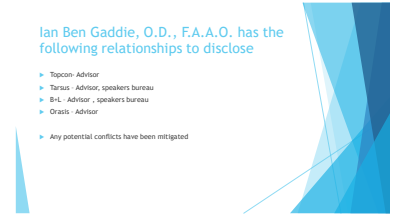


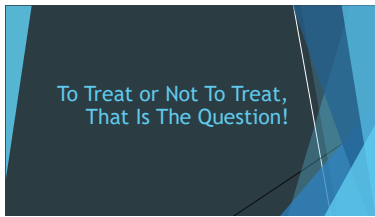
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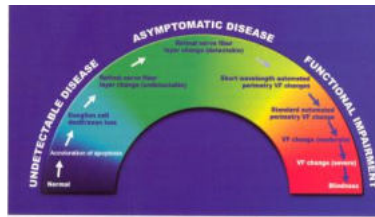
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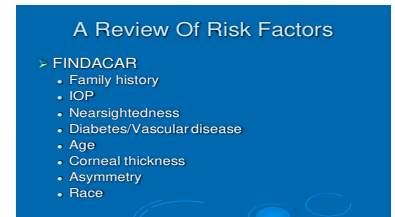
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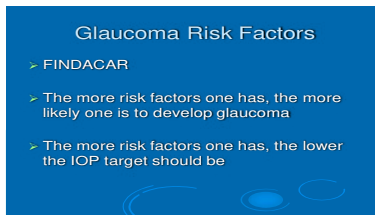
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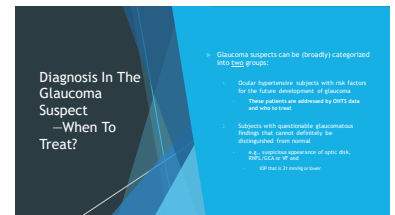
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9



Open Angle Glaucoma Suspect

- ▶ The Decision Tree:
- ▶ The patient without OCT, VF or OBT changes
- ▶ This may be someone with IOP < 21 or < 21 morning

10

Who do you treat? Options, Bias, Preferences

- ▶ Rather than a simplistic approach of treating everyone with an IOP of over 21 mmHg, treatment is held off until there is sufficient evidence of glaucoma damage at some level (OCT, VF, ...)
- ▶ This is a practice philosophy that can be followed for low-risk patients
- ▶ Or, we elect to treat those with the most significant risk factors.

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Glaucoma Suspect: The Ocular Hypertensive

- ▶ IOP 21-30+ mmHg with
 - ▶ Normal appearing of trabecular optic nerve and no glaucoma damage?
 - ▶ No visual field defects
 - ▶ None risk factors
- ▶ Follow OHTS Treatment Guidelines:

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Glaucoma Suspect: IOP under 21

- ▶ Management Options:
- ▶ An angle-comparable eye problem: none with any signs: (not recommended)
- ▶ Follow these patients every 3-6 months with observation and repeat: OHT, VF, OCT, IOP (not)
- ▶ High-risk combination of two (OCT or VF defect, OHT) (not)
- ▶ Or, Start Medical Therapy for those with 3 or more risk factors: positive family history,
 - ▶ OHTS 2.0 or greater, history of the nerve
 - ▶ Short duration, diurnal, etc.
 - ▶ Significant visual field defects, advancing OHT


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Patients Who Likely Require Therapy:

- ▶ At any IOP
 - ▶ Unexplained OHT Changes
 - ▶ As identified by you or a photograph and abnormal OCT
 - ▶ Abnormally abnormal, characteristics, and glaucoma OCT
 - ▶ "No other eye signs" (visual connection) there is no treatment over the same patient for other features)
 - ▶ Not used for "Not Observed"
 - ▶ Characteristics/Confirmed Visual Field Loss (not required for diagnosis)
- ▶ OHTN with IOP over 30 mmHg
 - ▶ None exceptions, eg very, high cornea

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Glaucoma diagnosis can be a very complex



- ▶ Requirements:
- ▶ Organized, step-by-step approach
- ▶ Sort and organize the data
- ▶ Identify good data
- ▶ Ignore bad/unreliable data
- ▶ Confirm data when necessary
- ▶ Sort and organize again
- ▶ No need to rush your decision
- ▶ Individualize to your patient
- ▶ Begin therapy (later) or monitor

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When you have enough compelling evidence - you treat!

- ▶ Look to the OHTS Study for guidance

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Ocular Hypertension

- When do you treat – sometime, all the never, never?
- Can OH progress to glaucoma if it is treated?
- What are the downsides to therapy?
- When NOT treat everyone w/ elevated IOP?

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Ocular Hypertension

- Definition of ocular hypertension
 - IOP ≥ 21 mm Hg or higher
 - Based upon the statistical definition of OHTA
 - Not based upon clinical findings
 - Visual field loss
 - Optic nerve considered fine
 - Optic nerve considered fine
 - The cost of definition is changing with OCT use allowing subtle optic nerve/ONH changes to be detected
- Consider therapy based upon risk of developing glaucoma over lifetime
 - Concept of risk assessment
- Therapy is often considered optional since true damage is not present
 - Optic nerve is only therapy before damage after long-term outcome
 - OHTA is used meant to answer this question

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The Swinging Pendulum of Therapy for Ocular Hypertension

- 1960s: IOP ≥ 21 mm Hg: Treat
- 1970s: IOP ≥ 21 mm Hg: No Tx
 - Decade of Ocular Hypertension
- 1980s: IOP ≥ 21 mm Hg: Tx/No Tx
 - 1993: Quigley paper field loss late sign DAG
 - Concept of risk factor analysis
- 1990s: IOP ≥ 21 mm Hg: Tx/No Tx
 - Earlier therapy once latanoprost introduced

