Title: The effect of Upneeq (oxymetazoline hydrochloride 0.1%) on palpebral fissure height, eye redness, and patient-reported eye appearance.

UMH Protocol Number: 20210199

NCT04831047

3/29/23

Protocol Title

The effect of Upneeq™ (oxymetazoline hydrochloride 0.1%) on palpebral fissure height, eye redness, and patient-reported eye appearance.

Objectives

Aim 1:
To determine the effect of Upneeq™ (oxymetazoline hydrochloride 0.1%) on palpebral fissure height.

Aim 2:
To determine the effect of Upneeq™ (oxymetazoline hydrochloride 0.1%) on eye redness.

Aim 3: To evaluate the effect of Upneeq™ (oxymetazoline hydrochloride 0.1%) on patient-reported eye appearance.

Hypothesis: We hypothesize application of Upneeq™ (oxymetazoline hydrochloride 0.1%) will cause an increase in subjects' palpebral fissure height, decrease in eye redness, and improvement in patient-reported eye appearance.

Background

Abnormal eyelid position often may be attributed to malfunctioning levator palpebrae superior muscle or Müller's muscle. Müller's muscle, a smooth muscle with a predominance of alpha-2 adrenergic receptors, contracts in response to sympathetic stimulation or topical adrenergic agonists.[1,2] Therefore, topical ocular administration of compounds that agonize adrenergic receptors causes an increase in interpalpebral fissure height via contraction of Müller's muscle, which helps mitigate ptosis effects as well as lending the cosmetically beneficial effect of an eye that is more open.[3] Compounds such as apraclonidine, a medication with mixed alpha-2 and weak alpha-1 agonist properties, have been shown to reverse ptosis caused by Horner's syndrome and botulinum injections and to help assess blepharoptosis preoperatively.[4,5] Although the primary mechanism of apraclonidine is alpha-2 agonism, which inhibits norepinephrine release from sympathetic nerve terminals, it is also a weak alpha-1 agonist, and allows for direct stimulation of smooth muscle. Multiple studies have observed the ability of topical apraclonidine to increase palpebral fissure height by elevating the upper lid.[6–8] Similarly, brimonidine, an alpha-2 adrenergic agonist with a much weaker affinity for the alpha-1 receptor,[9] has been used to decrease intraocular pressure by intensifying uveoscleral outflow and reducing aqueous humor inflow (brimonidine 0.2%)[10], reduce ocular redness through vasoconstriction with low dose medication, and dilate the pupil to camouflage anisocoria associated with Horner's syndrome.[9,11,12] In addition, brimonidine has been observed to elevate patients' eyelids via its alpha-1 and alpha-2 activation of Müller's muscle in prior literature assessing glaucoma patients.[13]

Similar to apraclonidine and brimonidine, oxymetazoline acts upon the alpha receptors as both an alpha-1 and alpha-2 receptor agonist.[14,15] Oxymetazoline has been used as nasal spray to promote decongestion through nasal vasoconstriction,[16–18] topical oxymetazoline has been used for

rosacea,[19] and ophthalmic oxymetazoline has been used for non-infectious conjunctivitis to improve hyperemia.[20–22] The combination of alpha-1 and alpha-2 agonist action of oxymetazoline may be more effective in acting upon Muller's muscle to increase palpebral height compared to apraclonidine and brimonidine, which primarily target the alpha-2 receptors with partial alpha-1 receptor activation. Two randomized Phase III trials have reported significant improvement in mean number of points visualized on peripheral field test and increase in marginal reflex distance,[23] leading to the FDA approval of Upneeq™ (oxymetazoline hydrochloride 0.1%) for ptosis. Of note, these studies have primarily examined patients with a relatively large degree of ptosis (mean baseline MRD1 1.09 mm). It is possible that patients with mild or minimal eyelid malposition may also benefit from oxymetazoline; however, this has not yet been evaluated.

While eyelid position has been shown as a recent indication for oxymetazoline ophthalmic use, oxymetazoline may result in ocular surface vessel vasoconstriction to improve eye redness, which may provide an alternative role for this medication beyond its effect on ptosis. Previous studies with the apraclonidine and brimonidine demonstrated improvement in eye redness through conjunctival blanching, likely through the alpha-2 agonist effect on the smooth muscle of ocular vessels to result in vasoconstriction.[11,24] Therefore, it is possible that oxymetazoline, which similarly has both alpha-1 and alpha-2 activity, may have similar effects on improving eye redness. Prior studies have reported improvement in hyperemia and eye redness in patients with non-infectious conjunctivitis following oxymetazoline use[20,21,25]; however, no study has yet evaluated the effect of oxymetazoline on reducing redness in healthy eyes, which may improve cosmesis.

