MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE

This activity is supported by independent educational grants from Aerie Pharmaceuticals, Inc., Alcon Pharmaceuticals Ltd. and Bausch & Lomb, Inc.
Demographics and POAG: Time to Consider Alternative Care Models

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Wilmer Eye Institute, Alfred Sommer Professor of Ophthalmology
Johns Hopkins University School of Medicine
Professor, Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
The Times They Are a Changin’

- Populations are aging
- Number of ophthalmologists is not adequate
- Cost of care is high and much of what we do during the care process is ineffective
- Technology is improving
Developed countries are aging and there will be fewer working age individuals. Who will see all of the glaucoma patients?
No New Ophthalmologists!!

The number of ophthalmologists in the United States will increase by about 2% and full time equivalents (FTE) will decrease over the next decade.
About 10% of Whites and over 15% of African-derived populations over 75 years of age

Nearly 100 million globally with glaucoma in 2020
Many More Need Monitoring

Patients

Large numbers with angle closure without glaucoma
Half of glaucoma care costs are for glaucoma visits
Current management is inefficient and often ineffective
Lots of Wasted Time and Effort

- Patient seen every 4 to 6 months
- IOP stable, field stable, nerve imaging stable
- 5 years later confirmed field loss

How much of the time spent with the patient was time well spent???
Visual Acuity
Intraocular Pressure
Anterior Chamber Angle
Anterior Chamber Angle
Fundus Photography

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Fundus Photography
NFL Imaging
Visual Field Testing
What about counseling?
Adherence in Clinic Patients


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
13 of 50 patients admitted to non-adherence in research interview

Physicians detected only 3 of them

### Determining Worsening???

<table>
<thead>
<tr>
<th>Clinician A</th>
<th>Definitely Stable</th>
<th>Probably Stable</th>
<th>Probably Progressing</th>
<th>Definitely Progressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Stable</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Probably Stable</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Probably Progressing</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Definitely Progressing</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Median weighted kappa for 5 clinicians = 0.32


**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
Technology can improve performance
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Photoscreening for DR
Local Testing at Remote Locations

• Better integration of data
• More resources allocated to interpretation
• Physician with better data and more time to interact with those who need time
• Rapid upgrade to better technology over time
A New Model of Care

• Testing using ancillary personnel for most visits
• Longer physician appointments when major clinical change is recommended

Health delivery systems can be improved in order to provide high quality care more efficiently and effectively
The Office of Tomorrow

• Data collected remotely
• Physician with multiple screens reviews
• Ancillary staff interact with the patient
• Longer visits with the doctor for change of care or change of status
The Future Is Here

• Populations are aging and growing
• Resources are finite
• Physician supply is not growing, technology is improving
• All that remains is to figure out the logistics
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE

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Recent Discoveries in the Pathophysiology of Glaucoma: Novel Treatments

W. Daniel Stamer, PhD

Joseph A. C. Wadsworth Professor of Ophthalmology
Professor of Biomedical Engineering
Duke University
Durham, NC
Which Currently Available Glaucoma Medications Secondarily Target the Conventional Outflow Pathway?

- **Prostaglandins** (direct, but secondary to changes in uveoscleral outflow pathway)
- **Pilocarpine** (indirect, via ciliary muscle contraction)
Aqueous Humor Dynamics: IOP Regulation

IOP = (F - U)/C + EVP

C = 1/R

Simplified Goldman Equation

IOP, intraocular pressure;
F, rate of aqueous formation;
U, uveoscleral outflow;
C, facility of aqueous outflow;
EVP, episcleral venous pressure

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Lowering Eye Pressure Is Neuroprotective


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

The lower the pressure... The better the outcome.
How Do We Medically Lower Eye Pressure?

\[ \text{IOP} = \frac{(F - U)}{C} + \text{EVP} \]

Simplified Goldman Equation

- **Decrease inflow**
  - ß-adrenergic blockers
  - Carbonic anhydrase inhibitors
  - \(a_2\)-adrenergic receptor agonists

- **Increase uveoscleral outflow**
  - Prostaglandin \(F_{2a}\) receptor agonists

- **Increase conventional outflow**
  - None currently available in US
Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis

Analysis of 114 Randomized Controlled Trials


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Higher Resistance to Conventional Outflow Causes Ocular Hypertension in Glaucoma


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Why Do We Need a Conventional Outflow Drug?

