The Glaucoma Compass

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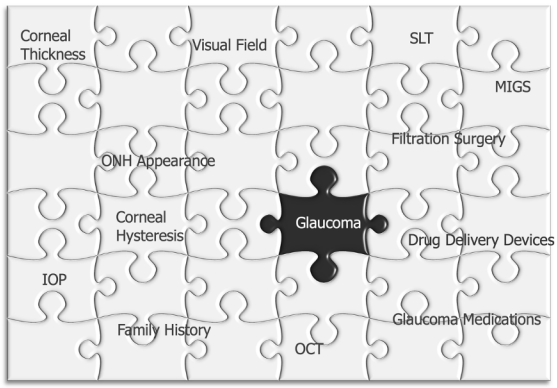
Disclosure Statement

- Aerie Pharmaceuticals
- Alcon
- Biotissue
- Diopsys
- Ivantis
- MacuLogix
- Nova Oculus
- Nidek
- Optovue
- Quantel
- Reichert
- RevolutionEHR
- Shire

2



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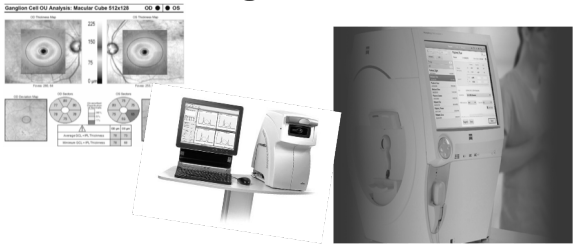
Diagnosis



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Lowering IOP Reduces the Risk of Disease Progression

Study	IOP	Progression (Tx/No Tx)
OHTS[2]	20% reduction	4.4%/9.5% (5 years)
EMGT[2]	25% reduction	45%/62% (6 years)
CNTGS[3]	30% reduction	12%/35% (7 years)
CIGTS[4] (medicine)	≈35% reduction	No progression (5 years)
CIGTS[4] (surgery)	≈48% reduction	No progression (5 years)
AGIS[5]	< 18 mm Hg	No progression (6 years)
AGIS[5]	> 18 mm Hg	1.93 units (7 years)

1. Kass et al. *Arch Ophthalmol.* 2002; 2. Heijl et al. *Arch Ophthalmol.* 2002; 3. CNTG Study Group. *Am J Ophthalmol.* 1998; 4. Lichter et al. *Ophthalmology.* 2001; 5. AGIS Investigators. *Am J Ophthalmol.* 2000.

5

CCT AS A RISK FACTOR

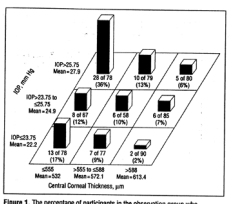

Figure 1. The percentage of participants in the observation group who developed primary open-angle glaucoma (median follow-up, 72 months) grouped by baseline intraocular pressure (IOP) of ≈23.75 mm Hg, >23.75 mm Hg to ≈25.75 mm Hg, and >25.75 mm Hg and by central corneal thickness measurements of ≈555 µm, >555 µm to ≈588 µm, and >588 µm. These percentages are not adjusted for length of follow-up. The means are not identical to those given in the text, which includes all participants in the Ocular Hypertension Treatment Study rather than just the observation group.

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Corneal Hysteresis (CH)

Corneal Hysteresis reflects the ability of the corneal tissue to dissipate energy [1]

Function of viscoelastic damping[2]

Provides insight into ocular properties that were not previously understood or conceived of

1. Luce DA. *J Cataract Refract Surg.* 2005;31:156-162.
2. Dupps WJ Jr. *J Cataract Refract Surg.* 2007;33:1499-1501.
3. Glass DH et al. *Invest Ophthalmol Vis Sci.* 2008;49:3919-3926.

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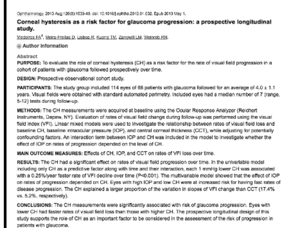
CH as a Predictor of Progression


Ophthalmology. 2013 Aug;120(8):1533-40. doi: 10.1016/j.ophtha.2013.01.032. Epub 2013 May 1.

Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study.

Medeiros FA[1], Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN.

Author information

Abstract

PURPOSE: To evaluate the role of corneal hysteresis (CH) as a risk factor for the rate of visual field progression in a cohort of patients with glaucoma followed prospectively over time.

DESIGN: Prospective observational cohort study.

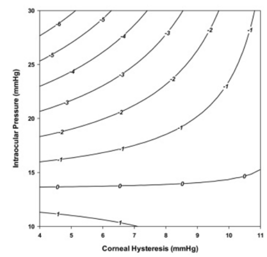
PARTICIPANTS: The study group included 114 eyes of 68 patients with glaucoma followed for an average of 4.0 ± 1.1 years. Visual fields were obtained with standard automated perimetry. Included eyes had a median number of 7 (range, 5-12) tests during follow-up.

METHODS: The CH measurements were acquired at baseline using the Ocular Response Analyzer (Reichert Instruments, Depew, NY). Evaluation of rates of visual field change during follow-up was performed using the visual field index (VFI). Linear mixed models were used to investigate the relationship between rates of visual field loss and baseline CH, baseline intraocular pressure (IOP), and central corneal thickness (CCT), while adjusting for potentially confounding factors. An interaction term between IOP and CH was included in the model to investigate whether the effect of IOP on rates of progression depended on the level of CH.

MAIN OUTCOME MEASURES: Effects of CH, IOP, and CCT on rates of VFI loss over time.

RESULTS: The CH had a significant effect on rates of visual field progression over time. In the univariable model including only CH as a predictive factor along with time and their interaction, each 1 mmHg lower CH was associated with a 0.25%/year faster rate of VFI decline over time (P<0.001). The multivariable model showed that the effect of IOP on rates of progression depended on CH. Eyes with high IOP and low CH were at increased risk for having fast rates of disease progression. The CH explained a larger proportion of the variation in slopes of VFI change than CCT (17.4% vs. 5.2%, respectively).

CONCLUSIONS: The CH measurements were significantly associated with risk of glaucoma progression. Eyes with lower CH had faster rates of visual field loss than those with higher CH. The prospective longitudinal design of this study supports the role of CH as an important factor to be considered in the assessment of the risk of progression in patients with glaucoma.



Medeiros FA et al. *Ophthalmology.* 2013;120:1533-1540.