Improvement in eyelid position and eye redness may lead to subjective patient-reported improvement in cosmesis, which may be important for improvement in self-confidence, psychological well-being, and increased comfort in social settings.[26] Prior studies investigating the effect of surgical ptosis repair have reported improvement in perceived eye appearance. However, no study has yet evaluated the effect of medical management of eyelid position on subjective eye appearance. The FACE-Q is a patient-reported outcome measurement developed to address the lack of instruments for facial aesthetic procedures.[27–30] FACE-Q has been previously reported as one of only 3 patient-reported outcome measures that met international recommendations for how such tools should be developed and validated per Oxford review of cosmetic surgery patient-reported outcome measures.[29] It has been used to evaluate patient-reported outcomes associated with multiple facial surgical procedures including botulinum toxin injections, blepharoplasties, and other cosmetic eye treatments.[29,31,32] Therefore, the FACE-Q may be a useful, well-validated method of measuring patient perception of eye appearance following administration of topical medications that may result in improved cosmesis.

To the authors' knowledge, there are currently no randomized control trials objectively observing the effects of oxymetazoline on eye redness. Additionally, further studies are needed to better evaluate the effect of oxymetazoline on palpebral fissure height and the potential variability of this effect in different individuals, including those with different eyelid positions. Lastly, no studies have evaluated patient-reported aesthetic appearance before and after oxymetazoline use. In this randomized controlled study, we aim to record changes in palpebral fissure height and eye redness before and after administration of 0.1% oxymetazoline ophthalmic solution, aiming to gain a deeper understanding of oxymetazoline's therapeutic potential as well as evaluate patient-reported subjective changes in appearance.

Inclusion and Exclusion Criteria*

Inclusion Criteria

- Adults age 18 and above able to provide informed consent to participate
- Subject with stable ocular health, defined as no ocular conditions requiring ongoing topical therapy or recent surgical intervention

Exclusion Criteria

- Adults unable to consent
- Individuals less than 18 years of age
- Prisoners
- Pregnant women.
- Patients will be asked if they are pregnant by research staff before participation in the study.
- Known contradictions or sensitivities to study medication (oxymetazoline)
- Ocular surgery within the past 3 months or refractive surgery within the past six months
- Grossly abnormal lid margins, anatomical abnormalities, previous eyelid or orbital surgery
- Variable ptosis or eyelid position (e.g., myasthenia gravis, thyroid eye disease, or blepharospasm)
- Significant pre-existing ptosis of any cause (defined as MRD1 < 1mm)
- Any ocular or systemic condition that, in the opinion of the investigator, would confound study data, interfere with the subject's study participation, or affected the subject's safety or trial parameters
- Presence of an active ocular infection
- Prior (within 5 days of beginning study treatment) use of eye whiteners (eg, vasoconstrictors), decongestants, antihistamines (including over the counter and herbal topical ophthalmic medications), phenylephrine dilating drops, any other topical ophthalmic agents
- Inability to sit comfortably for 15 – 30 minutes

Subject Identification and Recruitment

Potential subjects will be identified during their normal clinic visit at the Bascom Palmer Eye Institute, primarily within the Oculoplastics department. The attending physician will ask eligible patients if they are interested in hearing about the study. No phone calls for recruitment will be made prior to the regular clinic visit. Patients may additionally be referred from other providers within the Bascom Palmer Eye Institute during their regular visits or from the emergency room. Bascom Palmer employees and University of Miami Miller School of Medicine students would also be invited to participate if interested.

Participants who qualify for the study and express an interest in participating will have the study explained to them by a research study member and can ask questions. They will receive information on risks and benefits to research participation. They will receive a copy of the consent form and if desired may be able to take the consent form home prior to signing for

further consultation. Those who are interested in participation will be given a scheduled appointment to meet with research staff.

Upneeq™ Drug Product

Upneeq™ is an FDA approved drug for the treatment of ptosis. It is available in a drop formulation. This agent should be considered exempt from IND requirements as the study is using the drug in realm of FDA indications and meets the below IND criteria.

