A pilot study of the safety and feasibility of transcutaneous electrical nerve stimulation (TENS) for chronic ocular pain

Miami VA IRB: 1668339
Protocol version #: 4
Protocol version date: 08/18/2022
PI name: Elizabeth R. Felix, PhD

Abstract

Chronic ocular pain, which has historically been included under the diagnosis of "dry eye" (DE) disease, has recently been recognized as a unique condition that deserves specific study and targeted treatment. Alleviation of persistent ocular pain symptoms that are not linked to signs of tear dysfunction has proven difficult, likely because the mechanisms responsible for this pain are not fully understood. It has recently been theorized that mechanisms associated with neuropathic pain (defined as "pain caused by a lesion or disease of the somatosensory nervous system") may be the "missing link" in explaining idiopathic ocular pain symptoms. New approaches that specifically target peripheral and central somatosensory system mechanisms provide promising avenues to fill the gap in effective treatment options available to individuals with chronic NOP. We are interested in studying transcutaneous electrical nerve stimulation (TENS) for this purpose, as it has the potential to interfere with maladaptive nociceptive system mechanisms present in those with chronic ocular pain, and it is has been shown to be a low-risk, non-pharmacologic, non-addictive adjuvant therapy useful in several other chronic pain conditions To date, there have been no randomized control trials (RCTs) of TENS for ocular pain. Because NOP is a possible new indication for TENS, a pilot study is needed to assess its safety and feasibility in this patient population and to assess its potential effectiveness. The proposed SPiRE project is innovative in that it aims to overcome barriers to progress in this field and improve upon previous studies by: 1) completing a prospective evaluation of TENS as a novel treatment for NOP; 2) using a Sham TENS control for comparison; 3) evaluating both short- and mid-term safety, feasibility, and analgesic effectiveness; and 4) exploring potential mechanisms associated with response to TENS (e.g., NOP phenotypes, evoked pain sensitivity).Prospective, randomized, masked pilot study of Active TENS (intervention) vs Sham TENS (control/comparison). This is a scientifically-sound strategy to meet our goals of assessing the feasibility and safety of TENS, as well as assessing variability in [the time-course and] level of analgesic response across the target population.

New treatments for chronic ocular pain that target its presumed underlying mechanisms, are critically needed. If successful, our SPiRE pilot study will provide the preliminary data needed for submission of a Merit Review grant application of a fully-powered RCT of TENS for ocular pain. Results from this future RCT may provide the necessary evidence to support a non-invasive, non-pharmacologic, non-addictive, safe, and effective treatment option for the approximately 14% of Veterans with chronic ocular pain with underlying neuropathic mechanisms.

Introduction

a. Background and Significance

Chronic ocular pain, which has historically been included under the diagnosis of "dry eye" (DE) disease, has recently been recognized as a unique condition that deserves specific study and targeted treatment.[2] *[Almost 20% of US Veterans carry a DE diagnosis.[3] The majority of individuals with ocular pain rate their pain as at least moderate in intensity, and a substantial 20% rate their pain as severe.[4]]*

Alleviation of persistent ocular pain symptoms that are not linked to signs of tear dysfunction has proven difficult,[5,6] likely because the mechanisms responsible for this pain are not fully understood. It has recently been theorized that **mechanisms associated with neuropathic pain** (defined as "pain caused by a lesion or disease of the somatosensory nervous system"6) **may be the "missing link" in explaining idiopathic ocular pain symptoms**. Evidence supporting this assertion includes: 1) Ocular pain having characteristics that overlap with those of other types of neuropathic pain, such as spontaneous pain described as "burning" and presence of allodynia and hyperalgesia (evoked, or increased, pain due to wind/air puff or light);[7] 2) Patients with ocular pain often present with secondary hyperalgesia, described as exaggerated conjunctival or scleral pain along the trigeminal distribution;[8] and 3) Indications of abnormal corneal nerve morphology and corneal nerve dysfunction,[9-11] as well as central sensitization,[12] have been found in patients with ocular pain.

[*Approximately 70% of Veterans with symptoms of DE endorse one or more specific qualities associated with neuropathic pain.[4,7] Given that 20% of Veterans carry a DE diagnosis, this results in an estimated 14% of Veterans with at least mild and persistent ocular pain with neuropathic-like qualities – or "**neuropathic ocular pain" (NOP)**. Higher levels of NOP have been associated with increased psychological distress, greater prevalence of other chronic pain conditions, and decreased general health and well-being,[13] and treatment options for NOP are limited, often providing insufficient relief.[5,6]*]

New **approaches that specifically target peripheral and central somatosensory system mechanisms provide promising avenues to fill the gap in effective treatment options available to individuals with chronic NOP**. We are interested in studying **transcutaneous electrical nerve stimulation (TENS)** for this purpose, as it has the potential to interfere with maladaptive nociceptive system mechanisms present in those with chronic ocular pain, and it is has been shown to be a low-risk, non-pharmacologic, non-addictive adjuvant

therapy useful in several other chronic pain conditions.[14] [*There are a number of studies indicating that TENS can have both local/peripheral and central mediating effects on pain processes.[14,15] Results from studies targeting pain in areas outside of the eye indicate that these mechanisms can occur at the site of pain by increasing blood flow and decreasing inflammation, at the level of the spinal cord via interneurons that inhibit ascending pain information, and at the supra-spinal level via decreasing central excitability/sensitization and increasing activation of endogenous opioid and serotonin pathways.[16-18]*]

Although TENS has been studied for its ability to improve tear parameters associated with DE,[19,20] few investigators have reported the effects of electrical stimulation specifically for ocular pain. A study published in 1980 found that *subcutaneous* electrical stimulation in 25 individuals was effective for the short-term (2 weeks) treatment of postoperative ocular pain[21]; and a study from 1991 reported pain relief using TENS in 7 of 10 cases with various etiologies of ocular pain. These studies were small and did not include control groups, making them insufficient to provide an evidence basis in support of TENS for ocular pain in clinical practice.[22]

Innovation: To date, there have been no randomized control trials (RCTs) of TENS for ocular pain. Because NOP is a possible new indication for TENS, a pilot study is needed to assess its safety and feasibility in this patient population and to assess its potential effectiveness. The proposed SPiRE project is **innovative** in that it aims to overcome barriers to progress in this field and improve upon previous studies by: 1) completing a **prospective** evaluation of TENS as a novel treatment for NOP; 2) using a **Sham TENS** control for comparison; 3) evaluating both **short- and mid-term** safety, feasibility, and analgesic effectiveness; and 4) exploring **potential mechanisms** associated with response to TENS (e.g., NOP phenotypes, evoked pain sensitivity).

