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## Seeing your way to diagnosing and treating pain

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## Financial Disclosures For Marc R Bloomenstein, OD, FAAO

- |   |  |  |
|---|--|--|
| <ul style="list-style-type: none"> <li>■ Allergan-Speaker/Consultant</li> <li>■ Avellino-Consultant</li> <li>■ Azura-Consultant</li> <li>■ Bausch &amp; Lomb-Speaker/Consultant</li> <li>■ Bruder-Consultant</li> <li>■ Dompe-Speaker/Consultant</li> <li>■ EyeVance-Consultant</li> <li>■ Harrow-Speaker</li> <li>■ Iveric-Consultant</li> </ul> | <ul style="list-style-type: none"> <li>■ LENZ-Consultant</li> <li>■ Ocuphire-Consultant</li> <li>■ OcuSOFT-Consultant</li> <li>■ Olleyes-Consultant</li> <li>■ Oyster Point-Speaker/Consultant</li> <li>■ Novartis-Speaker/Consultant</li> <li>■ Reichert-Consultant</li> <li>■ Sydnexus-Consultant</li> <li>■ Sight Science-Speaker/Consultant</li> </ul> | <ul style="list-style-type: none"> <li>■ Visus-Consultant</li> <li>■ STAAR Surgical-Speaker/Consultant</li> <li>■ Sun-Speaker/Consultant</li> <li>■ Tarsus-Speaker/Consultant</li> <li>■ Thea-Consultant</li> <li>■ Topcon-Consultant</li> </ul> |
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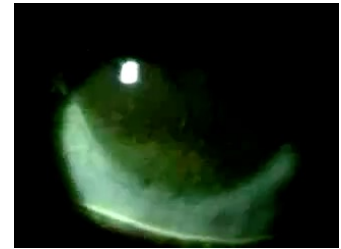
All financial relationships have been mitigated.

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## Neurotrophic keratitis



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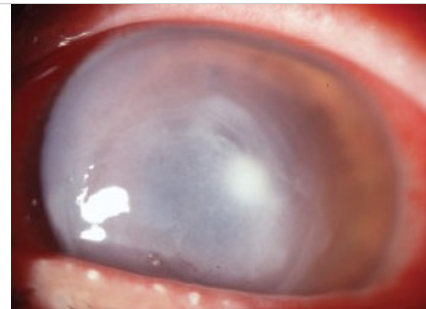
## Monday Morning Patient

- 71 yo Caucasian female
- 18-month history of dry eye, has seen 8 physicians
- Relatively sudden onset – shortly following uncomplicated cat sx, gradually worsening
- Primary symptoms: constant burning, moderate photophobia
- Treated with Restasis, Xiidra, ATs, Warm compresses, plugs, steroids, LipiFlow
- **"NOTHING HELPS!!"**



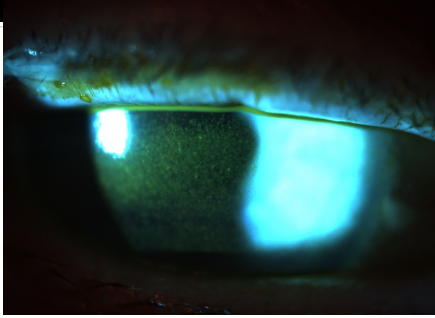
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## What we expect to see....



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What we expect to see....



7

What we actually see



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## Corneal Innervation

- Cornea is most highly innervated region in the body
- 21,668um/mm<sup>2</sup>
- 7000 nerve terminals per sq mm<sup>1</sup>
- Vast majority (70-80%) unmyelinated

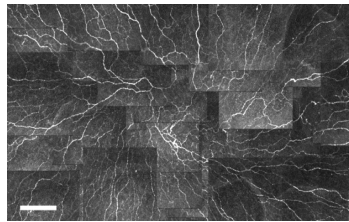


Photo: Cornea: Peter D. & McIlwain (2010) Dec 2010

1) Muller L.J. Exp Eye Res. May 2003  
2) Stepp MA. Gila. Jun 2017.

