# A Roadmap for the Medical Management of Glaucoman

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## Disclosures

- Murray Fingeret
  - Consultant
    - AbbVie, Bausch & Lomb, Carl Zeiss Meditec, Topcon
  - Ben Gaddie
    - Consultant
  - Eric Schmidt
    - Consultant

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## Glaucoma Therapy
## An Overview

- Chronic disease can be difficult to control
  - Person has the disease for the rest of their life
- Treatment often requires multiple medications and surgeries
- Treatment endpoints are poorly defined
- Treatment endpoints often difficult to achieve, even when defined
- Medication adherence is a challenge
  - Patients have difficulties taking medications for long periods of time
- Continuing need for new therapies and drug delivery techniques

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## When Do You Treat????

- Optic nerve changes consistent w glaucoma
  - With or without visual field loss
  - Regardless of IOP
- Glaucoma Suspect- consider therapy based in part on risk factors
  - Ocular hypertension
    - IOP > 21 mm Hg
  - Asymmetric IOP
    - 5 mm Hg or greater
  - Suspicious optic nerve
  - Visual field loss
  - Weigh risk factors
  - Treatment may be indicated at times
- Risk factors
  - Family history
  - Reduced corneal thickness
  - Reduced corneal hysteresis
  - Age
  - Race
  - Ocular history

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## Ocular Hypertension

- IOP 21 mm Hg or higher
- Visual Fields Full
- Optic nerve considered normal
- Consider therapy based upon risk of developing glaucoma over the lifetime
- If therapy is initiated, it is optional
- Not clear if early therapy alters outcome over time

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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 and EGPS
- What risk is too great to start therapy prophylactically?
- Uses concept from Framingham Heart Study and Cardiovascular disease
- Traditionally stage patient in regard to disease severity

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## Medical Therapy

- There are currently 6 classes of IOP-lowering medications
- Each works by altering one or more aspects of aqueous humor flow or production
- Beta-blockers and carbonic anhydrase inhibitors reduce the rate of aqueous production
- Prostaglandins increase outflow through the uveoscleral pathway
  - Vyzulta also works on TM outflow with nitric oxide
- Alpha-adrenergic agonists lower IOP by a dual mechanism
  - reducing aqueous production and increasing uveoscleral outflow
- There has been an unmet need for an IOP-lowering medication that works at the TM
  - the main site of outflow obstruction in glaucomatous eyes
- The site of outflow impairment—the TM – only recently has medications that influence this area
- ROCK inhibitors and Nitric Oxide (Vyzulta) work on trabecular meshwork directly through relaxation of cells
- Miotic class of drugs increase trabecular outflow, but only indirectly through action on the ciliary muscle
  - not through any direct effects on the TM itself
  - generally, poorly tolerated and not widely used in modern practice

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## Glaucoma Therapy Update

- Trend in topical eyedrop therapeutics is compounds with multiple targets and mechanisms of action (MOA) with single daily dosing
- Targets will include trabecular meshwork and uveoscleral outflow, aqueous humor production and episcleral venous pressure (EVP)

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## History of glaucoma drugs

- 1875 Cholinergic agents
  - Eserine (physostigmine)
    - Initially used for miosis during iridectomy which led to its use to break angle closure attacks
  - 1878 Pilocarpine introduced
  - 1946 diisopropyl fluorphosphae
  - 1957 echothiophate iodide (Phospholine iodide)
- 1904 Hyperosmotic agents
  - Hypertenoic saline, urea, mannitol, glycerol
- 1954 Carbonic anhydrase inhibitors –acetazolamide (Diamox)
- 1955 Adrenergic agonists – topical epinephrine

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## History of glaucoma drugs

