CASE FILES: THE GLAUCOMA CHRONICLES

Jessica Steen OD, FAAO, Dipl ABO

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JESSICA STEEN OD FINANCIAL DISCLOSURES

- Speakers Bureau-Carl Zeiss Meditec, Bausch and Lomb, Viatris, Thea Pharma, Alcon, Allergan, Astellas, Dompé
- Consultant-Bausch and Lomb, Balance Ophthalmics, Carl Zeiss Meditec, Opus Genetics, Viatris, Allergan, Astellas, Alcon, Radius XR, iCare, Glaukos, Eyenovia, Tarsus, Orasis, Topcon, Envision Health Technologies, LKC
- Shareholder-Clearside Biomedical, Annexon Bio (<0.01% ownership)
- *All relevant relationships have been mitigated*

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56 YEAR OLD AFRICAN AMERICAN FEMALE

- 56 year old African American female referred for evaluation due to suspicion of glaucoma secondary to optic disc appearance
  - No family history of glaucoma
  - No systemic diagnoses; no systemic medications

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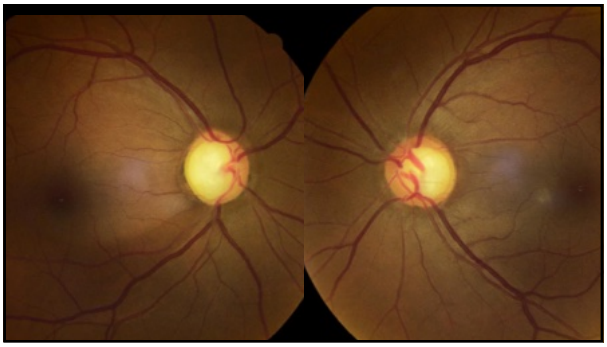

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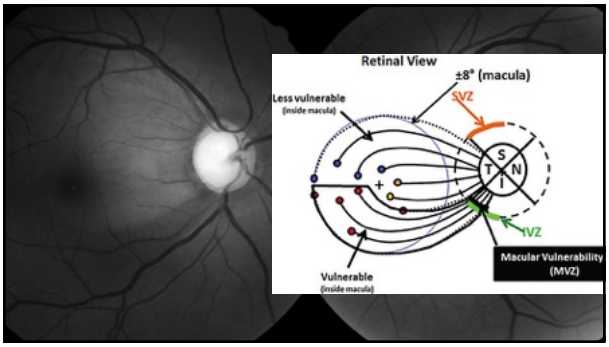

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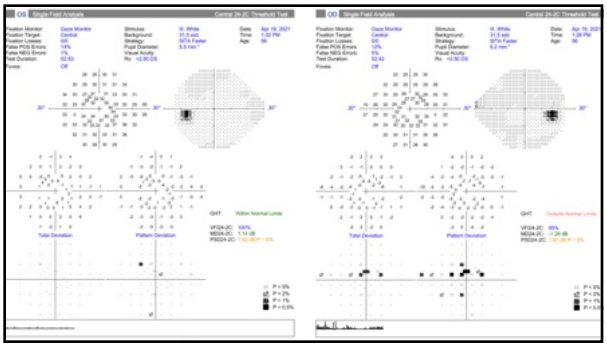

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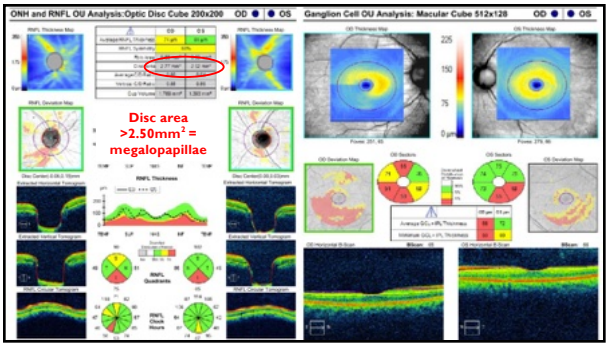

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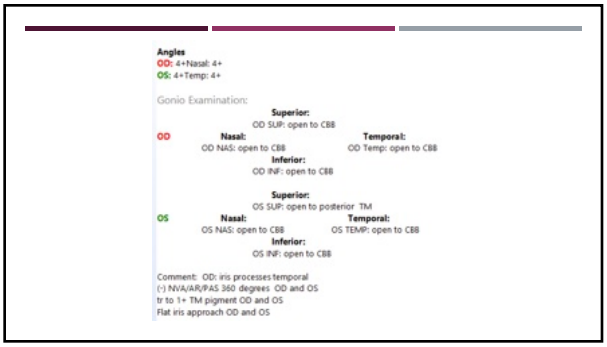

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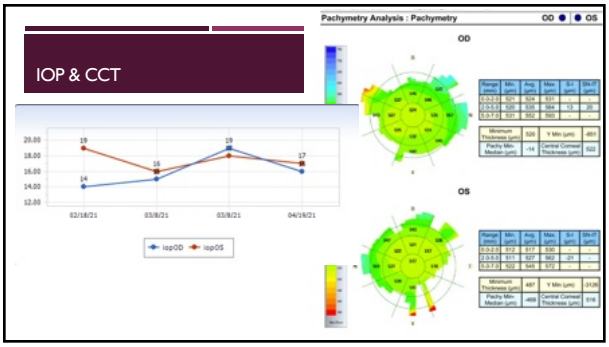
IOP & CCT



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*When **diagnosing** glaucoma, take IOP out of the equation*
*When **managing** glaucoma, bring IOP back in*

Ideally, 3 IOP readings prior to making or changing a treatment

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BUT—THE PRESSURE IS LOW

- But, the cornea is thin.
- Central corneal thickness impacts applanation tonometry measurement
  - Can lead to misdiagnosis or treatment changes
- Thin corneas are a risk factor for development of glaucoma in patients with ocular hypertension (OHTS)

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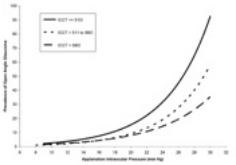
CENTRAL CORNEAL THICKNESS

- Persons with thin CCT had a significantly higher prevalence of OAG than did those with normal or thick CCTs at all levels of IOP
- **CCT is an important risk factor for the prevalence of glaucoma**
  - Los Angeles Latino Eye Study Group



Los Angeles Latino Eye Study, n = 5970

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Is Corneal Thickness an Independent Risk Factor for Glaucoma?

