A Roadmap for the Medical Management of Glaucoma

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Disclosures

- Murray Fingeret
  - Consultant - AbbVie, Allergan, Bausch & Lomb, Glaukos
- Ben Gaddie
  - Consultant
- Eric Schmidt
  - Consultant

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A Roadmap for the Medical Management of Glaucoma

1. Introduction - When do you treat
2. Ocular hypertension
3. Starting therapy with target IOP
4. Medical options
5. Drug delivery options
6. Management - when should patients return
7. Advancing therapy
8. Adherence
9. Dry eye and glaucoma

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ES

When do you treat?

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- Dr Schmidt is an advisor or consultant for the following:
  - Allergan
  - Tarsus
  - Eyenovia
  - Trukera
  - Thea Pharmaceuticals
  - Topcon
  - B&L
  - Sight Science
  - Avellino Labs
  - Visus

Disclosure Slide for Dr Eric Schmidt

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To Treat or Not To Treat, That Is The Question!

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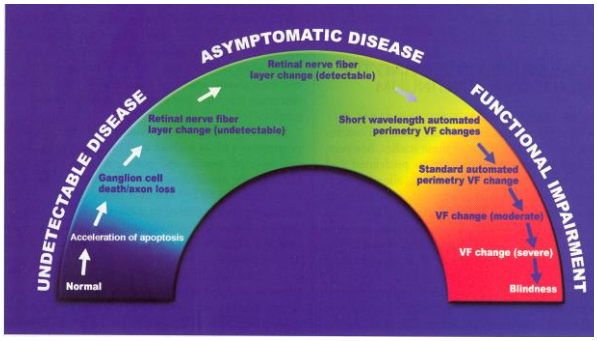

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A Review Of Risk Factors

- FINDACAR
  - Family history
  - IOP
  - Nearsightedness
  - Diabetes/Vascular disease
  - Age
  - Corneal thickness
  - Asymmetry
  - Race

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Glaucoma Risk Factors

- FINDACAR
- The more risk factors one has, the more likely one is to develop glaucoma
- The more risk factors one has, the lower the IOP target should be

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How Can We Make A Difficult Decision Less Difficult?

- Get Data
- What Data?
  - OCT
  - VF
  - FP
  - IOP
  - IOP
  - Pachymetry
  - Fam Hx
  - IOP

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- Glaucoma suspects can be (broadly) categorized into <u>two</u> groups:
  1. Ocular hypertensive subjects with risk factors for the future development of glaucoma
     - **These patients are addressed by OHTS data and who to treat**
  2. Subjects with questionable glaucomatous findings that cannot definitely be distinguished from normal
     - e.g., suspicious appearance of optic disk, RNFL/GCA or VF and
       - IOP that is 21 mmHg or lower

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Open Angle Glaucoma Suspect

- <u>**The Decision Tree:**</u>
  - The patient **without** OCT, VF or ONH damage
  - This may be someone with IOP >21 or <21 mmHg

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- 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 ***<u>low risk</u>*** patients
- **<u>Or, we elect to treat those with the most significant risk factors.</u>**

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- ***IOP 21-30+ mmHg with***
  - Normal appearing or suspicious optic nerve, <u>But NO definitive changes</u>!
    - no visual field defects
  - some risk factors
  - **Follow OHTS Treatment Guidelines:**

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- Management Options:
  - no single treatment plan nor guidelines, varies with every patient, must be individualized
1. Follow these patients every 3-6 months with observation and repeated: ONH, VF, OCT, IOP
   - Wait until confirmation of true OCT/VF defect, ONH *change*
2. Or, <u>may</u> initiate therapy for those with **3** or more risk factors: positive family history,
   - C/D ratio 0.8 or greater, asymmetry of the nerve heads
   - African American; diabetes, etc.
   - Questionable visual field defects, fluctuating IOP

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- At any IOP
  1. *Glaucomatous* ONH Changes
     - As identified by you or via photograph, OR
  2. Strongly abnormal, characterstic and *reliable* OCT
     - This must have some "clinical correlation"
     - Rarely do you treat based upon this *alone* (patient has other findings)
     - Watch out for "Red Disease"
  3. Characteristic/Confirmed Visual Field Loss
     - (*not required for diagnosis*)
- OHTN with IOP over 30 mmHg
  - Some exceptions; eg very, thick 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
- Look to Murray 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 Armaly statistical definition of OHTN
    - Not based upon clinical findings
  - Visual Fields Full
  - Optic nerve considered Full
    - This part of definition is changing with OCT use allowing subtle optic nerve/RNFL 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
- Still not clear if early therapy (before damage) alters long-term outcome
  - OHTS III was 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
  - 1982 Quigley paper field loss late sign OAG
  - 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 OHTN to glaucoma
- Those converting have greatest risk
  - thinner cornea, African American, larger cupping
- Led to the concept of risk assessment
- OHTS provided information on when to treat
  - European Glaucoma Prevention Study (EGPS) also provided risk information

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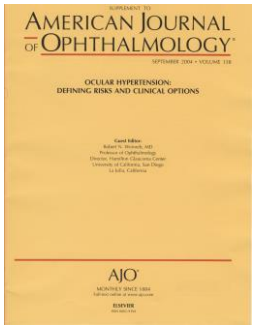

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Treating ocular hypertension Risk assessment

- Consider number of risks individual has 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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Risk Calculator in Glaucoma

- Whom and when to treat Ocular Hypertension (OHTN) is not well defined
  - OHTS study provides data on conversion rates
  - Use this data to determine when to treat
  - Still problem with OHTS study is that it was done primarily in Caucasian cohort
- Treatment of Hypertension and Elevated Cholesterol are similar to OHTN therapy
  - Coronary Heart Disease (CHD) and Glaucoma are chronic diseases w modifiable risk factors
  - Treatment outcomes differ between conditions
    - Glaucoma chronic
    - CHD can result in sudden death
  - Approach in developing prevention strategies is similar

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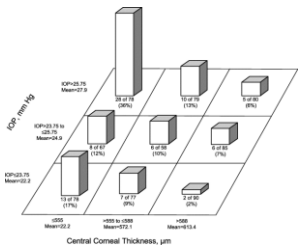
Risk Assessment

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



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iPhone Risk Calculator

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Risks

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

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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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Starting Therapy

Target IOP

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Medical Options

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Glaucoma Treatment Universe 2023

- 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???

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What Are You Trying To Achieve?

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

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Prostaglandin analogs

- Lower IOP by enhancing uveoscleral outflow
- They also reduce episcleral venous pressure
- PGAs work by causing up to a 26% reduction in resistance to outflow
- Breaks down collagen in the uveoscleral meshwork
- Create new channels for outflow

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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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Prostaglandin Side Effects

- Conjunctival hyperemia: Severe hyperemia
  - Lumigan 3.5%
  - Travatan 1.5%
  - Xalatan <1%
  - Vyzulta??
- Is this a transient phenomenon?
- Is it an allergic conjunctivitis?
- Is it worth stopping the drop?

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Conjunctival hyperemia

- PGAs have an effect on EP receptors which are vasodilators
- The stronger the drug binds to that receptor the more pronounced the vasodilation effect will be -
  Oh Really!!
- Will switching from 1 PGA to another decrease the hyperemia effect?

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Prostaglandin Side Effects

- Iris pigmentation
  - Is it reversible?
  - Is it pre-cancerous?
- Xalatan - 6.7% @ 6mths
  16% @ 12mths
- Travatan - 3% @ 12 mths
- Lumigan - 1.9% @ 12mths
- SO?