- 1978 Beta-adrenergic inhibitors – Timolol
- 1987 Alpha-adrenergic agonists – apraclonidine (Iopidine)
  - Initially approved for post-laser use and 1993 approved for chronic glaucoma
  - 1996 Brimonidine – quickly replaced apraclonidine
  - 1995 Dipivefrin (Propine) – prodrug adrenergic agonist
- 1995 Topical Carbonic Anhydrase Inhibitors – dorzolamide (Trusopt)
- 1996 – Prostaglandin analogs- latanoprost (Xalatan)
  - 2001 – Bimatoprost (Lumigan), Travoprost (Travatan Z)
  - 2000s – preservative–free versions PGs
- 2017 – Latanoprostene – bunod (nitric oxide donating PG)
- 2017- Netarsudil – Rhopressa (ROCK inhibitor)
- 2019 – Netarsudil-latanoprost - Rocklatan –March 2019

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## Starting Therapy

- Is therapy indicated?
  - Ocular Hypertension
  - Primary Open Angle Glaucoma
- Stage the condition regarding severity
  - One eye or both
  - Extent of Damage
- Consider age, family history, patient's attitude, ocular and medical history and determine target IOP
- Select therapy
  - Medications vs. SLT vs. Cataract surgery with MIGS vs. MIGS vs. Filter surgery
- Consider target pressure
  - IOP that should stabilize condition
  - Greater the amount of damage and higher the untreated IOP, lower pressure needs to be
  - Over time know at target pressure is stability seen
- Monitor

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## Choosing an Initial Agent (Primary)

- The medication will give the biggest IOP reduction
- Select medication with long duration of action without tachyphylaxis
- Medication should be compatible with other anti-glaucoma medications
- Medication should have few ocular or systemic side effects
- Use "Basic Principles":
  - Minimize number of medications
  - Minimize dosing frequency
- PG is usually the choice but not always

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## Therapy of Glaucoma
## Starting Therapy

- Communicate with patient about medication being selected
  - cost
  - side effects
  - dosage
- Think about target IOP and med selected
- Initiate therapy w one med at a time
- Communicate with individual's primary care doctor

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## Side Effects

- Adverse events vs. Tolerability
  - difference in significance
- Tolerability
  - Allergic conjunctivitis- Alpha agonists
  - Burning and stinging- Topical CAI
  - Hyperemia- PG, Rock inhibitors
- Stinging in part may be due to dry eye
  - tear substitute administered 5 minutes before reduces symptoms (burning)

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## When Should Patients Return?

- Baseline period
  - See 2-6 weeks after starting medication making sure the medication is tolerated and effective
  - Follow up period for 1st year
  - Examine every three months with fields and imaging done at 6 months and 1 year, 18 months, 2 years
- After First Year
  - May reduce frequency if stable
- Stable vs. Uncontrolled

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## Advancing Therapy

- Modify therapy when
  - Side effects/Adverse events noted
    - Hyperemia, irritation, pain, blur, tearing, itching
    - Rarely switch in class reduces problems
  - IOP not at target range
    - If close, may go to fixed combination agent
  - Progression noted either on OCT or Visual fields
- Aim is to not go past 2 bottles (3 medications) due to issues with adherence

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## Therapeutic Options

- Medications
  - Prostaglandins (PGs)
    - Travoprost – Travatan Z
    - Latanprost – Xalatan – generic
      - Preservative free
    - Bimatoprost – Lumigan (0.03)
    - Tafluprost – Zioptan (Preservative Free)
  - Prostaglandin with nitric oxide
    - Latanoprostene bunod
  - Beta Blockers – Timolol, Levonbunolol
    - Generic
  - Topical CAIs
    - Dorzolamide – Trusopt
    - Brinzolamide - Azopt
  - Alpha agonists
    - Apraclonidine, Brimonidine
  - Rho kinase inhibitors
    - Netarsudil – Rhopressa
  - Fixed Combination Agents
    - Timolol-dorzolamide
    - Timolol-brimondine
    - Brinzolamide-brimonidine
    - Latanoprost – netarsudil

