[1;2].
- The cornea is innervated by the somatosensory trigeminal system via branches of the ciliary nerve of the first division of the trigeminal nerve (V1) and terminate at higher centers of the somatosensory system. Due to peripheral and/or central plasticity in the trigeminal somatosensory system, this sensitization may become persistent, leading to spontaneous pain, allodynia (e.g. pain from typically non-noxious stimuli) and/or hyperalgesia (e.g. pain that is exaggerated in severity) [1;2].
- Persistent pain may result in chronic central nervous system (CNS) changes, prolonging pain signals that therefore becoming a challenge to treat[3;4;5;6].

- Mediators of this progression have been therapeutically targeted, and microglia has been identified as a glia-target treatment[7].
- Naltrexone, 17-(cyclopropylmethyl)-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one, is an μ- and k-opioid receptor antagonist that is approved by Food and Drug Administration (FDA) for the treatment of alcohol and opioid dependence[7;8].
- In low-doses ranging between1.5-5.0 mg, naltrexone acts as a neuromodulator with a neuroprotective effect via inhibition of microglial activation in the CNS, and therefore can inhibits the pro-inflammatory cascade that has neurotoxic effects on neurons[7;8].
- Low-dose Naltrexone further acts as a neuroimmunomodulator through another mechanism of action that results in upregulation of endogenous opioid production that has been demonstrated to provide neuropsychological benefits[7;8].
- Recent studies have explored the efficacy and safety of the off-label use of LDN for pain and inflammation in patients with auto-immune diseases (including MS and fibromyalgia)[9].

METHODS

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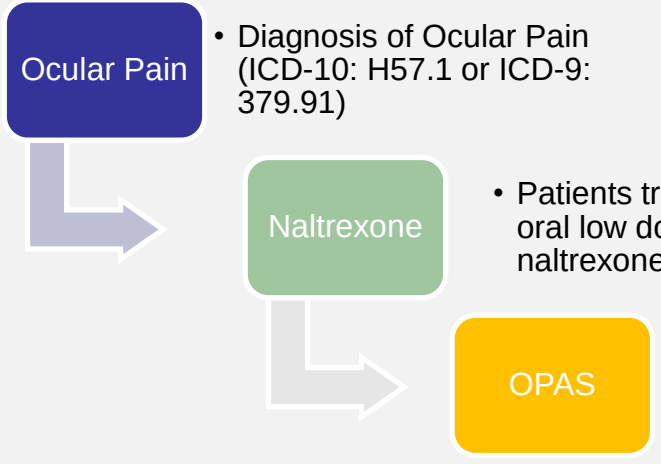
Charts reviewed between July 1, 2015 and March 31, 2019



Inclusion Criteria:

Diagnosis of NCP was based on medical history, discordance in clinical signs and symptoms, and corneal in vivo confocal microscopic findings.

Naltrexone use for at least four weeks with dose ranging between 1.5 mg to 4.5 mg based on treatment response and tolerability.

Completed at least question #1 of the OPAS at the visit where naltrexone was prescribed (termed "first visit" for the purposes of this study); 3) a completed question #1 of the OPAS at the most recent visit to our clinic or at the visit when naltrexone was discontinued (termed "last visit").

Exclusion Criteria:

1. Ocular pathology that might result in pain (e.g. active corneal infections, abrasions, recurrent erosion syndrome, angle-closure glaucoma, and anterior uveitis).
2. Complete resolution of symptoms after instillation of proparacaine drops (topical anesthetic)

RESULTS

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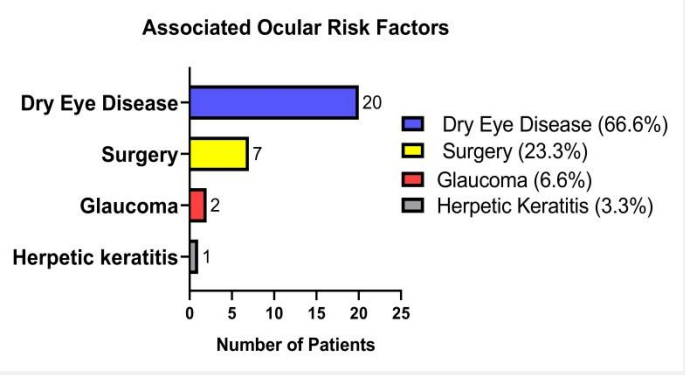