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Other Prostaglandin side effects

- CME
- Uveitis
- Reactivation of HSK
- Hypertrichosis
- Periorbital skin darkening
- Periorbital fat atrophy

- One must take into consideration the benefits of low IOP with the risks of the side effects

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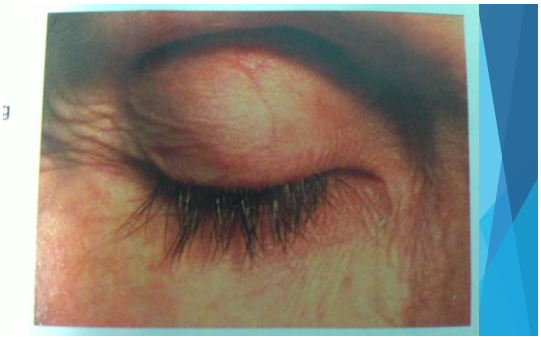

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Prostaglandins

- Oh sure, we know they are good, but just how good are they?
  - Average IOP drop of 34%
  - Improved compliance
  - Excellent safety profiles

- In general, PGAs are the initial therapy of choice.

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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 nitric oxide at the optic disk
- Some have BAK, others don't
- But does 1 work better than the others?

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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 Travaprost
- Also compared safety profiles of the 3 drugs
- Conclusions: All 3 drugs were comparable in their ability to lower IOP at all time periods.
  - Latanoprost exhibited greater ocular tolerability

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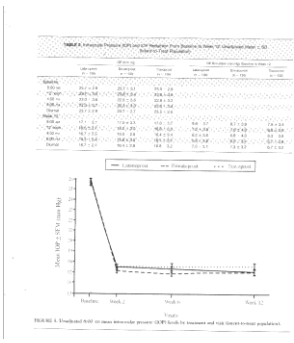

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- Reduces IOP by 32%
- 1.2mm HG lower than latanoprost
- Preserves VF better by 10%
- No loss of effect while sleeping
- Improved side effect profile
- Releases nitric oxide at the trabecular meshwork level

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- 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

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- 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?

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Are generics really as good as branded products?

What about when it comes to prostaglandins?

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But really… Is There Anything New??

Iyuzeh-
(latanoprost 0.005%)

Thea Pharmaceuticals

Let's talk about this…

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- 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??

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Iyuzeh – Phase 3 data

- Compared to Xalatan (Switch Study)
- Stable POAG pxs 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!!

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Iyuzeh – Phase 3 data-Adverse Effects

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

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- European data - Higher baseline IOP (24mm Hg)
  - IOP lowered to 15.5mm Hg
  - Same rate of adverse effects
- Bachrach data (2023 AGS)
  - 12 week trial comparing to Xalatan
  - Similar IOP reduction (as measured by ability to get IOP <18mm Hg)
  - 2% experienced redness or ocular irritation
  - 0% SPK

  Fewer ocular side effects (13.9% vs 22.5%)
- PASSY study
  - 97% tolerated drop
  - AT usage decreased 24%

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#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?

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

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Beta-blockers

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

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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
    - Anxiety
    - Confusion
    - Impotence
    - 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 pxs have contraindication to or significant side effect from beta-blocker
- Question, query and query some more!
- Be specific
- Remember the dose relationship so:
  - ¼% rather than ½%
  - QD rather than BID
- They are real (may be anecdotal)

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Works at the cellular level within the trabecular meshwork

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

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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 better at lowering IOP (as compared to itself) in pressures < 25mm Hg
- IOP lowering effect is maintained over 12 months
- Was given a broad label by FDA

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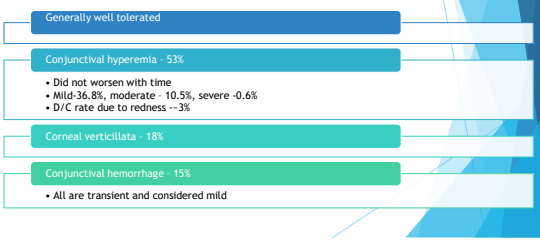

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New MOA so… it is absolutely different

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 pxs less than < 18mm Hg
  - <18mm -72.7 % (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

67.8-73.1% good or decent (physician response)

65-78% good or decent (Patient response)

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Roclatan – Aerie

- 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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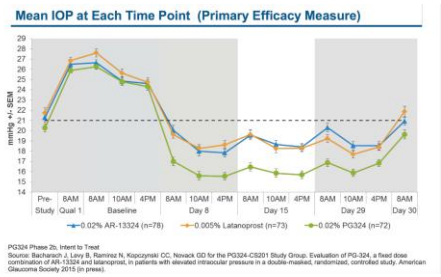

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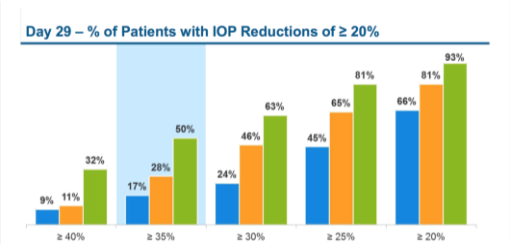

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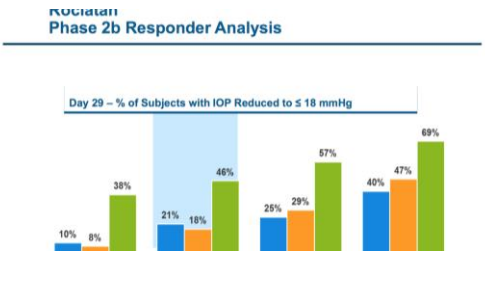

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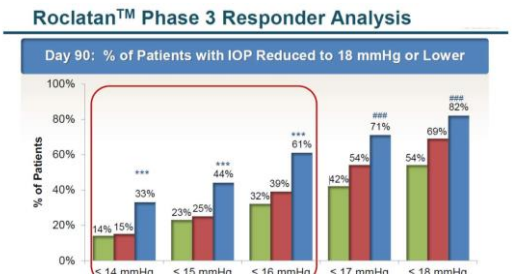

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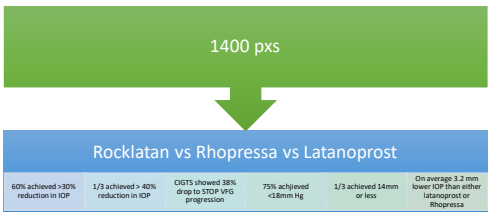
Newest Rocklatan Data



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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
  1. Reduce aqueous production
  2. Enhance outflow mechanisms
- 22-28% 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 pxs

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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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Drug Delivery Options

Is this where therapy is going?

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Drug Delivery

- Why
  - Reduce need for patient to take their drops
  - Host of studies have shown majority of eydrops 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 tacked into trabeculum
- Types – temporary vs. semi-permanent vs. permanent
- What are the downsides?
  - Cost? Does procedure and implant outweigh cost of eyedrop?
  - Side effects of medication
  - Complications for placing medication into eye

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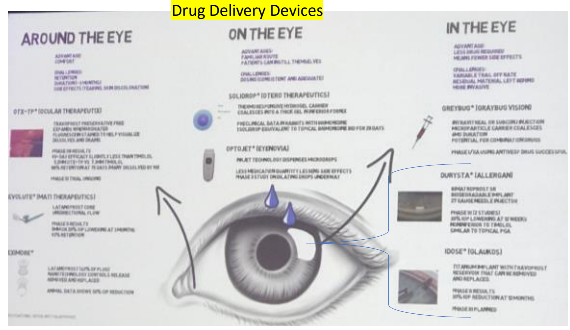
Drug Delivery Devices



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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

Seal JR, Robinson MR, Burke J, Bejanian M, Coote M, Attar M. J Ocul Pharmacol Ther. 2019;35:50–57.