- The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- The research is not intended to support a significant change in the advertising for the product.
- The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7.

Drug insert is available and attached to the IRB protocol.

Procedures Involved
We anticipate that procedures listed below will take about 30 to 40 minutes per patient. Except as noted, the procedures below are not considered standard of care and are being conducted for the study alone.

Part 1: Pre-treatment data collection

- Patients will complete a pre-treatment survey to evaluate the perceived baseline eye appearance.
- Patients will undergo pre-treatment baseline photography. Images will be taken in a room with the same conditions.

- An Ipad (Apple Inc, Cupertino, California, U.S.A.) with the Upneeq software app will be used. This app directs subjects to a standardized position and distance from the Ipad to measure the MRD1 and MRD2 in each eye. The subjects will focus on the Ipad with their eyes in primary gaze.

- All photographs will be taken with the dedicated Ipad camera, which will use standardized aperture, shutter speed, and exposure time.

- Photographs will be recorded and saved as JPG files (1200 9 797 pixels, 24-bit, RGB) in a locked folder. When not in use, the Ipad and accompanying software will be secured in a locked drawer.

Part 2: Upneeq™ application

- Subjects will be randomized to receive either Upneeq™ or balanced saline placebo in both eyes.
- Based on the randomization results, the examiner will apply Upneeq™ eye drops or saline to the subject's eyes.

Part 3: Post-treatment data collection

- Subjects will wait 2 hours after they receive eye drops.
- Subjects will be photographed at 2 hours after drop instillation according to the procedure described above. This will allow Upneeq to reach its average time for maximum effect.
- Patients will complete a post-treatment survey to evaluate the perceived change in eye appearance following Upneeq™ administration.

Part 4: Data analysis

- Data will be recorded and stored in a secure Microsoft Office Excel (Microsoft Corporation, Redmond, WA, U.S.A.) spreadsheet. Data will be graphically analyzed and represented with Adobe Photoshop (Adobe, Inc., San Jose, CA, U.S.A).
- Data assessed will involve assessing pre and post-treatment MRD1 and MRD2, investigator-assessed measurements of conjunctival color including the Validated Bulbar Redness Scale and patient-reported outcome measures such as those measured through the FACE-Q survey or other patient perceptions of the drop and changes in appearance before and after drop instillation.
- User performing analysis will be blinded to which patients received study drug or control.

No additional follow-up outside of the patient's next routine clinic visit will be needed. Patients who do have symptoms concerning any post-procedural complications will be instructed to notify study staff immediately. A phone number will be provided. Clinical examination post-procedure will be at Bascom Palmer Eye Institute.

Outcomes Measured

Primary outcome:

Outcome Measure Title: Change in palpebral fissure height

Outcome Measure Description: Palpebral fissure height will be calculated from the sum of marginal reflex distance 1 and 2 measured from the photograph by Ipad software and recorded by investigators.

Outcome Measure Timeframe: Baseline prior to drop administration, Day 1

Secondary outcomes:

Outcome Measure Title: Change in eye redness

Outcome Measure Description: Scoring of ocular redness from clinical photographs will be performed by investigators on a 0 - 100 unit scale as compared to standardized reference photographs (0 = no redness, 100 = very red). Images may also be analyzed quantitatively using software to calculate changes in redness between photographs.

Outcome Measure Timeframe: Baseline prior to drop administration, Day 1

Outcome Measure Title: Change in Patient-reported eye appearance

Outcome Measure Description: Patient-reported eye appearance will be assessed by patient completion of the FACE-Q Eye Module Survey. These surveys have a total raw score of 7 (worst) to 28 (best). Higher scores indicate greater satisfaction. These survey scores will be

assessed individually. Additionally patients will be queried regarding their perception of the drop including changes in eye appearance before or after drop instillation.
Outcome Measure Timeframe: Baseline prior to drop administration, Day 1

Adverse Events and Serious Adverse Events
Treatment-emergent adverse events, defined as any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment, will be monitored and reported throughout the study. Treatment emergent adverse scale will be graded as the following:

- Mild: Transient or mild discomfort (<48 hours) to the subject; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity of the subject; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity of the subject, some assistance usually required; medical intervention/therapy required including possible hospitalization.

Serious adverse events are defined as those which result in death, hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability), or congenital anomaly / birth defect.

Previously reported treatment-emergent adverse effects are described further in the risks section below.