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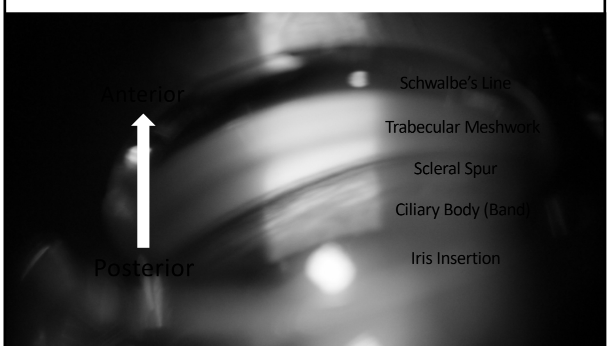

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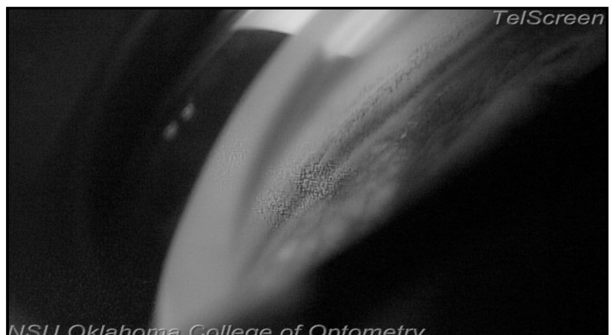

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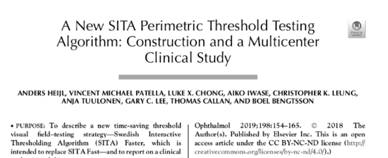
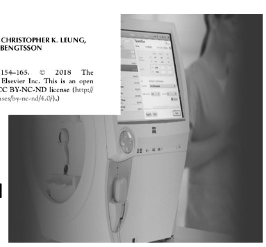

A New SITA Perimetric Threshold Testing Algorithm: Construction and a Multicenter Clinical Study

ANDERS HEIJL, VINCENT MICHAEL PATELLA, LUKE X. CHONG, AIKO IWASE, CHRISTOPHER K. LEUNG, ANJA TUULONEN, GARY C. LEE, THOMAS CALLAN, AND BOEL BENGTSSON

• PURPOSE: To describe a new time-saving threshold visual field–testing strategy—Swedish Interactive Thresholding Algorithm (SITA) Faster, which is intended to replace SITA Fast—and to report on a clinical evaluation of this new strategy.

Ophthalmol 2019;198:154–165. © 2018 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)



30.4% shorter than SITA Fast
53.5% shorter than SITA Standard

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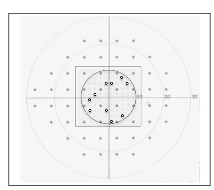
Resulting SITA Faster 24-2C Pattern on HFA3



Large Gray	24-2 pattern
Light Blue Dots	Ten additional 24-2C points
Small White	10-2 pattern

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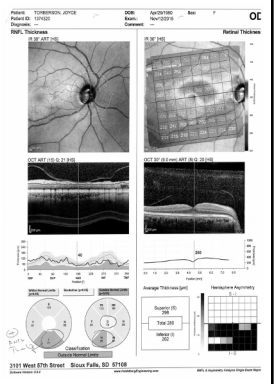
OCT

Pay attention to TSNIT curve.

Pay attention to the actual numbers in the segmentation plot

Pay attention to the numbers between eyes in the segmentation plot



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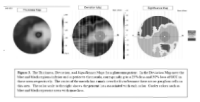
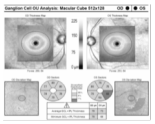
Macular Analysis

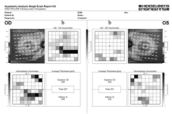


Optovue



Spectralis - macula

Cirrus OCT



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OCT Angiography: the Next Chapter in Posterior Imaging

- Images retinal microvasculature without dye injection
- Displays structure and function from a single imaging system

2002: Time Domain OCT

2006: Spectral Domain OCT

2014: OCTA

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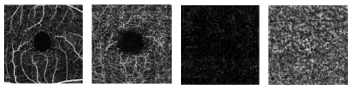
A New Approach to Visualizing Blood Flow

- Patient Benefits
  - Reduces patient burden to allow more frequent imaging
  - Avoid potential side-effects of fluorescein injection
- Clinical Benefits
  - Faster than a dye-based procedure
  - Ultra-high resolution imaging of retinal microvasculature
  - 3D visualization: segments retinal vasculature into individual layers



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OCT-A in our clinic

- Indications:

- AMD – dry vs. wet
- Diabetics -
- is there neo?
- is their non-perfusion (capillary dropout)?
- Vein Occlusions
- Glaucoma patients
- nerve perfusion?

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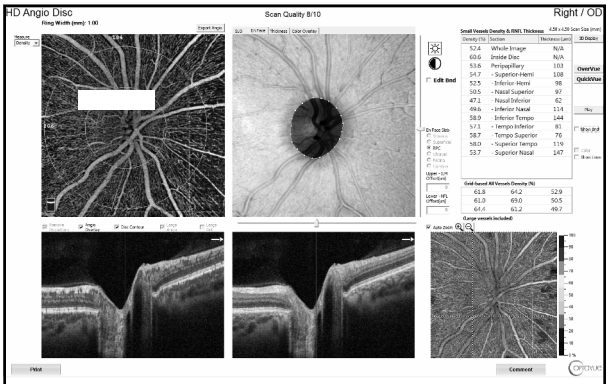

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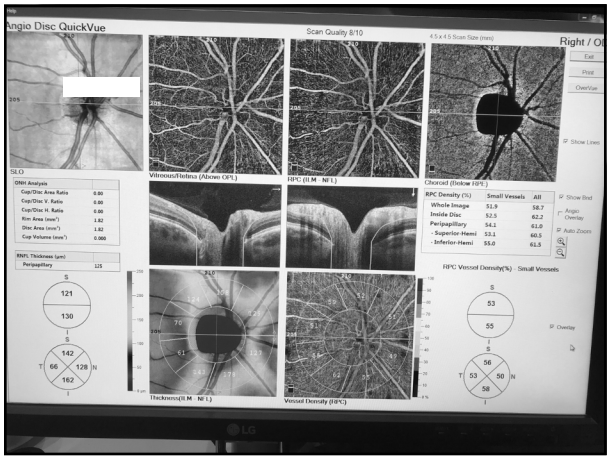

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Evaluating ERG Changes Associated with Glaucoma

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TABLE. Accuracy of AI Classification for Three Tests (N = 235)

TESTING PROTOCOL	NUMBER OF HEALTHY PATIENTS TESTED	NUMBER OF PATIENTS WITH PATHOLOGY TESTED	PATHOLOGY	SENSITIVITY	SPECIFICITY
PERG	70	70	Glaucoma	95%	92%
Chromatic Red/Blue Screening	15	12	Diabetic Retinopathy	93%	85%
Photopic-Negative Response	34	34	Glaucoma	94%	88%
Totals	119	116			

Abbreviation: PERG, pattern ERG

- possessing a higher sensitivity than specificity may be an advantage for a diagnostic screening tool because this makes false negatives less likely

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Pattern ERG (pERG)

- ERG's are electrical signals that are a measure of the electrophysiological activity at the retina
  - ***Mid-retinal layers, ganglion cell layer, and nerve fiber layer***
- Objectively measures retinal function**
- ERG's can help improve sensitivity and specificity in diagnosing optic neuropathies and maculopathies like glaucoma and macular degeneration when used in conjunction with other tests
- Can also help the clinician differentiate between retinal and optic nerve disorders when used in conjunction with Visual Evoked Potential (VEP).