By testing the safety and feasibility of implementing TENS as an at-home treatment for chronic NOP, we will advance the methodological knowledge necessary for conducting a scientifically-sound RCT of TENS for ocular pain. Successful completion of this pilot investigation is a critical step toward achieving the overall objective of our program of research: to prevent or alleviate chronic ocular pain. **This research is relevant to advancing the goal of the VA RR&D to maximize Veterans' functional independence and quality of life**, as reduction of chronic pain often translates into improved physical and mental functioning.[23]

b. Preliminary Studies

We have previously investigated the use of TENS retrospectively via medical record review in a small sample of our patient population. Our group has assessed the effect of the RS Medical RS4i Plus Sequential Stimulator® on ocular pain during an in-clinic test trial[24] (n=13) and, retrospectively in those who used the device at home over 3 to 14 months[25] (n=10). The RS4i was set at the 100Hz beat frequency stimulus protocol for 30 minutes, with two electrodes placed bilaterally along the ocular midline above the brow and two electrodes on the temple, to target the ophthalmic (V1) and maxillary (V2) nerves of the trigeminal system. We found that ocular pain intensity decreased by 55% (p=0.01) during the singular in-clinic trial,[24] and 9 of 10 patients who took the device home for treatment over 3 to 14 months reported they felt that TENS was helpful for their ocular pain.[25] We have also recently completed a retrospective review of medical records from some of Dr. Galor's (Co-I) patients with ocular pain exhibiting neuropathic features who were prescribed a Cefaly® TENS device. The Cefaly device is less bulky than the RS4i device, but delivers a similar stimulus frequency (60Hz). Overall, patients' (n = 15) ratings of eye pain intensity decreased by an average of 31.4% (p<0.01), and ratings of the intensity of "burning" quality of eye pain (a hallmark quality of neuropathic pain) were decreased by an average of 53.9% (p<0.01), on a 0 to 10 numerical rating scale (NRS) after six months of use. Additional analyses showed that significant decreases in pain emerged by three months of treatment.

Based on these evaluations, we are encouraged that TENS may be a feasible non-pharmacologic treatment for NOP. However, our previous studies were performed in a heterogeneous group of individuals with ocular pain, used retrospective study designs, and did not include a control condition. Thus, a prospective, placebo-controlled study will be needed to confirm the effectiveness of TENS for NOP and its mechanism(s)-of-action.

We have the ability to recruit and enroll individuals from the targeted study group. For a previous Merit Review award in people with DE and ocular pain (VA CSR&D: I01CX001089; PI: Galor), we recruited 513 individuals. Thus, we have a large patient population who are available and willing to participate in studies, including those we have recruited for prior studies, and the approximately 18,000 patients who receive services at the Miami VA eye clinic each year.

We have previous experience in qualitative and quantitative evaluations of ocular pain and investigating its underlying mechanisms. We have previously demonstrated the value of using pain questionnaires to assess eye pain in individuals with DE symptoms,[7,11,26,27] including pioneering the adaptation of the Neuropathic

Pain Symptom Inventory[28] (NPSI) for use in ocular pain patients (NSPI-Eye), and confirming its validity and reliability.[4] We have also demonstrated our ability to perform quantitative sensory testing (QST) to evaluate the integrity of somatosensory function and analyze relationships between these measures and ocular pain in our Veteran population: 1) We have found significant relationships between sensitivity to mechanical/air-puff stimulation at the cornea and the severity of NOP (i.e., corneal detection and pain thresholds were correlated with NPSI-Eye scores ($r = -0.21$ ($p = 0.01$) and -0.23 ($p = 0.02$) for detection and pain thresholds, respectively));[11] and 2) We have found significant associations between pain sensitivity at an unaffected remote site and the presence and severity of ocular pain (i.e., significantly lower pain thresholds measured at the forearm in participants with ocular pain compared to controls, and significant positive correlations between ratings of prolonged noxious stimulation at the forearm, indicative of central sensitization, and NPSI-Eye scores).[12] We will use some of the same QST methods to evaluate whether the purported analgesic mechanisms of TENS[14] can address the somatosensory system dysfunction present in NOP.

Our team has the experience to carry out the proposed pilot study. The study team will apply their training and experience to embark on a new direction for their program – moving from the investigation of mechanisms underlying ocular pain, to clinical trials of new treatment options for this pain condition. Dr. Felix (PI) has extensive experience with evaluation of chronic pain and its impact, assessments of evoked pain sensitivity (QST) and their relation to nociceptive system mechanisms, and is PI of a clinical trial of TENS for the prevention of chronic pain in persons with spinal cord injury [NCT03267810]. Dr. Galor (Co-I), an oculofacial pain specialist, has a history of funded research in DE and NOP and investigating their mechanisms using multiple approaches. Dr. Tang has worked with the team on previous projects and will oversee database quality control and statistical analyses. Drs. Felix and Galor will convene weekly lab meetings with study staff throughout the project, and supplemental meetings with Dr. Leung, as well as the Cefaly® team, with regard to trouble-shooting of the Active and Sham TENS protocols as needed.

Objectives

1) Evaluate the **safety and side-effect profile** of TENS for use in NOP patients.
Side-effect report: We have chosen to use an open-ended questionnaire of side-effects, so that we do not limit participants in their reports. Participants will be asked whether they had any changes in any physical or mental health symptoms immediately after application of TENS (for the initial in-lab TENS trial), or during the past two weeks (for the 6-month at-home trial, during bi-weekly phone assessments). They will be asked to indicate the intensity and unpleasantness of the symptoms, and whether and why they think symptoms are related to TENS device use. If discontinuation of the device occurs (see "Record of device use," above), the participant will be asked about their reasons for discontinuation. We **hypothesize** that no more than 10% of participants will experience side effects that are bothersome enough for discontinuation of use, and that no severe adverse events will occur.