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## Neuropathic pain & dry eye

**Hyperalgesia**-An increased sensitivity to feeling pain and an extreme response to pain. Ex. wind

**Allodynia**- pain due to a stimulus that does not normally provoke pain (feather touch)

**PhotoAllodynia**- Photophobia

Galor A, Moelin HR, Lee C, Rodriguez A, Felix ER, Sarantopoulos KD, Levitt BC. Neuropathic pain and dry eye. Ocul Surf. 2016 Jan;16(1):31-44. doi: 10.1016/j.jtos.2017.10.001. Epub 2017 Oct 12. PMID: 29031645; PMCID: PMC57756672.

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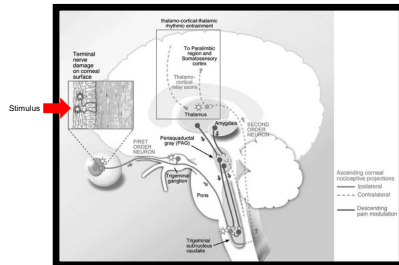
Photophobia  
Redness  
Tearing  
Burning

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Central vs peripheral

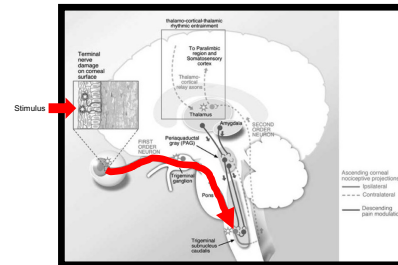
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## Corneal sensory pathway



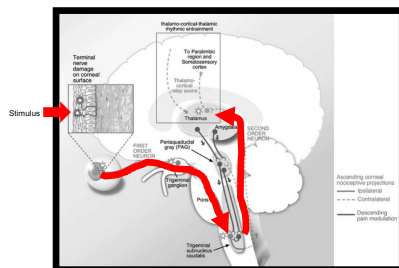
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## Corneal sensory pathway



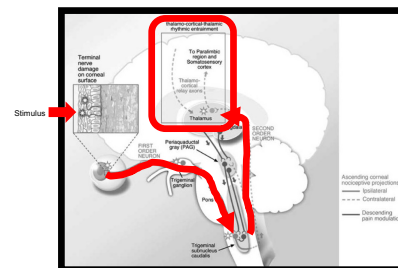
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## Corneal sensory pathway



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## Corneal sensory pathway



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<https://www.youtube.com/watch?v=ks5QzQdH3I>

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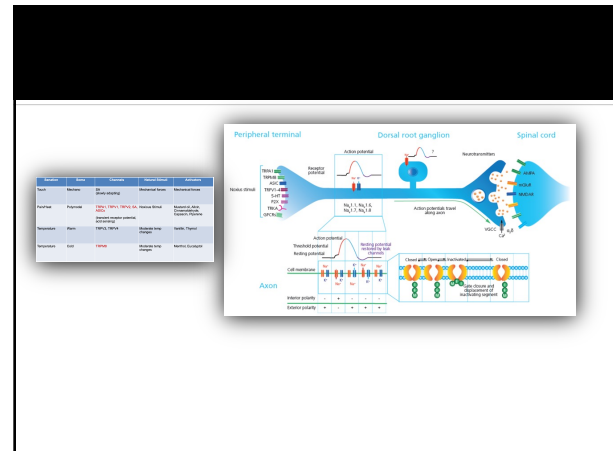
TRP channels

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## Corneal Sensory Receptors

Sensation	Soma	Channels	Natural Stimuli	Activators
Touch	Mechano	SA (slowly adapting)	Mechanical forces	Mechanical forces
Pain/Heat	Polymodal	TRPA1, TRPV1, TRPV2, SA, ASICs (transient receptor potential, acid sensing)	Noxious Stimuli	Mustard oil, Ailicin, Cinnamaldehyde, Capsacin, Piperene
Temperature	Warm	TRPV3, TRPV4	Moderate temp changes	Vanillin, Thymol
Temperature	Cold	TRPM8	Moderate temp changes	Menthol, Eucalyptol

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## Central vs peripheral

Most common ocular symptom:

1. Burning 0.73
2. Photophobia 0.72
3. Tearing 0.67
4. Redness 0.28

Kim J, Yoon HJ, You IC, Ko BY, Yoon KC. Clinical characteristics of dry eye with ocular neuropathic pain features: comparison according to the types of sensitization based on the Ocular Pain Assessment Survey. BMC Ophthalmol. 2020 Nov 18;20(1):456. doi: 10.1186/s12886-020-01733-1. PMID: 33208127; PMCID: PMC7672944.

