

The New Horizons of Medical Therapy in Glaucoma

An Update on Current and Near Future Medical Therapy in POAG



No Financial interest

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The ideal drug for treatment of POAG

- 
- ▶ effectively lower IOP
 - ▶ no adverse effects or systemic exacerbation of disease
 - ▶ inexpensive with once-a-day dosing.

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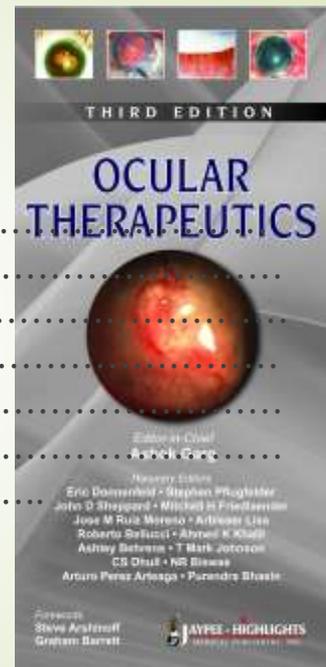
- ▶ Currently available drug classes often do not adequately fulfil these demands

The search continues for drugs with novel mechanisms of action that could lead to better treatment.

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After 20 Years, Major Medical Breakthroughs are coming to our doorsteps

- ▶ 1920s.....
-1970s.....
-1990s.....
-
-
-





Looking for

- ▶ compounds comprising multiple molecules/
mechanisms of action
- ▶ offer additivity and are complementary to
current therapeutics

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- ▶ Several new topical drop compounds directly targeting the trabecular meshwork/Schlemm canal (conventional outflow pathway) to reduce outflow resistance have obtained FDA approval in the past year. These include rho kinase inhibitors and nitric oxide donating compounds

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- ▶ Alternative therapies that offer long-term IOP lowering while removing the patient from the drug delivery system are moving forward in development. These include gene therapy and stem cell strategies, which could ease or eliminate the burden of topical drop self-administration for several years

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- ▶ Novel formulations and devices are in development that aim for controlled, steady state delivery of therapeutics over periods of months. The future of glaucoma therapy is focusing on an increase in specificity for the individual patient: their type of glaucoma; underlying mechanisms; genetic make-up; comorbid conditions; and rate of progression

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Here Comes the Rock

Rho Kinase Inhibitors

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Rho Kinase Inhibitors

- ▶ Serine/threonine kinases that regulate contraction of smooth muscle, vascular endothelial, and other cell types.
- ▶ Selective ROCK inhibitors can enhance fluid outflow through the TM by inhibiting TM/SC cellular contraction.

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Ripasudil hydrochloride hydrate

- ▶ Ripasudil hydrochloride hydrate (Glanatec, Kowa), is a specific ROCK inhibitor, studies by Prof. Tanihara, Kumamoto University, Japan
- ▶ approved for use in Japan since 2014, already **second-line drug for glaucoma treatment there**

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Netarsudil

- ▶ Rhopressa 0.02%; Aerie Pharmaceuticals, approved by the FDA in December 2017
- ▶ both a Rho-associated protein kinase (ROCK) inhibitor and a norepinephrine transport (NET) inhibitor; both novel pathways
- ▶ (Roclatan netarsudil 0.02% and latanoprost ophthalmic solution 0.005%, Aerie Pharmaceuticals)
The MERCURY 1 study: 65% of patients receiving Roclatan achieved a 30% reduction compared to 37% with latanoprost

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Rho Kinase Inhibitors

- ▶ reduces IOP specifically by improving outflow of the trabecular meshwork; the pathway from which most of the aqueous humor drains.
- ▶ decreasing production of aqueous humor
- ▶ decreasing episcleral venous pressure.
- ▶ Lowers low IOP (NTG)
- ▶ once daily

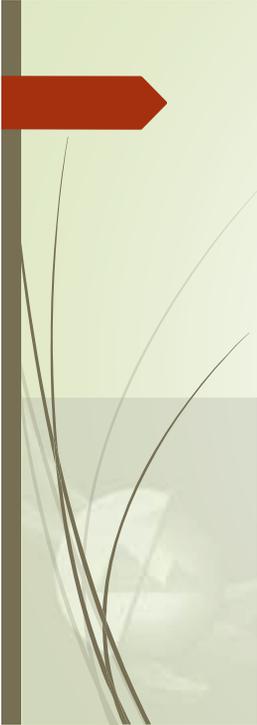
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Nitric oxide (NO)

- ▶ decreases IOP via relaxation of the TM and decreases in TM cell volume, reducing outflow resistance.
- ▶ plays a role in the assembly and disassembly of interendothelial adherens junctions, which affects endothelial permeability.

