Off Label Uses of Common Medications

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Process of Approval
- Company submits New Drug Application (NDA) to FDA
  - Looking for safety and effectiveness for its intended purpose
  - If application is approved
    - Indications
    - Contraindications
    - Dosage
    - Administration schedules
- But.......
- FDA does not have authority to regulate the practice of medicine

Process of Approval
- Supplemental New Drug Application (SNDA)
  - To apply for new indications
  - Lag between submission and approval

Off Label Use
- Statistics
  - Literature indicates >50% of ophthalmic medications used off-label
  - Annual US market for off-label medication use is $44 billion

Off Label Use
- Use of a medication or product for a different indication, age group, dosage, or administration than approved by the FDA.
- FDA Recommendations
  - Good medical practice and the best interests of the patient require that physicians use legally available drugs according to their best knowledge and judgment
- Off Label Use
  - Responsible to be well-informed about product
  - Base its use on firm scientific rationale and on sound medical evidence
  - Maintain records of product’s use and effects
Off Label Use
• Once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

US vs. Caronia
• Xyrem (Orphan Medical)
  • Indicated for the treatment of narcolepsy and to reduce cataplexy attacks
  • Promotion of medication by pharmaceutical rep and physician
  • Caught on tape promoting its use for treatment of insomnia, fibromyalgia, restless leg syndrome, Parkinson’s disease, and multiple sclerosis, and in unauthorized patient populations

• Orphan Medical and physician (Gleason) pled guilty
• Caronia was acquitted of misbranding, but convicted of conspiracy to introduce a misbranded drug into interstate commerce
• Orphan Medical was bought by Jazz Pharmaceuticals
• Caronia conviction overturned, citing 1st Amendment rights
  • Specifically, Caronia, a pharmaceutical sales representative, promoted the drug Xyrem for “off-label use,” that is, for a purpose not approved by the U.S. Food and Drug Administration (the “FDA”). Caronia argues that he was convicted for his speech -- for promoting an FDA-approved drug for off-label use -- in violation of his right of free speech under the First Amendment
  • Gleason committed suicide
  • Final FDA approval

US vs. Caronia
• Oral antibiotics
• Topical antibiotics
• Topical cyclosporine
• Topical corticosteroids
• Topical NSAIDs
• Topical anti-virals
• Others

Doxycycline Indications
Treatment of Susceptible Micro-organisms
• Rickettsiae
• Mycoplasma pneumoniae
• Agents of lymphogranuloma venereum
• Bartonella bacilliformis
• Borrelia recurrentis
• Haemophilus ducreyi
• Pasteurella pestis and Pasteurella tularensis
• Bartonella spp.
• Bartonella henselae
• Escherichia coli
• Enterobacter aerogenes
• Shigella species
• Bacillus anthracis
• Diplococcus pneumoniae
• Staphylococcus aureus
• Neisseria gonorrhoeae and N. meningitidis
• Treponema pallidum and Treponema pertenue
• Listeria monocytogenes
• Clostridium species
• Fusobacterium fusiforme
• Actinomyces species
• Other gram- and gram-positive species
• Other anaerobic (Gram-negative and clostridia)
• Other aerobic (anaerobic, and clostridia)
• Other anaerobic species

Doxycycline Contraindications
• Hypersensitivity to drug/class/compound
• Children under 8 years old
• Pregnancy Category D
• Caution with photosensitization, GI upset, diarrhea
Oral Antibiotics

- Antibiotic vs. anti-inflammatory
- Sub anti-microbial dose
- Mechanism of Action
  - reduce inflammation via anti-collagenolytic, anti-matrix-degrading metalloproteinase, and cytokine down-regulating properties

Doxycycline

- Ophthalmic uses
  - Ability to accumulate in oil glands
  - Regulates lipase
  - Ideal for conditions with inflammation surrounding oil glands

Other Uses- Recurrent Corneal Erosion

- Matrix metalloproteinase (MMP)
  - Name for group of enzymes that break down the structure of the extracellular matrix
  - Gelatinase
    - Composed of MMP-9 and MMP-2
    - Degrades collagen type IV and VII and Laminin
    - all major components of BM
  - Elevated levels of MMP-9 and MMP-2 have been observed in tears of patients with RCE
    - Higher levels of MMP may dissolve old and newly forming BM
  - Doxycycline inhibits MMP

Doxycycline

- Dosage
  - 20-50 mg twice daily
  - Maintenance dose

Topical Antibiotics

- Ciloxan
- Vigamox/Moxeza
- Zymaxid
- Besivance
- Tobradex ST
- AzaSite
Topical Fluoroquinolones