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## TRP channels

“AR-15512 has been shown to increase the activity of corneal cold thermoreceptor nerve fibers and tear production”

<https://aeriepharma.com/rd/ocular-surface-disease/ar-15512/>

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## Neuropathic pain & dry eye

“Control / eliminate inflammation and then use your regenerative therapies. The inflammation is what hypersensitizes the nerves in the first place”

Scott Hauswirth, OD

[https://www.youtube.com/watch?v=6VZAqNN\\_JoE](https://www.youtube.com/watch?v=6VZAqNN_JoE)

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## Neuropathic pain & dry eye

“Don’t prescribe stuff that continues to be an irritant to patients - if they don’t tolerate Restasis/Cequa/Xiidra or whatever don’t continue to push it, find an alternative”

Scott Hauswirth, OD

[https://www.youtube.com/watch?v=6VZAqNN\\_JoE](https://www.youtube.com/watch?v=6VZAqNN_JoE)

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## Optometric indications

- For ocular pain, process is usually acute
  - Need for pain relief for only 24-36 hours or less
- Most often, topical only may be enough
  - Cycloplegia
  - Topical NSAIDs
  - Bandage

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## Optometric Indications

- Corneal/conjunctival trauma
  - abrasion
  - foreign body
- Traumatic hyphema
- Surgery
  - Refractive
  - Cataract
  - Retinal

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## Before treatment

- Determine etiology of pain and treat **before** beginning pain management!
- Nature of pain:
  - FOLDAR: frequency, onset, location, duration, association, relief
  - Severity
- What have you done already that helps/doesn't help?

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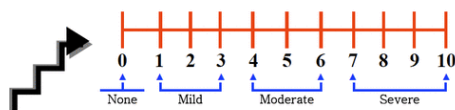
## Before treatment

- Assess the level of pain **before** initiating treatment
  - Numerical scale
  - Pictures: Wong-Baker
- Make sure level is **decreasing** with treatment

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## Before treatment

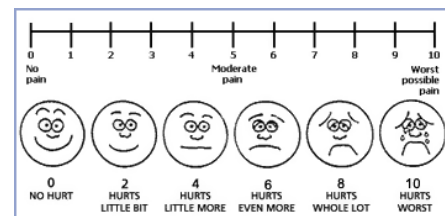
- Numerical Scale



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## Before treatment

- Wong-Baker Pain Classification Scale



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## Before treatment

- Medical history
  - pregnancy, alcohol use, anti-depressants
- Drug history
  - CNS medications, coumadin, digoxin, **OTC's**, etc.
- Allergy history
  - Esp. ASA etc.

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## Topical Pain Relievers

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## Topical Pain Relievers

- Cycloplegics
  - Block acetylcholine, a stimulatory neurotransmitter of the ANS
  - Cause pupillary dilation and relaxation of ciliary body
  - Relaxation of ciliary spasm causes pain reduction as well as stabilizes the blood-aqueous, decreasing inflammation

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## Topical Pain Relievers

- Cycloplegics
  - Tropicamide: 0.5-1%; qid; 4-6 hrs
  - Cyclopentolate: 0.5, 1, 2%; tid; 2-24 hrs
  - Homatropine: 2, 5%; bid-qid; 1-3 days
  - Scopolamine: 0.25%, bid, 3-7 days
  - Atropine: 0.5,1,2%; bid-tid; 6-12 days

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## Topical Pain Relievers

- NSAID's
  - Inhibition of prostaglandin synthesis by blockage of cyclooxygenase (COX)
  - Classic Triad effect
    - Reduced inflammation
    - Maintained pupil dilation
    - Induced analgesic effect