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latanoprostene bunod

- ▶ latanoprostene bunod 0.024% (Vyzulta)

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VYZULTA

- ▶ approved by the FDA in November 2017
metabolizing into two components: latanoprost acid and butanediol mononitrate, which breaks down into nitric oxide (NO), effectually increasing outflow through the trabecular meshwork and Schlemm canal
- ▶ demonstrated a mean IOP reduction of 7.5 to 9.1 mm Hg from baseline between 2 and 12 weeks of treatment

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Adenosine Agoists

- ▶ (Trabodenoson) is a highly selective adenosine A1 receptor agonist that engenders an upregulation of protease A and matrix metalloproteinase-2 (MMP-2) in target cells.
- ▶ The proteases digest and remove hydrolyzed collagen type IV, a major component of the resistive ECM in the TM

Phase II trials

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DRUG DELIVERY IMPLANTS

- ▶ The bimatoprost ring
- ▶ ENV515 (Envisia) is an intracamerally injected biodegradable proprietary Particle Replication In Non-Wetting Templates (PRINT) nanoparticle with an extended release formulation of travoprost.
- ▶ iDose (Glaukos) is another sustained release travoprost intraocular implant at the phase 2 clinical trial stage.

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Marijuana and Glaucoma

- ▶ No illegal or Cnnabiphilic interest

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- ▶ In 1974, Robert Randall, a 26-year-old man with advanced, poorly controlled glaucoma, observed that the haloes around lights he experienced because of his high IOP disappeared after he smoked marijuana.
- ▶ He eventually faced federal criminal charges for growing marijuana to relieve his symptoms
- ▶ he won a landmark court case later

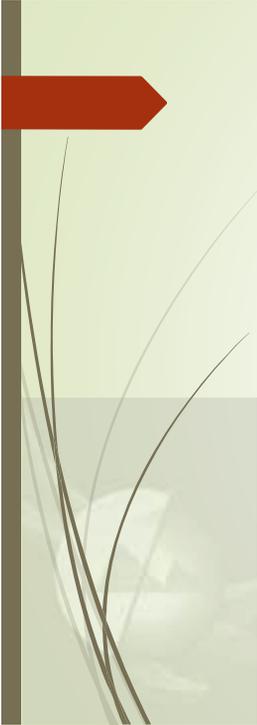
Marijuana and Glaucoma

- ▶ In 1971, first report that smoking marijuana could lower IOP

Hepler RS, Frank IR. Marijuana smoking and intraocular pressure. *JAMA* 1971;217(10):1392.



- ▶ Because of the drug's short duration of action, eight to 10 marijuana cigarettes would have to be smoked each day to provide 24-hour IOP control.
- ▶ This regimen would be unlikely to allow the patient to work or drive, and intermittent use could lead to disease progression.
- ▶ The cost of this regimen would also greatly exceed the cost of any current glaucoma drug.

- 
- ▶ To solve these problems, the University of British Columbia team developed a hydrogel filled with thousands of nanoparticles containing cannabigerolic acid (CBGA), a cannabis compound that has shown promise in relieving glaucoma symptoms
 - ▶ Tried on donated pig corneas, the drug was absorbed quickly and reached the back of the eye.

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“After 20 years of silence, there is a wave of newly introduced drug families already approved by drug regulating authorities around the world. Others are underway. This wave is coming to the aid of glaucoma patients and specialists..”

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“ Around our corner;
Rhopressa
Glanatec
Roclatan
VYZULTA ”

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Thank You