Felipe A. Medeiros, M.D., Ph.D. and **Robert N. Weinreb, M.D.**
Hamilton Glaucoma Center, University of California San Diego, La Jolla, CA

Ophthalmology. 2012 March ; 119(3): . doi:10.1016/j.ophtha.2012.01.018.

In conclusion, the results of Brandt et al suggest that the use of CCT correction formulas for GAT measurements is probably of little value in clinical practice. Instead of attempting to use these formulas, clinicians are probably better off incorporating risk information as provided by validated predictive models for glaucoma development.[6, 7] However, the conclusion that CCT is a true independent risk factor for glaucoma is not validated at this time and requires further investigations.

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Decoding the Cornea-Glaucoma Association: Evidence From Mendelian Randomization

Victor A. de Vries,[1,2] Anita Szabo,[3] Joëlle E. Vergroesen,[1,2] Siyin Liu,[3,4] Karin A. van Garderen,[1,2] Kirithika Muthusamy,[1] Petra Liskova,[5] Lubica Dudakova,[5] Anthony P. Khawaja,[6] Stephen J. Tuft,[3,4] Caroline C. W. Klaver,[1,2,7,8] Alice E. Davidson,[3,4] and Wishal D. Ramdas[1]

Conclusions. We found no evidence for a causal link between CCT and OAG. Nevertheless, CCT measurements are still valuable for population-based risk stratification. We found no clear relationship between FECD and OAG.

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Do not adjust IOP based on CCT measurements

Pachymetry measurement and conversion models may themselves be error sources

It's not that simple

No validated algorithm to correct IOP based on CCT

No proven association of CCT and any other structural abnormality

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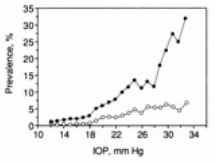
Intraocular Pressure

- This is the most significant risk factor overall
- IOP which is statistically abnormal is not necessary physiologically abnormal for an individual eye
- Conversely, IOP that is statistically normal is not necessarily physiologically normal for an individual eye
- **There is no clinically useful level of IOP to differentiate all normal from all people with glaucoma**



African American subjects, n = 4674 (closed circles; Caucasian subjects, n = 5700 (open circles)

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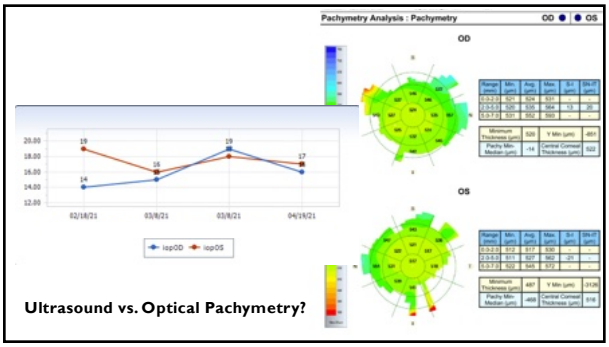

Ultrasound vs. Optical Pachymetry?

20

The Cupped Disc

Who Needs Neuroimaging?

David S. Greenfield, MD,[1] R. Michael Siatkowski, MD,[1] Joel S. Glaser, MD,[1,2] Norman J. Schatz, MD,[1,2] Richard K. Parrish II, MD[1]

Conclusions: Anterior visual pathway compression is an uncommon finding in the neuroradiologic evaluation of patients with a presumptive diagnosis of normal-tension glaucoma. Younger age, lower levels of visual acuity, vertically aligned visual field defects, and neuroretinal rim pallor may increase the likelihood of identifying an intracranial mass lesion. *Ophthalmology 1998;105:1866–1874*

- "Nothing notches a nerve like glaucoma"
- Disc hemorrhage, vertical cup elongation

I appreciate the opportunity to discuss this article because I feel so passionately about its conclusion. I agree with the authors: if it looks like normal-tension glaucoma, you do not have to do neuroimaging to sleep at night.

Richard Mills MD, MPH

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62 YEAR OLD FEMALE

- POAG OU; history of bilateral trabeculectomy with MMC
  - Clinical failure OS
- Latanoprostene bunod 0.024% QHS OS, netarsudil 0.02% QHS OS, dorzolamide-timolol BID OS
- Seropositive rheumatoid arthritis (200mg hydroxychloroquine BID x 4 years); Enbrel weekly
- BCVA 20/25 OS and OS
- IOP 5mmHg OD, 11mmHg OS (CCT 479um OD 467um OS)
- SPEED score 21

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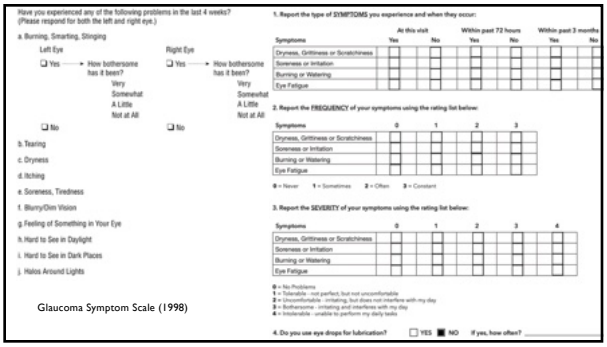

Glaucoma Symptom Scale (1998)

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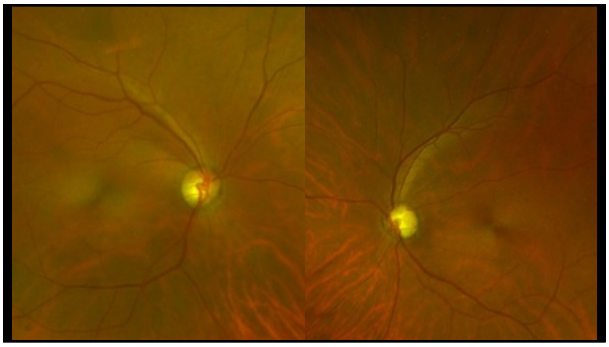