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Ocular Hypertension

- Many years ago, everyone with elevated IOP was treated
- Recognition that about 1% per year convert from OHTA to glaucoma
- Those with greater risk are more likely to convert
 - thinner cornea, African American, larger cupping
- led to the concept of risk assessment
- OHTA provided information on when to treat
 - European Glaucoma Prevention Study (EGPS) also provided risk information

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Treating ocular hypertension Risk assessment

- Consider number of risks (individuals) that increases chance for
 - Conversion of ocular hypertension to the development of glaucomatous damage
- Based upon evidence
- Studies include Ocular Hypertension Treatment Study (OHTS) and European Glaucoma Prevention Study (EGPS)
- If we are going to treat ocular hypertension, at what risk level?
 - 10% vs. 15% vs. 20%
 - Begin prophylactic therapy
- Uses concept from Framingham Heart Study

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OHTS – The Nitty Gritty

➤ The most predictive factors for conversion:

- Older age
 - 22% increase/decade
- Larger horizontal and vertical C/D
 - 32% increase/1 larger
- Higher baseline IOP
 - 10% increase/mm Hg
- Thinner corneas
 - 71% increase in risk/40 microns thinner

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Risk Assessment

- Risk Level Low <5%
 - Monitor
- Risk Level Moderate 5-15%
 - Consider Therapy
 - Discuss with patient
- Risk Level High >15%
 - Treat

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IOP 30mmHg, CCT 600µ

Glaucoma Risk Estimator

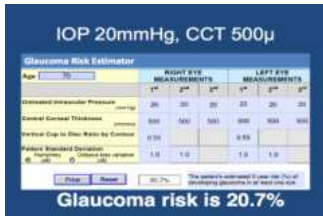
Age	RIGHT EYE MEASUREMENTS					LEFT EYE MEASUREMENTS				
	1 st	2 nd	3 rd	4 th	5 th	1 st	2 nd	3 rd	4 th	5 th
Unreated Intraocular Pressure (mmHg)	30	30	30	30	30	30	30	30	30	30
Central Corneal Thickness (µm)	600	600	600	600	600	600	600	600	600	600
Vertical Cup to Disc Ratio by Computer	0.00				0.00					0.00
Horizontal Cup to Disc Ratio by Computer	0.00				0.00					0.00
Patients Standard Deviation	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Print Reset 0.1%

The patient's estimated 5 year risk of developing glaucoma is 9.1%.

Glaucoma risk is 9.1%

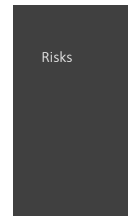
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29



30

- OHTS
 - IOP
 - Corneal thickness
 - Cup/Disc ratio
- Other risks
 - VF status
 - Family history
 - Race including Hispanic
- Newer risks
 - Alcohol use
 - Cigarette smoking
 - Diabetes?
 - Age at menopause
 - Ovarian surgery
 - Physical activity
 - Metabolic diseases
 - Hypertension, cholesterol, Cardiovascular diseases
 - Sleep apnea

Ocular Hypertension

- Treat when risk is significant but...
- Need to include patient in discussion about therapy
- Some patients would like OHTN to be treated when risk is present while others would rather not be treated
- Glaucoma is a slow-moving disease so can monitor those with OHTN safely without therapy
- Still not clear how soon therapy should be initiated

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Making the Diagnosis and Starting Therapy



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Glaucoma Clinical Trials: Study Design

Trial	N	Dr	Randomization	Follow Up
OHTS (OHT)	1630 pts	OHT	Medical Tx vs observation	5 years
EMGT (OHT)	200 pts	OHT	Tx (SLT + timololol) vs observation	4.9 years
CRISTOP (OHT)	140 eyes	NTG	Medical Tx versus surgery vs observation	7 years
CRISTOP (OHT)	607 pts	OHT	Medical Tx vs surgery	4 + years
AGIS (OHT)	738 eyes	OHT	ALT vs surgery	8 years

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IOP in Clinical Trials

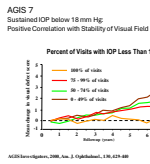
Study	IOP Reduction	Subprogression
• OHTS-20%	9.5%/4.5%	
• EMGT-25%***	62%/45%	
• CRISTOP-30%	35%/12%	
• AGIS	<1%; no progression	
• CRISTOP (meds) 38%	no progression	
• CRISTOP (surg) 45%	no progression	

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Advanced Glaucoma Intervention Study (AGIS)

- Long-term study with follow-up of patients with advanced glaucoma
 - exhausted all medical options
 - follow-up 7 years
 - 249 whites/ 332 black patients
- Results initially published July 1998 Ophthalmology
 - Therapeutic options and success vary by race
 - ALT Vs. Trabeculectomy as first procedure

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**Glaucoma Clinical Trials:
Summary of Implications**

- Treat newly diagnosed glaucoma^{1,2}
- Patients with early glaucoma should be treated to reach low pressures that reduce the risk of progression
- Both medical treatment and surgery effectively reduce IOP and risk of progression
- IOP needs to be consistently low³
- IOP fluctuation over long time periods increases risk of VF loss in glaucoma
- Results show that to be effective, patients need lower IOP
 - Need it lower consistently, all the time
- When pressures are low enough, patients on average have much lower risk of progression⁴

Determining the Target IOP

1. Estimating the amount of glaucoma damage.
 - This is based upon both structural/functional assessment.
2. Estimating the damaging IOP
 - One should make the best clinical assessment possible as to what the likely IOP was at which damage has already occurred. In some instances, multiple IOP measurements may help determine a baseline IOP and hence influence the initial determination of the target IOP

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Determining the Target IOP

3. Estimate the patient's life expectancy.
 - In general, the longer the patient's life expectancy, the lower the target IOP will need to be. Actuarial tables can be helpful, keeping in mind that any give patient may live much longer or shorter than the mean. When in doubt, err on the side of estimating a longer life expectancy. Nevertheless, on average, 40 year olds and 90 year olds may be treated differently.