• Majority of outflow (70%-90%) via conventional route, offering greater eye-pressure-lowering ability than PGAs

• Avoid interventional treatments (e.g. surgery, laser)

• Additive with current eye-pressure-lowering drugs: Current medical treatments do not lower eye pressure enough in most

• Restore function to conventional pathway
  – Diseased tissue
  – Better perfusion of tissues/cells
  – Possible stimulation of cell division and repopulation/remodeling of tissue
  – Dampen eye pressure fluctuations
Conventional Outflow Drugs/Current Status

• Rho kinase inhibitors
  – Netarsudil (Awaiting FDA approval in US)
  – Netarsudil/latanoprost (Phase III)
  – Ripasudil (Approved in Japan)

• Nitric oxide donors
  – Latanoprostene bunod (Recently approved in US)
  – Nipradilol (Approved in Japan)
Latanoprostene Bunod: Mechanism of Action

Nitric Oxide Lowers IOP by Increasing Outflow Facility

**Infusion**

- **97 µg/min Nitroglycerin**

- **Narrow-Angle Glaucoma (n = 9)**

- **Open-Angle Glaucoma (n = 5)**

**Graphs:**

1. **IOP, %**
   - **Minutes**
   - **Infusion**
     - **Narrow-Angle Glaucoma (n = 9)**
     - **Open-Angle Glaucoma (n = 5)**

2. **Flow Rate, µL/min**
   - **SNAP (n = 6)**
   - **NAP (n = 5)**
   - **Equations:**
     - $Y = 0.051x - 0.309$  \( R^2 = 0.956 \)
     - $Y = 0.031x - 0.198$  \( R^2 = 0.965 \)

**References:**


**Mechanisms of Pressure Relief in Glaucoma**
Rho Kinase Inhibitors: Mechanism of Action

MLC, myosin light chain.

**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
Netarsudil vs Latanoprost vs Netarsudil/Latanoprost (N = 292)


**Mechanisms of Pressure Relief in Glaucoma**
Mean Diurnal IOP Reduction


**Mechanisms of Pressure Relief in Glaucoma**
MERCURY 1, 12-Month Netarsudil/Latanoprost vs Individual Components (n = 718)


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
At Month 12: Percentage of Patients with IOP Reduced to 18 mmHg or Lower

![Bar chart showing the percentage of patients with IOP reduced to 18 mmHg or lower for different IOP levels and treatment groups.](http://investors.aeriepharma.com/events-and-presentations)

Source: [investors.aeriepharma.com/events-and-presentations](http://investors.aeriepharma.com/events-and-presentations).

*P < .05, **P < .01.
# 12 Month Phase III Safety Profile of Netarsudil vs Latanoprost vs Netarsudil/Latanoprost

<table>
<thead>
<tr>
<th>Adverse Events (≥5.0% in any group)</th>
<th>Netarsudil/Latanoprost N = 238</th>
<th>Netarsudil n = 243</th>
<th>Latanoprost N = 237</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>150 (63.0%)</td>
<td>125 (51.4%)</td>
<td>52 (21.9%)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>31 (13.0%)</td>
<td>44 (18.1%)</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Cornea Verticillata</td>
<td>42 (17.6%)</td>
<td>33 (13.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>27 (11.3%)</td>
<td>22 (9.1%)</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Punctate Keratitis</td>
<td>12 (5.0%)</td>
<td>18 (7.4%)</td>
<td>10 (4.2%)</td>
</tr>
<tr>
<td>Lacrimation Increased</td>
<td>17 (7.1%)</td>
<td>20 (8.2%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>13 (5.5%)</td>
<td>13 (5.3%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>11 (4.6%)</td>
<td>15 (6.2%)</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>14 (5.9%)</td>
<td>8 (3.3%)</td>
<td>5 (2.1%)</td>
</tr>
<tr>
<td><strong>Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instillation Site Pain</td>
<td>55 (23.1%)</td>
<td>60 (24.7%)</td>
<td>18 (7.6%)</td>
</tr>
</tbody>
</table>

*Reports as adverse events.


## MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Latanoprostene Bunod (LBN), Phase III Apollo Study


Mean IOP, mmHg

*P≤0.002 versus timolol at the same assessment point.
3-Month Latanoprostene Bunod, Voyager Phase III Trial (N = 396)

- Reduction in Mean Diurnal IOP, mmHg

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Reduction in Mean Diurnal IOP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBN 0.006%</td>
<td>-7.81</td>
</tr>
<tr>
<td>LBN 0.012%</td>
<td>-8.3</td>
</tr>
<tr>
<td>LBN 0.024%</td>
<td>-9 *</td>
</tr>
<tr>
<td>LBN 0.040%</td>
<td>-8.93 †</td>
</tr>
<tr>
<td>Latanoprost 0.005%</td>
<td>-7.77</td>
</tr>
</tbody>
</table>

*P = .005 vs latanoprost. †P = .009 vs latanoprost.

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
## Safety: 12-Month Latanoprostene Bunod Treatment in Japanese Subjects: The Jupiter Study

Incidence of Ocular Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects in the Study Eye or the Treated Fellow Eye (Safety Population)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Study Eye (N = 130) n (%)</th>
<th>Treated Fellow Eye (N = 126) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Ocular AE</td>
<td>76 (58.5)</td>
<td>78 (61.9)</td>
</tr>
<tr>
<td>≥1 Treatment-Related Ocular AE</td>
<td>62 (47.7)</td>
<td>61 (48.4)</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival Hyperemia*</td>
<td>23 (17.7)</td>
<td>21 (16.7)</td>
</tr>
<tr>
<td>Growth of Eyelashes</td>
<td>21 (16.2)</td>
<td>21 (16.7)</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>15 (11.5)</td>
<td>15 (11.9)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>13 (10.0)</td>
<td>13 (10.3)</td>
</tr>
<tr>
<td>Iris Hyperpigmentation</td>
<td>5 (3.8)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Blepharal Pigmentation</td>
<td>4 (3.1)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>3 (2.3)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>3 (2.3)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Asthenopia</td>
<td>3 (2.3)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>2 (1.5)</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

*Reported as adverse events.

Progressive Degeneration of the Trabecular Meshwork Drives Elevated IOP and Vision Loss in Glaucoma

Outflow Drugs Have the Potential to Improve Health of TM in Patients With Glaucoma

Healthy TM → Healthy TM

Cellular Stress
- Aging
- Oxidation

Reduced Fibrosis, Stiffness, Contraction

Less Cellular Stress

Increased Aqueous Perfusion Area

More Nutrients, Antioxidants

Reduced IOP → Preserve Vision

+ drugs that decrease contractility

Reducing Fibrosis, Increasing Trabecular Outflow Could Stop Degeneration of Outflow Tissues in POAG


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Summary: Take Home Messages

• Conventional outflow dysfunction causes ocular hypertension
• Effectively lowering IOP preserves vision
• No medication currently available primarily targets the conventional outflow pathway
• One drug that relaxes the trabecular meshwork and increases conventional outflow may soon be available, and another was recently approved for patients
  – Safe
  – Efficacious (additive with current medications)
  – Therapeutic potential
    ▪ Increase functionality of trabecular meshwork (i.e. ability to dampen IOP fluctuations)
    ▪ Increase blood flow to optic nerve head (evidence of vascular dysfunction in some forms of glaucoma)
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE
Mechanisms of Pressure Relief in Glaucoma: Pharmacologic & Surgical Advances for Refractory POAG or Non-Adherence

Steven J. Gedde, MD
John G. Clarkson Chair in Ophthalmology
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami Health System
Miami, FL
Treatment Algorithm

**Congenital Glaucoma**
- Goniotomy or Trabeculotomy
- Medical treatment is recommended during the waiting time prior to surgery

**Juvenile Glaucoma**
- Laser Trabeculoplasty
- Medical Therapy*

**POAG / XFG / PDG**
- Laser Trabeculoplasty
- Medical Therapy*
- Surgery

**Ocular Hypertension**
- Consider:
  - Medical therapy options on the basis of IOP values
  - Risk factors profile
- Discuss with the patient
- No treatment

If the above procedures not successful or feasible, consider repeat filtration surgery with anti-metabolites or long-tube drainage implant/cyclodestructive procedure

*Up to 2-3 different drugs. Do not add a drug to a non-effective one; consider switching.