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Table 1 Sustained release delivery platforms in various developmental stages, each indicated for the treatment of OAG and OHT

Delivery system	Product name	Developer	Drug	Route/site of administration	Development stage	Pros	Cons
External ocular insert	Bimatoprost Ocular Ring	Allergan, Dublin, Ireland	Bimatoprost	Peri-ocular ring (conjunctival cul-de-sac)	Phase 2: NCT02742649, NCT02358369	-Easy to place -Good retention -Non-invasive -Lasts up to 6mo	-Risk of dislodgment -Ocular discomfort -Cosmetic concerns
	Topical Ophthalmic Drug Delivery Device (TODD)	Amorphex Therapeutics, Andover, MA, USA	Timolol+Latanoprost	Upper fornix	Phase 1		
Puncal plug	Evolute	Mati Therapeutics, Austin, TX, USA	Latanoprost/travoprost	Punctum	Phase 2: NCT03318146, NCT02014142	-Non-invasive -Lasts for 30d or longer -May help dry eye	-Variable retention rates -Less effective than timolol to date -Tearing and discomfort -Risk of infection
	OTX-TP (development discontinued)	Ocular Therapeutix Inc., Bedford, MA, USA	Travoprost	Punctum	Phase 3: NCT02914509, NCT01845038		
Contact lens	Vitamin-E loaded	Peng et al[?], Hsu et al[?]	Timolol	Ocular surface	Preclinical	-Non-invasive -Established device platform	-High burst release -Low drug loading -Risk of microbial keratitis and ulceration -Short term dosing -Inability of patients to insert device
	Methafilcon lenses	Ciolino et al[?]	Latanoprost	Ocular surface	Preclinical		
Subconjunctival injection	Graybug GB-401	Graybug Vision Inc., Redwood City, CA, USA	Beta adrenergic prodrug	Subconjunctival or intravitreal injection	Phase 1/2a	-Largely avoids retention issues -Sustained IOP reduction to 6mo	-Inconsistent delivery -Risks associated with injection (*i.e.* pain, bleeding, and infection)
	Eye-D VS-101	BioLight Life Sciences, Tel Aviv, Israel	Latanoprost	Subconjunctival insert	Phase 1/2a: NCT02129673		
Intracameral implant	ENV515	Aerie Pharmaceuticles, Durham, NC, USA	Travoprost	Biodegradable intracameral implant	Phase 3: NCT02371746	- Lasts 4-6 months or more - Only FDA approved platform (Durysta/BimSR) -Avoids retention issues -Biodegradable implants do not need to be removed	-Invasive with risk of endophthalmitis -Long term therapy requires multiple injections -Risk of migration -Risk of corneal endothelial cell loss
	DURYSTA (BimSR)	Allergan, Dublin, Ireland	Bimatoprost	Biodegradable intracameral implant	Phase 3: NCT02250651, NCT02247804, NCT04285580, NCT02636946		
	iDose	Glaukos, San Clemente, CA, USA	Travoprost	Non-degradable intracameral implant	Phase 2: NCT02754596		
	OTX-TIC	Ocular Therapeutix Inc., Bedford, MA, USA	Travoprost	Biodegradable intracameral implant	Phase 1		

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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 resorbs over time
- Can be performed in the office
- Insert can be visualized in the inferior angle
- Ensures patient compliance

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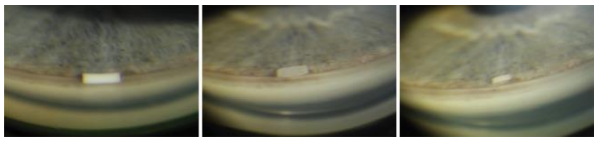

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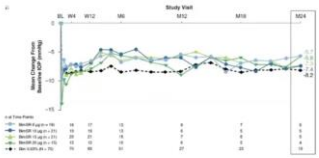
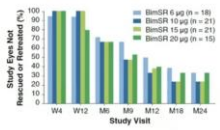
BIM SR (Durysta) Phase I/II Apollo Trial: Efficacy





Data censored after rescue or retreatment

Similar to topical bimatoprost 0.03% through 16 weeks
Second administration efficacy similar to first administration

Rescue or retreatment not required at
6 months – 68%
12 months – 40%
24 months – 28%

Craven ER, Walters T, Christie WC, et al. *Drugs*. 2020;80(2):167-179.

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Glaukos Announces Positive Results for *iDose TR* Exchange Trial, Highlighting Favorable Safety and Tolerability

January 10, 2023 04:05 PM Eastern Standard Time

ALISO VIEJO, Calif.--(BUSINESS WIRE)--Glaukos Corporation (NYSE: GKOS), an ophthalmic medical technology and pharmaceutical company focused on novel therapies for the treatment of glaucoma, corneal disorders and retinal diseases, today announced positive results for a prospective, multi-center clinical trial designed to evaluate the safety of the surgical exchange procedure for *iDose® TR (travoprost intraocular implant)* in subjects who had previously been administered an *iDose TR* in the Phase 2b clinical trial (referred to as the "exchange trial").

"We are pleased to clinically confirm the iDose TR exchange procedure is safe and facile. We look forward to including these positive data in our upcoming NDA submission to further support the safety and tolerability of redosing iDose TR patients over time".

Tweet this

Results from the exchange trial demonstrated a second administration of *iDose TR* and removal of the original *iDose TR* implant was safe and well-tolerated, with the second *iDose TR* demonstrating a favorable safety profile over a 12-month evaluation period. Additionally, no subject in the exchange trial exhibited a greater than 30% endothelial cell loss over the extended evaluation period of more than five years on average. Glaukos plans to include the exchange trial's positive data set in its upcoming U.S. Food and Drug Administration (FDA) New Drug Application (NDA) submission targeted for the first quarter of 2023.

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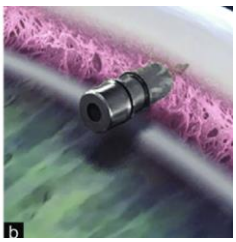

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What's new in the glaucoma world?
Glaukos Corporation has released positive results from a prospective, multi-center clinical trial assessing the safety of the iDose TR (travoprost intraocular implant) surgical exchange procedure in patients who were administered an iDose TR in a previous phase 2b clinical.

Tell me about the iDose TR.
The iDose TR is a biocompatible titanium implant administered during micro-invasive procedures that contains a novel formulation of travoprost—a prostaglandin analog used to lower IOP—which is released inside the anterior chamber.

By eluting the drug already inside the eye, the device can then bypass the corneal permeability barrier, enabling the release of micro-amounts of travoprost over time.

How long does the implant last?
Glaukos designed the iDose TR to continuously release therapeutic medication levels for at least 1 year. Once all the travoprost is released, the implant is removed and replaced with another implant.

What was the purpose of this trial?
The exchange trial was based on an FDA agreement and was created to assess the safety and feasibility of exchanging iDose TR implants in patients who had received an iDose TR in a previous trial.

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All News Releases

March 2, 2022

Johnson & Johnson Vision Care Receives FDA Approval for ACUVUE® Theravision™ with Ketotifen – World's First and Only Drug-Eluting Contact Lens

Novel technology combines ACUVUE® daily disposable contact lenses with an established antihistamine in FDA- first in its new category

JACKSONVILLE, FL –March 2, 2022 – Johnson & Johnson Vision Care, Inc.[1], a global leader in eye health and part of the Johnson & Johnson Medical Device Companies,[2] today announced that the U.S. Food and Drug Administration (FDA) has approved ACUVUE® Theravision™ with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen). Each lens contains 19 mcg ketotifen. Ketotifen is a well-established antihistamine. ACUVUE® Theravision™ with Ketotifen is the first in an entirely new category of contact lenses and brings forward a new wearing experience for contact lens wearers with allergic eye itch.