Withdrawal of Subjects
Patients may withdraw at any time at their discretion. Subject withdrawn from and/or terminated from research with or without their consent are those who are found to not meet inclusion/exclusion criteria, and/or are not able to complete the research protocol in its entirety, as well as those who suffer a treatment-emergent adverse effect requiring medication discontinuation. For any subjects who withdraw from research, including partial withdrawal from procedures, study data of the withdrawn subject will not be included in statistical analysis and will be shredded.

Data and Specimen Banking*
Not applicable.

Data Management*

Steps to Secure Data
The study coordinator will assign each patient a specific ID number and place this information on a separate spreadsheet. The study coordinator will collect the sex, patient's age, and dates of service, but no other identifiable information. No names will be used in the forms. Presentations and publications will not identify individual patients. Data from the subjects' medical records will be encrypted and stored securely as detailed below. Identifiable data will not be stored for future use beyond the timeframe of this study. The release of data will be only to study members and no other outside organization.

Data will be kept under lock and key in Dr. Wendy Lee's office at the Bascom Palmer Eye Institute Oculoplastics Research Laboratory on the 4th floor (900 NW 17th Street, Miami, FL 33136), data encoded in the computer will be password-protected and will be available only to study personnel, and protected health information will not be re-used or disclosed for other purposes. Study members will be trained on how to log in and log out of the computers. The study coordinator will assign each patient a specific ID number and the sex, patient's age and date of on a separate spreadsheet. The study coordinator will record the study results with the specific sample ID on another spreadsheet.

Statistical Analysis Plan

Statistical analysis will be performed by the researchers. A paired t-test will be used to analyze the difference in palpebral fissure height, eye redness, and patient-reported eye appearance as measured through the FACE-Q survey. 114 subjects will be required to perform perimetric statistics. Chi-squared testing will be used to assess categorical variables. $P < 0.05$ will be considered significant.

Risks to Subjects*

The primary risks to the subjects are adverse reactions to the medication. These risks are explained to patients prior to their arrival to the Oculoplastics Clinic. Previously described potential adverse reactions to include instillation site discomfort, punctate keratitis, and blurry vision although in general is well-tolerated.[21–23,33] Potential psychosocial risks to subjects include time taken from their day to undergo tests, potentially missing work, and anxiety or discomfort from the eye drop instillation process. This study is not collecting sensitive information, thus no potential risk to reputation or legal risks should occur.

Subjects will be instructed to call immediately for an appointment if they notice a change in their vision, eye redness, or the development of pain in either eye. Care will be taken by all study members to prevent the occurrence of any adverse events.

There are no well-controlled studies of oxymetazoline in pregnant women, and the risks to the fetus or embryo are unknown/unforeseen. One prior publication reported possible renal collecting system abnormalities after using inhaled oxymetazoline[34]; however, another larger prospective study found no increased risk of malformations associate with nasal inhalant use including oxymetazoline,[35] and no alterations in maternal or fetal circulation were found to be associated with oxymetazoline use.[36] No studies have been performed evaluating topical oxymetazoline ophthalmic solution. Oxymetazoline is classified as US FDA pregnancy category C.

- US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Participants will be informed of the above information and reserve the right to decline participation in the study. We will not be following pregnancy outcomes.

Unanticipated problems or complications will be reported to the IRB according to posted guidelines.

Risks of the study are listed above and will be minimized by the following:

- Study will be discontinued if subjects experience any negative effect from the medication
- Patients with a known sensitivity or history of adverse reaction to oxymetazoline or similar medications will be excluded from the study

As with any study, there is a risk of confidentiality breach. The research members will assign each patient a specific ID number and place this information on a separate spreadsheet. No names will be used in the forms. Presentations and publications will not identify individual patients.

Potential Benefits to Subjects*

There will be no direct benefit to patients participating in the study. Their involvement may provide satisfaction for aiding in future research, particularly if they would be interested in personally using the agent to increase their own palpebral fissure height or eye redness in the future.

Vulnerable Populations*

Bascom Palmer employees and Miller School of Medicine students are considered vulnerable populations as they would be invited to participate in the study if they were interested.

Setting

Study location will be at the Bascom Palmer Eye Institute.

Resources Available

Principal investigator will be in charge of the studies and has been involved in multiple human clinical trials at the University of Miami.

Resident physicians have extensive experience in clinical research, slit lamp examination, and obtaining clinical photographs, and data collection and analysis.

