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Quantitative assessment of light discomfort thresholds in a patient with photoallodynia treated with topical naltrexone 0.01 %☆

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ABSTRACT

Background: Photoallodynia is a rare but disabling condition in which mild non-painful light triggers pain. Novel reliable diagnostic tools and effective treatments are desirable.
Case presentation: A 68-year-old female patient with dry eye owing to Sjogren syndrome reported severe photoallodynia not controlled by a wide armamentarium of topical treatments (eyelid hygiene, lubricants, corticosteroids, cyclosporine, and autologous serum). Patient symptoms were evaluated using visual analogue scale (VAS). Light discomfort thresholds under different lighting conditions (continuous warm, continuous cold and flashing warm) were measured using the Lumiz 100 device (Essilor International, Paris, France). All the evaluations were performed at presentation (T0), after proparacaine test (T1), and after 1 month of therapy with naltrexone 0.01 % eye drops instilled 4 times/day (T2). At T0, VAS score was 10; light discomfort thresholds were 1.83 log10[lux] for continuous warm, 1.79 log10[lux] for continuous cold, and 1.87 log10[lux] for flashing warm. At T1, a partial improvement of symptoms was reported and VAS score decreased to 8; light sensitivity thresholds slightly increased to 2.06 log10[lux] for continuous warm, 2.02 log10[lux] for continuous cold, and 2.18 log10[lux] for flashing warm. At T2, patient experienced a clinically meaningful improvement of symptoms and VAS score decreased to 4; in parallel, light discomfort thresholds increased to 2.78 log10[lux] for continuous warm, 2.82 log10[lux] for continuous cold, and 2.66 log10[lux] for flashing warm.
Conclusions: Naltrexone 0.01 % eye drops successfully controlled a severe case of photoallodynia refractory to all previous treatments. This improvement was quantitatively detected by the increase of light discomfort thresholds under all lighting conditions.

1. Background

Dry eye disease (DED) is a common, chronic, multifactorial ocular disorder that can significantly impact patients' quality of life.[1] Among etiologic causes, Sjogren's syndrome (SS) represents the most common condition associated to the aqueous-deficient subtype of DED.[2] It is an autoimmune disease characterized by the progressive damage of exocrine glands that ultimately results in impaired lacrimal gland function and hyposecretion.[2] Beyond dryness and irritation, patients may also complain increased sensitivity to light up to photophobia and photoallodynia in most severe cases.[2] Despite not well-defined, photophobia is described as an increased sensitivity to normal levels of light. This symptom intensifies patient's ocular discomfort, making exposure to both natural and artificial light particularly challenging. Photoallodynia occurs when even mild non-painful light triggers pain. This condition can be associated with central sensitization or abnormal pain processing, and has a profoundly debilitating effect on patients, leading to lost work hours, impaired social interactions, frustration, and

☆ Claim of Priority
After conducting a literature review on (March 31st, 2025) utilizing PubMed, Google Scholar, and other search engines, using the key words (topical naltrexone, ded, dry eye), we did not find any prior reports.

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heightened anxiety and depression.[3]

Although various strategies including questionnaires,[4] scales,[5] and other tools,[6] have been employed in recent years to evaluate photosensitivity, the lack of standardized reliable measurements remain a diagnostic challenge. Lumiz 100 (Essilor International, Paris, France) is a novel device capable of providing rapid, reliable, and safe evaluation of light discomfort thresholds, which has been recently demonstrated to have a good feasibility and accuracy in analyzing patients' light discomfort.[7,8] Despite several therapeutical advances have been introduced for effectively managing DED,[9] light-related symptoms are often overlooked by ophthalmologists, remaining frequently undertreated or poorly controlled.[3]

The present case report describes the successful management of a refractory case of photoallodynia in a patient affected by DED owing to SS thanks to the use of topical low dose naltrexone and provides quantitative data on changes of light sensitivity thresholds after treatment.