2) Establish the **feasibility and acceptability** of our study design and of the Active and Sham TENS protocols.
Medical record review, screening, and enrollment: We will follow guidelines for pain clinical trials (CONSORT[35], IMMPACT[36]) with regard to collecting information on patient disposition. This will include keeping a record and count of all patients screened for eligibility, their demographic information (for comparison of characteristics of those who meet initial screening criteria and those who do not), and reasons for exclusion after screening procedures are completed. We will also keep detailed records of those who consent to participate in the pilot study and those who choose not to. These metrics will be used to estimate recruitment rate and recruitment strategies for a future RCT. We **hypothesize** that at least 50% of eligible participants will enroll in the study.
Checklist of appropriate use of TENS device: We have created a step-by-step checklist for proper application of the TENS device to be used during the training session of Visit 2. This checklist documents the number of times a participant needs to be reminded or corrected regarding how to perform each of the steps correctly. We **hypothesize** that 100% of participants will be able to demonstrate safe self-administration of TENS.
Record of device use: The Active and Sham TENS Cefaly® device is able to record the use of the device, including the date, time, duration, and amplitude of stimulation. We will download this information from the device at Visits 3 and 4. We **hypothesize** that ≥75% of enrolled participants will maintain a 75% compliance rate with treatments and be retained throughout the study period.
Allocation questionnaire: At the end of the in-lab TENS trial, and again at the end of the 6-month intervention, participants will be asked to report which intervention arm they think they were assigned to, their level of certainty, and what factor(s) affected their guess. Results from Sham TENS participants (n=16) will be used to evaluate

whether a sufficient degree of uncertainty is reported in the Sham TENS group for it to serve as a control condition in future RCTs, or what aspects of subject instructions should be altered to induce more uncertainty. We **hypothesize** that ≥ 50% of individuals will report some uncertainty in treatment allocation.

3) [*Estimate the **time-course of analgesic effect** of long-term use of TENS for NOP*.]
Ocular pain symptom severity / Measure of analgesic response: 1) The Defense and Veterans Pain Rating Scale (DVPRS)[37] was developed by the Department of Defense and Veterans Health Administration and will serve as our primary measure of ocular pain. Ratings will be collected for current pain intensity (Visit 2, in-lab trial), or for average pain intensity during the past week (at-home treatments). 2) The NPSI-Eye[4] will be used to evaluate the effect of TENS on neuropathic pain-specific characteristics of ocular pain. 3) Two validated questionnaires for DE symptoms will be used as secondary assessments of the effect of TENS: the Dry Eye Questionnaire-5 (DEQ5)[38] and Ocular Surface Disease Index (OSDI).[39] [*We **hypothesize** that: a) ≥30% reductions in pain will occur within three months of Active TENS intervention; b) responsiveness to Active TENS will be maintained until the end of the six-month treatment period; and c) Active TENS will produce a greater analgesic effect than the Sham TENS condition throughout the treatment period*.]

4) Explore **between-subject variability in feasibility, safety, and analgesic responsiveness** to TENS.
Corneal and cutaneous evoked pain sensitivity: QST techniques will be used to measure sensitivity to stimuli delivered to the cornea (affected area) and to the forehead (cutaneous area near the affected region) and the forearm (cutaneous area remote from the affected region). The Belmonte aesthesiometer and the Medoc TSA-II devices will be used to measure detection and pain thresholds at the cornea and at cutaneous sites, respectively, using procedures previously described by our group[11,12,32] These measures will be used to assess whether baseline sensitivity to noxious and non-noxious stimulation may be able to predict the analgesic effect of TENS.
Ocular exam metrics: Participants will be asked to refrain from taking any eye drops (i.e., artificial tears) for at least 2 hours prior to ocular exam assessment sessions (Visits 1, 3, and 4). Assessments will include: 1) Visual acuity; 2) Tear osmolarity (TearLAB, San Diego, CA); 3) Pheno Red Thread measures of tear volume for assessment of lacrimal function; 4) InflammaDry testing (Quidel, San Diego, CA); 5) Eyelid assessment; 6) Tear film break up time (TBUT); 7) Corneal staining; 8) Pain assessment pre- vs post- anesthesthetic eye drops; 9) Schirmer strips; 10) Meibum quality; 11) Confocal microscopy (Laser In Vivo Confocal Microscopy (IVCM) will be performed using the Rostock Cornea Module of the Heidelberg Retina Tomograph (HRT) III (Heidelberg Engineering, Germany)). These metrics will be used to screen out those with abnormal tear film parameters and to assess potential changes in these measures during the TENS intervention period.
Covariates of interest: We will collect information regarding demographic characteristics (age, gender), environmental factors (e.g., smoking, alcohol use), medication use, and physical and psychological co-morbidities (e.g., other chronic pain conditions, diabetes, hypertension, PTSD, depression).

Our goal for Objective 4 is to use the evoked pain sensitivity profiles, eye examination metrics, and covariates of interest, to assess relationships between these variables and the acceptability, feasibility, side-effects, and analgesic efficacy of TENS in our study sample. These assessments will help inform targeted recruitment strategies for future RCTs of TENS for ocular pain.

Study Procedure

a. Research design: Prospective, randomized, double masked pilot study of Active TENS (intervention) vs Sham TENS (control/comparison). This is a scientifically-sound strategy to meet our goals of assessing the feasibility and safety of TENS, as well as assessing variability in [*the time-course and*] level of analgesic response across the target population.

The data and results from this study are not intended to be used to change the label of the device: 1) This is a pilot study; 2) The study will be performed independently of the manufacturer of the device with the exception of their provision of a sham device, which is not commercially available. The investigators are paying the manufacturer standard cost for the devices to be used in the study, and the manufacturer will have no interaction with the investigators in regard to data collection or data analysis/results.

b. Population to be studied: We will recruit Veterans from the Miami VA and Non-Veterans from Bascom Palmer Eye Institute. **The study population will consist of patients who have moderate-to-severe chronic NOP [*without signs of tear dysfunction*]**, as detailed in the criteria listed below.