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## Topical Pain Relievers

- Non-steroidal Anti-inflammatory Agents
  - Ketorolac (Acular): 0.5%; qid
  - Diclofenac (Voltaren): 0.1%; qid
  - Bromfenac (Prolensa): 0.07%; QD
  - Bromfenac (Bromsite): 0.075% Bid
  - Nepafenac (Ilevro): 0.3%; QD
  - Flurbiprofen (Ocufen): 0.03%
  - Suprofen (Profenal): 1%
- Steroid options

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## Durezol (difluprednate 0.05%)

- First steroid to receive an indication for postoperative pain management
  - Also for postoperative inflammation
- FDA approved June 2008, available early 2009
  - Sirion Therapeutics
  - Acquired by Alcon March 2010
  - QID starting day after sx
- ≈\$100 per 5 ml

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## Lotemax 0.5% Ophthalmic Ointment

- Indications
  - Treatment of Post Operative Pain and inflammation following ocular surgery
- ½ inch ribbon qid x 2 weeks starting day after surgery

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## Lotemax 0.5% Ophthalmic Ointment

- In 2 studies of 805 patients:
  - less post-operative inflammation at post op day 8 vs. v
  - High 78%

Resolution of Anterior Chamber Cells and Flare and Pain at Visit 5: Integrated Intent-to-Treat Population<sup>2</sup>

	Lotemax ointment (n= 404)	Vehicle (n= 401)	Difference (95% CI) P value
Complete resolution of anterior chamber cells and flare	112 (27.7%)	50 (12.5%)	15.3% (9.6%, 20.9%) <0.0001
Grade 0 (no) pain	305 (75.5%)	173 (43.1%)	32.4% (25.7%, 39.0%) <0.0001

Lotemax, lotepredniol etabonate; CI, confidence interval.

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## Lotemax 0.5% Ophthalmic Ointment

- Contraindications:
  - Viral disease of cornea/conj (HSV), mycobacterial or fungal infection of eye
  - Should not be used in children
    - May interfere with amblyopia therapy by hindering ability to see out of operated eye
- Adverse effects:
  - AC reaction (25%): conjunctival hyperemia, corneal edema, eye pain (4-5%); HAs (1.5%)
  - IOP increased > 10 mm in 3 pts
    - Check IOP after 10 days of use

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## Diluted proparacaine?

- Small Canadian study evaluated 0.05% (or 1/10<sup>th</sup>) diluted proparacaine for corneal injuries
  - Proparacaine arm had significant improvement in pain reduction vs. AT's
    - No ocular complications
    - No delayed wound healing

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## Proparacaine in ER? Really?

..... 2010 Sep;12(5):389-96.

**Dilute proparacaine for the management of acute corneal injuries in the emergency department.**

[Garcia J, Rodriguez J, Gomez J, Rodriguez J, Rodriguez J.](#)

### CONCLUSION:

Dilute topical proparacaine is an efficacious analgesic for acute corneal injuries. Although no adverse events were observed in our study population, larger studies are required to evaluate safety.

[Acad Emerg Med.](#) 2014 Apr;21(4):374-82.

**Topical tetracaine used for 24 hours is safe and rated highly effective by patients for the treatment of pain caused by corneal abrasions: a double-blind, randomized clinical trial.**

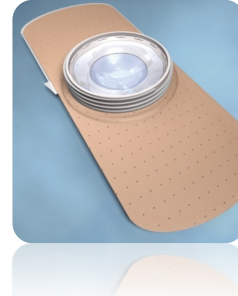
[Waldman N, Dersie JK, Herbison P.](#)

### CONCLUSION:

Topical tetracaine used for 24 hours is safe, and while there was no significant difference in patient VAS pain ratings over time, patient surveys on overall effectiveness showed that patients perceived tetracaine to be significantly more effective than saline.

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## Contact Lens or Shields



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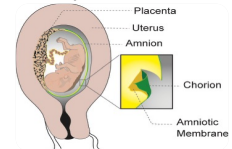
Wet or Dry...