2. Methods

2.1. Light discomfort evaluation

Light discomfort was evaluated through visual analog scale (VAS) and Lumiz 100 device. Briefly, VAS is a rating scale for acute and chronic pain in which scores are based on self-reported symptom measures, recorded by placing a single mark along a 10-cm line. The left end of the scale (0 cm) corresponds to "no pain" while the right end (10 cm) signifies "worst pain".[10] Lumiz 100 is a portable device that evaluates two thresholds of light discomfort: i) "just perceptible" discomfort threshold, and ii) "really disturbing" discomfort threshold. The patient indicated these discomfort thresholds by pressing a button when mild symptoms such as "tension in the eyelids or tingling" occurred and when the light became "really disturbing" requiring effort to keep the eyes open, respectively. Thresholds were determined under three lighting conditions: two of them are characterized by continuous light increases and the other one by discontinuous light increases. For continuous increase, light starts at 25 Lux for 5 seconds and increases every second using a 20 % increase step, using either warm light (4000 K color temperature) or cold light (6500 K color temperature). For discontinuous increases, light starts at 10 lux for 5 seconds followed by increases to 25 lux for half a second and then decreases back to 10 lux for 2 seconds, before a 44 % increase from the previous flash using warm light (4000 K). Since photosensitivity has a logarithmic relationship with light intensity, the lux thresholds were log-transformed by using the log10 (lux) thresholds. The mean of the two thresholds ("just perceptible" and "really disturbing") for each of the three lighting conditions was calculated. Diagnostic performance and measurement reliability of the device have been previously detailed.[7,8]

2.2. Preparation and storage of naltrexone 0.01 % eye drops

Naltrexone eye drops were prepared at a concentration of 0,1 mg/ml using naltrexone HCl (Galeno Srl). Naltrexone HCl was added and mixed under mechanical agitation in a sodium chloride 0.9 % sterile injection base (preserved with benzalkonium chloride: 0.02 % w/v). The entire process was conducted in a grade D cleanroom. The final solution of naltrexone 0.01 % was filtered through a 0.22 μm filter Stericup® Sterile Vacuum Filtration Systems (Merck Millipore, MC2, Clermont-Ferrand, France) under the laminar airflow of an ISO 4.8 (grade A) isolator. The sterile naltrexone eye drops were packaged in a 1 ml low-density polyethylene multidose eyedropper (Acef Spa) with a beyond use date of 3 days refrigerated or 45 days frozen.

2.3. Treatment tolerability

Treatment tolerability for naltrexone 0.01 % eye drops was investigated after 1 month of therapy by administering the Brief Ocular Discomfort Inventory (BODI) questionnaire (11-point scale, where 0 indicates no discomfort and 10 indicates extreme discomfort).[11]