Figure 1: Criteria for neuropathic pain diagnosis,[1] operationalized for neuropathic ocular pain

1. *Pain in a neuroanatomically plausible region[1] will be established by the report of chronic pain of at least moderate intensity on average (NRS ≥ 4) in one or both eyes.*

- AND -

2. *Pain history consistent with neurological disease or lesion[1] will be established based on:*
   a. *"burning" quality of pain (hallmark descriptor associated with neuropathic pain);*
   b. *elimination of probable non-neuropathic etiology (e.g. failure to adequately manage pain with medications that target ocular surface health; other diagnoses that explain ocular pain; measureable tear dysfunction – see "exclusion criteria," below); and/or*
   c. *failure of topical anesthetic to alleviate pain.*

- AND -

3. *Pain is associated with sensory signs in the same neuroanatomically plausible area[1] will be based on:*
   a. *Hypo- or hyper-sensitivity to mechanical stimulation of the cornea (based on > ± 1 SD for threshold measures in normative samples)*
   b. *Reported hypersensitivity to light or wind on the cornea*]

Inclusion Criteria: a) male or female; b) all races and ethnicities; c) ≥ 18 years of age; d) persistent eye pain for ≥6 months; e) average eye pain intensity of ≥4 on a 0-10 NRS; f) on a stable medication regimen for the past 3 months; g) naïve to TENS use for orofacial conditions; and h) neuropathic-like eye pain, [*based on the operationalized screening criteria for neuropathic pain[1] as it pertains to NOP presented in* ***Figure 1***.

Exclusion Criteria: a) presence of ocular diseases that are the likely cause of pain, such as corneal and conjunctival scarring, corneal edema, uveitis, iris transillumination defects, etc., as the pathophysiology of ocular pain in these individuals is likely different from those with NOP; b) contraindication to TENS (e.g., pacemaker, cardioverter defibrillator, neuro-stimulation (brain or spinal cord), bone growth stimulations, indwelling blood pressure monitors, epilepsy)[29]; [*c) patients with signs of tear dysfunction, including TBUT <5sec, staining >3 (out of a score of 15), and Schirmer <5mm wetting at 5 minutes (in either eye)*]; d) current participation in another study with an investigational drug or device within one month prior to screening; e) pregnant.

Feasibility of, and strategy for, participant recruitment and retention: We will enroll 50 people: 34 in the Active TENS treatment group, and 16 in the Sham TENS group (~2:1 ratio). In consultation with our study statistician, this ratio was chosen in order to include an adequate number of participants in the Active TENS group to evaluate its safety and tolerability [*(the primary outcome of interest for this pilot study, in accord with the SPiRE award mechanism objectives)*] while still keeping the total participant number low for this 2-year pilot study, [*given that each individual will have a 12-month study enrollment period*]. With 34 individuals in the Active TENS group, we will have a 97% probability of observing one or more specific adverse events if the true population incidence rate is 10%; and an 83% probability if the true incidence is 5%.

[*In addition, based on guidelines in the literature,[30] 15 individuals per treatment arm are needed to provide a large enough pilot sample size to guide estimates of variability and effect size for a future RCT with 90% power, α = 0.05, and a medium effect size (0.5).[30] Thus, our proposed sample size is feasible and appropriate because: a) We have a sizable target population to meet the pilot study needs; b) We have powered it to provide meaningful information on our primary safety outcome; c) Our sample size is within recommended guidelines for pilot studies; and d) We have kept the participant number low enough to successfully complete the study within the time and budgetary limitations of the SPiRE award mechanism.*

c. Recruitment methods

Research activities will start after IRB approval of the study. Potential study participants will be identified and may be approached by their medical provider (optometrist, ophthalmologist, primary care physician, neurologists, physical medicine, and rehabilitation physician) during their medical appointment and informed about the opportunity to participate in this study. From our participant pool, study staff will pre-screen individuals, and contact those who may qualify. The study will be described to potential volunteers including the time commitment, a description of the study details and goals, the requirement to provide informed consent, and randomization. The participating investigators who have access to the patient records will conduct screening procedures to ensure each potentially interested volunteer meets initial inclusion/exclusion criteria for this study prior to scheduling the baseline evaluation.

At the baseline visit, study personnel will explain the study goals, the required testing, and the potential risks. The study personnel will also explain the methods used to mitigate risk in the study, including protection of all

private information. Only subjects with the mental capacity to understand the study and the informed consent process will be recruited. Subjects will be asked for their voluntary participation and if they agree, adequate time will be given to read and review the informed consent. The investigators will be available to answer any questions the participant may have regarding the study before consenting. If the participants agrees to be in the study, he/she will sign and date the written informed consent document and study staff or PI (Dr. Felix) will document that consent was properly obtained with their own signature and date. After signature is obtained, the participant will be given his/her own copy of the signed consent and HIPAA documents. Study procedures will not be initiated until signed consent is obtained.

We have demonstrated our capability to recruit a large number (> 200) of participants for previous studies of eye pain,[4,31,32] and, [*based on demographic and detailed pain characterization data from these individuals, we have found that approximately 18% of individuals seen in Dr. Galor's clinic would meet the specific eligibility criteria detailed above*.] If enrollment numbers fall behind our projections, we will rapidly respond to these insufficiencies by: 1) Identifying individuals from other VA clinics (e.g., physical medicine and rehabilitation, neurology); 2) Schedule in-clinic appointments for possible candidates after performing thorough medical records review; and 3) Considering recruitment of non-Veterans. To minimize attrition, we will make bi-weekly phone calls to participants, we will provide payment for each study visit, and we will include a "bonus" payment for those who complete all study time points.

d. Procedures: [**Table 1** presents a timeline of procedures that each enrolled participant will follow.]

Visit 1 will include performance of the consenting process and completion of screening questionnaires and measures (medical history, ocular pain symptom history, and ocular surface exam metrics).