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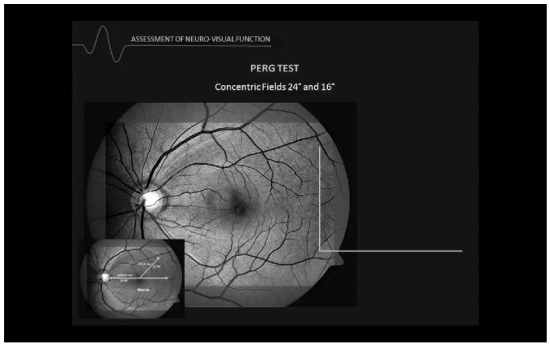

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Per NIH and Bascom-Palmer:

"In patients who are glaucoma suspects, pERG signal anticipates an equivalent loss of OCT signal by several years (as many as 8 years).

Invest Ophthalmol Vis Sci. 2013;54:2346-2352) DOI:10.1167/iovs.12-11026


Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects

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Glaucoma

Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects

CONCLUSION:

" There is an 8-year time delay between seeing a 10% reduction in potentially reversible PERG amplitude to seeing a 10% irreversible structural RNFL reduction (with OCT). This represents a substantial window for intervention before permanent loss of structure from glaucoma."

Banitt MR, Ventura LM, Feuer WJ, et al. Progressive loss of retinal ganglion cell function precedes structural loss by several years in glaucoma suspects. Invest Ophthalmol Vis Sci. 2013;54:2346-2352.

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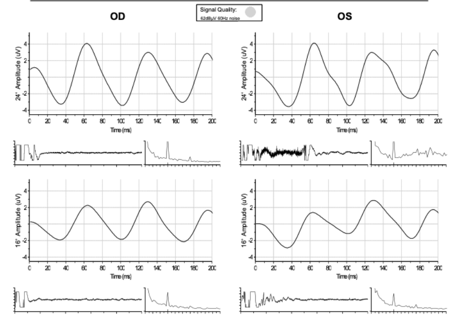
Exam Date: 2015-05-11 OD:+1.50 BCVA: 20/30
Exam Time:03:32:10 PM OS:+1.50 BCVA: 20/15



Parameter	OD 24°	OD 16°	OS 24°	OS 16°
Magnitude (uV)	3.90	2.45	3.73	2.28
MagnitudeD	3.66	2.31	3.61	2.09
MagD/Mag Ratio	0.94	0.94	0.97	0.92
SNR (dB)	14.3	10.9	14.1	9.6
Artifacts	1	0	5	2

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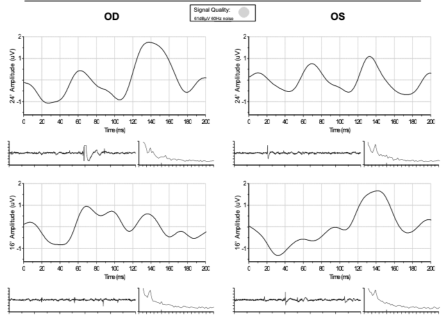
Exam Date: 2015-07-14 OD:+1.00 +0.75 x75 BCVA: 20/20
Exam Time: 01:16:32 PM OS:+1.00 +0.50 x95 BCVA: 20/20



Parameter	OD 24°	OD 16°	OS 24°	OS 16°
Magnitude (uV)	1.01	1.25	1.24	1.17
MagnitudeD	0.75	0.46	0.72	0.54
MagD/Mag Ratio	0.74	0.37	0.58	0.46
SNR (dB)	0.3	2.4	2.3	1.3
Artifacts	1	0	0	0

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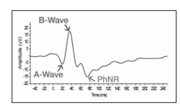
PHOTOPIC NEGATIVE RESPONSE (PHNR) | FLASH ERG WAVEFORM

- The PhNR of the ERG is a negative wave that occurs after the b-wave in response to a brief flash of light.[1]
- The PhNR has been found to originate mainly from the activity of retinal ganglion cells (RGC) and their axons.[2-5]



1.Frishman L, Sustar M, Kremers J, McAnany JJ, Sarossy M, Tzekov R, Viswanathan S. ISCEV extended protocol for the photopic negative response (PhNR) of the full-field electroretinogram. Doc Ophthalmol. 2018;136:207-211.
2.Viswanathan S, Frishman LJ, Robson JG, Walters JW. The photopic negative response of the flash electroretinogram in primary open angle glaucoma. Invest Ophthalmol Vis Sci. 2001;42:514–522.
3.Viswanathan S, Frishman LJ, Robson JG, Harwerth RS, Smith EL 3rd (1999) The photopic negative response of the macaque electroretinogram: reduction by experimental glaucoma. Invest Ophthalmol Vis Sci. 1999;40:1124–1136.
4.Kondo M, Kurimoto Y, Sakai T, Koyasu T, Miyata K, Ueno S, Terasaki H. Recording focal macular photopic negative response (PhNR) from monkeys. Invest Ophthalmol Vis Sci. 2008;49:3544-50.
5.Ueno S, Kondo M, Piao CH, Ikenoya K, Miyake Y, Terasaki H. Selective amplitude reduction of the PhNR after macular hole surgery: ganglion cell damage related to ICG-assisted ILM peeling and gas tamponade. Invest Ophthalmol Vis Sci. 2006;47:3545-9.

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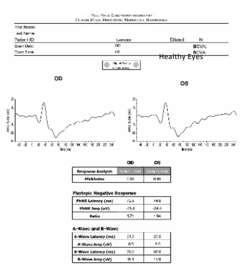
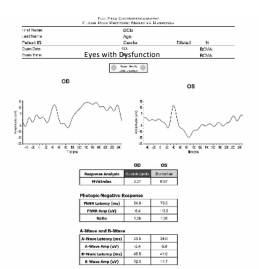
DIOPSYS FFERG/FLASH PLUS PHNR





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How do we treat glaucoma?