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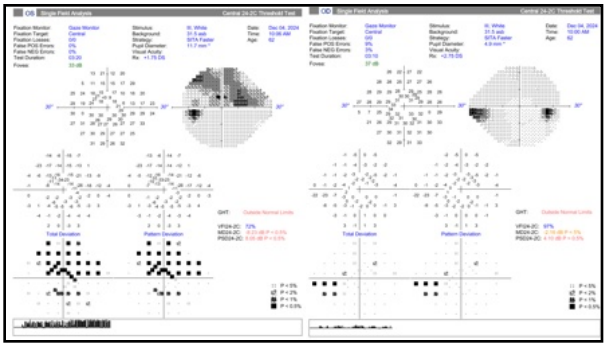

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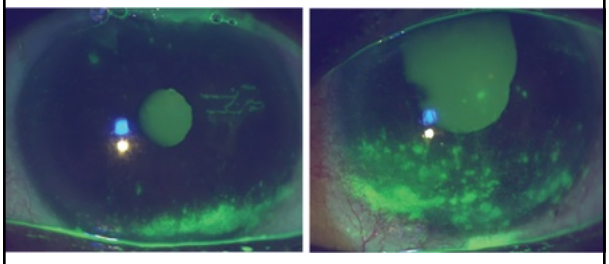

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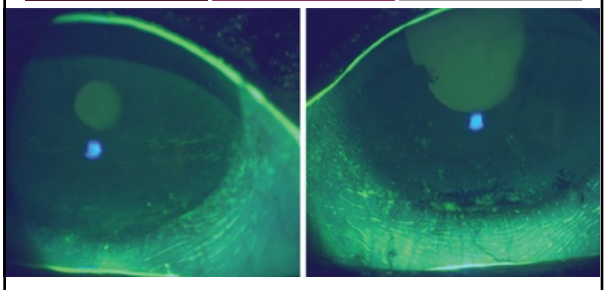

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Ocular surface disease is common

Around 60% of glaucoma patients are reported to have ocular surface disease…

Really…that's it?

It matters, but does not impact target IOP

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OCULAR SURFACE DISEASE AND GLAUCOMA

- Manage the ocular surface early
  - If patients are asymptomatic when clinical signs are apparent prior to initiation of therapy-expect symptoms to develop with therapy
- Long-term impact of benzalkonium chloride
  - Decreased density of goblet cells
    - Related to concentration of BAK

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ADDITIONAL OPTIONS

- Medication options
  - Non-BAK formulations
    - Travoprost 0.004% (Travatan Z) sofZia-teal colored cap
    - Latanoprost 0.005% ophthalmic emulsion (Xelpros) potassium sorbate
  - Preservative-free formulations
    - Tafluprost 0.0015% (Zioptan)-prostaglandin analog
    - Dorzolamide-timolol (Cosopt PF)
    - Timolol 0.25% and 0.5% (Timoptic in Ocudose)
    - Latanoprost 0.005% (Iyuzeh)

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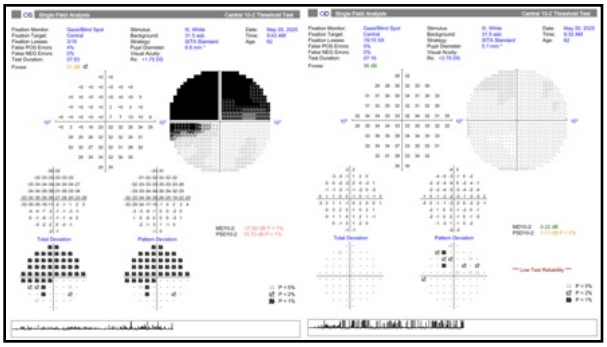

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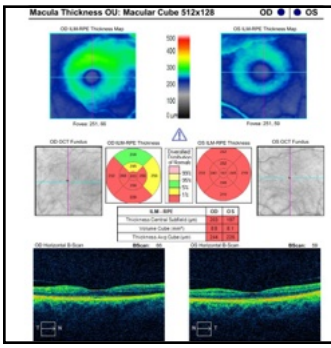

How can I monitor effectively for hydroxychloroquine toxicity?!

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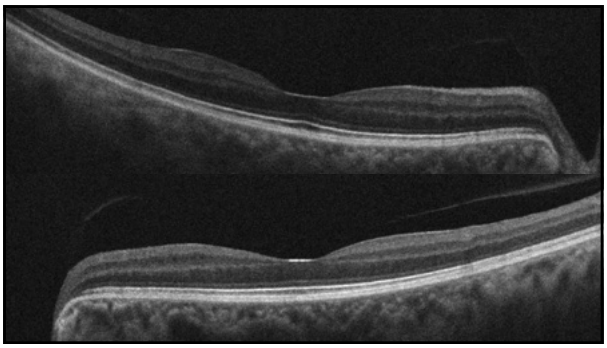

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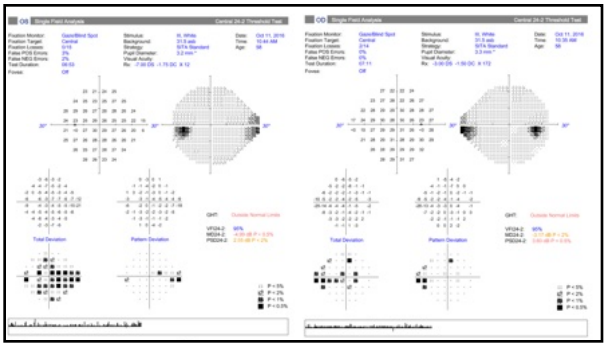

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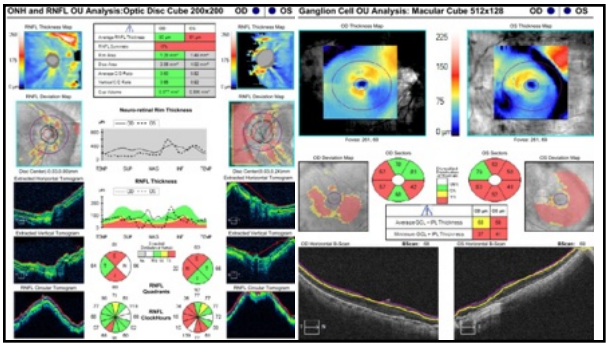