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## Therapeutics Options

- Fixed Combination Agents
  - Without PG
  - Cosopt – Timolol – Dorzolamide
  - Combigan – Timolol-Brimonidine
  - Simbrinza – Brimonidine – Brinzolamide
  - With PG
  - Rocklatan – Netarsudil with latanoprost
  - Xalcom – Timolol with Latanoprost (Not available in US)
  - Ganfort – Timolol with Bimatoprost (Not available in US)
  - Duotrav – Timolol with Travoprost (Not available in US)

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## Topical Prostaglandins

- Agents
  - Latanoprost – Generic
  - Bimatoprost (Lumigan)
  - Travoprost (Travatan Z)
    - Also generic
    - Cash pay model
  - Tafluprost (Zioptan) – Preservative free
- Reduce IOP through uveoscleral outflow
  - To smaller extent increase outflow through trabecular meshwork
- Highly selective FP prostaglandin receptor agonist
- Reduces IOP 25-35%
- Once per day w few side effects
  - While package insert mentions nighttime dose, can be taken anytime of day with similar efficacy
  - Want patient to be consistent when they use medication
  - Better compliance with AM dosage

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## Latanoprostone bunod (Vyzulta)

- 0.024% used once daily to reduced IOP
  - Bausch & Lomb
- Metabolized to latanoprost acid plus butanediol mononitrate
- Butanediol mononitrate is a nitric-oxide donating moiety NO molecule attached to latanoprost backbone to provide dual action
- Works over 24 hour period with >35% IOP reduction
- One molecule leads to IOP reduction via the uveoscleral and trabecular meshwork pathways
- NO is a signaling molecule that regulates outflow facility via the TM
- Can dilate blood vessels
- Modulates TM contractility, cell adhesion and the cytoskeleton leading to reduced IOP
- Medication acts on both the
  - Uveoscleral outflow pathway by altering the extracellular matrix in the ciliary muscle and the sclera
  - Trabecular meshwork outflow by inhibiting actomyosin contractility in trabecular meshwork cells thereby relaxing the meshwork

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## Rho Kinase (ROCK) Inhibitors

- Netarsudil 0.02% - Rhopressa
- Rho kinase inhibitors
- Reduce cellular stiffness in trabecular meshwork
  - Target trabecular meshwork cells to enhance outflow
  - May offer neuroprotective as well as anti inflammatory effects
  - Aerie
- Dual action Rho kinase (ROCK) + norepinephrine transport (NET) inhibitor
  - Also believed to reduce episcleral venous pressure which may allow it to better reduce IOP when it is below 21 mm Hg
- Once per day dosage
- Hyperemia is most common side effect

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## Latanoprostone bunod (Vyzulta)

- 0.024% used once daily to reduced IOP
  - Bausch & Lomb
  - Approved November 2017
- Metabolized to latanoprost acid plus butanediol mononitrate
- Butanediol mononitrate is a nitric-oxide donating moiety NO molecule attached to latanoprost backbone to provide dual action
- Works over 24 hour period with >35% IOP reduction
- One molecule leads to IOP reduction via the uveoscleral and trabecular meshwork pathways
- Latanoprost concentration 0.005%
- NO is a signaling molecule that regulates outflow facility via the TM
- Can dilate blood vessels
- Modulates TM contractility, cell adhesion and the cytoskeleton leading to reduced IOP
- Medication acts on both the
  - Uveoscleral outflow pathway by altering the extracellular matrix in the ciliary muscle and the sclera
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## Rho Kinase Inhibitors – Netarsudil 0.02%

- Rho kinase inhibitors
  - Rhopressa
- Reduce cellular stiffness in trabecular meshwork
  - Target trabecular meshwork cells to enhance outflow
  - May offer neuroprotective as well as anti inflammatory effects
  - Aerie
- Side effects
  - Hyperemia
    - conjunctival hemorrhages
  - Corneal verticillata
- Efficacy similar to timolol
- Once per day
- Dual action Rho kinase (ROCK) + norepinephrine transport (NET) inhibitor (Netarsudil 0.02%) - Rhopressa
  - Lowers IOP by enhance outflow through TM (ROCK) and inhibit aqueous production (NET)
  - Also believed to reduce episcleral venous pressure which may allow it to better reduce IOP when it is below 21 mm Hg
- Hyperemia most common side effect

