

# New Ideas in Glaucoma

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# New Ideas in Glaucoma

- IOP
  - 24-Hour IOP
    - Devices now FDA approved to measure 24-hour IOP
    - Implantable device approved in Europe and undergoing US review
  - Artificial Intelligence (AI)
    - How will it change how we use the OCT, visual fields and photographs to diagnose and manage glaucoma?
    - FDA reviews and approves AI software

# New Ideas in Glaucoma

- Optic Nerve/RNFL/Posterior pole
  - Advances in Optical Coherence Tomography
    - Faster units with better resolution
    - Swept Source OCT
    - OCT angiography
  - Topographic approach to analysis
  - Modifying how the results are displayed
    - Flipping the TSNIT allows easier recognition of loss
    - Improved Structure-Function
  - 50% of ganglion cells in central 4.5mm area
    - explains why central testing important
- Visual fields
  - Role of central fields in diagnosing and monitoring glaucoma
    - 10-2 pattern with  $2^{\circ}$  spacing
    - 24-2 pattern with  $6^{\circ}$  spacing
    - Test pattern combining 24-2 and 10-2 points - 24-2C
  - Faster tests – SITA Faster
  - Structure –Function
    - Incorporating fields with imaging results
    - Incorporating fields with retinal photography
  - Virtual Reality (VR) perimeter in development
    - When will it allow patients to test at home

Understanding our patient's IOP  
over 24 hours will allow us to  
precisely modulate therapy

IOP tends to be highest during nocturnal hours though not clear how  
clinicians can utilize this information

# Precision Medicine

- Nationwide Precision Medicine Initiative
  - Prevention and treatment strategies
    - Launched by President Obama in 2015 to search for creative solutions
  - Use science to enhance care
    - Genetics, proteomics, technologies including those in diagnosis

# The Genetics of Glaucoma

- Glaucoma now viewed as a complex genetic disease
- Family history plays a role in the screening process
- Genetic testing may one day be important
- Over 100 genes identified that cause either glaucoma or elevated IOP
- 40% of newly diagnosed OAG have first-degree relative
  - Parent or sibling
- 23 and me – genetic typing

# Intraocular Pressure (IOP)

- IOP currently monitored in office using isolated daytime measurements
- Current standard of care for glaucoma management includes measurement every 3-4 months (q. 6 mos for OHTN) during daytime hours
  - Even for patients with severe disease
- Treatment decisions often based upon single IOP readings
- However, we have known that IOP fluctuate throughout the day and night
  - Vary both in short-term (day to day) and long-term (over months to years)
- Recognizing that IOP as the primary modifiable risk factor may vary has led to a host of better ways to capture diurnal and nocturnal IOP variability

# Intraocular Pressure (IOP)

- Spikes in IOP often occur outside of office hours
  - Missing peak may lead to misdiagnosis or undertreatment
    - Individuals labeled as normal tension glaucoma may have higher IOP
- Reasons for IOP fluctuation are unknown
  - Speculation includes position, episcleral venous pressure, hormone levels and nitric oxide production
    - IOP higher in supine position
    - Sleeping in lateral decubitus position
    - Correlation b/w cortisol levels and IOP during psychological stress

# Intraocular Pressure (IOP)

- Patient-specific data outside of the office has been a powerful tool in treatment and decision making for diagnosis and management of other chronic conditions
  - Cardiovascular medicine – ambulatory blood pressure monitoring
- Amplitude and frequency of IOP fluctuations over 24-hours is difficult to predict based upon in-office measurements
- Home tonometry may be a relevant tool
- Home tonometry may also be useful in telemedicine and minimize office visits or if elevated IOP noted, patients may be brought into the office earlier to modify therapy

# How Much Does the IOP Vary During a Day?

Can We Measure the IOP During the Day When Not in the Office?

# 24-Hour IOP Monitoring

- How do we evaluate IOP if we are only measuring it briefly in office?
- Three approaches to measure IOP over 24-hour period
  - Self tonometry
    - iCare
  - Permanent continuous IOP monitoring
    - Implantdata Eyemata
  - Temporary continuous IOP monitoring
    - Measures a marker of progression, not IOP variation
    - Sensimed triggerfish

# Home IOP Monitoring

- Devices have been developed for home IOP monitoring
  - Triggerfish (Sensimed) contact lens device approved by FDA in 2016
    - Challenges with patient use, reimbursement, and measurement methods led to instrument not available in the US
  - Rebound tonometry with iCare tonometer
    - Fairly accurate reproducibility
    - iCare home tonometer approved by FDA in 2017
      - As an adjunct to routine clinical IOP monitoring for self use at home with doctor's prescription
      - Used after short training session for several days several times per day
- Role of home monitoring is to detect IOP variations despite in-office measurements that consistently are at target goal
- Still home monitoring not widely used which begs question should it become routine in cases of progression?