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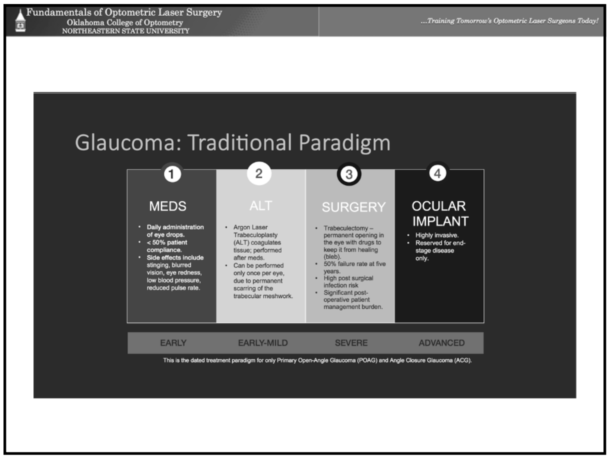

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Prostaglandin Analogs

- Latanoprost 0.005%
  - Xalatan (0.02% BAK)
  - Generic (0.02% BAK)
- Travaprost 0.004%
  - Travatan Z (SofZia)
  - Generic (0.015% BAK)
- Bimatoprost
  - Lumigan 0.01% (0.02% BAK)
  - Generic 0.03% (0.005% BAK)
- Tafluprost 0.0015%
  - Zioptan (unpreserved)
- Latanoprostene bunod 0.024%
  - Vyzulta (0.02% BAK)

Which prostaglandin analog do you choose first?

1. **Efficacy**
2. **Cost**
3. **Generic vs. Branded**
4. **Adverse Effects**
5. **Contraindications**
6. **Tolerability**

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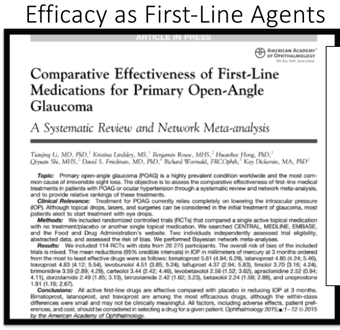
Efficacy as First-Line Agents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AMERICAN ACADEMY OF OPHTHALMOLOGY

Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma

A Systematic Review and Network Meta-analysis

Tianjing Li, MD, PhD,[1] Kristina Lindsley, MS,[1] Benjamin Rouse, MHS,[2] Hwanhee Hong, PhD,[3] Qiyuan Shi, MHS,[2] David S. Friedman, MD, PhD,[4] Richard Wormald, FRCOphth,[5] Kay Dickersin, MA, PhD[1]

Topic: Primary open-angle glaucoma (POAG) is a highly prevalent condition worldwide and the most common cause of irreversible sight loss. The objective is to assess the comparative effectiveness of first-line medical treatments in patients with POAG or ocular hypertension through a systematic review and network meta-analysis, and to provide relative rankings of these treatments.
Clinical Relevance: Treatment for POAG currently relies completely on lowering the intraocular pressure (IOP). Although topical drops, lasers, and surgeries can be considered in the initial treatment of glaucoma, most patients elect to start treatment with eye drops.
Methods: We included randomized controlled trials (RCTs) that compared a single active topical medication with no treatment/placebo or another single topical medication. We searched CENTRAL, MEDLINE, EMBASE, and the Food and Drug Administration's website. Two individuals independently assessed trial eligibility, abstracted data, and assessed the risk of bias. We performed Bayesian network meta-analyses.
Results: We included 114 RCTs with data from 20 275 participants. The overall risk of bias of the included trials is mixed. The mean reductions (95% credible intervals) in IOP in millimeters of mercury at 3 months ordered from the most to least effective drugs were as follows: bimatoprost 5.61 (4.94; 6.29), latanoprost 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.70 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), betaxolol 2.24 (1.59; 2.88), and unoprostone 1.91 (1.15; 2.67).
Conclusions: All active first-line drugs are effective compared with placebo in reducing IOP at 3 months. Bimatoprost, latanoprost, and travoprost are among the most efficacious drugs, although the within-class differences were small and may not be clinically meaningful. All factors, including adverse effects, patient preferences, and cost, should be considered in selecting a drug for a given patient. *Ophthalmology 2015;■:1–12 © 2015 by the American Academy of Ophthalmology.*

Ophthalmol, 2015

Mean IOP Reduction in mm Hg at 3 months

→ Bimatoprost 5.61
→ Latanoprost 4.85
→ Travoprost 4.83
Levobunolol 4.51
→ Tafluprost 4.37
Timolol 3.70
Brimonidine 3.59
Carteolol 3.44
Levobetaxolol 2.56
Aproclonidine 2.52
Dorzolamide 2.49
Brinzolamide 2.42
Betaxolol 2.24
Unoprostone 1.91

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Topical Glaucoma Drops

First Line

- Xalatan (Latanoprost 0.005%)
  - Generic available
- Travatan-Z (Travoprost (0.004%)
  - Generic available
- Lumigan (bimatoprost (0.03%)
  - Generic available
- Vyzulta (Latanoprostene bunod 0.024%)
- Roclatan (Latanoprost 0.005%/Netarsudil 0.02%)
- Xelpros (Latanoprost 0.005%)
- Selective Laser Trabeculoplasty (SLT)

Second Line/Additional Therapy

- Beta-blockers
- Alphagan P (Brimonidine 0.1% or 0.15%)
- Generic brimonidine 0.15% or 0.2%
- Rhopressa (Netarsudil 0.02%)
- Trusopt (dorzolamide 2%)
- Azopt (brinzolamide 1%)
- Combigan (timolol/brimonidine)
- Cosopt (timolol/dorzolamide)
- Simbrinza (brimonidine/brinzolamide)

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Vyzulta

- Latanoprostene bunod 0.024% ophthalmic solution
  - Nitric oxide donating donating prostaglandin
- Mechanism:
  - Increases uveoscleral outflow + increases TM outflow
  - NO relaxes the TM, enhancing the outflow of aqueous
- VOYAGER Study:
  - All studied concentrations compared to Xalatan
  - Greater IOP reduction
  - Superior diurnal reductions in IOP
  - Slightly higher adverse effects (usually mild)
    - Most common side effect - hyperemia
- Bausch & Lomb

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Rhopressa

- Netarsudil ophthalmic solution 0.02%
  - Rho Kinase inhibitor (ROCK inhibitor)/NET inhibitor
- Triple IOP lowering action
  1. Increases TM outflow
  2. Decreases aqueous production
  3. Lowers episcleral venous pressure (EVP)
- Dosing - QD
- Clinical Trials – Rocket 1, 2, 3, and 4
  - 5.5 mmHg IOP lowering
- Adverse effects:
  - No systemic effects
  - Conjunctival hyperemia - 48%
  - Corneal verticillata, conjunctival hemorrhage, blurred vision, erythema of eyelid
    - 3-5%
- Aerie Pharmaceuticals