Determining the Target IOP

4. Consideration of the other risk factors for progression.
 - Other proposed risk factors include severe damage in the other eye, family history of blindness from glaucoma, etc.
5. Guesstimate the Rate of Progression (ROP) of glaucoma damage, either disc and/or fields, based upon the assessment of damage already occurred vs time

IOP Often Not Lowered to Recommended Target Pressures

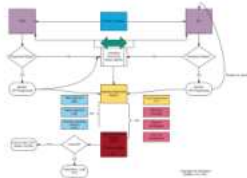
- Review of 395 POAG patient charts in 6 managed care plans
 - IOP often inadequately controlled
 - 54.6% of patients IOP > 20 mm Hg
 - 52.4% of visits IOP > 20 mm Hg
 - 21.1% of visits IOP > 18 mm Hg
 - Modestly to severe glaucoma
 - 45.3% of visits IOP > 17 mm Hg
 - 38.4% of visits IOP > 21 mm Hg

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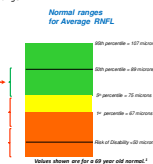
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Today's Treatment Algorithms



OCT and Progression Range

- Just like perimetry, the average patient can lose 0.3um/decade of RNFL or 1.5um/decade of IOP
- Normal person loses 2um/decade due to aging



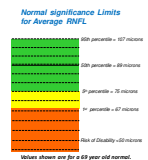
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SDOCT measurements are highly reproducible.

2-4 Steps in Range

- We can measure multiple steps of statistically significant change while a glaucoma suspect still is in the green normal range.



- Savary et al. Ophthalmology 2010; 117: 1247
- Rao et al. Ophthalmology 2011; 118: 2038
- Heuer et al. Ophthalmology 2010; 117: 2102
- Hsu et al. Ophthalmology 2014.

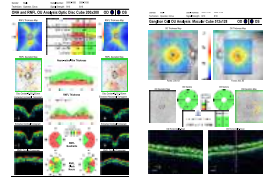
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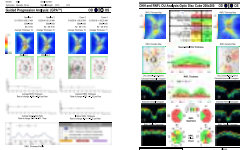
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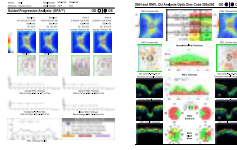
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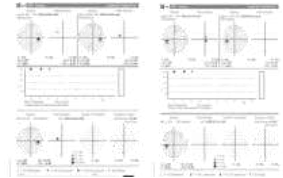
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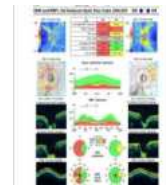
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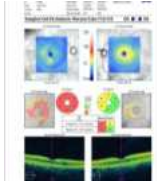
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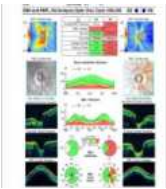
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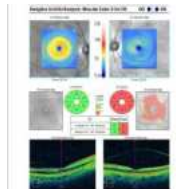
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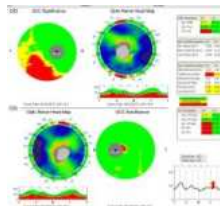
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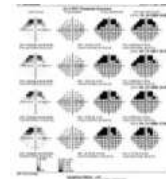
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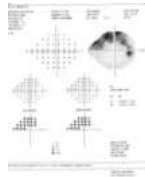
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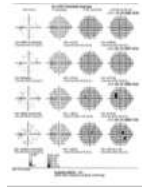
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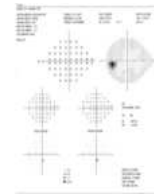
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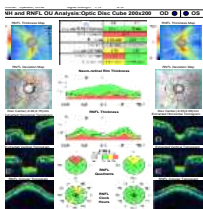
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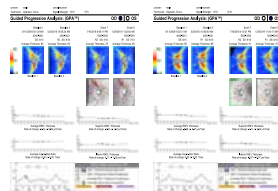
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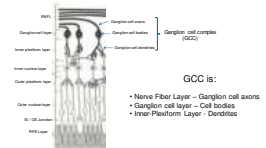


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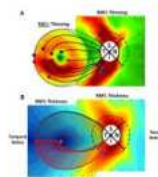
Retinal Ganglion Cells extend through three retinal layers



69

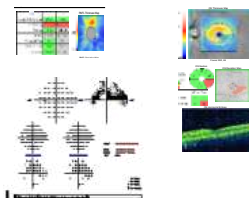
Macular Vulnerability Zone

Macular Vulnerability Zone

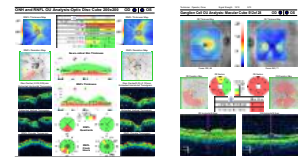
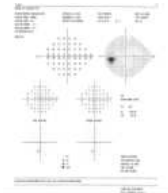
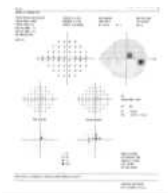
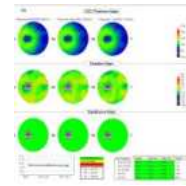
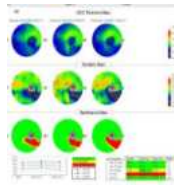
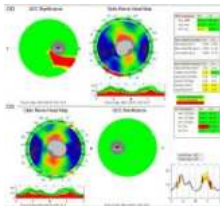
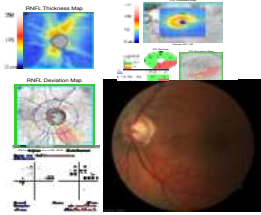