ACUVUE® Theravision™ with Ketotifen are daily disposable contact lenses indicated for the prevention of ocular itch due to allergic conjunctivitis and provide vision correction in patients who do not have red eyes, who are suitable for contact lens wear and who do not have more than 1.00 D of astigmatism.

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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

Beyond bimatoprost, the SpyGlass drug-eluting pads are uniquely designed to deliver additional drugs to address multiple ophthalmic indications

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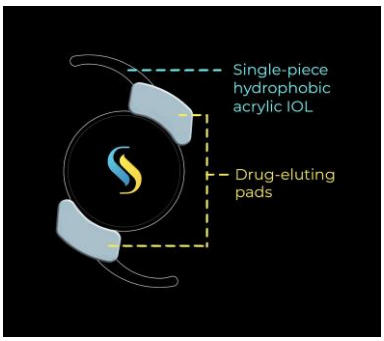

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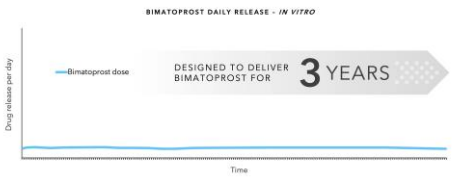
ES

Targeting three years of bimatoprost sustained delivery for glaucoma management



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Adherence

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

This is so not Cool…

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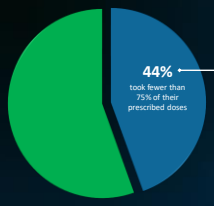
Adherence to IOP-Lowering Therapy Is Challenging

Over 3 months in a study of 196 patients with glaucoma taking an IOP-lowering medication in one or both eyes[1,2]:



Despite instruction, free medication, once-daily administration, use of a dosing aid, and electronic monitoring of adherence

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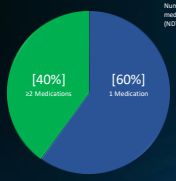
Individualizing the Target IOP

Target IOP should be individualized and updated as needed

- Periodically reassess the IOP target by comparing optic nerve status (optic disc appearance, quantitative assessments of disc and nerve fiber layer) and VF with previous examinations[1]
- Consider switching or adding medications if target is not yet achieved with initial therapy[1]
- Many patients require 2 or more medications to achieve target IOP[2]



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Adherence to IOP-Lowering Therapy Is a Complex, Multifaceted Problem[1,2]

Adherence includes both persistency and compliance issues[1]

Components of successful adherence[1]

- 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 Educators 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 some 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 pxs (way) higher than initially thought

60% of G pxs 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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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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BG

Advancing Therapy

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BG

Dry Eye and Glaucoma

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Ocular Hypertension

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

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Menopause. 2014 April ; 21(4): 391–398. doi:10.1097/GME.0b013e31829f4881.

The Risk of glaucoma after early bilateral oophorectomy

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Abstract

Objective—Because early estrogen deficiency may increase the susceptibility of the optic nerve to glaucoma, we studied the association of early bilateral oophorectomy with glaucoma.

Methods—We studied the risk of glaucoma in the Mayo Clinic Cohort Study of Oophorectomy and Aging, by comparing all women who underwent bilateral oophorectomy from 1950 to 1987 with age-matched reference women who did not undergo unilateral or bilateral oophorectomy. Glaucoma diagnostic codes were searched in the records linkage system of the Rochester Epidemiology Project. Hazards ratios (HR) were calculated over a median follow-up of 25.5 years. Analyses were stratified by age at the time of bilateral oophorectomy (in tertiles).

Results—Of 1,264 women who underwent bilateral oophorectomy before menopause, 147 developed glaucoma. Of 1,070 referent women, 133 developed glaucoma. Women who underwent bilateral oophorectomy showed no increased risk of glaucoma in the overall group (HR 1.12, 95% CI 0.89–1.42). However, women who underwent oophorectomy before age 43 years (n=344; the first tertile) had a significantly increased risk of glaucoma (HR 1.80, 95% CI 1.35–2.25). The results did not change after adjustment for hypertension, obesity, diabetes, or disorders of lipid metabolism at baseline. Approximately 11% of women with bilateral oophorectomy before age 43 years were treated with estrogen to age 50 years; however, treatment did not reduce the association (HR 1.59, 95% CI 0.81–3.13).

Conclusions—Bilateral oophorectomy before age 43 years may increase the risk of glaucoma, and estrogen treatment does not appear to attenuate the risk.

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Menopause exacerbates visual dysfunction in experimental glaucoma

Andrew J. Feola[a,b,*], **Jieming Fu**[a], **Rachael Allen**[a,b], **Victoria Yang**[a], **Ian C. Campbell**[a,b], **Amy Ottenmeyer**[a], **C. Ross Ethier**[c], **Machelle Pardue**[a,b]

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Abstract

Glaucoma is the leading cause of irreversible blindness worldwide. Recently, estrogen deficiencies caused by early menopause, alterations in estrogen-signaling via mutations in estrogen receptors, and polymorphisms along estrogen metabolic pathways have all been linked to an increased risk of developing glaucoma. Here, we examined how menopause and age impact visual function and retinal structure in an experimental model of glaucoma. Young (3–4 months) and aged (9–10 months) female Brown Norway rats were divided into pre- and post-menopausal cohorts by surgically inducing menopause via ovariectomy (OVX). After six weeks, ocular hypertension (OHT) was induced unilaterally for a period of eight weeks. Four cohorts were successfully followed to eight weeks: young sham (n = 8), young OVX (n =9), aged sham (n =10), and aged OVX (n =11) animals. Intraocular pressure (IOP) was monitored weekly in all groups. Prior to inducing OHT (baseline) and at four and eight weeks after inducing OHT, we assessed visual acuity via the optomotor response (OMR) and retinal structure using optical coherence tomography (OCT). OHT decreased the OMR in all cohorts. We found that spatial frequency thresholds decreased by 54% in OVX animals after OHT compared to sham animals after OHT, regardless of age ($p < 0.001$). We also found thinning of the retinal nerve fiber layer (RNFL) and loss of total retinal thickness after induction of OHT. Aged animals had more thinning of the RNFL and loss of total retinal thickness compared to young animals ($p < 0.001$). Overall, OHT caused significant changes in visual function and retinal structure. Observing that OVX in young and aged animals further decreased spatial frequency thresholds after OHT suggests that an estrogen deficiency may intensify visual impairment after OHT.

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The Association of Female Reproductive Factors with Glaucoma and Related Traits

A Systematic Review

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Topic: This systematic review summarizes evidence for associations between female reproductive factors (age at menarche, parity, oral contraceptive [OC] use, age at menopause, and postmenopausal hormone [PMH] use) and intraocular pressure (IOP) or open-angle glaucoma (OAG).

Clinical Relevance: Understanding the associations between female reproductive factors and glaucoma may shed light on the disease pathogenesis and aid clinical prediction and personalized treatment strategies. Importantly, some factors are modifiable, which may lead to new therapies.

Methods: Two reviewers independently extracted articles in MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials databases to identify relevant studies. Eligibility criteria included studies with human subjects aged > 18 years; a measured outcome of either IOP or OAG; a cohort, case-control, cross-sectional, or randomized controlled trial design; a reported measure of association, such as the hazard ratio, relative risk, odds ratio, or mean difference, with an associated confidence interval; and a measured exposure of at least 1 of the following variables: age at menarche, parity, OC use, age at menopause, or PMH use.

Results: We included a total of 27 studies. Substantial differences in study designs, exposure and treatment levels, treatment durations, and variable reporting precluded a meaningful quantitative synthesis of the identified studies. Overall, relatively consistent associations between PMH use and a lower IOP were identified. Estrogen-only PMH use may be associated with lower OAG risk, which may be modified by race. No significant associations were found with combined estrogen-and-progesterone PMH use. No strong associations between parity or age at menarche and glaucoma were found, but a younger age at menopause was associated with an increased glaucoma risk, and adverse associations were identified with a longer duration of OC use, though no overall association with OC use was found.