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## Rocklatan (latanoprost and Netarsudil)

- Combination of Rhopressa with latanoprost
- Dosed once daily with significant IOP lowering
- Few systemic side effects
- Limited ocular side effects that are similar to the use of the two medications
- Approved March 12, 2019

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## Beta Adrenergic Blockers

- Two types
  - Nonselective and selective
- Reduce aqueous production approx 22%
- First available 1978 w Timolol
  - Timoptic- Merck
- Changed glaucoma management when first introduced
- Generic affords cost effective agent

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## Non Selective β -Blockers

- Effects all beta receptors
  - beta 1- heart
  - beta 2- pulmonary system
- Reduce aqueous production leading to lowered IOP

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## Cardioselective B Blockers - Betaxolol

- Reduced Systemic Side Effects
  - Less affinity for beta-2 pulmonary receptors
- Reduced efficacy as compared to timolol
- Potential neuroprotective and blood flow properties

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## Non-Specific Adrenergics Mechanism of Action

- Effects of Epinephrine and Propine
  - aqueous humor flow
    - increase or decrease
  - trabecular outflow
  - uveoscleral outflow
- Weak efficacy
- Medications of historical importance
- Rarely used today

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## Brimonidine (Alphagan)

- Highly selective alpha 2-adreno-receptor agonist
  - stimulates class of cell surface receptors which reduce aqueous humor production
  - decreases IOP
  - also increases uveoscleral outflow
- Additive with other glaucoma medications
- Only $alpha_2$-adreno-receptor agonist approved by FDA for chronic use
- Indications
  - Open angle glaucoma
  - Ocular Hypertension
- Drug used as 2nd or 3rd line agent
- Allergy common
  - red eye

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## Brimonidine (Alphagan)

- IOP reduction approximately 22%
  - comparable to timolol 0.5%
- Peak and trough effects
  - reduced half life requiring tid dosage if used as sole agent
- Minimal IOP drift at one year
- Favorable ocular and systemic safety profile
  - CNS side effects reported 10% of time
    - Fatigue
  - Beware of its use in children as it causes lethargy

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## Systemic Side Effects of Adrenergic-Agonist Drugs

- Nonselective drugs
  - General
    - headaches (epinephrine)
  - Cardiovascular
    - arrhythmia (epinephrine)
    - hypertension (epinephrine)
    - tachycardia (epinephrine)
- $\alpha_2$–Adrenergic-agonist drugs
  - General
    - lethargy (brimonidine)
    - fatigue (brimonidine)
    - drowsiness (brimonidine)
    - dry mouth
    - dry nose
  - Cardiovascular
    - mild decrease in blood pressure (brimonidine)

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## Mechanism of Action
### Carbonic Anhydrase Inhibitors (CAI)

- $CO_2 + OH^- \leftrightarrow HCO_3^-$
- Reversible conversion of Carbon Dioxide and Bicarbonate requires carbonic anhydrase
- In ciliary processes, formation of $CO_2$ linked to secretion of $Na^+$ used to form aqueous humor
- Requires 99% inhibition of CA in target tissue

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## Topical CAI

- Primarily used as adjunctive agent
  - may be used bid as adjunct agent w 20% additional reduction
- If used as monotherapy, requires tid dosage
- Excellent efficacy when used in combination w other agents
  - Prostaglandins or Beta Blockers
- Used as second or third line drug
  - complements primary therapy
- Ocular side effects common
  - hyperemia 36%
- Systemic side effects
  - metallic taste- 27%
- Dorzolamide 2% (Trusopt)
  - Merck
- Brinzolamide 1% (Azopt)
  - Alcon
- Reduce IOP approximately 16-18%
  - Excellent as 2nd line agent
- Safe medication
  - neither bone marrow depression or aplastic anemia reported
- Burns upon instillation
  - less with brinzolamide