POAG, primary open-angle-glaucoma; XFG, exfoliative/pseudoexfoliative glaucoma; PDG, pigment dispersion glaucoma.

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MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
# Incisional Glaucoma Surgery

<table>
<thead>
<tr>
<th>Traditional glaucoma surgery</th>
<th>Minimally invasive glaucoma surgery (MIGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Trabeculectomy</td>
<td>- Ab interno trabeculectomy (Trabectome®)</td>
</tr>
<tr>
<td>- Aqueous shunts</td>
<td>- Trabecular microbypass stent (iStent®)</td>
</tr>
<tr>
<td>- EX-PRESS® implant</td>
<td>- Gonioscopy-assisted transluminal trabeculotomy (GATT)</td>
</tr>
<tr>
<td></td>
<td>- Kahook Dual Blade</td>
</tr>
<tr>
<td></td>
<td>- CyPass® Micro-Stent</td>
</tr>
<tr>
<td></td>
<td>- XEN® Gel Stent</td>
</tr>
<tr>
<td></td>
<td>- Trab™360</td>
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</table>

<table>
<thead>
<tr>
<th>Nonpenetrating glaucoma surgery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Deep sclerectomy</td>
<td></td>
</tr>
<tr>
<td>- Viscocanalostomy</td>
<td></td>
</tr>
<tr>
<td>- Canaloplasty</td>
<td></td>
</tr>
</tbody>
</table>

| Endoscopic cyclophotocoagulation (ECP)                |                                            |
|                                                      |                                            |
Trabeculectomy

• Scleral fistula allows drainage of aqueous humor into subconjunctival space creating a filtering bleb

• Only titratable glaucoma procedure

• Success enhanced with use of antifibrotic agents (MMC, 5-FU)

• Growing concern about bleb-related complications (leaks, infection, dysesthesia)
Surgical Trends


**Mechanisms of Pressure Relief in Glaucoma**
Aqueous Shunts

• Silicone tube shunts aqueous humor to end plate located in equatorial region of globe

• Design
  – Valved: Ahmed, Krupin
  – Nonvalved: Baerveldt, Molteno

• Traditionally used in eyes at high risk for filtration failure, but indications are expanding

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
PTVT Study

Cumulative Proportion Failing

Follow-up (Months)

Trabeculectomy Group
Tube Group

$P = .013$

0.3
0.2
0.1
0.0

17.3%
7.9%

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
EX-PRESS® Implant

- Nonvalved, stainless steel tube
- No sclerostomy or iridectomy required
- High rate of hypotony and extrusion prompted placement under a scleral flap
- Similar long-term safety and efficacy compared with trabeculectomy
XVT Study

- Trabeculectomy
- EX-PRESS®

**Percent Success**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Trabeculectomy</th>
<th>EX-PRESS®</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ P = 0.563 \]

\[ N_E = 59 \]
\[ N_T = 61 \]

**Mean IOP, mmHg**

\[ * \]

**Vision, logMAR**


**Mechanisms of Pressure Relief in Glaucoma**
Nonpenetrating Glaucoma Surgery

• Excision of corneoscleral tissue under scleral flap leaves thin window of trabecular meshwork (TM) and Descemet’s membrane to provide resistance to aqueous outflow
• Reduces risk of hypotony
• Technically difficult
• Types:
  – Deep sclerectomy
  – Viscocanalostomy
  – Canaloplasty
Nonpenetrating Glaucoma Surgery

Follow-up (Months)

Cumulative Proportion of Success

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 2 4 6 8 10 12 14 16 18 20 22

Trabeculectomy
Nonpenetrating deep sclerectomy

Intraocular Pressure

Preoperative 1 2 3 6 12 18

Follow-up (Months)

14 16 18 20 22 24 26 28 30

Trabeculectomy
Nonpenetrating deep sclerectomy


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Endoscopic Cyclophotocoagulation (ECP)

- Treatment of ciliary processes under direct visualization with endoscopic camera and laser
- Frequently combined with phaco
- Provides moderate long-term IOP reduction
- CME is most common cause of vision loss
Minimally Invasive Glaucoma Surgery (MIGS)

• Newer group of glaucoma procedures characterized by:
  – Ab interno approach
  – Minimal trauma to tissue
  – Modest efficacy
  – Excellent safety profile
  – Rapid postoperative recovery