3. Case presentation

A 68-year-old Caucasian female with a diagnosis of SS complains of photoallodynia in both eyes despite the use of hyaluronic-based lubricants, vitamin A ointment and eyelid hygiene. Upon presentation, slit lamp examination showed DED associated with meibomian gland dysfunction (MGD). In both eyes, corneal fluorescein staining was present (Oxford score 2), break up time (BUT) was 3 seconds (s), Schirmer's test measured 3 mm/5 minutes (min). Corneal sensitivity was reduced in both eyes (40 mm when measured with Cochet-Bonnet esthesiometer). Snellen best corrected visual acuity (BCVA) was 1 and intraocular pressure was 15 mmHg in both eyes. Warm compresses, autologous serum eye drops (6 times daily), fluorometholone 0.1 % (3 times daily), and cyclosporine 0.1 % (once daily) were started. Two months after the initiation of this therapy, MGD and DED conditions improved bilaterally with a reduction of corneal fluorescein staining to Oxford score 1 and an increase of BUT to 5 s and Schirmer's test to 6 mm/5 min. Corneal sensitivity remained unchanged. However, patient continued to report persistent photoallodynia that impaired dramatically her daily-life activities (Supplemental digital content 1, video 1). Patient's light sensitivity score evaluated with VAS measured 10. Light discomfort thresholds examined by means of Lumiz 100 device were 1.83 log10 [lux] for continuous warm, 1.79 log10[lux] for continuous cold, and 1.87 log10[lux] for flashing warm (Fig. 1A–C). One minute after the administration of a drop of proparacaine hydrochloride 0.5 %, the mean VAS score decreased to 8, while light sensitivity thresholds slightly increased to a value of 2.06 log10[lux] for continuous warm, 2.02 log10 [lux] for continuous cold, and 2.18 log10[lux] for flashing warm (Fig. 1D–F). The mild improvement of the photoallodynia after the anesthetic test revealed a mixed (central and peripheral) component of the symptom. Topical naltrexone 0.01 % was added 4 times daily to the ongoing treatment after receiving the signature of the informed consent from the patient for the off-label use. One month later, the patient reported a clinically meaningful improvement in photoallodynia with a near-normal restoration of her daily activities (Supplemental digital content 2, video 2). This improvement was confirmed by the VAS score that decreased to 4, and by Lumiz 100 examination that reported light discomfort thresholds of 2.78 log10[lux] for continuous warm, 2.82 log10[lux] for continuous cold, and 2.66 log10[lux] for flashing warm (Fig. 1G, H, 1I). Treatment was well tolerated by the patient with a BODI score of 2. All the other ocular surface parameters, including corneal sensitivity, did not show changes throughout the treatment period. Currently, 4 months after initial presentation, patient is still under topical naltrexone 0.01 % and reports continuous relief from light-associated symptoms (Supplemental digital content 3, video 3). Throughout the entire treatment period, no adverse events were observed.

Supplementary video related to this article can be found at doi:10.1016/j.ajoc.2025.102500

4. Discussion and conclusions

In the present case report, topical naltrexone provided a significant relief of photoallodynia in a patient affected by DED owing to SS who was unresponsive to conventional ocular surface therapies. The partial improvement of the photoallodynia after the proparacaine challenge test suggested a mixed (central and peripheral) component of the symptom. In these cases, both aggressive ocular surface treatment including anti-inflammatory options and systemic therapies with analgesics, tricyclic antidepressants, anticonvulsants, low dose naltrexone, and electrical neurostimulation are usually required to reduce pain. Before switching to systemic therapy, a therapeutical attempt with topical naltrexone was performed. One month after treatment, an