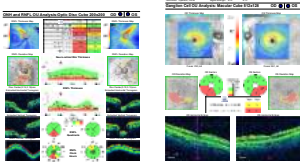
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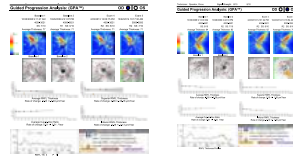


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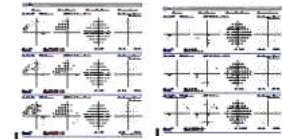




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Glaucoma Treatment Universe 2024

- ▶ Prostaglandins
- ▶ Alpha agonists
- ▶ Rho-kinase inhibitors
- ▶ Beta-blockers
- ▶ Carbonic Anhydrase Inhibitors
- ▶ Combo Agents
- ▶ SLT
- ▶ MIGS
- ▶ Glaucoma Surgery
- ▶ How Do You Know Which Category To Choose???

85

What Are You Trying To Achieve?

- ▶ Optimal IOP Reduction
- ▶ Minimal Side Effects
- ▶ Rigid Compliance
- ▶ Anything Else?

86

PGA

- ▶ QHS dosing
- ▶ Long duration of action
- ▶ Flatten diurnal curve
- ▶ Effective on trough and peak IOP
- ▶ No systemic side effects
- ▶ Little tachyphylaxis

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Prostaglandins

- ▶ All decrease IOP by increasing uveoscleral outflow
- ▶ All are effective at squashing the diurnal curve
- ▶ They have either no effect or a positive effect on retinal perfusion
- ▶ Some affect things outside at the optic disk
- ▶ Some have BAK, others don't
- ▶ But does 1 work better than the others?
- ▶ Is there really any reason to not start with a PGA?

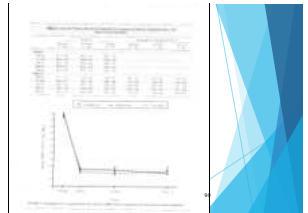
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XLT Study - Parrish, Palmberg, et. al. (AJO, May 2003, Vol. 135, No.5)

- ▶ Multicenter study to compare IOP lowering efficacy of Bimatoprost vs Latanoprost vs Travoprost
- ▶ Also compared safety profiles of the 3 drugs
- ▶ Conclusion: All 3 drugs were comparable in their ability to lower IOP at all time periods.
- ▶ Latanoprost exhibited greater ocular tolerability

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90



Vyzulta - A different kind of PGA

- Reduces IOP by 31%
- 1.2mm HG lower than latanoprost
- Preserves VF better by 10%
- No loss of effect while sleeping
- Improved side effect profile
- Releases nitric oxide at the trabecular meshwork level

91

Effect of latanoprostene bunod on Optic Nerve Head Flow

- Samaha, Diaconu et al, IOVS, Feb 2022, Vol 9, Iss 2 pp172-176
- Purpose was to evaluate effect of latanoprostene bunod on optic nerve blood volume and O2 saturation - *IN HEALTHY SUBJECTS*
- Measurements were taken before initiating therapy and then 7 days after QD therapy of both Latanoprost and latanoprostene bunod

92

- ONH saturated O2 levels were 4% higher with Vyzulta than latanoprost
- ONH blood volume was way higher with Vyzulta
 - 66% higher at Hr 1, 45% higher at Hr 2
- What is the clinical significance of this?

93

Are generics really as good as branded products?


What about when it comes to prostaglandins?

94

But really... Is There Anything New??

Iyuzeh- (latanoprost 0.005%)
Thea Pharmaceuticals

Let's talk about this...



95

- Does that sound familiar?
- Monoprost (in Europe) - the market leader in PGA in Europe
- This actually is PRESERVATIVE FREE latanoprost!!
- Single dose container
- But does it really work?!

96

Iyuzeh - Phase 3 data

- Compared to Xalatan (Switch Study)
- Stable POAG pax on Xalatan
- 8 day washout period
- 3 months on Iyuzeh
- IOP reduction was 4-8mm Hg on Xalatan
- IOP reduction was 3-8mm Hg on Iyuzeh
- Baseline IOP was 19mmHG!

97

Iyuzeh - Phase 3 data-Adverse Effects

- Xalatan group
 - Hyperemia - 31%
 - Eye Irritation - 34%
- Iyuzeh Group
 - Hyperemia - 34%
 - Eye Irritation - 19%
- ZERO reports of SPK

98

- European data - Higher baseline IOP (24mm Hg)
 - IOP lowered to 15.5mm Hg
 - Same rate of adverse effects
- Randomized data (2022 ASC)
 - 12 week trial comparing to Xalatan
 - Similar IOP reduction (as measured by ability to get IOP < 18mm Hg)
 - 26 reported adverse events in each treatment
 - US SPA
 - Preservative free side effects (S, R, W, 22.5%)
- Real world study
 - 1000 patients
 - 17% usage increased 2%

99



#What's The Big Deal??

- OSD is an epidemic in glaucoma
- Will this improve compliance?
- Will this cost \$1M?
- Is it better than what we have?

100

Are we going to see a trend towards Preservative free glaucoma drops??

101

Beta-blockers

- 40 year history of successfully lowering IOP
- Reduces aqueous humor formation
- Adrenergic agonists
- Lowers IOP 22-28%
- Ocularly well tolerated

102

Beta-blocker side effects

- Cardiac problems**
 - Bradycardia
 - Hypotension
 - Exercise intolerance
 - Heart block
- Respiratory problems**
 - Bronchospasm
 - Status asthmaticus

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Beta-blocker side effects

- CNS**
 - Often overlooked
 - ACID
 - Memory
 - Confusion
 - Depression
 - Depression
 - General decreased affect
- Diabetic problems**
 - Decreased sense of caloric need due to depressed adrenergic surge


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Beta-blocker side effects

- 22% of pts have contraindication to or significant side effect from beta-blocker
- Question, query and query some more!
- Be specific
- Remember the dose relationship so:
 - 1/5 rather than 1/5
 - QD rather than BID
- They are real (may be anecdotal)
- IS THERE REALLY ANY REASON TO USE A BETA-BLOCKER??