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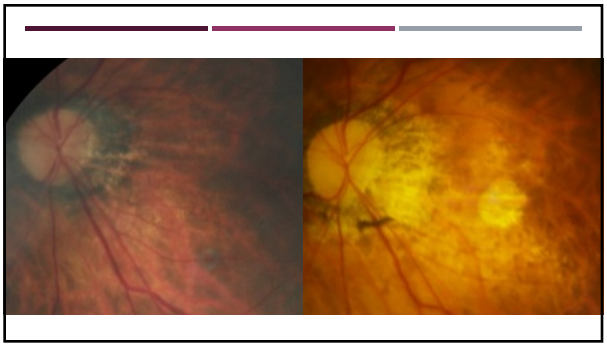

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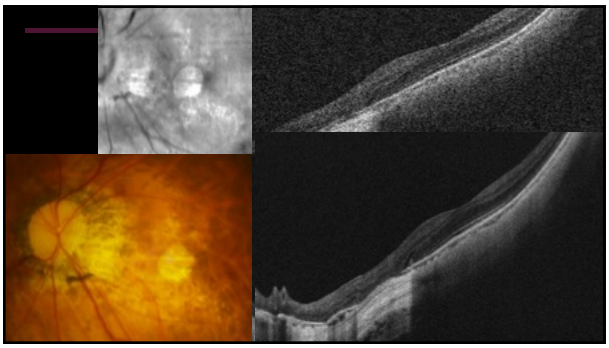

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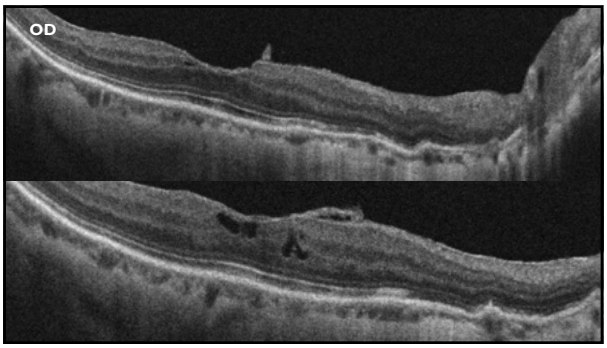

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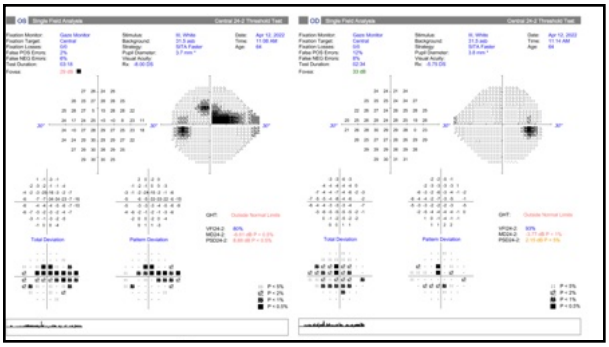

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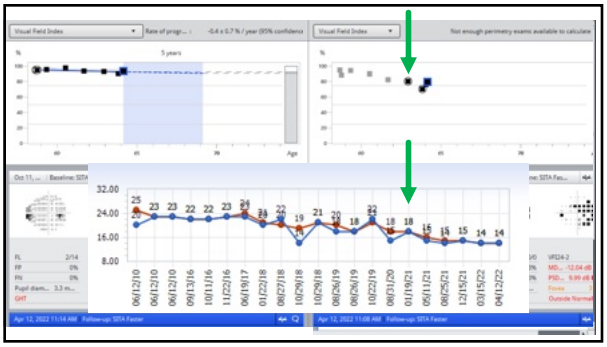

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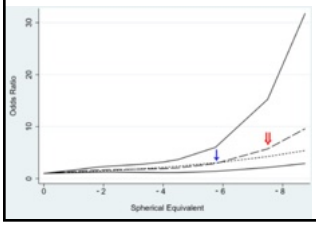
Degree of Myopia and Glaucoma Risk: A Dose-Response Meta-analysis

AHNUL HA[1], CHUNG YOUNG KIM[2], SUNG RYUL SHIM[3], IN BOEM CHANG[3], AND YOUNG KOOK KIM[2]



• CONCLUSIONS: For each unit (1-D) increase in myopia, the risk of glaucoma increases by approximately 20%. The risk more steeply increases in high-degree myopia, representing a significant nonlinear relationship. (Am J Ophthalmol 2022;236: 107–119. © 2021 The Authors. 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/))

Primarily mechanical

Axial elongation → stretching and thinning of the lamina

Disc tilt and oblique insertion → laminar strain

Overdiagnosis of glaucoma?

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67 YEAR OLD FEMALE

- History of primary open angle glaucoma of the left eye in 2022
- Presented taking latanoprost 0.005% QHS OU
- IOP in office 16mmHg OD 17mmHg
  - CCT 554 µm OD 560 µm OS
- ***Is this good?***

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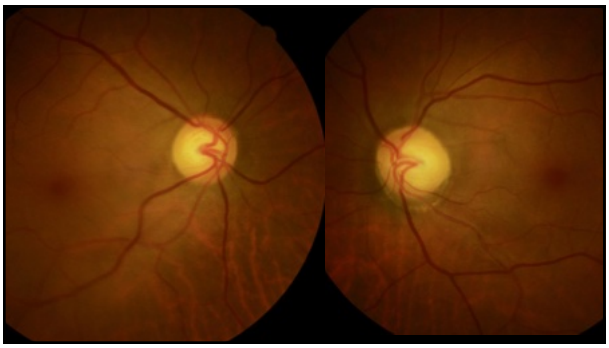

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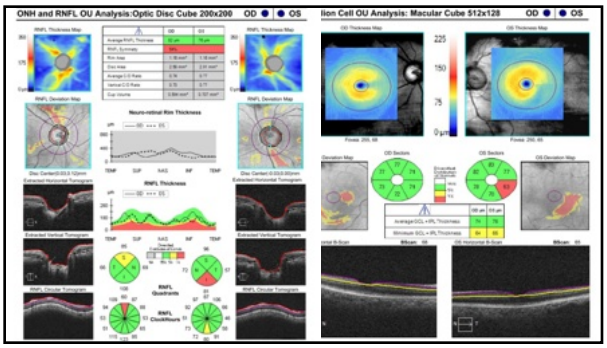