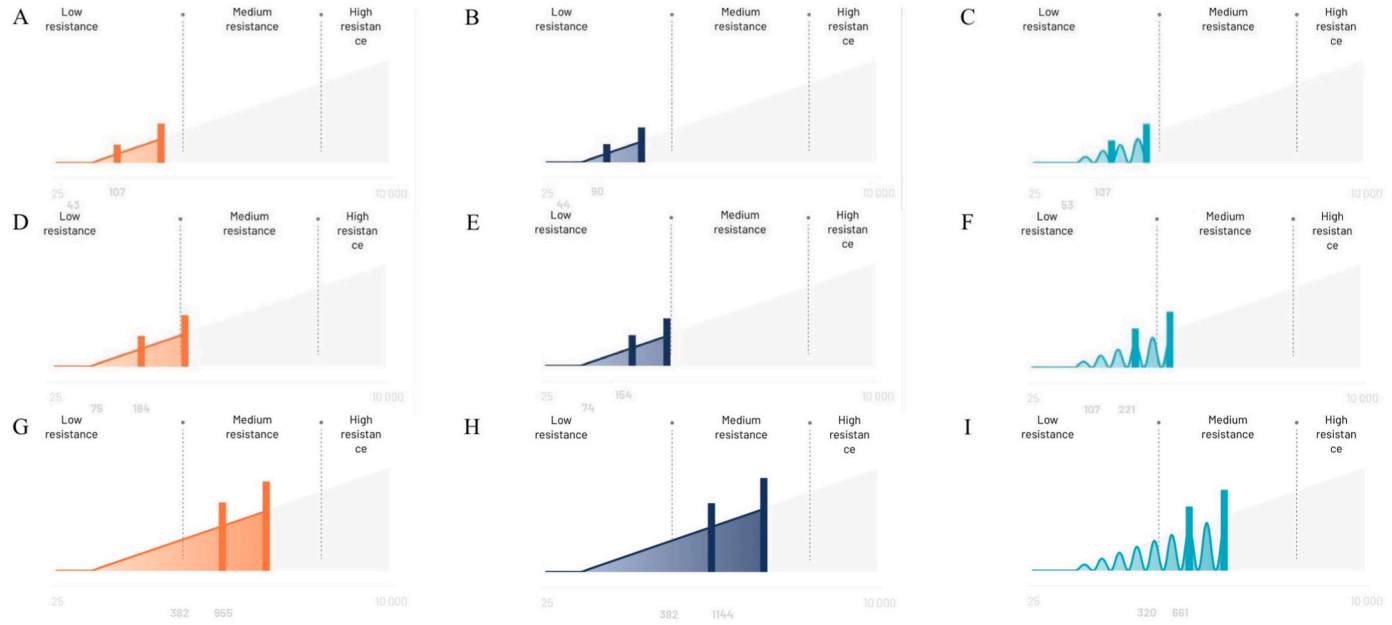

Fig. 1. Light discomfort thresholds for continuous warm, continuous cold, and flashing warm at baseline (respectively, A-C), after topical administration of benoxinate 0.4 % ophthalmic solution (respectively, D-F) and after 1-month treatment with naltrexone eye drops (respectively, G-I) in a 68-year-old female with Sjögren's syndrome-related dry eye and photoallodynia. For each lighting condition, the first vertical line indicates the onset of a just perceptible discomfort, while the second one represents the onset of a really disturbing discomfort.

improvement of photoallodynia assessed both subjectively and quantitatively was detected, opening a novel scenario of using topical naltrexone for this challenging condition avoiding the use of systemic therapies that can determine adverse or undesirable effects. Patients suffering from photoallodynia are usually unable to carry out activities of daily living, even when wearing dark glasses, resulting in loss of work productivity, impaired social functioning, frustration, and increased anxiety and depression. In our case, the patient was able to resume all daily activities after treatment with topical naltrexone, reporting a good tolerability for the topical product.

Among other ocular disorders, DED and MGD have been linked to both photophobia and photoallodynia.[3] Indeed, through a persistent irritation and inflammation of the trigeminal afferents that innervate the cornea, they can lead to a corneal neuropathy.[12] This condition, characterized by pain in response to different stimuli, including light, can be effectively assessed used in vivo confocal microscopy (IVCM).[12,13] In cases of peripheral dysfunction, the use of topical anesthetic (proparacaine challenge test) typically controls completely the pain 13. Conversely, in the present case only a partial improvement was documented after this test, suggesting a mixed component of the pain. Different pathways have been proposed to explain how light can activate pain circuits at central level. Digre and Brennan described potential interactions between conventional photoreceptors or intrinsically-photosensitive retinal ganglion cells with the thalamus and cortex, shedding light on "photophobia circuits".[3] Furthermore, photophobia in blind patients and after optic nerve resection in rodents demonstrates that an intact optic nerve is not essential for sensitivity to light, suggesting also other potential mechanisms implicated in light discomfort.[3] Hence, the pathophysiology of photophobia and photoallodynia are still not well understood.