**Vigamox/Moxeza**
- moxifloxacin HCl 0.5%
- Indications
  - Treatment of bacterial conjunctivitis by susceptible organisms
- Vigamox: TID x 7 days
- Moxeza: BID x 7 days

**Zymaxid**
- gatifloxacin 0.5%
- Indications
  - Treatment of bacterial conjunctivitis by susceptible organisms
  - Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1
  - Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7

**Besivance**
- besofloxacin 0.6% ophthalmic suspension
- Indications
  - Treatment of bacterial conjunctivitis by susceptible organisms
- Developed specifically for topical ophthalmic use
  - No widespread systemic, agricultural, or animal feed usage
  - Greatly reducing chance for resistance
  - Research shows some potential anti-inflammatory properties

Off Label Uses
- Corneal ulcers
- Corneal abrasions
- Empirical treatment of non-cultured ulcer
- Surgical prophylaxis of infection

Other Uses- Interface Keratitis
- Most sight threatening of interface disorders following LASIK
  - Rare but potentially devastating
  - Incidence:
    - Solomon et al 2003 – 0.03%
    - Moshirfar et al 2007 – 0.31%
    - Goev et al 2010 – 0.005% (71 eyes of 204,586 from 2002-2008)
  - Variety of organisms have been implicated
    - Staphylococcus
    - Pseudomonas
    - Atypical mycobacteria
    - Fungi
    - Acanthamoeba
    - HSV
    - Adenovirus

Infectious Keratitis
- Most common non-viral cause of infectious keratitis has evolved over time
  - More recently Methicillin-resistant Staph aureus has become more common in early postoperative period
  - Due to potential to develop resistance to fluoroquinolones
Infectious Keratitis

- Risk factors for IK
  - Blepharitis
  - Dry eye
  - Intraoperative epithelial defects
  - Excessive manipulation
  - Intraoperative contamination
  - Delayed postoperative re-epithelialization
  - Use of topical corticosteroids
  - Patients in health profession

Prevention

- Infectious lid disease and dry eye treated pre-operatively
- Intraoperative, strict adherence to aseptic techniques
- Lid scrub with povidone-iodine solution
- Use of different set of instruments for bilateral procedures
- Ensure sterile water being used to clean instruments
- Surgical prophylaxis

Tobradex ST

- Tobramycin 0.3% and dexamethasone 0.05%
- Indications
  - For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists
- Dosage
  - Instill one drop into the conjunctival sac(s) every four to six hours

Off Label Uses - Tobradex ST

- Anterior Blepharitis
  - Most common has inflammation and imbalance of normal lid bacteria
  - Red, irritated eyes
  - Burning/itching
  - Lid/lash debris
  - Tobradex ST QID x 2 weeks
  - Not specifically indicated for blepharitis
  - Concomitant therapy

AzaSite

- Azithromycin 1%
- Indications
  - for the treatment of bacterial conjunctivitis caused by susceptible isolates
- Dosage
  - Instill 1 drop in the affected eye(s) twice daily for the first two days and then 1 drop in the affected eye(s) once daily for the next five days

Off Label Uses - AzaSite

- Meibomian gland dysfunction / Blepharitis
  - Chronic obstruction and inflammation of meibomian glands
  - Interferes with microbial protein synthesis
  - 2008 Clinical Trial
    - Divided into 2 groups
      - Hot compresses twice daily x 10 minutes
      - 1 gtt BID OU x 2 days, then 1 gtt QD OU x 12 days
**Off Label Use- AzaSite**

- **Results**
  - 70% improvement in meibomian gland plugging vs. hot compresses alone
  - 44% of AzaSite users demonstrated no MG obstruction in at least 1 eye
  - 69% vs. 10% decrease in eyelid redness
- **Safety Profile**
  - Pregnancy Category B
  - Indication for patients > 1 year old

**Off Label Use- AzaSite**

- **Recurrent Corneal Erosion**
  - Inhibits MMP-9
  - BID x 2 weeks
  - QD x 1 month

**Lotemax Gel**

- **Indications**
  - Corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery
- **Dosage**
  - Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period.
- **Contraindications**
  - Contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures

**Lotemax Gel**

- **Muco-adhesive technology**
- **Dose Uniformity**
- **Low preservatives with 2 known moisturizers**

**Off Label Uses- Lotemax Gel**

- **Allergies**
- **Other ocular surgeries**
- **Dry Eye**
  - Induction therapy
  - Better penetration
  - QID x 2 weeks, then BID x 2-4 weeks

**Off Label Uses- Lotemax Ointment**

- **Indications**
  - Corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery
- **Dosage**
  - Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.
Off Label Uses - Lotemax Ointment