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## Topical Carbonic Anhydrase Inhibitors

| | | | |
|---|---|---|---|
| Brinzolamide | 1% Suspension | Three times per Day | Azopt |
| Dorzolamide | 2% Solution | Three times per day | Trusopt |

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## Systemic Side Effects of Carbonic Anhydrase Inhibitors

- Pulmonary
  - respiratory decompensation in COPD
- Gastrointestinal
  - cramps
  - diarrhea
  - epigastric burning
  - metallic taste
  - nausea
- Renal
  - nephrolithiasis
  - renal failure
- Hematologic
  - acute leukopenia
  - agranulocytosis
  - aplastic anemia
  - neutropenia

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## Fixed Combination Agents

- CoSopt
  - Timolol 0.5%- Dorzolamide
- Combigan
  - Timolol 0.5%- Brimonidine 0.2%
- Simbrinza – Brimonidine 0.2% - Brinzolamide .15%
- Combination Drugs - PGs
  - Rocklatan (Netarsudil-Latanoprost)
  - Xalcom (Latanoprost-Timolol)
  - DuoTrav (Travoprost-Timolol)
  - Ganfort (Bimatoprost-timolol combo)
  - Azarga (Brinzolamide-Timolol)
- Side effects comparable to single entities

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## Medical Therapy

- Begin with PGA
- Add other medications if PGA provides meaningful but inadequate IOP reduction
- Don't switch within class
- Add one medication at a time
- Number of medications, drops, bottles comprising maximum therapy will vary patient to patient
- Benefit of 3$^{rd}$ or 4$^{th}$ medication is often minimal

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## Dry Eye and Glaucoma

- Therapeutic options
  - Surgery including SLT/MIGS with cataract surgery
  - Non preserved agents
    - Zioptan (tafluprost ophthalmic sol 0.015%) Akorn
    - CoSopt PF (timolol 0.5%-dorzolamide 2% ophthalmic sol) Akorn
    - Timoptic in Ocudose (timolol 0.5%) Valeant
  - BAK free agents
    - Latanoprost (0.005% ophthalmic emulsion) Sun pharma

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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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## 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
- Phase III trial underway comparing SR to timolol
- Will there ever be a need for removal?
- Could it cause cataracts?

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## Target IOP Range

- Range of intraocular pressures at which further damage to optic nerve is deemed unlikely
- Problems with definition
  - impossible to know w certainty what IOP or range of IOPs will stabilize condition
  - other factors besides IOP may be involved in causing glaucomatous damage
- Need to be flexible
- Regularly reassess target IOP range
  - comparisons to baseline and previous optic nerve and visual field evaluations important
- Think in terms of Per Cent Reduction from highest IOP reading
- Greater the damage, lower the IOP needs to be

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## Target IOP

- There is no validated algorithm for the determination of a target IOP. This does not, however, negate its use in clinical practice.
- If one elects to use the target IOP then it should be recorded so that the clinicians can readily use it on subsequent patient visits.
- The use of a target IOP in glaucoma requires periodic re-evaluation, entailing the detection of the presence or absence of glaucomatous progression, the effect of the therapy upon the patient's QOL, and whether the patient has developed any new systemic illness that might affect the risk/benefit ratio of therapy.

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## Target IOP

- During the re-evaluation, the clinician will conclude that either the target is appropriate and should not be changed, that the target needs to lowered, or that the target should be raised.
- It should be emphasized that the target IOP is only an estimate, and must be continually reassessed in relation to the patient's condition, needs, and wishes.

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## Target IOP

- The target IOP merely reflects a goal set by the treating clinician, based on estimated measures of the patient's risk and the current understanding of glaucoma.
- Some patients will continue to have unacceptable rates of disease progression despite apparent achievement of their target IOP, and many who do not achieve their target IOP will not be adversely affected by their glaucoma.
- Therefore, in many cases, clinicians may choose not to advance treatment in patients who have not met their target IOP, always balancing the burdens of therapy against the risks of glaucoma.

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