The lack of precise definition and quantification methods, beyond to the absence of readily available therapies, makes the medical management of light-related symptoms challenging in most cases.[3] Conventionally, VAS score is a measurement scale used to assess subjectively pain intensity. It is simple to use and provides a quantifiable way to detect changes in patient's condition over time. Nonetheless, it presents different limitations including the individual variation and the lack of precise assessment of the different components of pain 10. To obtain a quantitative assessment of light sensitivity, the Lumiz 100 device was used in the present case at three different time points: i) patient presentation, ii) 1 min after proparacaine challenge test, iii) after one month of naltrexone 0.01 % eye drops. This innovative tool provides a simple and accurate assessment of light sensitivity thresholds, enabling scalable measurements for effective monitoring of photophobia variations over multiple examinations.[7,8] Specifically, a large cohort study demonstrated that the Lumiz 100 is a safe and rapid method for evaluating light sensitivity thresholds in healthy subjects.[7,8] Moreover, recent studies reported significant changes of light sensitivity thresholds in patients with age-related cataract and DED.[14,15]

In the present case a stepwise approach was used to control patient's symptoms. After the failure of first-line therapy, warm compresses, autologous serum eye drops, topical steroids and cyclosporine were started, providing only partial relief of symptoms. Blood-derived tear preparations contain growth factors and cytokines that can increase nerve density and restore corneal nerve topography, resulting in an improvement of photoallodynia, as already reported in patients with no concurrent ocular surface diseases.[12] Furthermore, either topical anti-inflammatory therapies (corticosteroid and cyclosporine), and warm compresses can improve ocular surface status and lessen trigeminal irritation by reducing ocular surface inflammation and improving meibomian gland function, respectively. However, the partial improvement of patient's symptoms recorded in the patient despite long-lasting use of these therapies suggests that ocular surface optimization was insufficient to restore patient's conditions. The marked and persistent reduction of photoallodynia during therapy with topical naltrexone highlights a distinct therapeutic contribution of this agent despite a synergistic effects with the other ongoing topical therapies cannot be fully excluded. Naltrexone, a nonselective opioid antagonist approved by the Food and Drug Administration for treatment of alcohol and opioid addiction disorders at doses of at least 50 mg, has showed to reduce pain when used at lower doses.[16] By transiently blocking opioid receptors, naltrexone increases endogenous endorphin levels, thereby reducing pain perception. Additionally, by binding the Toll-like receptor (TLR)-4 on glial cells throughout the central and peripheral nervous

system, naltrexone exhibits a further *anti*-neuroinflammatory effect. In this context, Dieckmann and colleagues investigated the use of low dose naltrexone (4.5 mg), administered orally in patients with corneal neuropathic pain, demonstrating a significant reduction in pain scores along with a good tolerability profile.[16] Animal studies have also explored the outcomes of topical application of naltrexone. Zagon et al. reported that topical naltrexone dissolved in Vigamox® eye drops could restore tear production, ocular sensitivity and reversing corneal surface within hours of a single instillation on diabetic rodents.[17,18] Similarly, McLaughlin and colleagues showed that 20 μg/ml of topical naltrexone effectively recovered tear film deficits and restored corneal surface sensitivity in diabetic rats with DED without causing toxic side effects.[19] Elevated levels of opioid growth factor (OGF) like enkephalin in diabetic animals and humans contribute to impaired cell replication and corneal sensitivity. Hence, by blocking OGF-OGF receptor interactions, naltrexone accelerates cell replication, promotes corneal repair, restores sensitivity, and reverts ocular surface diseases.[19] It is conceivable that the combination of this mechanism action with the above-mentioned central activity has led to improvement of photoallodynia in the present case report. Literature data on the topical application of this product in humans are poor. A randomized double-blind phase I study has investigated naltrexone eye drops use in healthy individuals. This study demonstrated that escalating doses of topical naltrexone (up to 5×10^{-5} M) applied to the corneal surface were well-tolerated over 24 hours and remained safe without adverse effects over a 7-day observation period.[20] Another study included 30 diabetic patients who were randomized to placebo or topical naltrexone 0.002 % for the evaluation of signs and symptoms of DED. Although efficacy results have not been published, the topical formulation demonstrated a good safety profile, with no adverse events reported in the treatment group; in addition, VAS score was lower in the naltrexone-treated group compared to the placebo group (16.27 ± 22.82 vs 25.07 ± 31.32, respectively).[21] While these findings are encouraging, it is important to point out that the evidence is still limited. Most available studies highlight positive outcomes, but some gaps remain. For example, robust placebo-controlled trials in humans are lacking, and the reproducibility of animal results in clinical practice is uncertain. Moreover, alternative strategies for photophobia management, including systemic neuropathic pain agents, neuromodulation, tinted lenses, and behavioral therapies, are not consistently effective, often yielding variable outcomes across patients.[3] This underscores the complexity of the management of photophobia and photoallodynia, for which treatment must be individualized and often multidisciplinary.