Conclusions: The association between PMH use and lower IOP or OAG risk is a potentially clinically relevant and modifiable risk factor and should be investigated further, although this needs to be interpreted in the context of a high risk of bias across included studies. Future research should examine associations with IOP specifically and how the relationship between genetic factors and OAG risks may be influenced by female reproductive factors. *Ophthalmology Glaucoma 2022;5:628-647 © 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/).

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Age at Menopause

The epidemiologic literature does not consistently support an overall association between age at menopause and POAG; however, several subgroup analyses suggest a higher risk of POAG in those with an earlier age at natural menopause. A lower risk of POAG was also found in a large subgroup analysis of older women (> 65 years) who underwent menopause at a later age, suggesting that a longer duration of estrogen exposure may reduce the POAG risk.[18] Although no association between the age at menopause and OAG with elevated IOP (specifically, > 21 mmHg) was identified, no study directly assessed the relationship with IOP, and this represents an avenue for future investigation. 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,[46] but the specific effects of each are not yet fully understood.[47] The number of studies reporting each of these subtypes individually did not make a subanalysis realistic in this review, although an effort was

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Age at Menarche

A younger age at menarche should theoretically confer greater overall lifetime estrogen exposure, which would lead to a hypothetically lower risk of POAG. Evidence from the included observational studies,[14,19,22–24] however, suggests no clear association between the age at menarche and risks of POAG. This may be owing to the inability to meta-analyze the various studies, leading to this review being underpowered to identify a true association. 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 POAG (IOP < 22 mmHg),[14] suggesting that a potential association between menarche age and glaucoma may occur via non–IOP-mediated mechanisms. The relationship between age at menarche and POAG should be further investigated, more completely accounting for the entire female reproductive and postreproductive history.

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ARTICLE OPEN

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

Asahi Fujita[1,2✉], Yohei Hashimoto[1,2], Hiroki Matsui[2], Hideo Yasunaga[2] and Makoto Aihara[1]

BACKGROUND/OBJECTIVES: Although lifestyle habits may represent modifiable risk factors of glaucoma, the association between lifestyle factors and glaucoma is not well understood. The aim of this study was to investigate the association between lifestyle habits and the development of glaucoma.
SUBJECTS/METHODS: Participants who underwent health check-ups from 2005 to 2020 using a large-scale administrative claims database in Japan were included in the study. Cox regression analyses were performed where glaucoma development was regressed on the lifestyle (body mass index, current smoking, frequency and amount of alcohol consumption, eating habits, exercise habits and quality of sleep), age, sex, hypertension, diabetes mellitus and dyslipidaemia.
RESULTS: Among the 3,110,743 eligible individuals, 39,975 developed glaucoma during the mean follow-up of 2058 days. Factors associated with increased risk of glaucoma were overweight/obese (vs. moderate weight: hazard ratio, 1.04 [95% confidence interval, 1.02–1.07]), alcohol consumption of 2.5–4.9 units/day, 5–7.4 units/day, and ≥7.5 units/day (vs. <2.5 units/day: 1.05 [1.02–1.08], 1.05 [1.01–1.08] and 1.06 [1.01–1.12], respectively), skipping breakfast (1.14 [1.10–1.17]), late dinner (1.05 [1.03–1.08]) and daily walking of 1 h (1.14 [1.11–1.16]). Factors associated with decreased risk of glaucoma were daily alcohol consumption (vs. rarely: 0.94 [0.91–0.97]) and regular exercise (0.92 [0.90–0.95]).
CONCLUSIONS: Moderate body mass index, having breakfast, avoiding late dinner, limiting alcohol intake to <2.5 units/day, and regular exercise were associated with a reduced risk of developing glaucoma in the Japanese population. These findings may be useful for promoting glaucoma prophylaxis.

Eye; https://doi.org/10.1038/s41433-023-02535-7

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

Moon Jeong Lee, BS,[1] Jiangxia Wang, MS,[2] David S. Friedman, MD, PhD,[1] Michael V. Boland, MD, PhD,[1] Carlos G. De Moraes, MD, MPH,[1] Pradeep Y. Ramulu, MD, PhD[1]

Purpose: To determine the association between physical activity levels and the rate of visual field (VF) loss in glaucoma.
Design: Longitudinal, observational study.
Participants: Older adults with suspect or manifest glaucoma.
Methods: Participants wore accelerometers for 1 week to define average steps per day, minutes of moderate-to-vigorous activity, and minutes of nonsedentary activity. All available VF measurements before and after physical activity assessment were retrospectively analyzed to measure rates of VF loss.
Main Outcome Measures: Pointwise changes in VF sensitivity associated with physical activity measures.
Results: A total of 141 participants (mean age, 64.9±5.8 years) were enrolled. Eye mean deviation (MD) at the time of physical activity assessment was −6.6 decibels (dB), and average steps per day were 5613±3158. The unadjusted average rate of VF loss as measured by pointwise VF sensitivity was 0.36 dB/year (95% confidence interval, −0.37 to −0.35). In multivariable models, slower VF loss was observed for patients demonstrating more steps (+0.007 dB/year/1000 daily steps, $P = 0.001$), more moderate-to-vigorous activity (+0.003 dB/year/10 more minutes of moderate-to-vigorous activity per day, $P < 0.001$), and more nonsedentary activity (+0.007 dB/year/30 more minutes of nonsedentary time per day, $P = 0.005$). Factors associated with a faster rate of VF loss included older age, non-white race, glaucoma surgery, cataract surgery, and moderate baseline VF damage (−6 dB ≥ MD > −12 dB as opposed to mild VF damage (MD > −6 dB). Similar associations between baseline accelerometer-measured physical activity and rates of VF loss were observed over other time periods (e.g., within 1, 3, and 5 years of activity assessment).
Conclusions: Increased walking, greater time spent doing moderate-to-vigorous physical activity, and more time spent in nonsedentary activity were associated with slower rates of VF loss in a treated population of patients with glaucoma, with an additional 5000 daily steps or 2.6 hours of nonsedentary physical activity decreasing the average rate of VF loss by approximately 10%. Future prospective studies are needed to determine if physical activity can slow VF loss in glaucoma or if progressive VF loss results in activity restriction. If the former is confirmed, this would mark physical activity as a novel modifiable risk factor for preventing glaucoma damage. *Ophthalmology 2019;126:958-964* © *2018 by the American Academy of Ophthalmology*

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

Victoria L. Tseng, MD, PhD,[1] Fei Yu, PhD,[1,2] Anne L. Coleman, MD, PhD[1,3]

