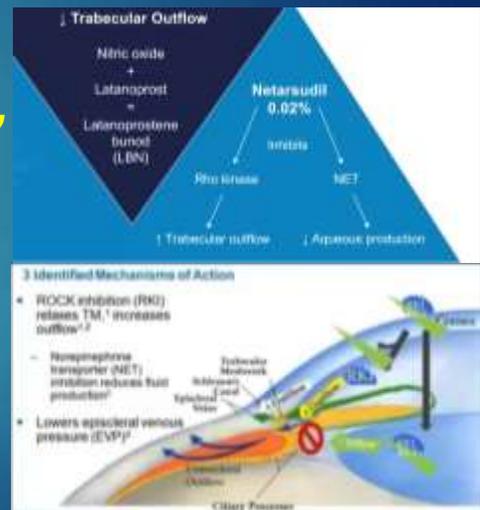


New Drug Delivery Systems In Glaucoma

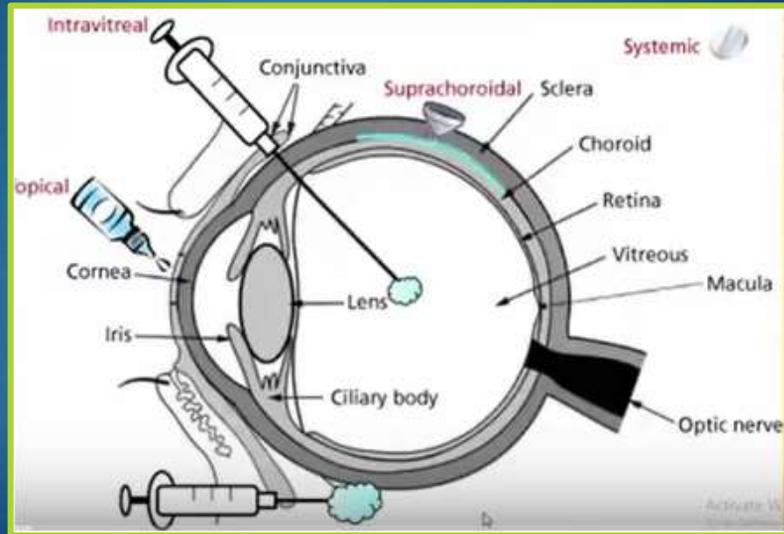
BY :
HANY ELIBIARY, M.D.

New Medications (2018)

- ▶ Nitric oxide donators:
“*Latanoprostene bunod*”
- ▶ Rho kinase inhibitors:
“*Netarsudil*”



Do we need them??



Do we need them??

- ▶ Reduction of IOP is still the **standard therapy** for glaucoma.
- ▶ Excellent drugs but need to be **applied** frequently & correctly.
- ▶ Less than **50%** of patients can **adhere properly** to **1** medication.

*“Sorry Doctor but I forgot to
put my medication last
Night”*

Problems with eyedrops:

- ▶ **Inefficient:** 25-50 ul/ drop in a 7ul space.
- ▶ Less than 1% of applied drug reaches AC (barriers).
- ▶ Systemic absorption.
- ▶ Limited **residence time** on eye .
- ▶ **Pulsatile** delivery.
- ▶ Needs **manual** dexterity.
- ▶ **Ocular surface** signs and symptoms.
- ▶ May not reach target tissue in therapeutic doses
“ **Neuroprotective drugs**”

New Drug Delivery Systems:

- ▶ Independent on / or improve **patient adherence**.
- ▶ Reduce side effects.
- ▶ Increase efficacy
- ▶ Reach target tissues in a better way.
- ▶ Open the field for drugs not suitable for conventional routes of administration.
“**eg; Neuroprotective drugs**”

Neuroprotective Drugs:

▶ **I- Small molecules:**

Statins, memantine , progesterone , cyclosporin A

▶ **II- Large molecules :**

Neurotrophic proteins as **GDNF & CDNF**

- large size
- enzymatic susceptibility
- systemic side effects

thus:

- failure to cross cornea & blood brain barriers
- Rapid degradation.

Neuroprotective Drugs:

- ▶ **Transfection of retinal cells** with viral or non viral particles carrying genes of interest.
- ▶ Transplantation of **stem cells** in the retina engineered to produce the required neurotrophic factor.
- ▶ Under trial: **CNTF implants** for RP.