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Roclatan

- Netarsudil/latanoprost ophthalmic solution 0.02%/0.005%
  - Rho Kinase inhibitor (ROCK inhibitor)/NET inhibitor/prostaglandin analogue
- Quadruple IOP lowering action
  1. Increases TM outflow
  2. Decreases aqueous production
  3. Lowers episcleral venous pressure (EVP)
  4. Increases uveoscleral outflow
- Dosing – QD
- Clinical Trials – Mercury 1, 2, and 3
  - Superior to each of its components by up to 3 mmHg
- Aerie Pharmaceuticals

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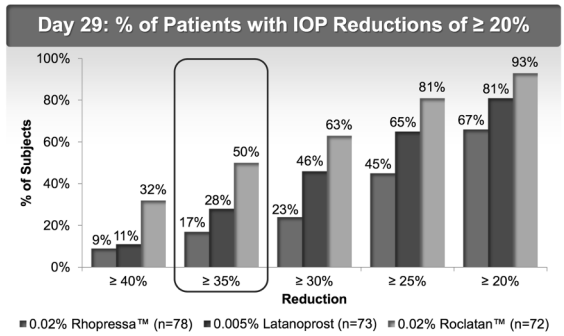
Roclatan™ Phase 2b Responder Analysis: Goal is to Achieve Lowest IOP Possible



Source: Lewis RA, Levy B, Ramirez N, Kopczynski CC, Usner DW, Novack GD for the PG324-CS201 Study Group. Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension. Br J Ophthalmol 2015;0:1–6. doi:10.1136/bjophthalmol-2015-306778

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Fundamentals of Optometric Laser Surgery
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Are there reasons for choosing options other than drops?

- Glaucoma is progressing in a pt on max meds
  - Something else needs to be done
  - Surgery not wanted yet
- Compliance issues
- Cost issues
- Convenience/quality of life issues
- Ocular Surface Disease
- Systemic side effect issues of drops
- Doctor preference

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SLT Indications

- After maximum medications?
- When adding second/third drop?
- First line?

40

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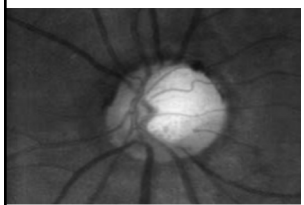

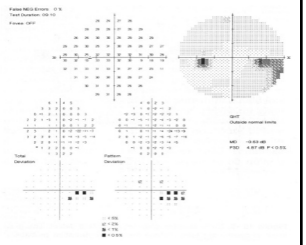

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SLT Studies

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Selective Laser Trabeculoplasty Versus Medical Therapy as Initial Treatment of Glaucoma: A Prospective, Randomized Trial

L. Jay Katz, MD, William C. Steinmann, MD,† Azad Kabir, MD,‡ Jeanne Molineaux, COA,* Sheryl S. Wizov, COA,* and George Marcellino, PhD§ the SLT|Med Study Group*

J Glaucoma • Volume 21, Number 7, September 2012

- SLT Med Study (2012)
  - Dr. Katz @ Wills Eye in Philadelphia
    - J Glaucoma 2012;21:460-468
  - SLT (100 applications over 360 degrees of TM) vs. prostaglandin analog
  - Primary outcome -> IOP
  - Secondary outcome -> # of treatment steps

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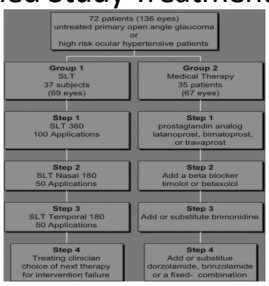
SLT Med Study Treatment Arms



43

SLT vs. Prostaglandins

- SLT Med Study (2012)

Results:

1. IOP reduction:
   - SLT – 25.7% IOP reduction
     - IOP reduced from 24.5 to 18.2 (6.3 mmHg reduction)
   - Prostaglandin – 28.3% IOP reduction
     - IOP reduced from 24.7 to 17.7 (7.0 mmHg reduction)
2. # of treatment steps:
   - SLT group - 11% of eyes required additional SLT
   - Prostaglandin group -> 27% of eyes required additional medication

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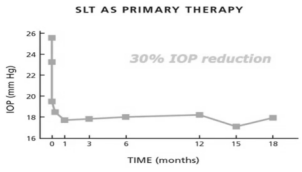
SLT Med Study

Conclusions: IOP reduction was similar in both arms after 9 to 12-months follow-up. More treatment steps were necessary to maintain target IOP in the medication group, although there was not a statistically significant difference between groups. These results support the option of SLT as a safe and effective initial therapy in open-angle glaucoma or ocular hypertension.

45

SLT as Primary Therapy

- IOP decreased by 30% (7.7 mmHg), from 25.5 to 17.9 mmHg over the f/u period
- Forty eyes (89%) had a decrease of 5 mmHg or more



"Selective laser trabeculoplasty is effective and safe as a primary treatment for patients with ocular hypertension and open-angle glaucoma."

Arch Ophthalmol. 2003;121: 957-960

46

SLT as first line?

- American Academy of Ophthalmology Preferred Practice Patterns
  - "Laser trabeculoplasty can be considered as initial therapy in selected patients."

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SLT as first line?

- UpToDate
  - "Once the decision has been made to treat a patient with open-angle glaucoma, we recommend pharmacologic or laser therapy as first line treatment."
  - Grade 1B evidence

UpToDate
PROVIDING ANSWERS TO CLINICAL QUESTIONS

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SLT as first line?

- 2015 Meta-Analysis (Oi Man Wong et. al)
  - "Robust evidence that SLT may be...offered as a primary treatment to patients with OAG."

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- **Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial**

Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Anurag Garg, Victoria Vickerstaff, Richael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Neil Nathwani, Keith Barton, Gary Rubin, Marta Buszewicz, on behalf of the LiGHT Trial Study Group*

Summary

Background Primary open angle glaucoma and ocular hypertension are habitually treated with eye drops that lower intraocular pressure. Selective laser trabeculoplasty is a safe alternative but is rarely used as first-line treatment. We compared the two.

Methods In this observer-masked, randomised controlled trial treatment-naive patients with open angle glaucoma or ocular hypertension and no ocular comorbidities were recruited between 2012 and 2014 at six UK hospitals. They were randomly allocated (web-based randomisation) to initial selective laser trabeculoplasty or to eye drops. An objective target intraocular pressure was set according to glaucoma severity. The primary outcome was health-related quality of life (HRQoL) at 3 years (assessed by EQ-5D). Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety. Analysis was by intention to treat. This study is registered at controlled-trials.com (ISRCTN32038223).