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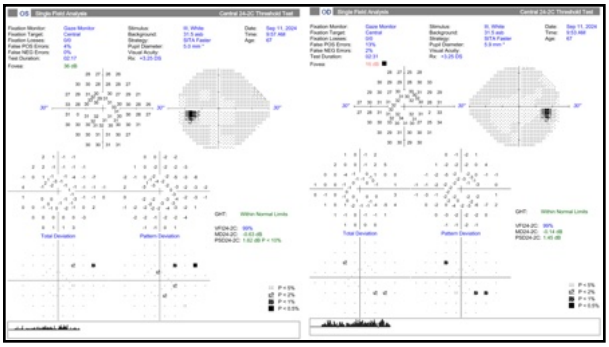

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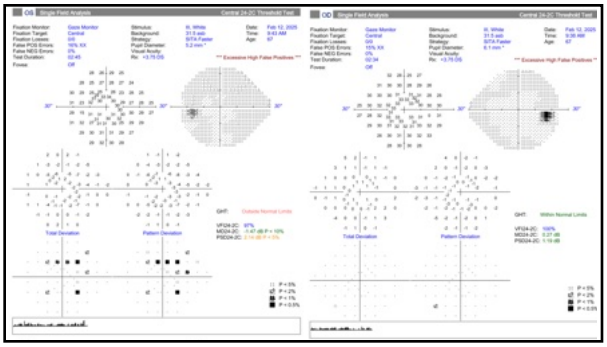

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Is this good?!

Peak untreated IOP 18mmHg OD and 18mmHg

Treated IOP 16mmHg and 17mmHg OS

Blood pressure: 115/80mmHg on treatment

History of TIA 2011, stroke 2010
Bilateral hip replacement: 2016 & 2017
Fibromyalgia 2018

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Now what?

Adherence?

Discontinue treatment

IOP 1 month later: 16mmHg OD 15mmHg OS

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Evaluation of data gathered on that day—and <u>most</u> importantly, compared to previous data for change over time

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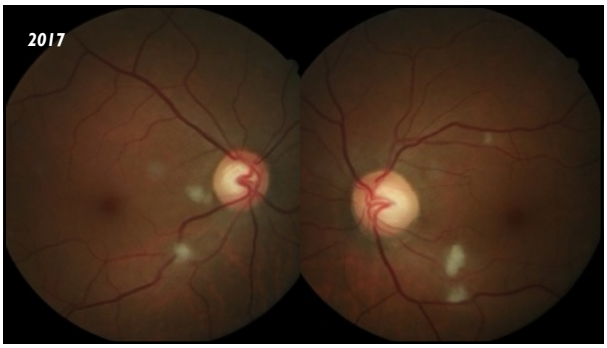

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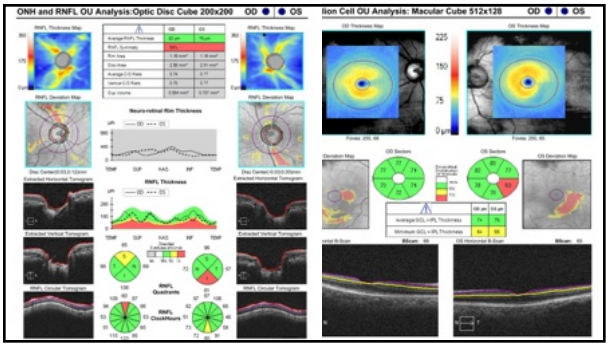

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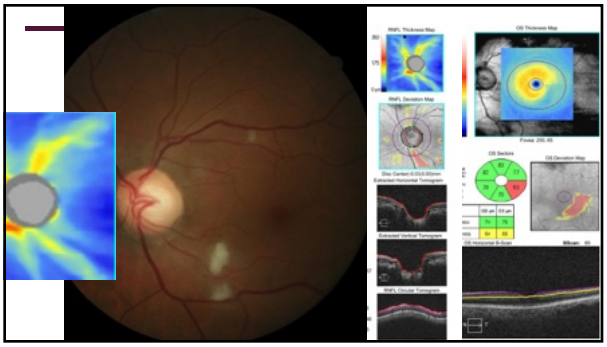

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What else can cause RNFL defect?

Retinal ischemia

Diabetes mellitus, hypertension, systemic lupus erythematosus

Nonarteritic ischemic optic neuropathy

Optic disc drusen

…

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63 YEAR OLD WHITE MALE

- History of "narrow angles" and bilateral LPI
  - 25 years ago (1999)-at the age of 38
- Latanoprost QHS OU (teal cap)
  - Reported peak untreated IOP high 20s
- Systemic hypertension and anxiety
  - Lisinopril
  - Clonazepam
    - No events of significant blurred vision, haloes around lights, significant nausea, or headache

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63 YEAR OLD WHITE MALE

- BCVA 20/20 OD and OS
  - +2.00D OD and OS
- Patent LPI 1:00 OD and OS
  - What does LPI do?!
    - Reverse or prevent pupil block
- Moderately deep central anterior chamber
  - Anterior trabecular meshwork 360 degrees OD; 270 degrees OS with no structures temporal
    - Convex iris approach; no PAS, AR, NVA
    - 1+ pigment with compression

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OCT Evaluation of the Anterior Chamber

No inadvertent compression

May be performed in complete darkness

Most valuable to determine if the angle is open or closed

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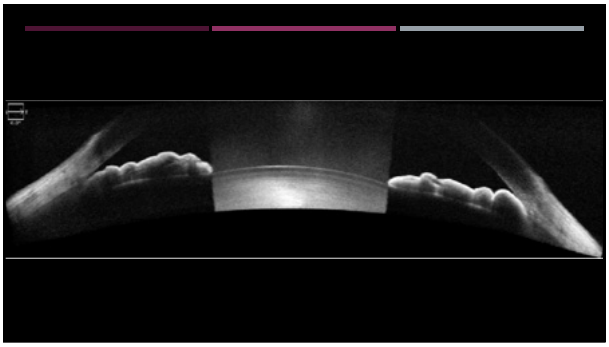