Prolonged Drug Delivery: (History)

▶ Timolol gel :

- Once a day
- Discomfort & blurring

▶ Ocuserts :

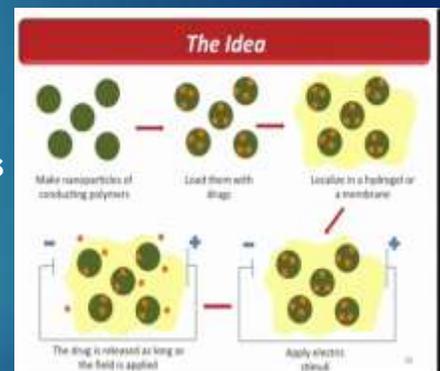
- Pilocarpine once a week
- Timolol
- Discomfort & frequent dislodgement



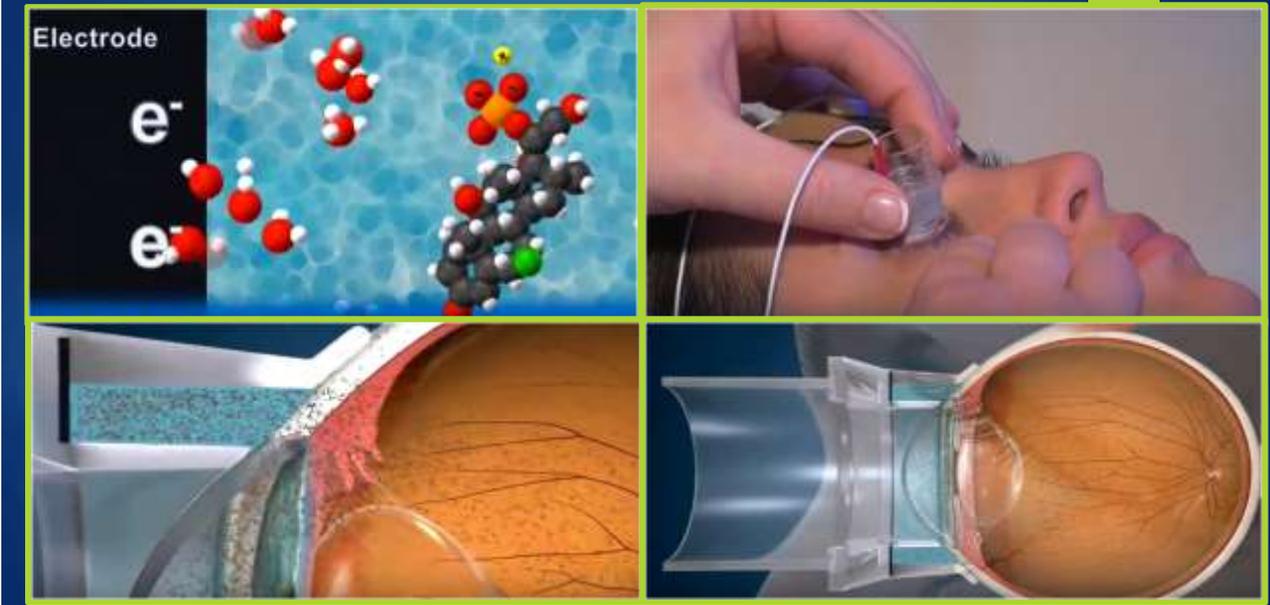
Prolonged Drug Delivery:

▶ Liposomes & Nanosphere delivery:

- To attach the drug to a carrier to improve its ocular penetration & prolong its residence time in the target tissue.
- May reduce number of required applications of certain drugs to once a day
- Carrying particles may be positively or negatively **charged** to control penetration in the eye.
- **Electrically Controlled Drug Delivery**



Eyegate (Iontophoresis)



Prolonged Drug Delivery:

► Gel forming drops:

- Pentablock made of **5 polymers** which can be coupled with a variety of glaucoma medications.
- **Thermal responsive hydrogel** sheds water at body temp to change from liquid to gel form.
- Eye drops instilled change to **a soft non-washable gel** at body temp under lower lid.
- **Opaque , non degradable** & retained in inferior fornix and may release drug for **4-6 m.**
- **Manually removed** and replaced.
- **UPMC** : brimonidine once/month.