105

Rhopressa (netarsudil) -MOA



Works at the cellular level within the trabecular meshwork.

ROCK inhibitors improve outflow by relaxing contraction and stress fibers at the l.u.m.

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What Do We Know About Rhopressa (netarsudil 0.02%)

- Rhopressa QD is non-inferior to timolol 0.5% BID in lowering IOP
- Expected IOP reduction 3.7 - 7.0mm Hg
- Rhopressa seems to be better at lowering IOP (as compared to itself) in pressures < 20mm Hg
- IOP lowering effect is maintained over 12 months
- Was given a broad label by FDA

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Rhopressa - Adverse Effects

- Generally well tolerated
- Conjunctival hyperemia - 53%
 - Did not worsen with time
 - Mild 36.8%, moderate - 10.5%, severe - 0.6%
 - ADIC rate due to redness - 3%
- Corneal verticillata - 18%
- Conjunctival hemorrhage - 15%
 - All are transient and considered mild

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What's to like about Rhopressa?

- New MOA so... it is absolutely different
- It should be additive
- Definitely works better at lower IOP
- What about side effects?

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M.O.S.T. Study

- Real World Open Label Phase 4 Study
- ASCRS 2020
- To determine efficacy of Rhopressa as an adjunct med
- Investigator's Choice – Rhopressa + any other agent
- 24.4% African-American participants


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M.O.S.T. Results

Rhopressa + PGA - IOP 21.1 > 16.9 mmHg (20% reduction)

Rhopressa + 2 meds – 20.6 > 16.6 mmHg (20% reduction)

Notice the low baseline IOP






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More M.O.S.T. Results

- % of patients less than < 18mm Hg
 - < 18mm - 72.3% (from 34.4%)
 - < 17mm - 65% (from 25.2%)
 - < 15mm - 40.6% (from 15.9%)
 - < 14mm - 30.1% (from 11.3%)
- 2/3 of all patients achieved IOP < 17mm Hg

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M.O.S.T. Tolerability rates

-  **Hyperemia – 20.* %**
-  **D/C rate – hyperemia 3.4%**
-  **Tolerability rating**
 67.6-73.1% good or decent (patient response)
 65-78% good or decent (patient response)

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Roclatan – Alcon

- Fixed Combination drug – Rhopressa + latanoprost
- QD dosing
- "Quadruple acting" MOA – (adds increased uveoscleral outflow)
- IOP lowering better than either of its components
- Potential to be very effective – lowered IOP an additional 2-3 mm compared to Rhopressa (and other PGAs)

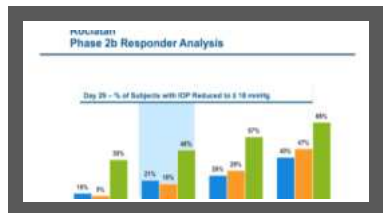
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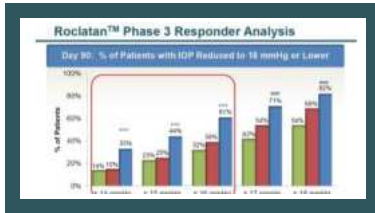
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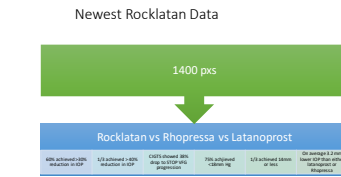
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Newest side effect data

- No tachyphylaxis at 12 months
- No unexpected A.E.
- Very few serious A.E. - majority are mild
- 58% hyperemia but 5% d/c rate
- 20% Instillation pain – 0% d/c
- 10% subconj heme – 0% d/c

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Adrenergic Agonists

- Dual mechanism of action
- Reduce aqueous production
- Enlarge outflow mechanism
- 22-25% IOP reduction
- Short duration of action
- TID dosage
- Avoid in kids

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Mechanism of Action of Brimonidine-PURITE®

- Complements PGAs because it decreases aqueous production
- Complements timolol because it increases uveoscleral outflow

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Brimonidine side effects

- 10-20%
 - Hyperemia
 - Allergic conjunctivitis
 - Ocular pruritis
- 5-9%
 - burning sensation,
 - conjunctival folliculosis,
 - ocular allergic reaction,
 - oral dryness,
 - visual disturbance
- Do these worsen with time?
- How do you know if the drops are the culprit?

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Alphagan systemic side effects

- Dry mouth (~20%)
- Fatigue (1-2%)
- Drowsiness
- Decreased BP
- This drug can cross blood-brain barrier, esp in older and younger pts

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Brimonidine questions

- What is the correct dosage?
- Which of the 3 products should be prescribed?
- Can it be used as stand alone therapy?
- Effect on diurnal curve?
- What Happens if Hypersensitivity To 0.2% Brimonidine Occurs?

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Let's talk (quickly) about combo drops!

- What are their advantages?
- What about their side effects?
- Are they twice as good as their individual components?