Research fellow at the Bascom Palmer Eye Institute has experience with data collection and analysis.

Prior Approvals

None.

Recruitment Methods

Wendy Lee, MD, the principle investigator of this study, will assess patients for study eligibility by reviewing the medical record. These patients will be coming in during their normal visit at the Bascom Palmer Eye Institute Oculoplastics Clinic. Dr. Lee will ask eligible patients if they are interested in hearing about the study. No phone calls for recruitment will be made prior to the regular clinic visit. Other subjects may additionally be referred from other providers within the Bascom Palmer Eye Institute during their regular visits. Bascom Palmer employees and University of Miami Miller School of Medicine students would also be invited to participate if interested. No payment will be provided to patients for their participation.

Subjects who qualify for the study and express an interest in participating will have the study explained to them by a research study member and have the opportunity to ask questions. They will receive information on risks and benefits to research participation. They will receive a copy of the consent form and if desired may be able to take the consent form home prior to signing for further consultation. Those who are interested in participation will be given a scheduled appointment to meet with research staff.

Local Number of Subjects

The goal of this pilot study is to assess the ability of Upneeq™ in patients as an agent to increase eyelid height as well as possibly improve eye redness and patient-reported eye appearance. The time and resource constraints of our current pilot study allow for only approximately 114 participants.

Confidentiality

Check all that apply:

Data obtained or created for this research will be stored on an encrypted electronic device or system owned by the University of Miami or on a cloud storage system that has been approved by the University of Miami for storage or research data.

The Investigator (or research staff) will record (e.g. write down, abstract) data collected in a manner that **does not include** any indirect or direct identifiers and the recorded data **will not be linked to the individual's' identity.**

The investigator (or research staff) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of the subject. The investigator **will assign a code to each subject and link the code to the subject's identity**. The research team will maintain the link to the subject's identity on a document separate from the research data. Both documents will be stored in separate files on a University of Miami encrypted device or on a

University of Miami approved cloud storage system. The research team will destroy the identifiers at the earliest opportunity.

The research team will maintain the research data for at least three years.

Bio-Specimens obtained for this research will be stored without any direct or indirect identifiers.

Bio-Specimens obtained for this research will be stored in a de-identified coded manner.

When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

Authorization for Use and Disclosure of Protected Health Information (HIPAA)

If the research team will access patient medical records or other identifiable health information for this research, you must obtain a waiver of the requirement for written authorization from the patients to access their medical records.

Type of Request:
Waiver of Authorization for access to medical record for subject identification/recruitment.
Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.
I confirm

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible. ***I confirm***

Provisions to Protect the Privacy Interests of Subjects

An adequate plan to protect identifiers from improper use and disclosure is included in our study. Patient data will be collected under patient initials only. Data will be kept under lock and key in Dr. Wendy Lee's office at the Bascom Palmer Eye Institute Oculoplastics Research Laboratory on the 4th floor (900 NW 17th Street, Miami, FL 33136), data encoded in the computer will be password-protected and will be available only to study personnel, and protected health information will not be re-used or disclosed for other purposes. Separation of identifiers and data during storage, use and transmission will be implemented. Additionally, paper shredding and erasure of electronic data will be done at the earliest opportunity.

Consent Process

After identifying eligible study subjects, those who are interested in participating will be given a scheduled appointment to meet with research staff to review the consent form. The consent process will take place at Bascom Palmer Eye Institute. Adequate time will be devoted to the consent discussion; the patients will be given ample time to review the consent form and ask questions. If patients have a different language than English, such as Spanish, as their native language, a translator will be used to explain the research process. A separate consent translated in that appropriate language will be created prior to signing the consent. A witness will be used if the patient has vision impairment and is unable to read the consent.

Process to Document Consent in Writing

Consent of the subject will be documented in writing.