Findings Of 718 patients enrolled, 356 were randomised to the selective laser trabeculoplasty and 362 to the eye drops group. 452 (91%) returned the primary outcome questionnaire at 36 months. Average EQ-5D score was 0·89 (SD 0·13) in the selective laser trabeculoplasty group versus 0·90 (SD 0·10) in the eye drops group, with no significant difference (difference 0·01, 95% CI −0·01 to 0·03; p=0·23). At 36 months, 74·2% (95% CI 69·3–78·6) of patients in the selective laser trabeculoplasty group required no drops to maintain intraocular pressure at target. Eyes of patients in the selective laser trabeculoplasty group were within target intraocular pressure at more visits (93·0%) than in the eye drops group (91·3%), with glaucoma surgery to lower intraocular pressure required in none versus 11 patients. Over 36 months, from an ophthalmology cost perspective, there was a 97% probability of selective laser trabeculoplasty as first treatment being more cost-effective than eye drops first at a willingness to pay of £20 000 per quality-adjusted life-year gained.

Interpretation Selective laser trabeculoplasty should be offered as a first-line treatment for open angle glaucoma and ocular hypertension, supporting a change in clinical practice.

Funding National Institute for Health Research, Health and Technology Assessment Programme.

Published Online March 6, 2019 http://dx.doi.org/10.1016/S0140-6736(18)32213-X

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(19)31013-4

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Recent Ground Breaking 3-Year LiGHT Clinical Trial

SLT vs Eye Drops

CLINICAL CONCLUSION

"Selective Laser Trabeculoplasty (SLT) should be offered as first-line treatment for open angle glaucoma and ocular hypertension, supporting a change in clinical practice."

3 Years	n=652	5x LESS	78.2%	Surgical Intervention
MULTI-CENTER RANDOMIZED	SLT 329 DROPS 323	Adverse Events SLT 30 DROPS 150	SLT DROP FREE @ 3 YEARS	SLT 0 DROPS 11

*Data available in reference article below

QUALITY OF LIFE The trial supports a longer drop-free period for patients when treated with SLT, which may confer significant benefits to your patient's quality of life.

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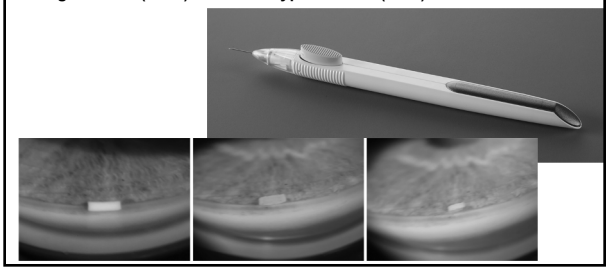
Bimatoprost Implant Overview

Indications and Usage

Durysta™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).



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Bimatoprost Implant: Sustained-Release, Biodegradable Intracameral Implant

Drug delivery platform: Can be modified to provide different release profiles[1]

Biodegradable Polymers[2]

- **Ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant**
- **Bimatoprost implant should not be readministered to an eye that received a prior bimatoprost implant**
- **Intracameral implant containing 10 mcg in the drug delivery system**

1. Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147. 2. Lee, et al. *Pharm Res*. 2010. 27:2043-2053. 3. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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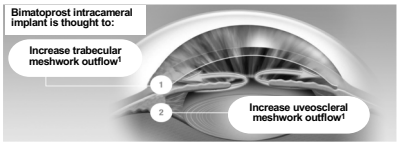
Bimatoprost Implant: Mechanism of Action

- Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity
- Bimatoprost is believed to lower IOP in humans by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional)
  - Elevated IOP presents a major risk factor for glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss



1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Bimatoprost Implant

Efficacy Results from Clinical Trials

55

24 Month Phase I/II Clinical Trial

bimatoprost pellet
(6, 10, 15, or 20 micrograms)

75 subjects

topical bimatoprost 0.03%

Craven ER, Walters T, Christie WC, Day DG, et al. 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients.
Drugs. 2020 Feb;80(2): 167-179.

56

24 Month Phase I/II Clinical Trial

bimatoprost pellet
(6, 10, 15, or 20 micrograms)

topical bimatoprost 0.03%

16 weeks – IOP reduction
7.5, 7.3, 7.3, 8.9 mm Hg

16 weeks– IOP reduction
of 8.2 mm Hg

No Rescue or Retreatment
68% - 6 mos.
40% - 12 mos.
28% - 24 mos.

Craven ER, Walters T, Christie WC, Day DG, et al. 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients. Drugs. 2020 Feb;80(2): 167-179.

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ARTEMIS

Study Background

Design	Two multicenter, randomized, parallel-group, patient and efficacy evaluator masked active controlled 20- month studies including eight month follow-up conducted in patients with OAG or OHT
Treatments	Twice daily topical timolol 0.5% or bimatoprost implant
Outcomes	**Co- Primary Endpoint:** • Mean IOP by Treatment Group • Treatment Difference in Mean IOP

IOP = intraocular pressure; OAG = open angle glaucoma; OHT = ocular hypertension

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020. 2. . U.S. National Library of Medicine ClinicalTrials.gov. Retrieved from website: www.ClinicalTrials.gov. ClinicalTrials.gov Identifiers: NCT02247804, NCT02250651 Accessed 11/1/20

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Artemis I and II

- Two identical, phase 3 trials
- 742 subjects
- 20 months

- Bimatoprost implant (Durysta) implanted q4 months
  - Initial implant, another one week 16, 3rd and final one week 32
- Vs. Timolol BID

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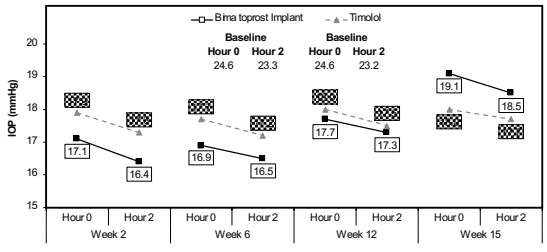
ARTEMIS Study 1

Mean IOP by Treatment Group and Treatment Difference in Mean IOP

Primary Endpoint



Bimatoprost Implant vs. Timolol (95% CI)

Hour 0	-0.8 (-1.47, -0.14)	-0.8 (-1.47, -0.21)	-0.3 (-1.09, 0.43)	1.1 (0.22, 1.89)
Hour 2	-0.9 (-1.50, -0.31)	-0.7 (-1.27, -0.04)	-0.2 (-0.90, 0.46)	0.9 (0.10, 1.64)