## Amniotic Membrane

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## Amniotic Membrane

- Amniotic membrane is the inner most lining of the placenta (amnion) and shares the same cell origin as the fetus
- Contains cytokines and growth factors
  - Anti-Inflammatory (protease inhibitors)
  - Anti-Angiogenic
  - Aids in rapid wound healing and re-epithelialization
  - Anti-Scarring

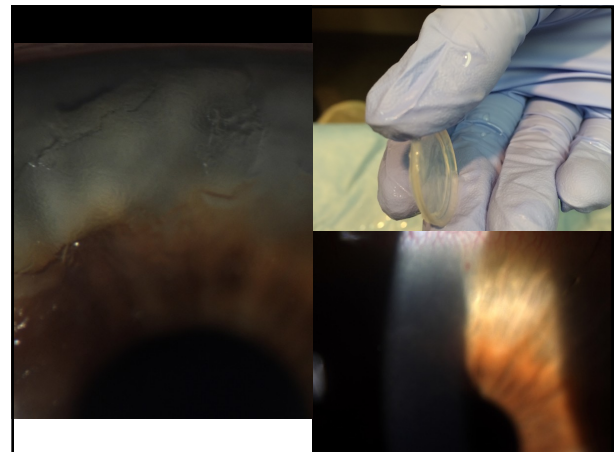


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**Cryopreserved amniotic membrane is a biologic therapy that can:**

- Promote regenerative healing
- Reduce inflammation
- Minimize scar formation
- Inhibit angiogenesis
- Minimize pain

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Ocul Surf. 2018 Jan;16(1):132-138. doi: 10.1016/j.jos.2017.10.003. Epub 2017 Oct 13.

**Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain.**

Morkin M<sup>1</sup>, Hammish P<sup>2</sup>

Author information

**Abstract**

**PURPOSE:** Treatment of neuropathic corneal pain (NCP) remains intricate, and involves a long-term combined multistep approach. The self-retained cryopreserved amniotic membrane (PROKERA<sup>®</sup>, Bio-Tissue, Miami, FL) has been utilized for multiple ocular surface disorders. We evaluate the efficacy, safety, and tolerability of ProKera<sup>®</sup> Slim (PKS) and ProKera<sup>®</sup> Clear (PKC) in the treatment of NCP.

**METHODS:** Retrospective case series of 9 patients who received PKS/PPKC for the acute treatment of NCP. Patient demographics, prior therapies, clinical examination, duration of PKS/PPKC retention, changes in pain severity, corneal subbasal nerve density and morphology by in vivo confocal microscopy (IVCM, HRT3/RCM, Heidelberg Engineering, Heidelberg, Germany), and adverse events were recorded.

**RESULTS:** PKS/PPKC were placed in 10 eyes of 9 patients. Pain severity improved by 72.5 ± 8.4% (from 6.3 ± 0.8 to 1.9 ± 0.6, scale 1-10,  $p = 0.0003$ ) after retention for 6.4 ± 1.1 days. Despite shorter retention for 4.0 ± 0.7 days in patients with ring dysesthesia (4 eyes) or premature implant disengagement (2 eyes), pain severity still improved by 63.1 ± 12.5% (from 6.8 ± 1.0 to 2.4 ± 0.9,  $p = 0.009$ ). During a follow-up of 9.3 ± 0.8 months, two patients reported recurrence of pain after 2.3 and 9.6 months respectively, treated effectively with additional PKS/PPKC. IVCM showed a 36.6 ± 17.6% increase in total nerve density, from 17,700.9 ± 1315.7 to 21,891.3 ± 2040.5  $\mu\text{m}/\text{mm}^2$  ( $p = 0.047$ ), while the fellow PKS/PPKC-untreated eyes did not show a significant interval change. Main nerve trunk and branch nerve densities were not statistically different. Dendritiform cell density decreased from 46.0 ± 8.2 to 32.0 ± 6.0 cells/ $\text{mm}^2$  ( $p = 0.01$ ).

**CONCLUSIONS:** PKS/PPKC provide a safe and effective treatment approach to achieve sustained pain control in patients with NCP.