[*Individuals who are found to meet all inclusion criteria based on the Visit 1 screening evaluation, will be randomized, and entered into the intervention trial and scheduled for Visit 2*.] **Visit 2** will begin with completion of demographic and other covariate information questionnaires and measures of current ocular pain symptoms and of corneal and cutaneous evoked pain sensitivity. Subjects will then be read a standard script describing the treatment procedure, the possible sensations that will be felt when the TENS device is turned on, and the safety features of the device. In order to introduce ambiguity about the randomized assignment, instructions include a statement that the sensations the participant might feel are variable from person to person and that the perceptibility of the sensations may fade during the course of the treatment. The initial, in-lab 20-minute Active or Sham TENS (depending on the participant's randomized intervention assignment) trial will then occur. The presence and severity of side-effects and of current ocular pain symptoms will be queried at 5, 30, 60, and 120 minutes post-TENS. Corneal and cutaneous sensitivity measures will also be re-assessed so that a comparison of before vs. after TENS can be made to investigate both the potential mechanism-of-action of TENS and potential predictor variables for responsiveness to at-home TENS treatment. Participants will also be queried regarding which treatment allocation they think they received and their confidence in their guess.

Visit 2 will conclude with a demonstration and instructions on how to properly apply the electrode and initiate activation of the device for the self-administration of TENS at home. The participant will then be required to apply and activate the device by him/herself as the study staff member evaluates their performance..

Participants will be called every two weeks ("bi-weekly") during the at-home treatment period. These phone calls will be used to collect side-effect reports, ocular pain ratings, and information on frequency of TENS use and barriers to use. Participants will come back to the lab for [***Visit 3** at the 3-month intervention time point, and again for **Visit 4** at the 6-month end-of-treatment time point*], for completion of ocular pain questionnaires, eye exams, and QST. At the end of their 6-month participation, the participant will be made aware of their study treatment assignment. Those who received a sham device during the intervention period, they will be prescribed an active TENS device by Dr. Galor, if they decide they want it. An in-clinic trial with the new active device for the 16 participants in the sham group will be performed to ensure the individual has been fully instructed on how to use the device. Thereafter, follow-up phone interviews will occur once per month, until the 12-month time point, to document safety, feasibility, and effectiveness until the 12 month time point. After 12 months have concluded, the participant may keep the device if they so choose.

If the participant does not experience pain relief or wishes to terminate participation in the study, they may do so. They will receive continued care at the eye clinic with Dr. Galor, who will decide future treatment options. The goal of this pilot study is to assess feasibility of TENS thus dropout rates are part of the data collected.

Table 1: Overview of participant study procedures and assessments

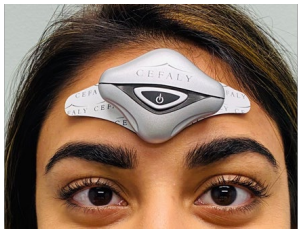
	Screen	Baseline	Initial, in-lab intervention trial (Week 0)					Home intervention (6 months)		Post-intervention
ASSESSMENT/ MEASURE	VISIT 1	VISIT 2						HOME USE Phone calls	VISITS 3 & 4	FOLLOW-UP Phone calls
	Screening	Baseline/ Pre-intervention	In-lab initial intervention trial	Minutes post-intervention				TENS education & training	Day 1 and bi-weekly	End of Month 3, and end of Month 6	Monthly (months 7-12)
				5	30	60	120				
Medical record review	X										
Informed consent	X										
Covariates of interest		X									
Ocular exam metrics and topical anesthetic challenge	X									X	
Intervention			X						X		
Checklist of appropriate and safe use of device								X			
Side-effect report				X	X	X	X		X	X	X
Self-report of frequency of TENS use									X	X	
Obtain device record of TENS use										X	
Allocation questionnaire							X			X	
Ocular pain severity	X	X		X	X	X	X		X	X	X
Corneal and cutaneous evoked pain sensitivity		X					X			X	

TENS – transcutaneous electrical nerve stimulation

e. Intervention details: Fifty enrolled individuals will be randomly assigned, in a ratio of 2:1 (Active:Sham), according to a computer-generated randomization schedule, using a variable (n=6) blocked randomization sequence. Participants and all study staff involved in participant evaluations will be blinded to treatment allocation. Each device will have the stimulation program pre-set according to the randomization assignment. The randomization assignment will be held by the study statistician (Dr. Tang), and one of the research staff members will be responsible for dispensing the Active vs. Sham TENS devices according to the randomization document. This research staff member will *not* conduct any of the outcome measurement evaluations. Each treatment (including the initial in-lab trial session and each at-home session) will consist of a 20-minute stimulation period. The intervention period will consist of 3 (or more, if the participant chooses) weekly sessions of TENS over a 6-month period. The maximum use of the device is one 20-minute sessions daily for 6 months regardless of persistent pain.

Intervention device: The Cefaly Dual® (Cefaly Technology, Belgium; **Figure 2**) was chosen as the TENS device for this pilot study because it is compact, having only one bipolar electrode with no protruding wires, and it targets stimulation of the trigeminal nerve. In addition, Cefaly is FDA cleared for migraine prevention[33] and we have demonstrated that migraine and ocular pain have shared pathophysiological mechanisms.[34] We have discussed the use of the Cefaly device with Cefaly Technology and have confirmed availability of both Active and Sham TENS devices for purchase. These devices record all activity, which we will download at Visits 3 and 4, allowing for the accurate assessment of compliance with the treatment protocol. TENS (active or sham) will be delivered via an external self-adhesive electrode (30 mm by 94 mm) which is placed along the midline of the forehead, bilaterally covering the origins of the supraorbital nerves (branches of 1st trigeminal division).

Figure 2: Demonstration of Cefaly ® TENS position



Active TENS: For the Active TENS intervention, a constant current generator (maximum skin impedance of 2.2KΩ) generates biphasic rectangular impulses (impulse width 250μS, frequency 60Hz) for 20 minutes, with a slow increase in intensity to a maximum of 16mA.