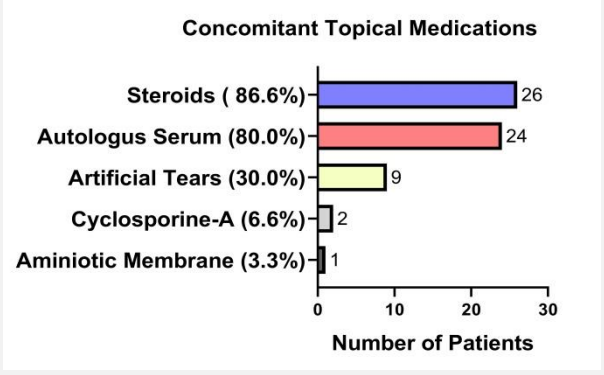

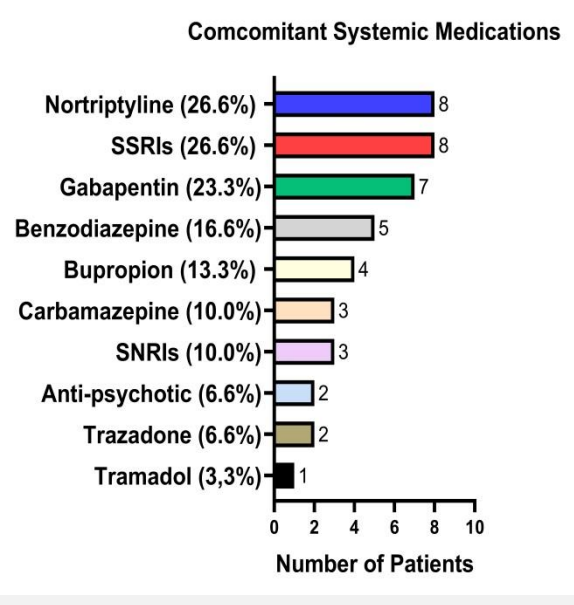

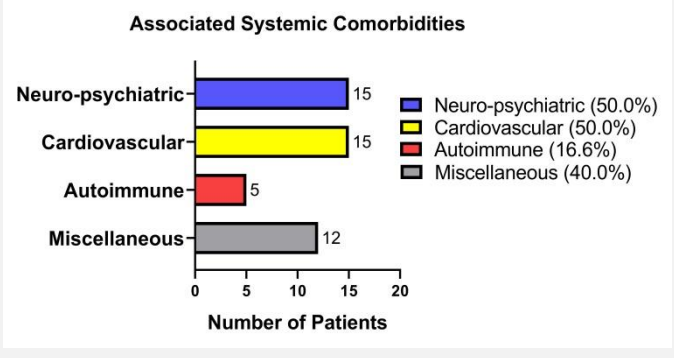

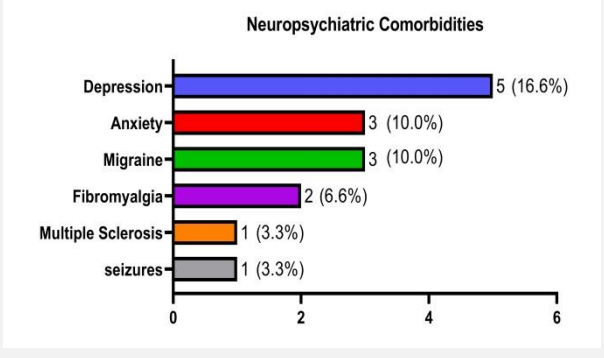

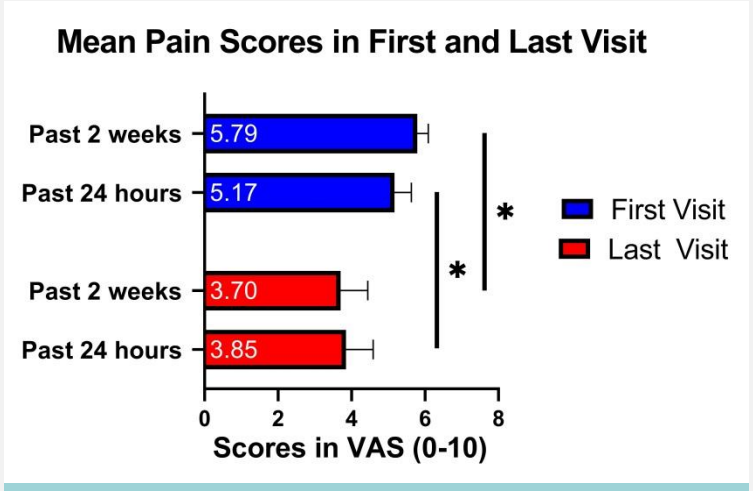

Figure 3. Change in pain scores based on OPAS questions #4 to #6 (pain levels for the past 24 hours) and #7 to #9 (pain levels for the past 2 weeks)(n=16)

- Low-dose naltrexone was effective in reducing pain(≥ 50%) in 16 out of 30 patients. There was a significant improvement in quality of life scores in the last visit compared to the first visit.
- Low-dose naltrexone is effective and well tolerated among NCP patients
- Retrospective nature and relatively small sample size are the main limitations of this study, as well as the lack of a double-blinded, randomized, placebo-controlled study.

Low-dose Naltrexone is effective and well tolerated among NCP patients as an adjunctive therapy.

REFERENCES

AAO2019

1. Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. Ophthalmology. 2017;124(11s):S34-s47.

2. Goyal S, Hamrah P. Understanding Neuropathic Corneal Pain--Gaps and Current Therapeutic Approaches. Seminars in ophthalmology. 2016;31(1-2):59-70.

3. Galor A, Moein HR, Lee C, et al. Neuropathic pain and dry eye. The ocular surface. 2018;16(1):31-44.

4. Galor A, Batawi H, Felix ER, et al. Incomplete response to artificial tears is associated with features of neuropathic ocular pain. Br J Ophthalmol. 2016;100(6):745-749.

5. Crane AM, Feuer W, Felix ER, et al. Evidence of central sensitisation in those with dry eye symptoms and neuropathic-like ocular pain complaints: incomplete response to topical anaesthesia and generalised heightened sensitivity to evoked pain. Br J Ophthalmol. 2017;101(9):1238-1243.

6. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32:1-32.

7. Haight ES, Forman TE, Cordonnier SA, James ML, Tawfik VL. Microglial Modulation as a Target for Chronic Pain: From the Bench to the Bedside and Back. Anesth Analg. 2019;128(4):737-746.

8. Trofimovitch D, Baumrucker SJ. Pharmacology Update: Low-Dose Naltrexone as a Possible Nonopioid Modality for Some Chronic, Nonmalignant Pain Syndromes. Am J Hosp Palliat Care. 2019;36(10):907-912.

9. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014;33(4):451-459.

10. Qazi Y, Hurwitz S, Khan S, Jurkunas UV, Dana R, Hamrah P. Validity and Reliability of a Novel Ocular Pain Assessment Survey (OPAS) in Quantifying and Monitoring Corneal and Ocular Surface Pain. Ophthalmology. 2016;123(7):1458-1468.