Purpose: To examine the association between exercise intensity and glaucoma in the National Health and Nutrition Examination Survey (NHANES) population.
Design: Retrospective, cross-sectional study.
Participants: Adult participants of the 2005–2006 NHANES aged 40 years and older.
Methods: Objective exercise intensity was assessed based on measurements from accelerometers worn by participants over 1 week. Subjective exercise intensity was assessed with questionnaire responses. Glaucoma was defined with 2 definitions based on (1) the Rotterdam criteria and (2) ophthalmologist grading of optic disc photographs for characteristic features of glaucoma. Covariates included age, gender, ethnicity, blood pressure, body mass index, and spherical equivalent. Logistic regression was performed to assess associations between objective and subjective exercise intensity and glaucoma while controlling for all covariates. All data were weighted based on the NHANES multistage sampling design.
Main Outcome Measures: Prevalence of glaucoma based on the 2 definitions described.
Results: The study included a sample of 1387 participants, of whom 68 (4.9%) had glaucoma based on Rotterdam criteria and 7 (0.5%) had glaucoma based on disc image grading. This translated to a weighted estimate of 702 46 180 individuals, with an estimated prevalence of glaucoma of 3.1% based on the Rotterdam criteria and 0.3% based on disc image grading. After adjusting for covariates, each 10-count increase in accelerometer intensity was associated with decreased odds of glaucoma using both criteria (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.95–0.99 for Rotterdam; OR, 0.90; 95% CI, 0.85–0.95 using disc image grading). With Rotterdam criteria, participants who spent the day standing or walking versus sitting had 58% decreased odds of glaucoma (OR, 0.42; 95% CI, 0.25–0.70). With disc image grading, participants who performed moderate amounts of vigorous activity had 95% decreased odds of glaucoma compared with those who performed no vigorous activity (OR, 0.05; 95% CI, 0.01–0.56).
Conclusions: In the 2005–2006 NHANES adult population, increased exercise intensity is associated with decreased odds of glaucoma. Further population-based studies are needed to examine associations between additional aspects of exercise and glaucoma. *Ophthalmology Glaucoma 2020;3:393–402* © *2020 by the American Academy of Ophthalmology*

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Clinical science

Smoking and progressive retinal nerve fibre layer thinning in glaucoma

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ABSTRACT
Backgroundlaims To investigate the relationship between smoking and smoking intensity, and the rate of retinal nerve fibre layer (RNFL) thinning in patients with primary open angle glaucoma (POAG).
Methods In this longitudinal study, patients with POAG who had at least 3 years of follow-up with a minimum of 5 visits of optical coherence tomography (OCT) were enrolled. The smoking intensity was calculated as the pack-year at the baseline OCT. Univariable and multivariable linear mixed models were used to determine the effect of each parameter on the rates of RNFL thinning over time. Non-linear least-squares estimation with piecewise regression model was used to investigate the cut-off point for the relationship between cumpapillary RNFL thinning and smoking intensity.
Results A total of 466 eyes of 314 patients were included over the mean (95% CI) follow-up of 6.6 (6.4 to 6.7) years. Of the 314 patients, 121 (39%) had reported any history of smoking. Greater smoking intensity was associated with faster RNFL thinning (−0.06 (95% CI −0.11 to 0.00) µm/year per 10 pack-year higher; p=0.031) after adjusted for confounding factors. RNFL thinning became significantly faster when smoking intensity was >8 pack-year.
Conclusions Smoking intensity is associated with faster rates of RNFL thinning. Evaluation of smoking intensity might add information to the assessment of risk of glaucoma progression. Future studies are required to explore if withdrawing smoking as a modifiable risk factor can decrease progression in patients with glaucoma.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The association between smoking and glaucoma progression has not been well known.

WHAT THIS STUDY ADDS
⇒ Greater smoking pack-year index was associated with faster rates of retinal nerve fibre layer thinning over time in patients with glaucoma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Smoking pack-year index might add information to the assessment of risk of glaucoma progression.

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ABSTRACT
Background/Aims To investigate the relationship between smoking and smoking intensity, and the rate of retinal nerve fibre layer (RNFL) thinning in patients with primary open angle glaucoma (POAG).
Methods In this longitudinal study, patients with POAG who had at least 3 years of follow-up with a minimum of 5 visits of optical coherence tomography (OCT) were enrolled. The smoking intensity was calculated as the pack-year at the baseline OCT. Univariable and multivariable linear mixed models were used to determine the effect of each parameter on the rates of RNFL thinning over time. Non-linear least-squares estimation with piecewise regression model was used to investigate the cut-off point for the relationship between cumpapillary RNFL thinning and smoking intensity.
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Conclusions Smoking intensity is associated with faster rates of RNFL thinning. Evaluation of smoking intensity might add information to the assessment of risk of glaucoma progression. Future studies are required to explore if withdrawing smoking as a modifiable risk factor can decrease progression in patients with glaucoma.

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Clinical and Epidemiologic Research

Alcohol Consumption, Genetic Risk, and Intraocular Pressure and Glaucoma: The Canadian Longitudinal Study on Aging

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Purpose. The purpose of this study was to examine the association of alcohol consumption with intraocular pressure (IOP) and glaucoma and to assess whether any associations are modified by a glaucoma polygenic risk score (PRS).
Methods. Cross-sectional analysis of data from the Canadian Longitudinal Study on Aging Comprehensive Cohort, consisting of 30,097 adults ages 45 to 85 years, was done. Data were collected from 2012 to 2015. Alcohol consumption frequency (never, occasional, weekly, and daily) and type (red wine, white wine, beer, liquor, and other) were measured by an interviewer-administered questionnaire. Total alcohol intake (grams/week) was estimated. IOP was measured in mm Hg using the Reichert Ocular Response Analyzer. Participants reported a diagnosis of glaucoma from a doctor. Logistic and linear regression models were used to adjust for demographic, behavioral, and health variables.
Results. Daily drinkers had higher IOP compared to those who never drank ($\beta = 0.45$, 95% confidence interval (CI) = 0.05, 0.86). An increase in total weekly alcohol intake (per 5 drinks) was also associated with higher IOP ($\beta = 0.20$, 95% CI = 0.15, 0.26). The association between total alcohol intake and IOP was stronger in those with a higher genetic risk of glaucoma (P for interaction term = 0.041). There were 1525 people who reported being diagnosed with glaucoma. Alcohol consumption frequency and total alcohol intake were not associated with glaucoma.
Conclusions. Alcohol frequency and total alcohol intake were associated with elevated IOP but not with glaucoma. The PRS modified the association between total alcohol intake and IOP. Findings should be confirmed in longitudinal analyses.

Keywords: alcohol, intraocular pressure (IOP), glaucoma, genetic, Canadian longitudinal study on aging (CLSA)

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The Association of Alcohol Consumption with Glaucoma and Related Traits

Findings from the UK Biobank

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Purpose: To examine the associations of alcohol consumption with glaucoma and related traits, to assess whether a genetic predisposition to glaucoma modified these associations, and to perform Mendelian randomization (MR) experiments to probe causal effects.

Design: Cross-sectional observational and gene–environment interaction analyses in the UK Biobank. Two-sample MR experiments using summary statistics from large genetic consortia.

Participants: UK Biobank participants with data on intraocular pressure (IOP) (n = 109 097), OCT-derived macular inner retinal layer thickness measures (n = 46 236) and glaucoma status (n = 173 407).

Methods: Participants were categorized according to self-reported drinking behaviors. Quantitative estimates of alcohol intake were derived from touchscreen questionnaires and food composition tables. We performed a 2-step analysis, first comparing categories of alcohol consumption (never, infrequent, regular, and former drinkers) before assessing for a dose-response effect in regular drinkers only. Multivariable linear, logistic, and restricted cubic spline regression, adjusted for key sociodemographic, medical, anthropometric, and lifestyle factors, were used to examine associations. We assessed whether any association was modified by a multitrait glaucoma polygenic risk score. The inverse-variance weighted method was used for the main MR analyses.

Main Outcome Measures: Intraocular pressure, macular retinal nerve fiber layer (mRNFL) thickness, macular ganglion cell–inner plexiform layer (mGCIPL) thickness, and prevalent glaucoma.

Results: Compared with infrequent drinkers, regular drinkers had higher IOP (+0.17 mmHg; $P < 0.001$) and thinner mGCIPL (-0.17 μm; $P = 0.049$), whereas former drinkers had a higher prevalence of glaucoma (odds ratio, 1.53; $P = 0.002$). In regular drinkers, alcohol intake was adversely associated with all outcomes in a dose-dependent manner (all $P < 0.001$). Restricted cubic spline regression analyses suggested nonlinear associations, with apparent threshold effects at approximately 50 g (~6 UK or 4 US alcoholic units)/week for mRNFL and mGCIPL thickness. Significantly stronger alcohol–IOP associations were observed in participants at higher genetic susceptibility to glaucoma ($P_{interaction} < 0.001$). Mendelian randomization analyses provided evidence for a causal association with mGCIPL thickness.