Sham TENS: Cefaly Technology has developed a Sham TENS device which is identical in appearance to, and makes the same sound as, the Active device. The user manual included with both devices are the same. The Sham TENS device delivers a 1 HZ, 1mA stimulation for the 20-minute treatment period. The SHAM TENS device has previously been used in RCTs of the device for migraine.[33]

If device malfunctions: All participants will be given instructions to contact the study coordinator or PI at any time if they have any questions or malfunctions with device. A study staff member will also call each participant every two weeks during the active intervention phase of their study participation to collect data and inquire about any issues with the device or side effects. Thus, if the participant fails to notify us immediately when they may be unsure of something, we will still be able to identify the issue relatively quickly, and in time to remedy the situation to resume the intervention for the majority of the 6-month period. Lastly, at each in-person visit, the device will be queried to capture the frequency of use of the device and will be able to identify any issues with its operation. If a device is found to be malfunctioning, the study staff will contact the manufacturer to trouble shoot and attempt to fix the device. If this is unsuccessful, a study staff member will contact the study statistician so that he may distribute a new device with the same active or sham stimulation (according to the randomization protocol).

f. Data collection and analysis: We have listed the pilot study's objectives above ("Objectives" section) along with the data collection tools/assessments and analyses that will be used to address each objective ("Objectives: section, pp 2-3). (Also refer to **Table 1,** above, for an overview and timing of each assessment.)

***g. Timetable*:**

Study event	YEAR 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Finalize protocol, IRB								
Train personnel								
Participant recruitment (goal number)		**12**	**22**	**16**				
Data collection/intervention/follow-up								
Data processing and analysis								
Merit Review writing and submission								
Publication								

Potential problems and alternative strategies*:* Our research methodology has several limitations, which we recognize and will try to address. First, we have chosen specific assessments and testing protocols, and it is possible that other measures would also be suitable for this study. However, we chose our measures based on: (1) using measures that have been shown to be valid and reliable, and 2) assessing important factors while minimizing patient burden. Second, while our study is designed to assess the safety and feasibility of TENS as a potential treatment for chronic ocular pain, our data may not fully support our stated hypotheses. Thus, we also plan to conduct secondary analyses (Objective 4) to evaluate which factors relate to acceptability of use of the device, adherence to the protocol, side-effects, and efficacy. These analyses will assist with planning follow-up studies in targeted patient subgroups as necessary. Finally, we realize that individuals may suspect to which group they are assigned (Active vs Sham), and we may not meet our goal of obtaining uncertainty of treatment allocation in 50% of Sham participants. To avoid easy identification of treatment arm, we have made the Active and Sham protocols as similar as possible, including using identical looking devices, and we will only recruit individuals who are naïve to TENS treatment for orofacial conditions.

Implications for our findings on advancing scientific knowledge and clinical practice: New treatments for chronic ocular pain that target its presumed underlying mechanisms, are critically needed. If successful, our SPiRE pilot study will provide the preliminary data needed for submission of a Merit Review grant application of a fully-powered RCT of TENS for ocular pain. Results from this future RCT may provide the necessary evidence to support a non-invasive, non-pharmacologic, non-addictive, safe, and effective treatment option for the approximately 14% of Veterans with chronic ocular pain with underlying neuropathic mechanisms.

Privacy and Confidentiality

Sources of Materials: A waiver of HIPAA will be requested for initial screening purposes. After recruitment and completion of the informed consent process, including signing of the HIPAA form, data will be collected and recorded for the study. The primary sources of data for the research study will include: 1) Medical record review to record current medications and co-morbid diagnoses; 2) self-report questionnaires of pain characteristics and side-effects of TENS (see "Appendix_4_Data Collection Forms" for study questionnaires); 3) measurements recorded on paper during ocular exam; 4) measurements recorded during quantitative sensory testing (QST) for pain thresholds; 5) download of transcutaneous electrical nerve stimulation (TENS) device for dates, times, and durations of device use.

Potential Risks:

1. Filling out questionnaires regarding pain poses no physical risk to subjects. However, there is a potential for emotional distress as the participant reflects on the severity of their pain and the impact that it has on his/her life. The likelihood of this risk is low, and the severity is expected to be mild, with only temporary impact to the individual.

2. QST will involve the assessment of pain thresholds by using air puff delivered to the cornea, and via a contact thermode delivering heat stimuli to the skin of the forehead and forearm. There is no risk of damage to the cornea or skin with testing, as the devices have limits regarding stimulus intensity and duration based on safety cut-offs. Subjects do experience transient unpleasant sensations, and occasionally redness of the skin, due to the nature of the testing (i.e., the goal of measuring evoked pain threshold, and the use of a hot temperature to do so). The risk of experiencing unpleasantness is high, though it is not a serious risk as the severity of the unpleasantness and/or redness is mild and its duration is short.

3. There are certain side effects that are possible with the therapeutic use of TENS, These include: the possibility that TENS would increase headache or ocular pain; skin irritation due to the adhesive used on the electrode; unpleasant sensation with higher amplitude of TENS. These side-effects occur infrequently, are usually mild, and are transient once TENS is stopped.

4. As in all studies, there is a risk that non-authorized individuals will gain access to patient information. With required protections in place and the previous experience of the study team in protecting such information, we consider this risk to be highly unlikely, and severity of this risk to be moderate if it does occur because the data collected for the study are not of a sensitive nature.

2. Adequacy of Protection from Risk

b. *Protection Against Risk*: For each of the Potential Risks enumerated above, the below procedures will be used to prevent or minimize these risks.

1. To mitigate the potential stress induced by filling out pain questionnaires, we will explain the nature of the questionnaires prior to administration so that the participant is not caught off-guard. In order to improve data quality and to evaluate potential stress induced by the questionnaires, the study personnel will capture questionnaire responses using an interview format (i.e., the participants will not be left alone to fill out the questionnaires by themselves). If an individual does become distressed, we will offer to set up psychological or psychiatric assessment as needed.

2. The QST procedures to be used in this study have previously been used by our study team on hundreds of other Veterans in our research laboratory. We have only had occasional, brief instances of erythema on the skin surface. To minimize risks, we manually hold the thermal stimulus probe against the skin during testing, and remove it off of the skin between each test trial (we do not use the elastic stimulator strap that comes with the machine and holds the stimulus probe against the skin throughout the testing). For anyone who does experience erythema, we contact them via phone 24 hours after their study visit to confirm that the skin tone has returned to normal and there is no lasting irritation (we have never had a subject report continued irritation).