Bibliography/References Cited

1. Esmaeli-Gutstein B, Hewlett BR, Pashby RC, Oestreicher J, Harvey JT. Distribution of adrenergic receptor subtypes in the retractor muscles of the upper eyelid. *Ophthal Plast Reconstr Surg*. 1999;15(2):92-99. doi:10.1097/00002341-199903000-00005

2. Skibell BC, Harvey JH, Oestreicher JH, et al. Adrenergic receptors in the ptotic human eyelid: correlation with phenylephrine testing and surgical success in ptosis repair. *Ophthal Plast Reconstr Surg*. 2007;23(5):367-371. doi:10.1097/IOP.0b013e3181462a2e

3. Munden PM, Kardon RH, Denison CE, Carter KD. Palpebral fissure responses to topical adrenergic drugs. *Am J Ophthalmol*. 1991;111(6):706-710. doi:10.1016/s0002-9394(14)76775-3

4. Park SJ, Jang SY, Baek JS, Chin S, Jang JW. Distribution of Adrenergic Receptor Subtypes and Responses to Topical 0.5% Apraclonidine in Patients With Blepharoptosis. *Ophthal Plast Reconstr Surg*. 2018;34(6):547-551. doi:10.1097/IOP.0000000000001095

5. Wijemanne S, Vijayakumar D, Jankovic J. Apraclonidine in the treatment of ptosis. *J Neurol Sci*. 2017;376:129-132. doi:10.1016/j.jns.2017.03.025

6. Kirkpatrick CA, Shriver EM, Clark TJE, Kardon RH. Upper Eyelid Response to Topical 0.5% Apraclonidine. *Ophthal Plast Reconstr Surg*. 2018;34(1):13-19. doi:10.1097/IOP.0000000000000843

7. Yazici B, Beden U. Use of 0.5% apraclonidine solution in evaluation of blepharoptosis. *Ophthal Plast Reconstr Surg*. 2008;24(4):299-301. doi:10.1097/IOP.0b013e31817f526a

8. Koc F, Kavuncu S, Kansu T, Acaroglu G, Firat E. The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis. *Br J Ophthalmol*. 2005;89(11):1442-1444. doi:10.1136/bjo.2005.074492

9. Torkildsen GL, Sanfilippo CM, DeCory HH, Gomes PJ. Evaluation of Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution, 0.025% for Treatment of Ocular Redness. *Curr Eye Res*. 2018;43(1):43-51. doi:10.1080/02713683.2017.1381269

10. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. *Arch Ophthalmol Chic Ill 1960*. 1995;113(12):1514-1517. doi:10.1001/archopht.1995.01100120044006

11. McLaurin E, Cavet ME, Gomes PJ, Ciolino JB. Brimonidine Ophthalmic Solution 0.025% for Reduction of Ocular Redness: A Randomized Clinical Trial. *Optom Vis Sci*. 2018;95(3):264-271. doi:10.1097/OPX.0000000000001182

12. deSousa J-L, Malhotra R. Brimonidine for anisocoria. *Ophthalmology*. 2007;114(7):1419. doi:10.1016/j.ophtha.2006.08.021

13. Burroughs JR, Anderson RL, Patrinely JR, Weinberg DA, McCann JD, McMullan TFW. Preoperative assessment of the eye and periocular region. *Semin Plast Surg*. 2007;21(1):5-17. doi:10.1055/s-2007-967742

14. Hsia E, Tian M, Gil D. Reduction in ultraviolet B light-induced erythema by oxymetazoline and brimonidine is mediated by different α-adrenoceptors. *Exp Dermatol*. 2018;27(7):763-768. doi:10.1111/exd.13557

15. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. *Fundam Clin Pharmacol*. 2010;24(6):729-739. doi:https://doi.org/10.1111/j.1472-8206.2009.00805.x

16. Graf P, Hallén H. Effect on the Nasal Mucosa of Long-Term Treatment With Oxymetazoline, Benzalkonium Chloride, and Placebo Nasal Sprays. *The Laryngoscope*. 1996;106(5):605-609. doi:https://doi.org/10.1097/00005537-199605000-00016

17. Graf P, Juto J-E. Decongestion Effect and Rebound Swelling of the Nasal Mucosa during 4-Week Use of Oxymetazoline. *ORL*. 1994;56(3):157-160. doi:10.1159/000276633

18. Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. 2011;127(4):927-934. doi:10.1016/j.jaci.2011.01.037

19. Draelos ZD, Gold MH, Weiss RA, et al. Efficacy and safety of oxymetazoline cream 1.0% for treatment of persistent facial erythema associated with rosacea: Findings from the 52-week open label REVEAL trial. *J Am Acad Dermatol*. 2018;78(6):1156-1163. doi:10.1016/j.jaad.2018.01.027

20. Breakey AS, Cinotti AA, Hirshman M, Skowron RA, Samson CR, Danzig MR. A double-blind, multi-centre controlled trial of 0.25% oxymetazoline ophthalmic solution in patients with allergic and non-infectious conjunctivitis. *Pharmatherapeutica*. 1980;2(6):353-356.