Conclusions: Alcohol intake was consistently and adversely associated with glaucoma and related traits, and at levels below current United Kingdom (< 112 g/week) and United States (women, < 98 g/week; men, < 196 g/week) guidelines. Although we cannot infer causality definitively, these results will be of interest to people with or at risk of glaucoma and their advising physicians.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology Glaucoma 2023;6:366-379*

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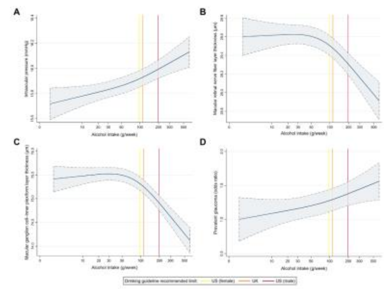

Figure 4. Maximally adjusted restricted cubic spline regression models for the association between alcohol intake and **A**, intraocular pressure; **B**, macular retinal nerve fiber layer thickness; **C**, macular ganglion cell–inner plexiform layer thickness; and **D**, glaucoma in regular drinkers. Vertical lines represent current UK (112 g/week) and US (women 98 g/week; men 196 g/week) recommended alcohol drinking guidelines.[41,42]

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Background polygenic risk modulates the association between glaucoma and cardiopulmonary diseases and measures: an analysis from the UK Biobank

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ABSTRACT

Aims To assess whether associations of cardiopulmonary conditions and markers with glaucoma differ by background genetic risk for primary open angle glaucoma (POAG).

Methods We constructed a POAG polygenic risk score (PRS) using genome-wide association study summary statistics from a large cross-ancestry meta-analysis. History of glaucoma (including self-report and codes for POAG, 'other glaucoma' or unspecified glaucoma), history of common cardiopulmonary conditions and cardiopulmonary measures were assessed in the UK Biobank. Stratifying by PRS decile 1 (lowest risk) versus decile 10 (highest risk), separate multivariable models were estimated to assess the associations of cardiopulmonary diseases or factors with glaucoma, adjusting for age, sex, smoking and medication use. A Bonferroni correction was used to adjust p values for multiple comparisons.

Results Individuals in POAG PRS decile 1 (417 cases, 44458 controls; mean age 56.8 years) and decile 10 (2135 cases, 42413 controls; mean age 56.7 years) were included. Within decile 1, glaucoma cases had significantly higher glycated haemoglobin (38.5 vs 35.9 mmol/mol) and higher prevalence of diabetes (17.5% vs 6.5%), dyslipidaemia (31.2% vs 18.3%) and chronic kidney disease (CKD) (6.7% vs 2.0%) than controls (adjusted p<0.0013 for each). Within decile 10, glaucoma was associated with higher prevalence of dyslipidaemia (27.7% vs 17.3%, p=6.9E-05). The magnitude of association between glaucoma and diabetes, CKD and glycated haemoglobin differed between deciles 1 and 10 (contrast test p value for difference <0.05).

Conclusion The relations between systemic conditions and glaucoma vary by underlying genetic predisposition to POAG, with larger associations among those who developed glaucoma despite low genetic risk.

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Key messages

What is already known on this topic
⇒ Glaucoma has been associated with several cardiopulmonary diseases.

What this study adds
⇒ This study found that the association between glaucoma and cardiometabolic diseases differed by background genetic risk for glaucoma.
⇒ Those who developed glaucoma despite having low genetic risk tended to have a higher prevalence of cardiometabolic disease, particularly diabetes, chronic kidney disease, chronic obstructive pulmonary disease and cholesterol level.

How this study might affect research, practice or policy
⇒ An individual's genetic risk for glaucoma may modulate the relative impact of environmental or other genetic risk factors for cardiopulmonary disease.
⇒ These findings may have implications for glaucoma or cardiometabolic disease screening as the use of genotyping becomes more common in the clinical setting.

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The Association between Serum Lipids and Intraocular Pressure in 2 Large United Kingdom Cohorts

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Purpose: Serum lipids are modifiable, routinely collected blood test features associated with cardiovascular health. We examined the association of commonly collected serum lipid measures (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides) with intraocular pressure (IOP).

Design: Cross-sectional study in the UK Biobank and European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohorts.

Participants: We included 94 323 participants from the UK Biobank (mean age, 57 years) and 6230 participants from the EPIC-Norfolk (mean age, 68 years) cohorts with data on TC, HDL-C, LDL-C, and triglycerides collected between 2006 and 2009.

Methods: Multivariate linear regression adjusting for demographic, lifestyle, anthropometric, medical, and ophthalmic covariables was used to examine the associations of serum lipids with corneal-compensated IOP (IOPcc).

Main Outcome Measures: Corneal-compensated IOP.

Results: Higher levels of TC, HDL-C, and LDL-C were associated independently with higher IOPcc in both cohorts after adjustment for key demographic, medical, and lifestyle factors. For each 1-standard deviation increase in TC, HDL-C, and LDL-C, IOPcc was higher by 0.09 mmHg (95% confidence interval [CI], 0.06–0.11 mmHg; $P < 0.001$), 0.11 mmHg (95% CI, 0.08–0.13 mmHg; $P < 0.001$), and 0.07 mmHg (95% CI, 0.05–0.09 mmHg; $P < 0.001$), respectively, in the UK Biobank cohort. In the EPIC-Norfolk cohort, each 1-standard deviation increase in TC, HDL-C, and LDL-C was associated with a higher IOPcc by 0.19 mmHg (95% CI, 0.07–0.31 mmHg; $P = 0.001$), 0.14 mmHg (95% CI, 0.03–0.25 mmHg; $P = 0.016$), and 0.17 mmHg (95% CI, 0.06–0.29 mmHg; $P = 0.003$). An inverse association between triglyceride levels and IOP in the UK Biobank (−0.05 mmHg; 95% CI, −0.08 to −0.03; $P < 0.001$) was not replicated in the EPIC-Norfolk cohort ($P = 0.30$).

Conclusions: Our findings suggest that serum TC, HDL-C, and LDL-C are associated positively with IOP in 2 United Kingdom cohorts and that triglyceride levels may be associated negatively. Future research is required to assess whether these associations are causal in nature. *Ophthalmology 2022;129:986-996*

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Plasma metabolite profile for primary open-angle glaucoma in three US cohorts and the UK Biobank

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Glaucoma is a progressive optic neuropathy and a leading cause of irreversible blindness worldwide. Primary open-angle glaucoma is the most common form, and yet the etiology of this multifactorial disease is poorly understood. We aimed to identify plasma metabolites associated with the risk of developing POAG in a case-control study (599 cases and 599 matched controls) nested within the Nurses' Health Studies, and Health Professionals' Follow-Up Study. Plasma metabolites were measured with LC-MS/MS at the Broad Institute (Cambridge, MA, USA); 369 metabolites from 18 metabolite classes passed quality control analyses. For comparison, in a cross-sectional study in the UK Biobank, 168 metabolites were measured in plasma samples from 2,238 prevalent glaucoma cases and 44,723 controls using NMR spectroscopy (Nightingale, Finland; version 2020). Here we show higher levels of diglycerides and triglycerides are adversely associated with glaucoma in all four cohorts, suggesting that they play an important role in glaucoma pathogenesis.