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## Oral Analgesics

- Three main categories
  - Over-the-counter
    - Aspirin, tylenol, advil
  - Non-Narcotic prescription
  - Narcotic prescription

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## Over-The -Counter

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## Non-Narcotic Prescription

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## Oral Narcotic Agents

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## DEA Schedules

- Schedule I
  - High Abuse potential
  - No approved medical use
    - Only available for investigational use
  - Ex: MJ, LSD, heroin
- Schedule II
  - High Abuse potential
  - **Written prescription only with no refills**
  - Ex: amphetamines, cocaine, **hydrocodone**

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## DEA Schedules

- **Schedule III**
  - **Moderately high abuse potential**
  - **Written or telephone prescriptions with refills allowed**
  - **ex: Tylenol with codeine**
- Schedule IV
  - Moderate abuse potential
  - Written or telephone prescriptions with refills allowed
  - ex: phenobarbital

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## DEA Schedules

- Schedule V
  - Low abuse potential
  - No prescription needed
  - ex: Robitussin A-C (contains less than 100 mg codeine per 100 ml)

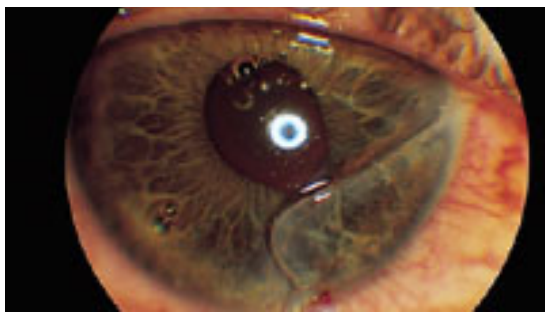
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## Case 1



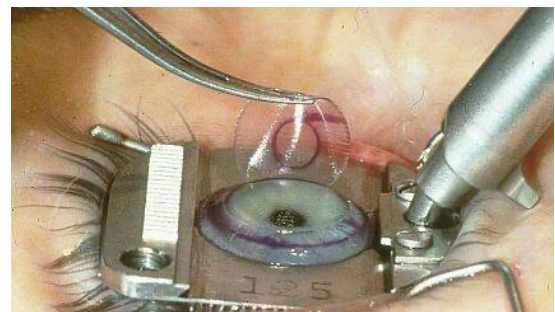
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## Case 2



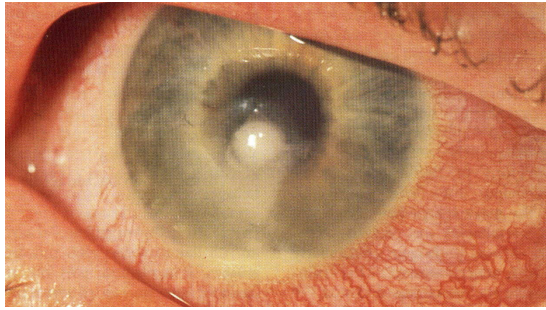
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## Case 3



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Case 4



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Case 5



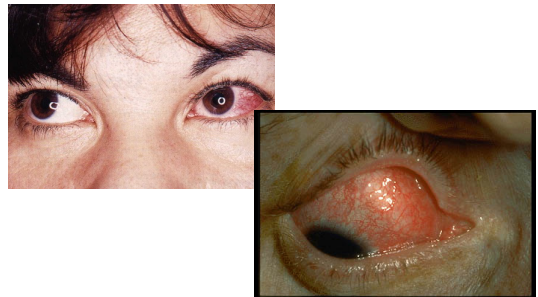
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Case 6



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Case 7



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Case 8



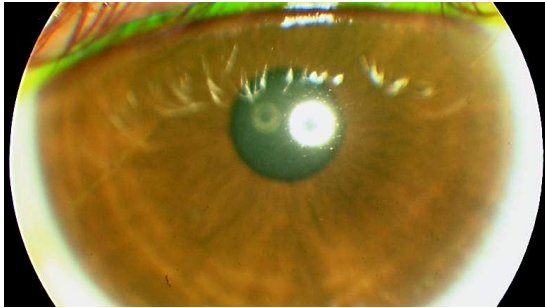
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Case 9



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## Case 10



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**Thank You!!!**

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