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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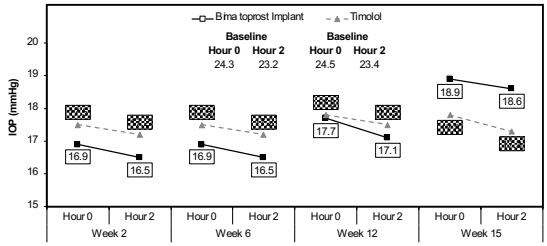
ARTEMIS Study 2

Mean IOP by Treatment Group and Treatment Difference in Mean IOP

Primary Endpoint



Bimatoprost Implant vs. Timolol (95% CI)

Hour 0	-0.6 (-1.30, 0.13)	-0.6 (-1.35, 0.17)	-0.1 (-0.88, 0.72)	1.0 (0.15, 1.94)
Hour 2	-0.7 (-1.38, -0.05)	-0.6 (-1.36, 0.06)	-0.3 (-1.11, 0.42)	1.2 (0.35, 2.06)

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Artemis I and II

- Two identical, phase 3 trials
- 742 subjects
- 20 months

- Bimatoprost implant (Durysta) implanted q4 months
  - Initial implant, another one week 16, 3rd and final one week 32
- Vs. Timolol BID

- Baseline IOP = 24
- IOP week 12 = 17
  - 30-33% IOP reduction from baseline over 12-week primary efficacy period

Conclusion: Noninferior to timolol administered as an eye drop twice a day.

*70-80% - additional 12 months without retreatment

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Artemis I and II

- Adverse Events:

Most Common Ocular Adverse Events	DURYSTA™ (n = 372)	Timolol 0.5% BID (n = 370)
Conjunctival hyperemia	102 (27.4)	62 (16.8)
Foreign body sensation in eyes	38 (10.2)	13 (3.5)
Eye pain	36 (9.7)	17 (4.6)
Photophobia	32 (8.6)	4 (1.1)
Conjunctival hemorrhage	29 (7.8)	24 (6.5)
Dry eye	27 (7.3)	16 (4.3)
Eye irritation	26 (7.0)	28 (7.6)
Intraocular pressure increased	25 (6.7)	10 (2.7)
Corneal endothelial cell loss	20 (5.4)	1 (0.3)
Vision blurred	19 (5.1)	11 (3.0)
Iritis	19 (5.1)	1 (0.3)
Most Common Nonocular Adverse Reaction	**DURYSTA™ (n = 372)**	**Timolol 0.5% BID (n = 370)**
Headache	19 (5.1)	12 (3.2)

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Important Safety Information

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Contraindications

- **Contraindications:**
  - Active or suspected ocular or periocular infections
  - Corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy)
  - Prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK])
  - Absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment
  - Hypersensitivity to bimatoprost or any other components of the product

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Warnings and Precautions

- **Warnings and Precautions:**
  - **Corneal adverse reactions:** The presence of bimatoprost implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of bimatoprost implant should be limited to a single implant per eye without retreatment. Caution should be used when prescribing bimatoprost implant in patients with limited corneal endothelial cell reserve.
  - **Iridocorneal angle:** Bimatoprost implant should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g. scarring) that may prohibit settling in the inferior angle.
  - **Macular edema:** Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including bimatoprost implant. Bimatoprost implant should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Warnings and Precautions

- **Warnings and Precautions (Continued):**
  - **Intraocular inflammation:** Prostaglandin analogs, including bimatoprost implant, have been reported to cause intraocular inflammation. Bimatoprost implant should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.
  - **Pigmentation:** Ophthalmic bimatoprost, including bimatoprost implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with bimatoprost implant can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.
  - **Endophthalmitis:** Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering bimatoprost implant, and patients should be monitored following the administration.

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Adverse Reactions

- In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia.
- Other common adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Bimatoprost Implant

Dosage and Administration

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Dosage and Administration

- **General Information:**
  - Bimatoprost implant is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant. Bimatoprost implant should not be readministered to an eye that received a prior bimatoprost implant.
- **Administration:**
  - The intracameral injection procedure must be performed under magnification that allows clear visualization of the anterior chamber structures and should be carried out using standard aseptic conditions for intracameral procedures, with the patient's head in a stabilized position. The eye should not be dilated prior to the procedure.
  - Remove the foil pouch from the carton and examine for damage. Then, open the foil pouch over a sterile field and gently drop the applicator on a sterile tray. Once the foil pouch is opened, use promptly.

IOP = intraocular pressure
1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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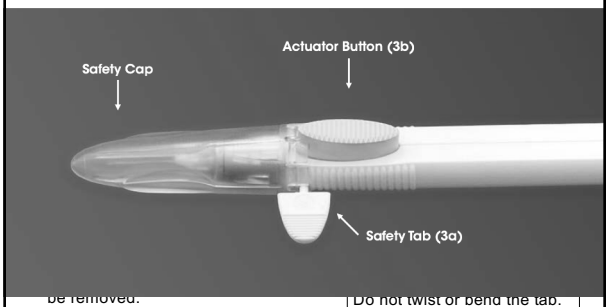
Pre-operative Care

- 2-3 drops of Proparacaine
- Ophthalmic Betadine 5% lavage (2-3 drops)
- 1 drop of topical antibiotic
- Maintaining proper aseptic technique through

71

Administration (Continued)



be removed.

Do not twist or bend the tab.

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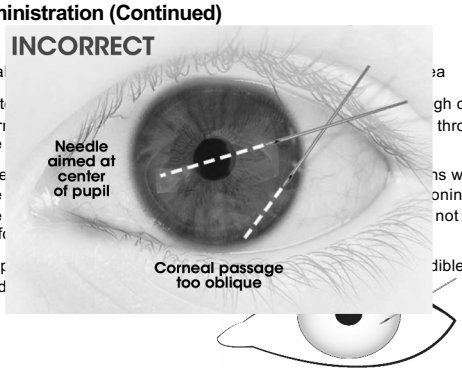
Administration (Continued)



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- Ent… …gh clear cor… …through the…
- The… …ns with the… …oning the… …not bent bef…
- Dep… …dible and…

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Administration (Continued)

- Following the release of the implant, remove the needle via the same track in which it was inserted and tamponade the opening. The implant should not be left in the corneal injection track.
- Check for injection site leaks; make sure that it is self sealing and the anterior chamber is formed.
- After injection, **do not** recap the needle. Dispose of the used applicator in a sharps disposal container in accordance with local requirements.
- Instruct the patient to remain upright for at least one hour after the procedure so the implant can settle.
- Some degree of eye redness and discomfort is expected following administration. However, it is recommended to instruct patients that if the eye becomes progressively red, sensitive to light, painful, or develops a change in vision, they should immediately contact the physician.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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Post-operative Care

- 1-2 drops of topical antibiotic in-office
- Check for a Seidel sign
- Discontinue PGA drops (or drops altogether)
- RTC 1 week for implant into the other eye

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Summary

- Bimatoprost implant is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT)
- Efficacy has been demonstrated in two Phase 3 studies with an IOP reduction of approximately 5 - 8 mmHg in patients with a mean baseline IOP of 24.5 mmHg
- The most common ocular adverse reaction observed in two randomized controlled clinical trials with bimatoprost implant in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients

Please also see the Durysta full prescribing information.