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Dry Eye and Glaucoma

Considerations on Glaucoma and Dry Eye

Preservatives in Glaucoma Medications

- Same age range as chronic dry eye
- Preservatives in PGAs and also combo medications
 - QD vs. BID vs... TID etc
- Preservative Free Glaucoma Medications
 - Effect of preservative on hydrolyzation of drug
- Blepharitis/PGA's

- BAK ranges depending on agent
- At once/day PGA BAK seems innocuous
- Adjunct drugs containing BAK
 - Beta Blockers, CAI's, Brimonidine, RhoKinase
- Mostly BAK; others such as Sofzia and "P" for Alphagan P

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OSD and Glaucoma

Non Preserved PGA's

- Strategies
 - Go with non preserved PGA
 - Consider SLT
 - Single treatment can last 5 years
 - Consider Durysta
 - Consider Cat S+ +MIGS when appropriate
 - Avoid multiple time/day drugs w/ BAK
 - Treat OSD/Blepharitis in addition to glaucoma
 - Medications
 - MIGS procedures (IFU/Lipiflow/Rear Care etc)
 - Amniotic membranes

- Zioptan (Tafuprost) Thea
- Iuzeh (Latanoprost) Thea



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Miebo Phase 3 Program

Two phase 3 studies evaluating the safety and efficacy of MIEBO for the treatment of DED

100% of participants had DED and clinical signs of OSD (OSD severity) at baseline (Day 1)

Participants randomized 1:1 to MIEBO or saline (control) DED

All 4 participants received MIEBO

OUTCOMES

- Significant improvement in total OSD severity (OSD) at Day 12 (secondary) and Day 24 (primary)
- Change from baseline in total OSD severity (OSD) at Day 12 (secondary) and Day 24 (primary)

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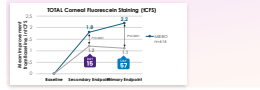
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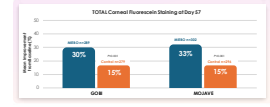
100% of Patients Had DED and Clinical Signs of MGD

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
<ul style="list-style-type: none"> 66-month and reported history of DED GDJ score 3 or 4 Topical MGD score 3 Based on observation of conjunctivae on lower eyelid Each eyelid from 0 to 3 0 = normal 1 = mild redness/inflammation 2 = possible 3 = redness/inflamed 	<ul style="list-style-type: none"> Active blepharitis Contact lens wear Recent history of puncture/plug or MGD procedure Use of topical steroids, other Rx DED drugs, secretions, or glaucoma medications Other ocular products (not artificial tears or "friction" devices)

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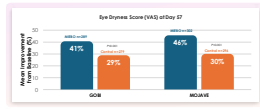
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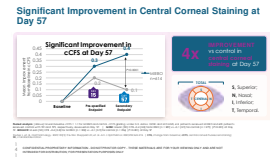
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Rosacea and Demodex Blepharitis

The following are the clinical signs and symptoms of Rosacea and Demodex Blepharitis:

- Redness of the eyelids
- Itching or burning of the eyelids
- Swelling of the eyelids
- Crusting of the eyelids
- Discharge from the eyelids
- Stinging or burning of the eyes
- Blurred vision
- Sensitivity to light
- Darkening of the eyelids
- Enlargement of the eyelids
- Changes in the shape of the eyelids
- Changes in the color of the eyelids
- Changes in the texture of the eyelids
- Changes in the appearance of the eyelids

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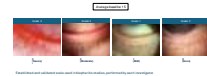


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Lid Margin Erythema Scale Used in Saturn-1



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Erythema Cure and Response

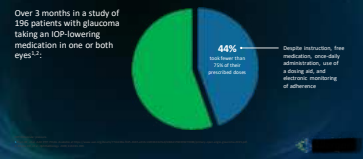


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And Now It's Time To Talk About Compliance!!!!

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Adherence to IOP-Lowering Therapy is Challenging

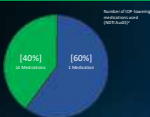


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Individualizing the Target IOP

Target IOP should be individualized and updated as needed

- Periodically assess the IOP target by comparing optic nerve status, optic disc appearance, quantitative assessments of RNFL and nerve fiber layer) and VF with previous examinations³
- Consider switching or adding medications if target is not yet achieved with initial therapy³
- Many patients require 2 or more medications to achieve target IOP³



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Adherence to IOP-Lowering Therapy is a Complex, Multifaceted Problem^{1,2}

Adherence includes both persistency and compliance issues³

Components of successful adherence³

- Successfully obtain medication
- Correctly instill drops into eye
- Use drops at appropriate times
- Use drops every day without gaps

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Compliance really is a hot topic

Dr David Friedman – OGF Education Meeting 9/19

Looked at compliance studies in glaucoma found that 70% compliance with medications was average

But is that good enough to preserve VF?

Friedman also showed that those who said they missed their drops none of the time, actually used their drops ~50% of the time.

That was much worse than those who say they never miss their drops

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Predictors of Poor Adherence – Friedman 2019

- Gaps in Visits
- Patients Don't Understand Severity Of Disease
- Cost of Drops (25%)
- Those who Travel A Lot
- Younger Pxs and Very Old Pxs
- African-Americans
- Those In Poor Health
- These drop adherence to <60%

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Compliance, adherence and side effects of therapy

- Compliance decreases the more bottles Rx'd
- Robin – Each extra bottle used decreased compliance by 1/3
- The more topical meds used the more ocular side effects occur
- OSD in G px (way) higher than initially thought
- 60% of G px use ocular lubricants

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What are the biggest barriers to proper compliance?

1. Forgetfulness
 2. Ability to put drops in
 3. Unaware of the importance of the drops
- Cost was not in the top 5!!!

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Ways To Improve Compliance

- See Pxs more frequently... especially early in treatment
- Improve tracking system – better identify no shows
- Call/email appointment reminders
- Reminders to pxs to take their drops
- Change Dr/Patient intervention
- G pxs ask 3.2 questions at visit whereas in other chronic diseases pxs ask ~ 6 questions/visit

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Question Time

MF

Drug Delivery Options

Is this where therapy is going?