Some limitations of the present report must be acknowledged. Firstly, as a single-patient observation without a control group, the generalizability of the results is limited. Secondly, considering the lack of pharmacokinetic data, the exact mechanisms underlying the action of topical naltrexone remain speculative and warrant further investigations. As serum naltrexone levels were not measured, the possibility of systemic absorption contributing to the therapeutic effect cannot be excluded. Even when administered topically, small-molecule drugs may penetrate the conjunctiva and nasal mucosa, potentially reaching systemic circulation. If this occurred, part of the clinical improvement might be attributable to systemic mechanisms, such as central opioid receptor modulation, rather than local corneal effects alone. This uncertainty limits the ability to clearly differentiate local versus systemic contributions. Moreover, other confounding factors including the natural variability of the disease, the role of the concomitant therapies used or a placebo effect should be considered. Indeed, when clinical trials analyze pain reduction, a certain rate (about 30 %) of placebo effect is reported. Additionally, corneal nerve assessment was not performed. In detail, IVCM examination of the sub-basal nerve plexus of the cornea would have provided stronger mechanistic support by documenting potential changes of the nerve status before and after treatment, thereby clarifying whether the improvement was mediated locally at the ocular surface. Future studies should incorporate such technique to better elucidate the relationship between corneal nerve alterations and clinical outcomes.

In conclusion, topical naltrexone was safe, well-tolerated and effective in controlling a single case of photoallodynia resistant to various treatments, including autologous serum eye drops and anti-inflammatory agents. Despite the exploratory nature of our findings, this ophthalmic formulation could represent a novel promising strategy to manage extreme cases of light sensitivity that are often inadequately addressed. Moreover, the use of the Lumiz 100 device, thanks to the reliable quantification of light discomfort thresholds, allowed for staging the severity of the condition and monitoring the therapeutical response over time.

Future research including placebo-controlled trials conducted on larger samples of patients with photoallodynia or corneal neuropathic pain should be performed to confirm these promising results. Key design elements should encompass specific diagnostic inclusion criteria, standardized treatment protocols, predetermined therapy duration with multiple assessment points, and controlled testing conditions with standardized lighting during threshold measurements. Additionally, prospective controlled clinical trials comparing topical and systemic low-dose naltrexone would help clarify their relative efficacy, underlying mechanisms of action, and safety profiles.

CRediT authorship contribution statement

Filippo Lixi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giulia Coco:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Valerio Calabresi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Livio Vitiello:** Visualization, Validation, Supervision, Resources, Data curation, Conceptualization. **Claudia Corda:** Methodology, Investigation, Data curation. **Mario Verdiglione:** Methodology. **Silvia Costa:** Methodology. **Giuseppe Giannaccare:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

Formal ethics committee approval was not required for a single patient. This case report was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the off-label use of naltrexone.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images or videos.

Availability of data and materials

No datasets were generated or analysed during the current study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

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Abbreviations

VAS	Visual analogue scale
DED	Dry eye disease
SS	Sjogren's syndrome
BODI	Brief Ocular Discomfort Inventory
MGD	Meibomian gland dysfunction
BUT	break up time
BCVA	Best corrected visual acuity
IVCM	in vivo confocal microscopy
TLR	Toll-like receptor
OGF	opioid growth factor

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