Reservoir Systems:

- ▶ Systems to deliver medications predictably over time are not totally new to Ophthalmology .
- ▶ **Gancyclovir** (Ultrisert 1990)
- ▶ **Ozurdex** (6m) , **Retisert** (1m) for uveitis
- ▶ In the eye , the **limited available space** accommodates only small sized delivery systems and hence small amount of drug so the drug must be:
 - **potent** in small doses
 - **not rapidly metabolized**

Reservoir Systems:

- ▶ **Drug releasing CL:**
 - Continuous wear
 - Discomfort
 - Corneal problems
- ▶ **CL like devices:**
"TODD"



Reservoir Systems:

Amorphex Therapeutics

TODDD™

- Topical plastic device* inserted and concealed under the eyelid
- Worn continuously for weeks and then replaced
- Drug is polymerized into the plastic
- Drug molecule unaffected by this proprietary* process
- Drug releases slowly over many weeks



Punctal Plugs:

► Ocular Therapeutics:

- Hydrogel implants (anti-infective, steroids, etc.)
- Travoprost : OTX-TP2 (2 -3 m drug delivery)
- Finally resorbs & pass NLD

► Mati Therapeutics:

- Latanoprost



Punctal Plugs:

► Limitations:

- **FB** : irritation, might move or fall
- Difficult to see by patient
- Need **preservative** like BAK to prevent bacterial build up
- Should maintain **constant rate** of drug delivery



Suprachoroidal Injection:

To utilize the potential **suprachoroidal space** as a drug reservoir

The suprachoroidal space provides a novel approach with possible treatment opportunities*



Targeted

The back of the eye is the location of many irreversible and debilitating visual impairments!



Expandable

The suprachoroidal space can extend in a volume-dependent manner, diffusing fluid into the back of the eye, then naturally return to its original thickness.



Bioavailable

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug.

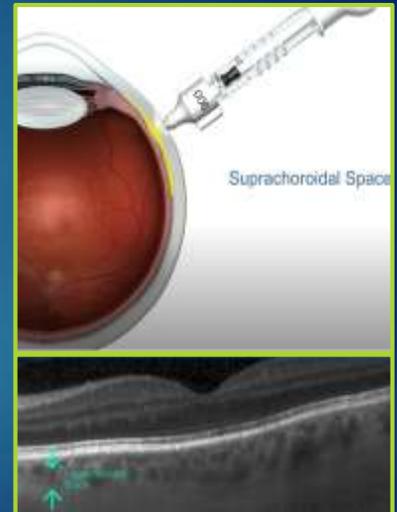


Compartmentalized

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non diseased tissues!

Suprachoroidal Injection:

- ▶ Special injectors and microneedles are designed for safe injection
- ▶ Enhanced depth OCT is useful for imaging and monitoring of the choroid
- ▶ Superior in Uveitis and macular edema
- ▶ Glaucoma ????
- ▶ Neuroprotective drugs ????



Implants & Injectables:

- ▶ Subconjunctival implants:
e.g; Durasert (pSivida) bioerodible latanoprost implant injected by 25g needle SC.
- ▶ Scleral implant:
(Euclid systems) 2x4mm scleral collagen implant releasing latanoprost for up to 6m.
- ▶ A C implants:
 - latanoprost (Icon bioscience)
 - Travoprost
 - Bimatoprost

Implants & Injectables:

OTX-TIC is designed to be a bioresorbable intracameral implant containing micronized travoprost that is injected into the anterior chamber of the eye and is intended for patients with glaucoma with a target duration of drug delivery of four to six months. Preclinical studies in beagles have demonstrated an acceptable safety profile, maintenance of drug levels in the aqueous humor and a sustained lowering of intraocular pressure. OTX-TIC is designed to directly address compliance issues by delivering travoprost over the course of several months with a single implant.

May 2018, the first patient was treated with OTX-TIC in a Phase 1, multi-center, open-label, prospective, proof-of-concept clinical trial.

Envisia Therapeutics Releases Interim ENV515 (Travoprost XR) Phase 2 Data Demonstrating 11-Month Duration-of-Action After a Single Dose in Patients With Glaucoma

Implants & Injectables:

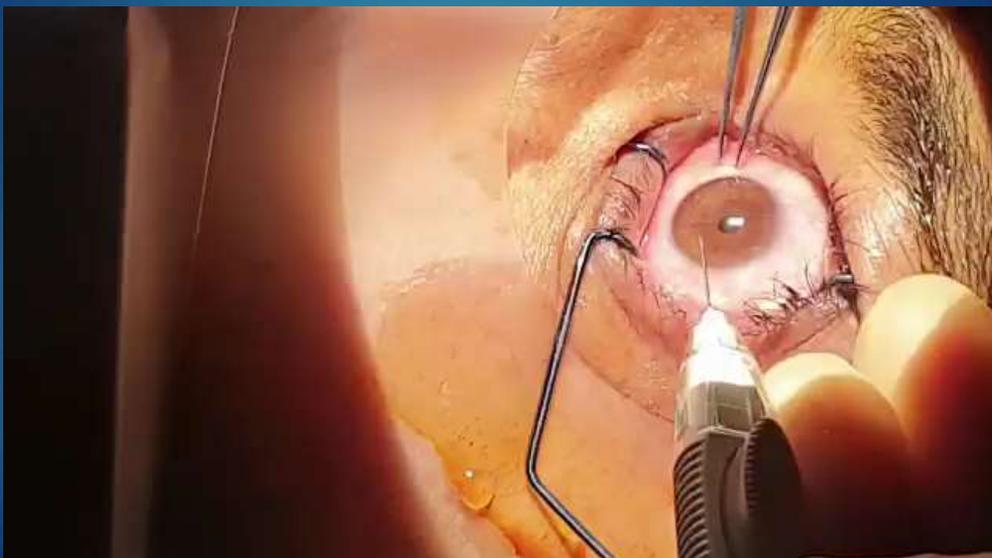


OTX-TIC resides in iridocorneal angle

Implants & Injectables:



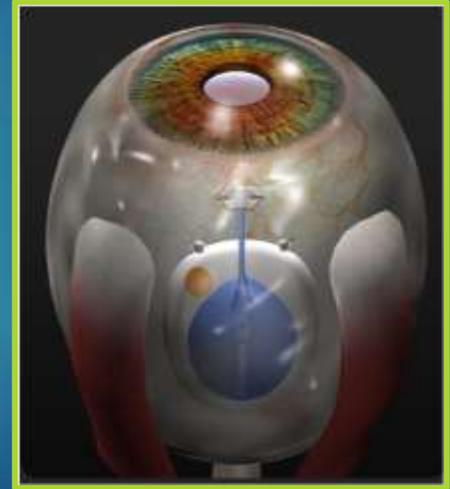
Implants & Injectables:



Drug Pumps:

► Ophthalmic Micropump (Replenish, Inc.):

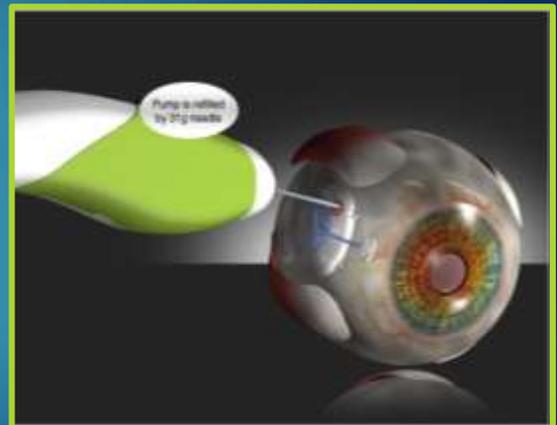
- Fixed on sclera
- Holds 6 – 12 m supply of drug
- Programmed to dispense **nanoliter-sized** doses of drug at **set** times
- **One way valve** to prevent reflux
- Flow **sensor**



Drug Pumps:

► Ophthalmic Micropump (Replenish, Inc.):

- Refillable with **31g needle**
- **Wireless** recharging
- **Wireless** reprogramming
- Flow sensor (feed-back)
- Optional cannula with pars plana clip for **intra-vitreous** drug delivery



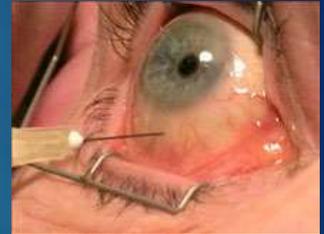
New Long-acting Drugs:

► Anecortave acetate :

- *Anecortave acetate* is a relatively new drug that has been shown in case series and clinical trials to effectively lower intraocular pressure (IOP) for up to several months following delivery into the subtenons space via an anterior juxtasceral depot injection.

- *Anecortave acetate* is a cortisol derivative that lacks both glucocorticoid and mineralocorticoid activity. "It is not anti-inflammatory, does not raise intraocular pressure, and does not cause cataracts.

- The mechanism by which *anecortave acetate* lowers IOP remains unclear, but it probably facilitates outflow. This molecule is relatively insoluble in the subtenons space, and this may contribute to its extended duration of action.



Thank You

Thank You