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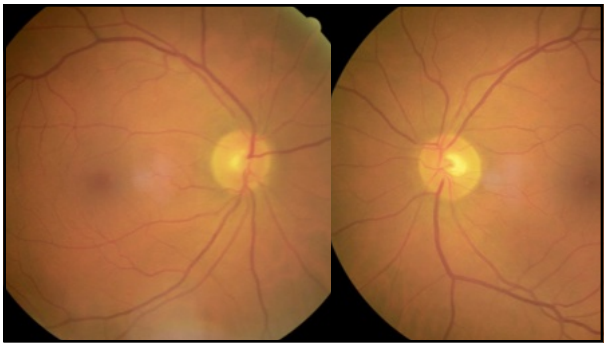

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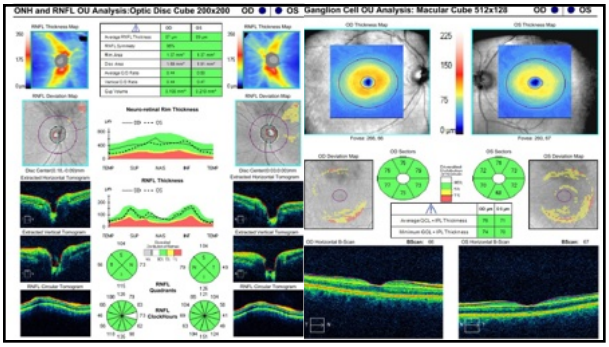

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Does this patient need to be on treatment?

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TERMINOLOGY

- **1) Primary angle closure suspect**
- 2) Primary angle closure
- 3) Primary angle closure glaucoma
- 4) Acute angle closure crisis

Either open or closed
There is no such thing as "narrow angle glaucoma"

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PRIMARY ANGLE CLOSURE SUSPECT

- Discontinue latanoprost: 18mmHg OD/17mmHg OS at follow up
- Advocate for early cataract surgery

- ***Does this patient meet EAGLE inclusion criteria?***

63

Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial

Augusto Azuara-Blanco, Jennifer Burr, Craig Ramsay, David Cooper, Paul J Foster, David S Friedman, Graham Scotland, Mehdi Javanbakht, Claire Cochrane, John Norrie, for the EAGLE study group

- Removal of clear lenses in eyes with PACG with IOP > 21 mmHg or eyes with PAC (without glaucoma) and IOP >30mmHg vs. LPI (and medications); greater than 50 years of age
  - Clear lens extraction patients had greater IOP control and improved quality of life
  - Patients who underwent lens extraction had fewer IOP lowering medications
    - Only 1 needed trabeculectomy after phaco whereas 24 patients in the LPI group needed trabeculectomy
  - Cost-effective at 3 years; savings by 10 years
    - Fewer procedures, fewer office visits
- Clear lens extraction can be considered

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Local Coverage Determination (LCD)

Cataract Surgery

L34413

In general, cataract surgery is performed to alleviate visual impairments attributable to lens opacity.

"There are uncommon situations when lens extraction becomes medically necessary for anatomic reasons rather than optical reasons"

"These include induced angle closure (e.g. microspherophakia)"

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Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial

Mingguang He, Yuzhen Jiang, Shengsong Huang, Dolly S Chang, Beatriz Munoz, Tin Aung, Paul J Foster*, David S Friedman*

- Zhongshan Angle Closure Prevention (ZAP) trial
- Purpose: to determine if laser iridotomy is superior to observation in primary angle closure suspects in China over a 6 year period
  - PACS = 6 or more clock hours where posterior trabecular meshwork was not visible
    - Without elevated IOP, disc change, or peripheral anterior synechiae
- Endpoint: elevated IOP--used dark-room prone provocative testing (compared pre-test IOP to IOP measured after 15 minutes in a dark room in prone position), PAC, acute angle closure
- Outcome: 889 eyes treated. 50% reduction in risk for development of primary angle closure over 6 years, but only 4% of untreated eyes progressed to primary angle closure
  - Acute angle closure: 5 patients untreated, 1 treated (3 control eyes and one LPI eye were after dilation)
  - Authors determined that laser peripheral iridotomy was not justified in smaller populations

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14-Year Outcome of Angle-Closure Prevention with Laser Iridotomy in the Zhongshan Angle Closure Prevention Study: Extended Follow-Up of a Randomized Controlled Trial

Results: During the 14 years, 390 LPI-treated eyes and 388 control eyes were lost to the follow-up. A total of 33 LPI-treated eyes and 105 control eyes reached primary endpoints (P <0.01). Within them, twelve eyes developed AAC or primary angle closure glaucoma (AAC: five control eyes and one LPI-treated eye; PACG: four control eyes and two LPI-treated eyes). The hazard ratio for progression to PAC was 0.31 (95% confidence interval, 0.21–0.46) in LPI-treated eyes compared with control eyes. At the 14-year visit, LPI-treated eyes had severer nuclear cataract, higher IOP, larger angle width and limbal anterior chamber depth (LACD) than control eyes. Higher IOP, shallower LACD, and central anterior chamber depth (CACD) were associated with an increased risk of developing endpoints in control eyes. In the treated group, eyes with higher IOP, shallower LACD, or less IOP elevation after dark room–prone provocative tests (DRPPT) were more likely to develop PAC after LPI.

Yixiong Yuan, MD, Wei Wang, PhD, Rulin Xiong, MD, Jian Zhang, MPH, Cong Li, MD, Shaopeng Yang, MD, David S. Friedman, PhD, Paul J. Foster, PhD, Mingguang He, PhD

Endpoint: PAC, PAS, IOP>24mmHg or AAC

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EMERGENCY VISIT

- IOP determined to be 30mmHg OD and 32mmHg OS at a comprehensive eye examination
- ***What is the mechanism for elevated intraocular pressure?***

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What about the clonazepam?

CONTRAINDICATIONS

Klonopin should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

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Now what?

1. Lower the pressure
   Is this an acute emergency?
   Medical therapy is NOT disease-modifying
2. Arrange for cataract surgery?
   How soon?

70

57 year old female

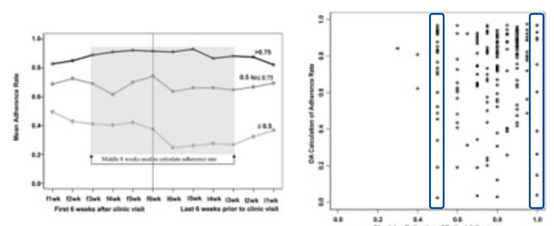
Peak untreated IOP 21mmHg OD 26mmHg OS

Transferred care for 5 years; returned taking latanoprost QHS OU…misses about 2 night per week due to irritation

"Do I have glaucoma?"
"Do I need to keep taking these eyedrops?"