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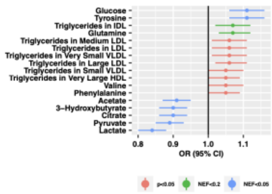

Fig. 4 | Individual metabolites (out of $N = 168$) that were at least nominally significantly associated with prevalent glaucoma in the UK Biobank (2238 cases, 44,723 controls). Data are presented as odds ratios and 95% confidence intervals estimated with logistic regression models. The logistic regression model includes adjustment for age, gender, smoking status, physical activity, BMI, ethnicity, spherical equivalent, coffee consumption, tea consumption, alcohol intake, systolic blood pressure, cholesterol level, diabetes, coronary artery disease, and statin use. All statistical tests are two-sided, and we accounted for multiple comparisons by using p-values based on number of effective tests (NEF). Source data with exact values are provided as a Source Data file.

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Glaucoma

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

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Purpose. Observational studies have suggested that individuals with pre-existing sleep apnea (SA) have up to double the risk of developing glaucoma than individuals without SA. Understanding risk factors for glaucoma is important to assist with well-structured screening, early intervention, and efficient allocation of specialist consultation. The objective of this study is therefore to use genetic data to determine whether SA is a causal risk factor for glaucoma.

Methods. Two-sample Mendelian randomization (MR) analyses were performed to assess the association between genetically predicted SA and glaucoma susceptibility using genome-wide association study (GWAS) of 25,062 SA cases, 313,372 controls derived from 23andMe and summary data from a glaucoma GWAS meta-analysis (20,582 cases, 119,318 controls), including individuals of European descent, mainly from the UK Biobank.

Results. Inverse variance weighted regression of genetic susceptibility for SA on risk of glaucoma revealed no strong evidence for an association between SA and glaucoma (OR = 0.95, 95% confidence intervals = 0.84–1.07), results were consistent across all MR predictors.

Conclusions. We found little genetic evidence supporting a causal association between SA and glaucoma. Our results refute the possibility of a large effect (glaucoma OR > 1.5 per doubling of odds on SA) between SA and glaucoma.

Keywords: glaucoma, sleep apnea, Mendelian randomization, genetics

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Open access | Original research

BMJ Open

Association of sleep behaviour and pattern with the risk of glaucoma: a prospective cohort study in the UK Biobank

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Based on the UK Biobank data, this is the first large prospective cohort study to comprehensively assess the association of sleep behaviours and patterns with glaucoma.
⇒ The application of cluster analyses (ie, multiple correspondence analysis (MCA) and a k-means clustering algorithm) enabled us to extract the most informative sleep patterns that inherently existed in the study population. Consequently, the exposed and reference groups in our analyses are realistic and mutually exclusive, leading to the most meaningful comparisons.
⇒ A wide range of important confounders were considered in the analyses since detailed information was available on sociodemographic factors, lifestyle, and somatic comorbidities.
⇒ The data were obtained from the UK Biobank but are not a representative sample of the entire UK population. The generalisation of our findings to the entire UK or other populations needs further assessment.

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BMC Medicine

RESEARCH ARTICLE | Open Access

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

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Abstract

Background: Sleep apnoea, a common sleep-disordered breathing condition, is characterised by upper airway collapse during sleep resulting in transient hypoxia, hypoperfusion of the optic nerve, and spike in intracranial pressure. Previous studies have reported conflicting findings on the association of sleep apnoea with glaucoma, and there are limited reports on the link between sleep apnoea and age-related macular degeneration (AMD).

Methods: Middle-aged and older participants from the longitudinal United Kingdom (UK) Biobank (n = 502,505) and the Canadian Longitudinal Study on Aging (CLSA; n = 24,073) were included in this analysis. Participants in the UK Biobank and the CLSA were followed for 8 and 3 years, respectively. Participants with diagnosed glaucoma or AMD at baseline were excluded from the analysis. In the UK Biobank, sleep apnoea and incident cases of glaucoma and AMD were identified through hospital inpatient admission, primary care records, and self-reported data. Multivariable Cox proportional hazards models were used to explore associations of sleep apnoea with incidence of glaucoma or AMD.

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Results: During the 8-year follow-up in the UK Biobank, glaucoma incidence rates per 1000 person-years were 2.46 and 1.59 for participants with and without sleep apnoea, and the AMD incidence rates per 1000 person-years were 2.27 and 1.42 for participants with and without sleep apnoea, respectively. Multivariable adjusted hazard ratios of glaucoma and AMD risk for sleep apnoea were 1.33 (95% confidence interval [CI] 1.10–1.60, P = 0.003) and 1.39 (95% CI 1.15–1.68, P < 0.001) relative to participants without sleep apnoea. In the CLSA cohort, disease information was collected through in-person interview questionnaires. During the 3-year follow-up, glaucoma incidence rates per 1000 person-years for those with and without sleep apnoea were 9.31 and 6.97, and the AMD incidence rates per 1000 person-years were 8.44 and 6.67, respectively. In the CLSA, similar associations were identified, with glaucoma and AMD odds ratios of 1.43 (95% CI 1.13–1.79) and 1.39 (95% CI 1.08–1.77), respectively, in participants with sleep apnoea compared to those without sleep apnoea (both P < 0.001).

Conclusions: In two large-scale prospective cohort studies, sleep apnoea is associated with a higher risk of both glaucoma and AMD. These findings indicate that patients with sleep apnoea might benefit from regular ophthalmologic examinations.

Keywords: Sleep apnoea, Glaucoma, Age-related macular degeneration, UK Biobank, CLSA, Cohort study

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Original Study

Associations Between Niacin Intake and Glaucoma in the National Health and Nutrition Examination Survey

Précis: This study examined the association between dietary niacin intake and glaucoma in the 2005-2008 National Health and Nutrition Examination Survey (NHANES). Increased niacin intake was associated with lower odds of glaucoma overall and among women.

Purpose: To examine the association between dietary niacin intake and glaucoma in the 2005-2008 NHANES.

Materials and Methods: This cross-sectional study included adult participants of the 2005-2008 NHANES. The exposure was dietary niacin intake, which was examined as a continuous and categorical variable. The outcome was glaucoma as defined by regraded disc images. Covariates included age, sex, race/ethnicity, education level, income, body mass index, smoking status, alcohol use, cardiovascular disease, diabetes mellitus, daily energy intake, vitamin B2 and B6 consumption, and macular degeneration. Adjusting for all covariates, logistic regression was performed to examine the association between niacin intake and glaucoma in the overall population and stratified by sex.

Results: The weighted population included 5371 individuals (109,734,124 weighted), of whom 55 (1.0%) had glaucoma. Each 1 mg increase in niacin intake was associated with a 6% decreased odds of glaucoma odds [adjusted odds ratio (aOR) = 0.94, 95% CI = 0.90, 0.98]. Among women, increased niacin intake was associated with decreased odds of glaucoma both with niacin as a continuous (aOR = 0.89, 95% CI = 0.80, 0.99 per 1 mg increase in niacin intake) and binary variable (aOR = 0.35, 95% CI = 0.14, 0.90 for higher vs lower niacin intake).

Conclusions: In the 2005-2008 NHANES population, higher levels of niacin intake were associated with decreased odds of glaucoma overall and in women. Further studies are needed to examine the potential protective effects of niacin on glaucoma risk.

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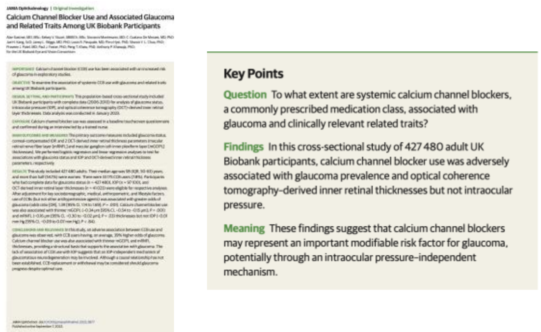

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Thank You!!!

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