• Frequently performed in combination with phaco

• Growing in popularity

Ab Interno Trabeculectomy (Trabectome®)

- Electrocautery removes a strip of TM and Schlemm’s canal

- Meta-analysis
  - 31% reduction in IOP
  - 66% success rate at 2 years

- Prior laser trabeculoplasty and trabeculectomy does not appear to influence results


Courtesy of Brian Francis.
Ab Interno Trabeculectomy (Trabectome®)


**Mechanisms of Pressure Relief in Glaucoma**
Trabecular Micro-Bypass Stent (iStent®)

- Snorkel-shaped device made of heparin-coated titanium is inserted into Schlemm’s canal
- FDA-approved for use with CE in patients with mild-moderate glaucoma
- RCTs show greater reduction in IOP and medical therapy than phaco alone
- Multiple stents may provide greater IOP reduction than single stent

Courtesy of Ike Ahmed.
Trabecular Micro-Bypass Stent (iStent®)

IOP ≤21 mmHg Without Meds

<table>
<thead>
<tr>
<th>Month</th>
<th>Stent + Cataract</th>
<th>Cataract Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>12</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>LOCF</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

IOP Reduced ≥20% Without Meds

<table>
<thead>
<tr>
<th>Month</th>
<th>Stent + Cataract</th>
<th>Cataract Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>12</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>LOCF</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
CyPass® Micro-Stent

• Flexible 6.35 mm fenestrated micro-stent with internal lumen of 300 micron

• Inserted with a guidewire

• Shunts aqueous humor from the AC to the suprachoroidal space

• Pressure gradient drives flow through device

Courtesy of Ike Ahmed.
CyPass® Micro-Stent


**IOP ↓ ≥20% vs Baseline (% of Group)**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Control</th>
<th>Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>66%</td>
<td>82%</td>
</tr>
<tr>
<td>24</td>
<td>60%</td>
<td>77%</td>
</tr>
</tbody>
</table>

***P<.001, **P<.01.


**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
XEN® Gel Stent

- 6 mm tubular collagen implant placed translimbally
- 27-gauge needle inserter
- Drains aqueous into subconjunctival space
- High needling rate (32%-47%)

Courtesy of Joseph Panarelli.

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
XEN® Gel Stent

Qualified Success at IOP 6-14

Qualified Success at IOP 6-17

Qualified Success at IOP 6-21

Proportion Successful

Months

0.0 0.2 0.4 0.6 0.8 1.0

Microstent 185 168 122 85 41 20 10
Trab 169 153 135 100 60 40 23


Mechanisms of Pressure Relief in Glaucoma
Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)

• Microcatheter or suture used to perform 360° trabeculotomy
• Hyphema is most common complication

Courtesy of Davinder Grover.
GATT, gonioscopy-assisted transluminal trabeculotomy.

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Kahook Dual Blade

- Removal of TM using dual blade
- Single use ophthalmic blade
- Blade composition
  - Pointed tip easily pierces TM
  - Ramp elevates and stretches TM
  - Dual blade excises strip of TM
  - Foot plate prevents damage to collateral tissue

Courtesy of Malik Kahook.
**TRAB™360**

- Cannula used to incise TM and introduce flexible trabeculotome 180°
- Filament is retracted back into device and procedure is repeated in other direction
- 360° goniotomy performed
Investigational

- Translimbal implant
  - InnFocus MicroShunt®
- Schlemm’s canal implants
  - Hydrus™ Microstent
  - iStent inject®
- Suprachoroidal shunts
  - Gold Micro Shunt
  - iStent Supra®
In Summary

• Surgical options for managing glaucoma are rapidly expanding

• Traditional glaucoma surgery (tubes and trabs) provide excellent IOP reduction, but surgical complications are common (generally transient and self-limited)

• MIGS are newer procedures that offer an improved safety profile, but reduced efficacy
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE
In the Pipeline: New Approaches to Drug Delivery for Glaucoma

David S. Friedman, MD, MPH, PhD

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Wilmer Eye Institute, Alfred Sommer Professor of Ophthalmology
Johns Hopkins University School of Medicine
Professor, Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Modest Advances in Medical Therapy: Largely Stagnant Over Last 20 Years