3. TENS devices have been used for decades for other pain conditions, and the Cefaly Dual device has previously been used for migraine prevention and treatment both in research studies, and clinically, for several years. It has been cleared by the FDA for use in migraines. The Cefaly Dual device is automatically programmed to a maximal amplitude that is of a safe intensity (16 mAmps), and which cannot be increased beyond that level (but can be manually reduced or arrested at a lower level by the user). We will perform the first use of the TENS device in the research lab, with the study research assistant present for the entire time, and participants will remain under observation, and data will be collected regarding side effects for 2 hours after this first 20-minute TENS session. We have also included in our protocol a training session for the self-administration of the TENS device. The participant will not be allowed to leave with the TENS unit, or participate in the at-home treatment portion of the study until he/she demonstrates the correct use of applying, starting, and removing the device. One of the primary outcomes of the study is the report of side-effects. Thus, we will be closely monitoring the presence and severity of side-effects throughout the study on at least a weekly basis. In addition, the study participants will have the PI's (Dr. Felix) and the study physician's (Dr. Galor) after-hours phone numbers in case any serious adverse events do occur.

4. We will mitigate risks to confidentiality and data security by keeping all sensitive information behind locked doors, in locked filing cabinets, and electronic files with any potential identifiers will be password protected on computers that require login credentials from authorized users.

3. Potential Benefits of Research

The study imposes some transient and mild risks in relation to its potential benefits. This project has potential direct benefit to subjects who are randomized to the Active TENS treatment arm, as TENS has been found beneficial in the treatment of chronic non-ocular pain and also beneficial for ocular pain in our retrospective review of patient records.

4. Importance of Knowledge to be Gained

Treatments for chronic ocular pain with a presumed neuropathic component are currently lacking, and a large number of Veterans suffer reduced quality of life due to their persistent eye pain. The proposed research is important in that it will allow for the further testing of a non-pharmacological, non-invasive, and non-addictive treatment therapy to potentially be integrated into clinical care.

5. Data and Safety Monitoring Plan

There will be three levels of participant safety and data quality oversight during the pilot study:
1) Ongoing timely evaluations by the clinical trial team, including oversight of data entry and data quality by the study statistician
2) Institutional oversight by the IRB
3) Oversight by a Medical Monitor (Dr. Caralis)

Data protection and integrity: Measures will be taken to protect the privacy of human subjects and maintain confidentiality of study data. Only study team members will have access to study records. Each subject will be assigned a study identification (ID) number in the format ###-AAA**.** The 3 digit numeric code numbers patients consecutively**.** The 3 letter alpha code will be an identifier, which will not be the participant's initials, assigned as a redundancy check. All data will thus be de-identified to protect patient privacy, and an electronic file with the link between the study ID and the patient identity will be maintained by the study coordinator in a password-protected file on the VA server. Once the study has been completed, this linking document will be deleted.

All source documents will be de-identified to the greatest extend possible (no personal identifiers in records) and kept in a locked file cabinet in a locked room. Data recorded in electronic databases will be completely de-identified and access limited to approved individuals. The study coordinator will input participant data into the electronic database which will then be independent verified from a second study member. Datasets will be stored and backed up on a secure server with "rights and permissions" limited to individuals qualified, trained and approved for specific functions to support for data collection, database management, quality control, quality assurance and analyses. Under the supervision of Mr. Feuer, staff will be trained in necessary activities related to data collection, management, quality assurance and quality control. Edit checks, such as missing data and out-of-range values, will be clarified during quality control. If missing data occurs, analyses will be performed by last observation carried forward, excluding variables when missing data for a variable are extensive.

The study team for this project has spent the last 10 years building the infrastructure needed to carry out the standardized examinations proposed herein. The PI (Dr. Felix) will train and oversee any study staff who administers questionnaires/conducts interviews and QST procedures. Standardized participant instructions are printed and maintained in the lab for reliable repeatability of QST measurements obtained. Dr. Galor will ensure that clinical examination reliability will be maintained by having one research member perform all ocular surface testing. The Manual of Procedures (MOP) will be available to all study investigators, along with all necessary forms for conducting the planned research.

Plan for low recruitment: We have a large population with chronic ocular pain and do not anticipate problems with recruitment. However, if stated enrollment goals fall behind projections, we will rapidly respond to these insufficiencies by: 1) Identifying individuals from other clinics, such as physical medicine and rehabilitation, neurology; 2) Calling individuals based on review of medical records; and 3) Consider recruitment of non-Veterans.

Risk Management and Emergency Response: Patients will be assured that refusal to participate in the study will in no way compromise the care they receive. All adverse events (AEs) will be recorded, graded and attribution assigned. The study technicians, coordinators and investigators will meet at least bi-weekly to review the progress of the study, including all AEs. Expected protocol-related AEs (e.g. transient irritation) will be reported to the IRB during annual ongoing reviews. Unexpected and severe adverse events (SAE) include hospitalization, life-threatening condition, permanent or substantial disability, falls, any important medical event, and death will be reported to the IRB in an expedited fashion according to IRB regulations. The PI will ensure accurate documentation, investigation and follow-up of all possible study-related AEs. The cumulative incidence of adverse events (AEs) will be recorded and unexpected trends will be evaluated further for study intervention relatedness. Protocol amendments will be considered if any study related safety concerns are identified. Both adverse as well as non-specific treatment effects will be monitored and reported to the Data Safety and Monitoring Board as part of the study.

6. Inclusion of Women, Minorities, and Children

Participants **will not be excluded** based on gender, race, or ethnicity. Children **will be excluded** from the study as ocular pain is not common in children and its pathophysiology likely differs from that encountered in adults.