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Drug Delivery

- Why
 - Reduce need for patient to take their drops
 - Most of studies have shown majority of eyedrops not taken
 - Leads to worsening of condition
- Different ways to get medication into eye
 - Inject into AC
 - Contact lens
 - Punctal plug
 - Mist spray/thicken drug increasing contact time
 - Reservoir tucked into trabeculum
- Types – temporary vs. semi-permanent vs. permanent
- What are the downsides?
 - Cost (one procedure and implant outweigh cost of eyedrop)
 - Side effects of medication
 - Complications for placing medication into eye

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Drug Eluting Ocular Implants

- Unmet needs; Compliance, Compliance, Compliance!
 - Forgetfulness, physical or cognitive disability
 - cost
 - side effects
- Locations:
 - Subconjunctiva, Lacrimal puncta
 - higher concentration, must cross ocular barrier; cornea, sclera
 - periocular side effects may be similar to topical application
 - Intraocular
 - lower quantity of drug required, higher concentration at target tissues, fewer barriers, fewer periocular side effects
- Challenges – biocompatible device, sufficient drug content, constant drug release, ease of implantation

Seel JR, Robinson MR, Burke L, Bejarian M, Conte M, Altar M. J Ocul Pharmacol Ther. 2019;33:50-57

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Table 1. Comparison of clinical studies comparing the efficacy of Durysta (Bimatoprost SR) with marketed IOLs. Last updated 10/1/2024

Study ID	Study Name	Study Design	Comparison	Primary Endpoints	Results Summary
1	APOLLO	Phase I/II	Durysta vs. First Admin	IOP, Efficacy	Similar to first admin through 18 weeks
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Bimatoprost SR (Durysta)

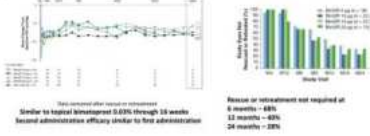
- Allergan
- Sustained release bio erodible implant that lasts 4-6 months with similar efficacy to eyedrops
- Small dissolvable pellet is injected into the anterior chamber
- Sits in/near the angle that reabsorbs over time
- Can be performed in the office
- Insert can be visualized in the inferior angle
- Ensures patient compliance

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BIM SR (Durysta) Phase I/II Apollo Trial: Efficacy



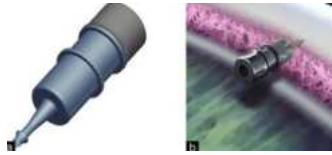
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Glaucoma Assessment Positive Results for Durysta SR Exchange Trial, Highlighting Favorable Safety and Tolerability

Glaucoma Assessment Positive Results for Durysta SR Exchange Trial, Highlighting Favorable Safety and Tolerability

Results from the exchange trial demonstrated a consistent improvement in IOP... The exchange trial... The safety and tolerability... The efficacy of Durysta SR...

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What's new in the glaucoma world?
 Durysta SR is a new sustained-release, bio-erodible, multi-center clinical trial assessing the safety of the Durysta SR...
 How long does the implant last?
 The Durysta SR is a bio-erodible, multi-center clinical trial...
 What was the purpose of this trial?
 The exchange trial was based on an FDA agreement and was created to assess the safety and efficacy of exchanging Durysta SR...

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Approved for Durysta SR
 Approved for Durysta SR
 Approved for Durysta SR
 Approved for Durysta SR

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Drug Delivery

The SpyGlass Platform combines the heritage and performance of a single-piece IOL and the ability to secure innovative, drug-eluting pads to the haptics of the IOL, prior to loading and implantation.

Regional pharmacists, the SpyGlass drug-eluting pads are uniquely designed to deliver sustained drug release with low drug loss and minimal toxicity.

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Targeting three years of bimatoprost sustained delivery for glaucoma management



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MF

When Should Patients Return? Managing Glaucoma

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When Should Patients Return?

- Baseline period – making the diagnosis whether it is OHTN or Glaucoma
 - Important to have good quality visual fields and OCT as therapy is initiated
 - If therapy is initiated, then see 2-6 weeks afterwards
 - Making sure the medication/procedure is tolerated and effective
 - Having only one post therapy IOP measurement can be misleading
 - If not at target IOP, see sooner
 - Follow up period is for first year
 - If the person has mild to moderate glaucoma, examine every three months
 - Fields and imaging done at 6, 12, 18, 24 months
 - If stable and good quality can reduce interval for both doing fields/imaging and when to examine patient
- Stable vs. Uncontrolled

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Ocular hypertension

- See on 6-month basis with imaging/fields done yearly
- May reevaluate over time

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When Should Patients Return?

- Is there a need to do visual fields after the initial assessment if the patient is stable?
 - If OCT is stable, why do a field?
- Which fields to do?
 - 24-2 vs. 24-2C vs. 10-2
 - SITA Standard vs. Fast vs. Faster
 - What about bundling fields
 - Do 2 SITA Faster fields at one visit separating by few minutes

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Advancing Therapy

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Dry Eye and Glaucoma

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Ocular Hypertension

- New risks are being discovered
- Cigarette smoking
- Alcohol
- Time for menopause

The Risk of Glaucoma after Early Menarche

Abstract Glaucoma risk is thought to increase with age at menarche and PMAIG. However, several subgroup analyses suggest a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Menopause can occur naturally or can be induced by surgery or radiation. Each of these types of menopause can influence the age at menopause, but the specific effects of each are not fully understood. The results of studies reporting each of these subtypes individually did not make a metaanalysis realistic in this review, although an effort was

Menopause associated with glaucoma in epidemiologic studies

Abstract The association between menopause and glaucoma is complex. Evidence from observational studies, including the Rotterdam Study, suggests a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

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The Association of Female Reproductive Factors with Glaucoma and Related Traits
A Systematic Review

Abstract The association between female reproductive factors and glaucoma is complex. Evidence from observational studies, including the Rotterdam Study, suggests a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Age at Menopause