# Self Tonometry

- Patients would monitor their IOP over time with easy-to-use devices
- Easiest approach in regard to continuous monitoring
- Adapt current device such as Noncontact tonometer or Rebound tonometer
- May be difficult for some patients to perform
- Not easy to obtain 24-hour IOP
- Icare Home tonometer

# Temporary Continuous IOP monitoring Triggerfish Contact Lens IOP Device

- A soft, disposable silicone contact lens with an embedded micro-sensor that captures circumferential changes near the corneoscleral junction
- Lens worn for 24 hours and discarded
- Consists of a clear, silicone contact lens ringed by a strain gauge and a microprocessor and antenna that transmits data to an external receiver
- The gauge continuously monitors the shape of the cornea
- The microprocessor is powered by an induction loop which uses a magnetic field around the eye to generate the tiny amounts of required electricity
  - Induction loops are also used to power hearing-aid implants
- Triggerfish is measuring ocular volume change over a 24 hour period
- Ocular volume change is associated with the eyes ability to handle increases in pressure as they are related to tissue elasticity and is related to risk of progression
- FDA Approved but never marketed in US

# Permanent Continuous IOP Monitoring

- Provide daytime and nighttime IOP measurements through self-contained implant
- Accessed remotely with wireless technology
- Ideal for advanced glaucoma
- Would not be measuring the surface but rather taking IOP measurements directly inside the eye
  - Subject to less noise
- Incorporates telemetric IOP device with IOL
- Digital signal sent from IOL to external device
- Alarm raised at certain point
- Long-term stability is unknown

Artificial Intelligence (AI),  
Deep or Machine learning

# Artificial Intelligence or Deep Learning

- Can a computer surpass a clinician in diagnosing glaucoma or recognizing change?
  - AI is used by dermatology to detect skin cancers
- Initially computers used pattern recognition with key features programmed in
- Artificial intelligence (AI) is now the way computers are developed to perform a task
- Has been successful in prediction of diseases

# Artificial Intelligence (AI)

- Simulation of human intelligence by machine
- Combines large amounts of data with fast and intelligent algorithms
- Neural network is an information processing unit inspired by the way the brain processes information
- Consists of a large number of interconnected units (like neurons) suitably trained to solve specific tasks
- With deep learning (AI), you did not need to program features but rather need training examples
- The computer then identifies the key features statistically
- The computer improves detection with large datasets

# Artificial Intelligence (Deep Learning)

- Recent paper performed by google scientists examining diabetic retinopathy used 9963 images from 4997 patients to train a computer
  - 97.5% sensitivity with 93.4% specificity
- AI could be used a screening tool with clinicians examining failures
  - Can tie to telemedicine

# FDA Approved AI Software for Devices

- 14 approvals to date
  - 11 Radiology
  - 2 to detect atrial fibrillation
  - 1 for ophthalmic devices
    - Diabetic detection – IDx-Rx fundus camera software

# Home VR Visual Field Testing

- Home field testing using VR goggles
  - More tests make tests more reliable - concept of home testing
- Provide feedback on each trial
  - track high interest areas with denser testing
- Provide automated training

# 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**

# Glaucoma Therapy Update - Current Issues

- Issues we are currently dealing with
  - Prior authorization
    - Approved 90% of time
    - Some optometry practices do not have infrastructure to manage prior auth
    - Companies like PARx help
- Will the government get involved with cost of medications?
  - System with the PBMs is crazy
  - Negotiated rebates paid by drug manufacturers
- Costs when medications are not covered can be large
- In the US, we pay more for medications
  - Will anything like Medicare for All ever happen?
    - Can it include a mechanism to allow newly approved drugs to be reimbursed?

# Glaucoma Therapy Update

- Therapy
  - Generics
  - Do glaucoma medications work around the clock
    - FDA does not require 24-hour testing
    - Timolol and brimonidine do not work during nocturnal hours
  - Fixed combination agents have moved up to 2<sup>nd</sup> line agents
    - Rocklatan, Simbrinza, Combigan, Cosopt (generic)
  - SLT as first-line therapy
    - LIGHT study has given this new impetus
  - Glaucoma surgical devices such as iStent inject, Hydrus
    - MIGS type devices
    - Now account for approximately 58% of glaucoma surgical costs
  - Recently approved medications
    - Vyzulta, Rhopressa, Rocklatan
  - Newly approved drug delivery device
    - Bimatoprost SR
  - MIGS reimbursement – will there be a fee reduction in 2022?
  - Neuroprotection – when will it happen?

# Glaucoma Therapy Update

- In the future, like cardiologists we may discuss with our patient's smoking cessation, altering diet, weight loss, and increased physical activity as additional therapies for glaucoma
- Most of the new therapies will revolve around surgical devices with reduced complications or drug delivery directly via some form of injection (doctor) or insertion (patient)
  - Still, we have relatively three new medications

# Significant changes in the glaucoma market landscape in recent years

- The arrival of a generic latanoprost in 2011 significantly altered the market landscape.
  - While branded products still contribute >60% of revenue, <40% of IOP-lowering drops are branded products
  - Increasing hurdles for reimbursement
- Arrival of compounding pharmacies
- Arrival of MIGS
  - First approval of iStent (Glaukos) in 2012
  - Approval of XEN (Allergan) in Nov. 2016
  - Instent inject and Hydrus in 2018

# Glaucoma Therapy Update

- 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

# 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 fluorophosphate
  - 1957 echothiophate iodide (Phospholine iodide)
- 1904 Hyperosmotic agents
  - Hypertonic saline, urea, mannitol, glycerol
- 1954 Carbonic anhydrase inhibitors –acetazolamide (Diamox)
- 1955 Adrenergic agonists – topical epinephrine

# 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

# 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)

# Bimatoprost SR (Durysta)

- Allergan
- Sustained release bioerodible implant that lasts 4-6 months with similar efficacy to eyedrops
- Small disolvable 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?