References:

1. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain.* 2016;157(8):1599-1606.
2. Galor A, Moein HR, Lee C, et al. Neuropathic pain and dry eye. *Ocul Surf.* 2018;16(1):31-44.
3. Galor A, Feuer W, Lee DJ, et al. Depression, post-traumatic stress disorder, and dry eye syndrome: a study utilizing the national United States Veterans Affairs administrative database. *Am J Ophthalmol.* 2012;154(2):340-346 e342.
4. Farhangi M, Feuer W, Galor A, et al. Modification of the Neuropathic Pain Symptom Inventory for use in eye pain (NPSI-Eye). *Pain.* 2019;160(7):1541-1550.
5. Goyal S, Hamrah P. Understanding Neuropathic Corneal Pain--Gaps and Current Therapeutic Approaches. *Semin Ophthalmol.* 2016;31(1-2):59-70.
6. Giacomazzi S, Urits I, Hoyt B, et al. Comprehensive Review and Update of Burning Eye Syndrome. *J Patient Cent Res Rev.* 2021;8(3):255-260.
7. Kalangara JP, Galor A, Levitt RC, et al. Characteristics of Ocular Pain Complaints in Patients With Idiopathic Dry Eye Symptoms. *Eye Contact Lens.* 2017;43(3):192-198.
8. Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD. Neuropathic ocular pain: an important yet underevaluated feature of dry eye. *Eye (Lond).* 2015;29(3):301-312.
9. Benitez-Del-Castillo JM, Acosta MC, Wassfi MA, et al. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2007;48(1):173-181.
10. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2005;46(7):2341-2345.
11. Spierer O, Felix ER, McClellan AL, et al. Corneal Mechanical Thresholds Negatively Associate With Dry Eye and Ocular Pain Symptoms. *Invest Ophthalmol Vis Sci.* 2016;57(2):617-625.
12. Galor A, Levitt RC, McManus KT, et al. Assessment of Somatosensory Function in Patients With Idiopathic Dry Eye Symptoms. *JAMA Ophthalmol.* 2016;134(11):1290-1298.
13. Crane AM, Levitt RC, Felix ER, Sarantopoulos KD, McClellan AL, Galor A. Patients with more severe symptoms of neuropathic ocular pain report more frequent and severe chronic overlapping pain conditions and psychiatric disease. *Br J Ophthalmol.* 2017;101(2):227-231.
14. Vance CG, Dailey DL, Rakel BA, Sluka KA. Using TENS for pain control: the state of the evidence. *Pain Manag.* 2014;4(3):197-209.
15. Bi Y, Wei Z, Kong Y, Hu L. Supraspinal neural mechanisms of the analgesic effect produced by transcutaneous electrical nerve stimulation. *Brain Struct Funct.* 2021;226(1):151-162.
16. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. *J Pain.* 2003;4(3):109-121.
17. Sluka KA, Lisi TL, Westlund KN. Increased release of serotonin in the spinal cord during low, but not high, frequency transcutaneous electric nerve stimulation in rats with joint inflammation. *Arch Phys Med Rehabil.* 2006;87(8):1137-1140.
18. Sluka KA, Vance CG, Lisi TL. High-frequency, but not low-frequency, transcutaneous electrical nerve stimulation reduces aspartate and glutamate release in the spinal cord dorsal horn. *J Neurochem.* 2005;95(6):1794-1801.
19. Pedrotti E, Bosello F, Fasolo A, et al. Transcutaneous periorbital electrical stimulation in the treatment of dry eye. *Br J Ophthalmol.* 2017;101(6):814-819.
20. Cai MM, Zhang J. Effectiveness of transcutaneous electrical stimulation combined with artificial tears for the treatment of dry eye: A randomized controlled trial. *Exp Ther Med.* 2020;20(6):175.
21. Ticho U, Olshwang D, Magora F. Relief of pain by subcutaneous electrical stimulation after ocular surgery. *American journal of ophthalmology.* 1980;89(6):803-808.
22. Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. *The Cochrane database of systematic reviews.* 2019;4:CD011890.
23. Vetter TR. A primer on health-related quality of life in chronic pain medicine. *Anesth Analg.* 2007;104(3):703-718.
24. Sivanesan E, Levitt RC, Sarantopoulos CD, Patin D, Galor A. Noninvasive Electrical Stimulation for the Treatment of Chronic Ocular Pain and Photophobia. *Neuromodulation.* 2018;21(8):727-734.

25. Zayan K, Aggarwal S, Felix E, Levitt R, Sarantopoulos K, Galor A. Transcutaneous Electrical Nerve Stimulation for the Long-Term Treatment of Ocular Pain. *Neuromodulation.* 2020;23(6):871-877.
26. Galor A, Zlotcavitch L, Walter SD, et al. Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. *Br J Ophthalmol.* 2015;99(5):665-668.
27. Galor A, Covington D, Levitt AE, et al. Neuropathic Ocular Pain due to Dry Eye is Associated with Multiple Comorbid Chronic Pain Syndromes. *J Pain.* 2016;17(3):310-318.
28. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain.* 2004;108(3):248-257.
29. Johnson MI, Jones G. Transcutaneous electrical nerve stimulation: current status of evidence. *Pain Manag.* 2017;7(1):1-4.
30. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res.* 2016;25(3):1057-1073.
31. Ong ES, Felix ER, Levitt RC, Feuer WJ, Sarantopoulos CD, Galor A. Epidemiology of discordance between symptoms and signs of dry eye. *Br J Ophthalmol.* 2018;102(5):674-679.
32. 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.
33. Riederer F, Penning S, Schoenen J. Transcutaneous Supraorbital Nerve Stimulation (t-SNS) with the Cefaly((R)) Device for Migraine Prevention: A Review of the Available Data. *Pain Ther.* 2015.
34. Diel RJ, Mehra D, Kardon R, Buse DC, Moulton E, Galor A. Photophobia: shared pathophysiology underlying dry eye disease, migraine and traumatic brain injury leading to central neuroplasticity of the trigeminothalamic pathway. *Br J Ophthalmol.* 2020.
35. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63(8):e1-37.
36. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2003;106(3):337-345.
37. Buckenmaier CC, Galloway KT, Polomano RC, McDuffie M, Kwon N, Gallagher RM. Preliminary validation of the Defense and Veterans Pain Rating Scale (DVPRS) in a military population. *Pain Medicine.* 2013;14(1):110-123.
38. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye.* 2010;33(2):55-60.
39. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118(5):615-621.