21. Rybiczka R, Mauracher E. Oxymetazoline ophthalmic solution versus naphazoline solution in non-infectious conjunctivitis. *Pharmatherapeutica*. 1983;3(6):376-381.

22. Fox SL, Samson CR, Danzig MR. Oxymetazoline in the Treatment of Allergic and Non-Infectious Conjunctivitis. *J Int Med Res*. 1979;7(6):528-530. doi:10.1177/030006057900700609

23. Slonim CB, Foster S, Jaros M, et al. Association of Oxymetazoline Hydrochloride, 0.1%, Solution Administration With Visual Field in Acquired Ptosis: A Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Ophthalmol*. Published online October 1, 2020. doi:10.1001/jamaophthalmol.2020.3812

24. Ackerman SL, Torkildsen GL, McLaurin E, Vittitow JL. Low-dose brimonidine for relief of ocular redness: integrated analysis of four clinical trials. *Clin Exp Optom*. 2019;102(2):131-139. doi:https://doi.org/10.1111/cxo.12846

25. Nayak BK, Kishore K, Gupta SK. Evaluation of oxymetazoline and naphazoline in benign red eyes : A double blind comparative clinical trial. *Indian J Ophthalmol*. 1987;35(4):190.

26. Maisel A, Waldman A, Furlan K, et al. Self-reported Patient Motivations for Seeking Cosmetic Procedures. *JAMA Dermatol*. 2018;154(10):1167-1174. doi:10.1001/jamadermatol.2018.2357

27. Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and Psychometric Evaluation of the FACE-Q Satisfaction with Appearance Scale: A New Patient-Reported Outcome Instrument for Facial Aesthetics Patients. *Clin Plast Surg*. 2013;40(2):249-260. doi:10.1016/j.cps.2012.12.001

28. Klassen A, Cano S, Scott A, Snell L, Pusic A. Measuring Patient-Reported Outcomes in Facial Aesthetic Patients: Development of the FACE-Q. *Facial Plast Surg*. 2010;26(04):303-309. doi:10.1055/s-0030-1262313

29. Klassen AF, Cano SJ, Grotting JC, et al. FACE-Q Eye Module for Measuring Patient-Reported Outcomes Following Cosmetic Eye Treatments. *JAMA Facial Plast Surg*. Published online January 19, 2017. doi:10.1001/jamafacial.2016.1018

30. Klassen AF, Cano SJ, Schwitzer JA, Scott AM, Pusic AL. FACE-Q scales for health-related quality of life, early life impact, satisfaction with outcomes, and decision to have treatment: development and validation. *Plast Reconstr Surg*. 2015;135(2):375-386. doi:10.1097/PRS.0000000000000895

31. Chang BL, Wilson AJ, Taglienti AJ, Chang CS, Folsom N, Percec I. Patient Perceived Benefit in Facial Aesthetic Procedures: FACE-Q as a Tool to Study Botulinum Toxin Injection Outcomes. *Aesthet Surg J*. 2016;36(7):810-820. doi:10.1093/asj/sjv244

32. Chen B, Song H. Measuring satisfaction with appearance: Validation of the FACE-Q scales for double-eyelid blepharoplasty with minor incision in young Asians- retrospective study

of 200 cases. *J Plast Reconstr Aesthet Surg*. 2017;70(8):1129-1135. doi:10.1016/j.bjps.2017.05.028

33. Samson CR, Danzig MR, Sasovetz D, Thompson HS. Safety and toleration of oxymetazoline ophthalmic solution. *Pharmatherapeutica*. 1980;2(6):347-352.

34. Menezes GA, Araujo Júnior E, Lopes J, Belmonte S, Tonni G, Werner H. Prenatal diagnosis and physical model reconstruction of agnathia-otocephaly with limb deformities (absent ulna, fibula and digits) following maternal exposure to oxymetazoline in the first trimester. *J Obstet Gynaecol Res*. 2016;42(8):1016-1020. doi:10.1111/jog.13014

35. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol*. 1997;100(3):301-306. doi:10.1016/S0091-6749(97)70241-0

36. Rayburn WF, Anderson JC, Smith CV, Appel LL, Davis SA. Uterine and fetal Doppler flow changes from a single dose of a long-acting intranasal decongestant. *Obstet Gynecol*. 1990;76(2):180-182.