74

Adherence during known monitoring



Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, Friedman DS. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. Ophthalmology. 2009 Feb;116(2):191-9.

75

Sustained delivery options

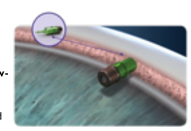
Bimatoprost implant 10mcg Equivalent to about 2-3 drops of bimatoprost 0.01%
Drug release complete in 3-4 months

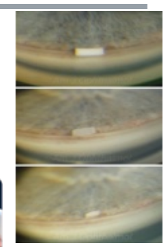
197 eyes, 94.9% pseudophakic, 41.6% prior SLT, mean age 80.4
Effect approximately 1 year; reduction in medication use
16.9% underwent SLT within first 12 months

Travoprost titanium implant
FDA approved December 14, 2023
Not refillable

36 month data: 70% (fast-release) and **68% (slow-release)** fewer or same medications as baseline

Mean IOP reduction: 8.3mmHg (fast-release) and 8.5mmHg (slow-release)





Teymoorian S, Craven ER, Nguyen L, Werts E. Real-World Study of the Effectiveness and Safety of Intracameral Bimatoprost Implant in a Clinical Setting in the United States. Clin Ophthalmol. 2024 Jan 19;18:187-199. Berdahl JP, Sarkisian SR Jr, Ang RE, Doan LV, Kothe AC, Usner DW, Katz LJ, Navratil T; Travoprost Intraocular Implant Study Group. Efficacy and Safety of the Travoprost Intraocular Implant in Reducing Topical IOP-Lowering Medication Burden in Patients with Open-Angle Glaucoma or Ocular Hypertension. Drugs. 2024 Jan;84(1):83-97.

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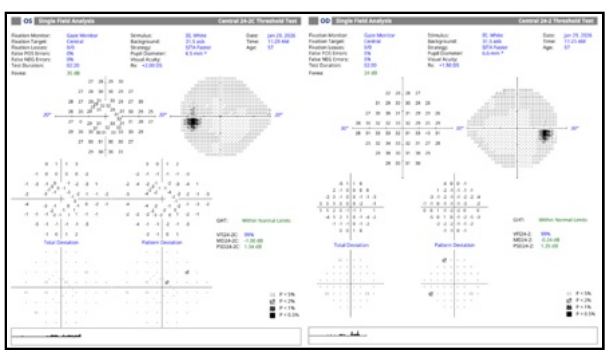
"Do I ~~really~~ need to use these eyedrops?

In office: 16mmHg OD and 17mmHg OS
CCT 555 µm OD 562 µm OS

Medication holiday

IOP 21mmHg OD and 22mmHg OS

77



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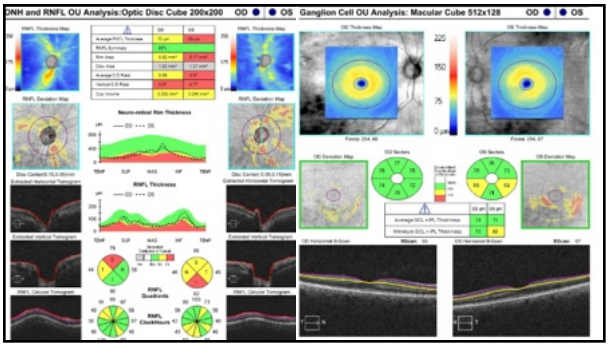

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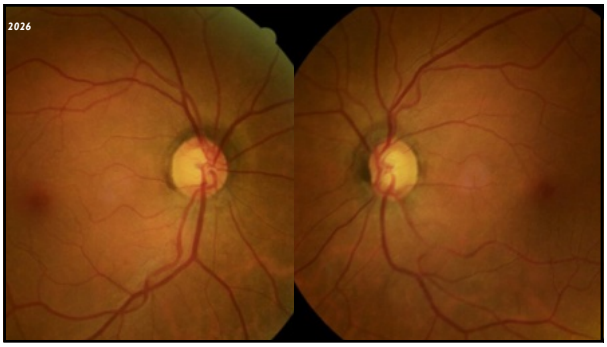

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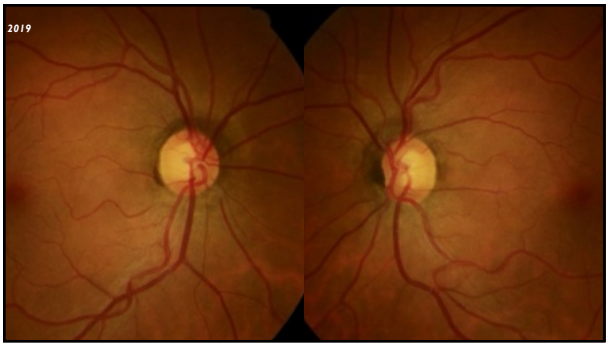

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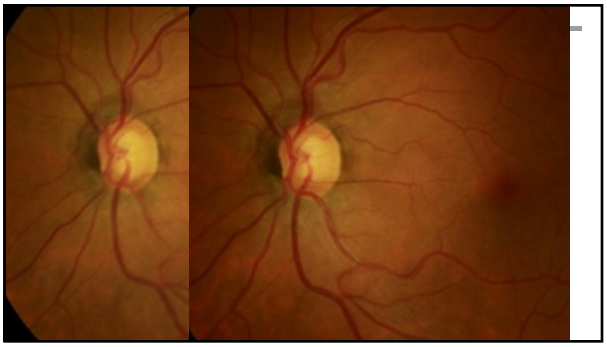

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57 year old female

Primary open angle glaucoma, left eye

Treatment options?

Primary SLT? Latanoprost 0.005% (BAK-preserved, preservative-free)

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Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

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, Rachael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Neil Nathwani, Keith Barton, Gary Rubin, Marta Buszewicz, on behalf of the LiGHT Trial Study Group*

- ***No game-changing data; But did provide good quality evidence for what was already known***

SLT: at target 93% of visits, 91.3% in the medication group (3 years)
What happens if one eye is drop-free, but the other isn't?