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

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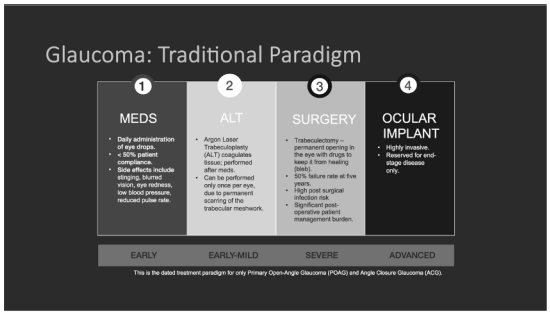

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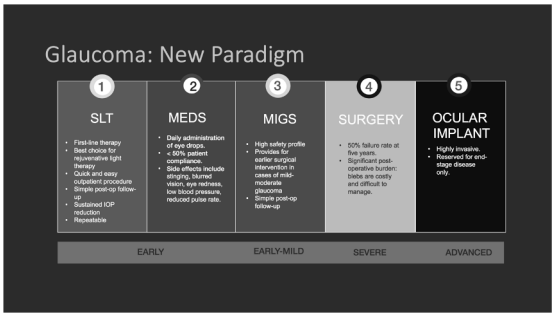

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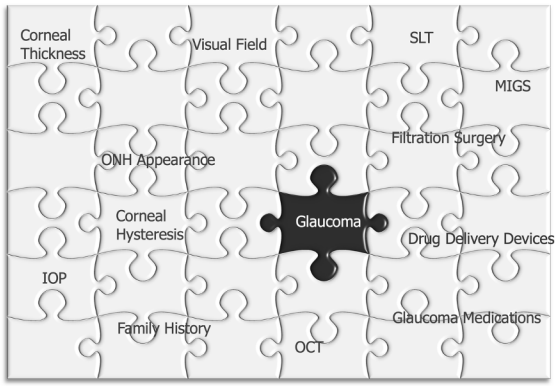

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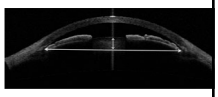
A Simplified Classification Scheme

1. Anatomically narrow (PACS)
   - Indentation gonioscopy opens angle
   - Normal IOP
   - Heightened suspicion

80

How narrow is too narrow?

- Gonioscopy: iridotrabecular contact in at least 180 degrees
  - Iridotrabecular contact = failure to see posterior meshwork
- AS-OCT: angle opening is less than 5-10 degrees
  - Visante: use lens vault measurement



81

A Simplified Classification Scheme

1. Anatomically narrow (PACS)
   - Indentation gonioscopy opens angle
   - Normal IOP
   - Heightened suspicion

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A Simplified Classification Scheme

1. Anatomically narrow (PACS)
   - Indentation gonioscopy opens angle
   - Normal IOP
   - Heightened suspicion
2. Anterior synechiae and/or elevated IOP (PAC)
   - Minimal natural history data
3. Closed angles and glaucomatous damage (PACG)

(Fourth category: Acute symptomatic angle closure)

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PI or not to PI……ZAP Study

- **Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. (ZAP Study)**
- He, et al Lancet 2019
- 889 patients with prophylactic PI followed for six years for incidence of angle closure

- Screening 11,991 patients
- 1087 were classified as Primary Angle Closure Suspects (PACS)
  - 9.1%
- 889 entered the study
  - PI in one eye
  - Observation in the other

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PI or not to PI……ZAP Study

- ZAP study:
  - Primary outcome was:
    - Development of Primary Angle Closure (PAC) over 6 years
      - Peripheral anterior synechiae (PAS) of 1 clock hour or greater
      - Elevated IOP
      - Acute angle closure
  - 889 eyes received a PI — 889 eyes received observation
    - 19 developed PAC — 36 developed PAC
    - 2.14% — 4.05%
  - 47% reduction in the risk of developing PAC in the eyes that underwent PI
  - Statistically significant
  - But…..

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PI or not to PI……ZAP Study

- ZAP study:
  - Final Conclusions:
    - "Laser peripheral iridotomy had a modest, albeit significant, prophylactic effect"
    - "The number needed to treat was 44 to prevent one case of new primary angle closure disease over 6 years, the vast majority of which were not acute attacks."
      - Treat 44 PACS patients with laser PI to prevent 1 from going to PAC
    - "Assuming that these primary angle closure cases have a 35% risk of developing sight loss from glaucoma over a further 5 years, and assuming that prevention of sight loss would be the ultimate goal of prophylactic laser iridotomy, then the total number needed to treat (over approximately a decade) would be around 126 people."
      - Treat 126 PACS patients with laser PI to prevent 1 from losing vision from PAC or PACG
    - "Widespread prophylactic laser peripheral iridotomy for primary angle-closure suspects is not recommended"

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Risk of PACS Developing Acute Primary Angle Closure

- ZAP Study
  - 889 followed for up to 6 years
  - 19 in LPI group
  - 36 in control group
- Guangzhou China
  - 485 followed for 4.8 years (1-6 yrs)
  - 6 (1.2%)
- Chicago Study
  - 129 followed for 2.7 years (1-6 yrs)
  - 8 (6.2%)
- Vellore India
  - 48 followed for 5 years
  - none

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Risk factors for primary angle closure - race

- 0.1-0.6% - Whites/Hispanic/Black
- 0.6% in Chinese but as high as 7% is some sub-groups
- Some estimates = 50% of Vietnamese have "occludable angles"

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Risk factors

- **Age** – rare under the age of 40 but prevalence increases with each decade over 40
  - Due to the increase in lens thickness with age
- **Gender** – occurs 2 to 4 times more common in females than it does in males
  - Females tend to have shorter anterior segments than do males
- **Family history** – increased in first degree relatives
  - 3 to 6 times greater risk

Hyperopia

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When to recommend prophylactic LPI

- Narrow angle and presence of any:
  - Peripheral anterior synechiae and/or elevated IOP (PAC)***
  - Optic nerve damage (PACG)***
  - Retinal disease
  - Family history
  - Unreliable patient that does not seek routine care
  - Symptomatic patient
- Narrow angle without any of these: discuss risks, involve patient in decision

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Thank You!

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