- Combination therapies
- Preservative free
Adherence in Clinic Patients Monitored Electronically


**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
Drops Are Not Ideal

- Half of new scripts are not filled after 6 months, low adherence
- Administrative errors
- Local and systemic side effects
Ideal Glaucoma Medical Treatment

- Patient-proof
- Few symptoms
- Can achieve the IOPs we need
- Cost effective
Drug Delivery Through a Scleral Ring

• Ability to incorporate drugs into polymer
• Phase 2 trials completed
Consistent Performance in Clinical Trials:
Four Phase 1 (N = 73) and Four Phase 2 (N = 251)

- Uneventful safety profile
- Regulatory pathway: NDA in 2019
- Topical, comfortable (90%), well-retained (90% at 6 months)
- One ring provides clinically significant IOP reduction for 6 months
- 85% of patient recommend insert
- 80% of doctors prefer insert to drops
- Validated platform for fixed combination glaucoma, allergy, dry eye, other pipeline

Mean Diurnal IOP with Bimatoprost Insert: Phase I Efficacy Results (N = 27)

- Mean IOP reduction: 4.7 to 6.5 mmHg from washout

Scleral Ring Pros and Cons

• Comfort???
• Cosmesis???
• Medication can be placed by the patient (no physician involvement needed)
• Possible compliance issues
• Local side effects???
Drug Delivery Into Suprachoroidal Space

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Ongoing Research

• Currently focused on macular edema and neovascular age-related macular degeneration

• One Phase I/II study completed

• Phase II and III studies on macular edema ongoing

• Injections every 12 weeks

• Planned research on delivery of glaucoma medicines using this technology
Suprachoroidal Delivery Pros and Cons

• Likely to eliminate many local side effects
• Low drug requirement
• Harm to retina and choroid unknown???
• Dosing frequency may exceed visit frequency
• Patient acceptance of “injection” unknown
Intracameral Injection of Printed Particles
Intracameral Injection of Printed Particles: Early Development

- Current product includes printed travoprost
- Ongoing Phase II study
- Novel design: enrolling patients scheduled for phaco within 60 days
- Evidence of efficacy >6 months in dogs

Graph:
- IOP, mmHg
- Baseline
- Placebo
- ENV515
- 30% change from baseline

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Intracameral Delivery Pros and Cons

• Likely to eliminate many local side effects
• Evidence of long duration of action
• Possibility of infection, harm to cornea, other?
• Difficulty removing implant if side effects occur
• Patient acceptance of “injection” unknown
Bioerodible Subconjunctival Implant

Two views and their delivery system

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA
Bioerodible Subconjunctival Implant

- Ongoing Phase I/II study
- Retinal products: duration of action as long as three years
Bioerodible Subconjunctival Implant: Pros and Cons

• Potentially long duration of action
• Avoids intraocular injection
• Possibility of removing implant if side effects occur
• May still have normal drug side effects
• Patient acceptance of “injection” unknown
• Possible adverse effect on later glaucoma surgeries
Bioerodible Tear Duct Plug
Bioerodible Tear Duct Plug

• Phase III trial completed for dexamethasone implant after cataract extraction
• Completed Phase I study comparing travoprost plug vs timolol
• IOP lowering noted for 3 months with minimal side effects
Bioerodible Tear Duct Plug: Pros and Cons

• Easy to insert
• Likely to be accepted by patients
• No possibility of removing implant if side effects occur
• May still have normal drug side effects, could fall out
• Dosing frequency may be > visit frequency
Biodegradable Nanoparticles

ENCAPSULATED DRUG

Biodegradability
Biocompatibility
Bioabsorbability

Polymer Modified to Reduce Inflammation

Mechanisms of Pressure Relief in Glaucoma
Subconjunctival Dorzolamide Particles Lowered IOP for 30 Days in Normotensive Rabbits

*Outliers more than 1.5x the interquartile range from the median.
Particles Potentially Useful for Delivering Neuroprotective Agents as Well


**MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA**
Medical Therapy Likely to Be a Rapidly Evolving Field

- Multiple new drug delivery platforms emerging
- Doctor and patient acceptance as well as business models will influence uptake
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE

This activity is supported by independent educational grants from Aerie Pharmaceuticals, Inc., Alcon Pharmaceuticals Ltd., and Bausch & Lomb, Inc.