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AMERICAN ACADEMY OF OPHTHALMOLOGY

Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial

Six-Year Results of Primary Selective Laser Trabeculoplasty versus Eye Drops for the Treatment of Glaucoma and Ocular Hypertension

Conclusions: Selective laser trabeculoplasty is a safe treatment for OAG and OHT, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma and cataract surgery over 6 years. *Ophthalmology 2023;130:139-151 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

No difference in health-related quality of life scores: mobility, self-care, usual activities, pain or discomfort.

Minimal difference in Glaucoma Symptom Scale-did not translate to difference in HRQoL

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AMERICAN ACADEMY OF OPHTHALMOLOGY

Six-Year Rate of Visual Field Progression in the Laser in Glaucoma and Ocular Hypertension Trial

Giovanni Montesano, MD, PhD,[1,2] David P. Crabb, PhD,[2] David F. Garway-Heath, MD, FRCOphth,[1] David M. Wright, PhD,[3] Evgenia Konstantakopoulou, PhD,[1,4] Neil Nathwani, BSc (Hons), DipTp(IP),[1] Giovanni Ometto, PhD,[1,2] Gus Gazzard, MD, FRCOphth[1]

Results: Data from 710 eyes (482 with OAG and 354 in the SLT-first arm) were analyzed. The 2 arms had similar baseline MD ($P = 0.7$). The average intraocular pressure (IOP) during follow-up was 16.1 [14.2–18.2] for the drops-first arm and 16.8 [14.6–18.6] in the SLT-first arm (median [interquartile range], $P = 0.057$). The mean [95% credible interval] MD rate was −0.37 [−0.43 to −0.31] decibels (dB)/year in the drops-first arm and −0.26 [−0.31 to −0.21] dB/year in the SLT-first arm ($P = 0.007$). When stratified by severity, this difference was significant only in mild OAG ($P = 0.035$, the largest sub-group). The secondary analyses largely confirmed the main results. The difference in MPD rate was also significantly slower in the SLT-first arm ($P < 0.001$).

26% of med-first eyes were fast-progressors vs. 15% in SLT-first

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JAMA Ophthalmology | Original Investigation

Selective Laser Trabeculoplasty After Medical Treatment for Glaucoma or Ocular Hypertension

Evgenia Konstantakopoulou, PhD; Gus Gazzard, MA, MD, MBBChir; David Garway-Heath, MD; Mariam Adeleke, PhD; Gareth Ambler, PhD; Victoria Vickerstaff, PhD; Catey Bunce, DSc; Neil Nathwani, BSc; Keith Barton, MD; for the LiGHT Trial Study Group

Patients were randomized to SLT or medication first (LiGHT)-then after 3 years patients were allowed to have secondary SLT (to reduce medication load) or to escalate therapy if needed

65% of 320 taking drops chose to continue medical therapy!

Patients "trust" eyedrops and prefer non-procedures—even though they don't take them as much as we would like…

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57 year old female

Opts for preservative-free latanoprost 0.005%

88

59 YEAR OLD FEMALE

- Diagnosed with POAG in Haiti about 10 years ago
  - Latanoprost QHS OU
- IOP 16-18mmHg range OD and OS
  - CCT 560um OD 540um OS
- Hypertension
  - Labetalol

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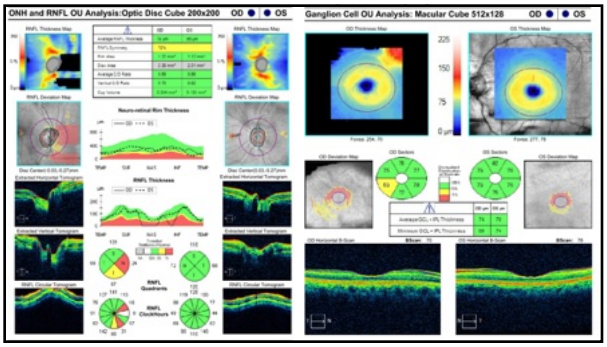

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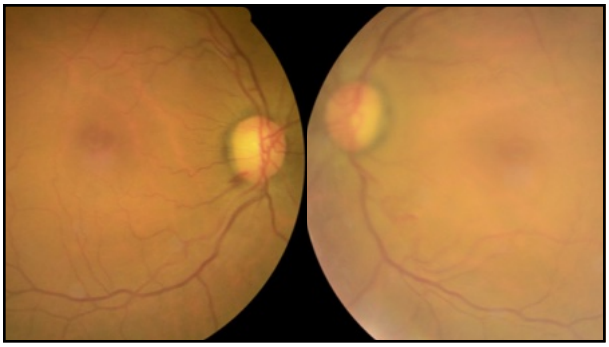

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Ischemic stress? Or mechanical stress?

110

Ocular perfusion pressure

OPP is the difference between blood pressure and IOP

Indirect assessment of ocular blood flow

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Labetalol(?!)

May be initial therapy in severe disease-or used to treat hypertensive crisis

Non-selective beta blocker; also has alpha blocking activity

Selective beta-blockers: atenolol, metoprolol

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Does Timing of Antihypertensive Medication Dosing Matter?

Disregard the reported data from the HYGIA project: blood pressure medication not to be routinely dosed at bedtime

Bedtime hypertension chronotherapy best reduces cardiovascular disease risk as corroborated by the Hygia Chronotherapy Trial. Rebuttal to European Society of Hypertension officials

How can evening medication reduce NON-cardiovascular deaths?!

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Hypertension

Volume 80, Issue 7, July 2023; Pages 1544-1554

https://doi.org/10.1161/HYPERTENSIONAHA.122.20862

Timing of Antihypertensive Drug Therapy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Muhammad Haisum Maqsood, Franz H. Messerli, Adam H. Skolnick, Jonathan D. Newman, Jeffrey S. Berger, and Sripal Bangalore

Conclusions: Evening dosing of antihypertensive drugs significantly reduced ambulatory BP parameters and lowered cardiovascular events but the effect was mainly driven by trials by Hermida group. Unless the intention is to specifically lower night-time BP, antihypertensive drugs should be taken at a time of day that is convenient, optimizes adherence, and minimizes undesirable effects.

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Bottom line

We know more about glaucoma pathophysiology than we sometimes give ourselves credit for

Take the time you need to establish a diagnosis and when making treatment decisions

Understand the impact of therapeutic selection on the bigger picture

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