The epidemiologic literature does not consistently support an overall association between age at menopause and PMAIG. However, several subgroup analyses suggest a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Age at Menarche

A younger age at menarche should theoretically confer greater overall lifetime estrogen exposure, which would lead to a hypothesized lower risk of PMAIG. Evidence from the included observational studies,^{1,17,18,21} however, suggests no clear association between the age at menarche and risks of PMAIG. This may be owing to the inability to meta-analyze the various studies, leading to the review being underpowered to identify true associations. Although no studies directly examined the association between age at menarche and IOP, a secondary analysis of the NHS found that a later age of menarche was associated with a slightly higher risk of the normal-tension subtype of PMAIG (OR = 2.1 mmHg), suggesting that a potential association between menarche age and glaucoma may occur via non-IOP mediated mechanisms. The relationship between age at menarche and PMAIG should be further investigated, most completely accounting for the entire female reproductive and postreproductive history.

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Association between lifestyle habits and glaucoma incidence: a retrospective cohort study

Abstract The association between lifestyle habits and glaucoma incidence is complex. Evidence from observational studies, including the Rotterdam Study, suggests a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Greater Physical Activity is Associated with Slower Visual Field Loss in Glaucoma

Abstract The association between physical activity and glaucoma is complex. Evidence from observational studies, including the Rotterdam Study, suggests a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

Association between Exercise Intensity and Glaucoma in the National Health and Nutrition Examination Survey

Abstract The association between exercise intensity and glaucoma is complex. Evidence from observational studies, including the Rotterdam Study, suggests a higher risk of PMAIG in those with an earlier age at natural menopause. A lower risk of PMAIG was also found in a larger subgroup analysis of older women (> 45 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the PMAIG risk. Although no association between the age at menopause and OAGI with elevated IOP (especially > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigations. Such a study may, however, prove logistically challenging, as it would require measuring IOP values before and after the menopausal transition and adjusting for age.

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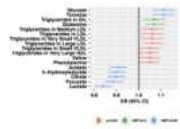


Fig. 1 Estimated heritability (h²) of 166 traits were in three genetically distinctively correlated sub-population groups in the UK Biobank. (2018)

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Is Genetic Risk for Sleep Apnea Causally Linked With Glaucoma Susceptibility?

Nathan Aspinall¹, Adam J. Cohen², Xiao Ren³, Jun Wang (Jing) Tang (Jianzhong)⁴, David A. Hinds⁵, Rajesh B. Sood⁶, Shantanu D. Joshi⁷, and Robert Horowitz⁸

Abstract Sleep apnea is a common respiratory disorder characterized by repetitive episodes of partial or complete upper airway obstruction during sleep. It is associated with an increased risk of cardiovascular disease, stroke, and cognitive decline. Glaucoma is a leading cause of blindness, characterized by progressive optic neuropathy and retinal ganglion cell loss. We investigated whether genetic risk for sleep apnea is causally linked to glaucoma susceptibility using Mendelian randomization analysis in the UK Biobank. We identified 10 independent genetic variants associated with sleep apnea and used them as instruments to estimate the causal effect on glaucoma. We found a significant causal effect of sleep apnea on glaucoma, suggesting a causal link between the two conditions.

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Abstract Associations of sleep behavior and patterns with the risk of glaucoma in the UK Biobank. This is the first large prospective cohort study to comprehensively examine the association of sleep behavior and patterns with glaucoma. We used a novel machine learning approach to identify sleep patterns that were most strongly associated with glaucoma. We found that irregular sleep patterns and shorter sleep duration were associated with an increased risk of glaucoma. These findings suggest that sleep health may be an important modifiable risk factor for glaucoma.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Based on the UK Biobank data, this is the first large prospective cohort study to comprehensively examine the association of sleep behavior and patterns with glaucoma.
- The application of cluster analysis to multiple correspondence analysis (MCA) and a k-means clustering algorithm enabled us to extract the most informative sleep patterns that were most strongly associated with glaucoma. We examined and validated groups in our analysis and included multiple models, leading to the most robust MCA representations.
- A wide range of important confounders were considered in the analyses using detailed information available in the biobank, including factors like age, sex, and genetic contribution.
- The data were obtained from the UK Biobank but are not representative enough of the entire UK population. The generalization of our findings to the entire UK or other populations needs further assessment.

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Associations of sleep apnoea with glaucoma and age-related macular degeneration: an analysis in the United Kingdom Biobank and the Canadian Longitudinal Study on Aging

Abstract Sleep apnoea is a common respiratory disorder characterized by repetitive episodes of partial or complete upper airway obstruction during sleep. It is associated with an increased risk of cardiovascular disease, stroke, and cognitive decline. Glaucoma is a leading cause of blindness, characterized by progressive optic neuropathy and retinal ganglion cell loss. We investigated whether genetic risk for sleep apnoea is causally linked to glaucoma susceptibility using Mendelian randomization analysis in the UK Biobank and the Canadian Longitudinal Study on Aging. We identified 10 independent genetic variants associated with sleep apnoea and used them as instruments to estimate the causal effect on glaucoma. We found a significant causal effect of sleep apnoea on glaucoma, suggesting a causal link between the two conditions.

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Key Points

- To date, no study has systematically examined the association between calcium channel blockers, a commonly prescribed medication class, associated with glaucoma and clinically relevant outcomes.
- Using a large-scale mendelian study of 427 480 adult UK Biobank participants, calcium channel blocker use was inversely associated with glaucoma prevalence and optical coherence tomography-defined inner retinal thickness but not intraocular pressure.
- However, these findings suggest that calcium channel blockers may represent an independent modifiable risk factor for glaucoma, potentially through an intraocular pressure-independent mechanism.

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Thank You!!!

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