- Atopic dermatitis
  - Caused by variety of allergic reactions and autoimmune diseases
  - Contact with cosmetics, shampoos, hair care products

- Dry Eye
  - Induction therapy
  - Complementary with Restasis
  - QHS x 1 month

Restasis

- Indications
  - topical immuno-modulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca

- Contraindications
  - in patients with known or suspected hypersensitivity to any of the ingredients in the formulation

- Dosage
  - 1 gtt in affected eye Q12H

Off Label Uses - Restasis

- Inhibits activation of T-cell lymphocytes
  - T-cells play a central role in orchestrating various immune responses, including immunologic rejection of foreign tissue
  - Has no impact on IOP, wound healing, viral replication
  - Steroids?

- Vernal keratoconjunctivitis (VKC)
  - a seasonal form of allergic conjunctivitis
  - severe itching, redness, sensitivity to light, and discharge
  - VKC has the potential to lead to corneal ulcers, keratoconus, and permanent vision loss
  - Histopathological studies showed T-lymphocytes in the conjunctival papillae
    - CD4+ subset of lymphocytes is known to produce IL-2

Off Label Uses - Restasis

- Studies have proven that topical cyclosporine, with the correct formulation and concentration, will likely provide relief for both acute VKC and the recurrences of the disease
- VKC may be a chronic condition that requires long-term anti-inflammatory treatment
  - Decreased symptoms (91%), decreased clinical signs (68%)

Off Label Uses - Restasis

- Herpes Stromal Keratitis
  - not active viral infection but viral antigens initiating a T-lymphocytic destruction of the stroma
  - Studies show topical steroids effective
    - Concerns?
- May limit herpetic reactivation
Off Label Uses - Restasis

- Corneal transplantation
  - Reduces inflammation, does not increase the susceptibility to infection
  - Eliminates the issues surrounding the potential for a steroid response
  - A study by Panda et al showed cyclosporine-treated grafts have been found to contain significantly fewer T-lymphocytes. This indicates that the topical cyclosporine actively inhibits the entry of T cells into the grafts, which may make it effective in reducing the risk of allograft rejection in high-risk patients.

- Meibomian Gland Dysfunction
- Recurrent Corneal Erosions
- Improves tear film
- Controls MGD
- Refractive Predictability Following LASIK

- Atopic Keratoconjunctivitis
- Graft vs. Host Disease
- Ocular Rosacea
- Thygeson’s Superficial Punctate Keratitis
- Superior Limbic Keratoconjunctivitis
- Pterygium Recurrence Prevention
- Ocular Myositis

Bottom Line

- Topical cyclosporine is an excellent and safe alternative to topical corticosteroids.
- Useful where patients may require long term or high dose topical steroids.
- No impact on IOP or viral replication.
- Does not slow wound healing or cause cataracts.

Durezol

- Indications
  - For the treatment of inflammation and pain associated with ocular surgery.
  - For the treatment of endogenous anterior uveitis.

- Contraindications
  - In most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

- Approved in 2008
- First steroid to receive specific indication that includes pain
- Formulated as an emulsion for greater bioavailability
- Consistent dosing
- Can be dosed at half of typical Pred Forte
- No BAK
**Durezol**

- **Jamal and Callanan (2009)**
  - Durezol equivalent at clearing anterior chamber cells compared to PF

**Off Label Uses- Durezol**

- **Cystoid Macular Edema**
  - Causes
    - Medication-side effects
    - Trauma/injury
    - Diabetes
    - AMD
    - Cataract surgery

- **Diffuse Lamellar Keratitis (DLK)**
  - Interface inflammation following LASIK

- **Other uses**
  - Anterior segment surgery
  - Glaucoma surgery
  - Corneal grafting

- **Benefits**
  - More convenient dosing
  - Higher potency

- **Watch IOP and side effects**

**Topical NSAIDs**

- **Acular**
  - Indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of post-operative inflammation in patients who have undergone cataract extraction

- **Acular LS**
  - Indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery

- **Nevanac**
  - Indicated for the treatment of pain and inflammation associated with corneal refractive surgery

- **Voltaren**
  - Indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery

- **Bromday**
  - Indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction

- **Prolensa**
  - Indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction

- **Ilevro**
  - Indicated for the treatment of pain and inflammation associated with cataract surgery
Off Label Uses- Topical NSAIDs

- Typically labeled for 2 weeks of post-operative use, starting treatment up to 1 day pre-operatively
- Commonly prescribed to start up to 3 days preoperatively, with treatment continuing for 4 to 6 weeks in uncomplicated cases
- Prescribed off-label for prevention of CME
- Pain control
  - Corneal ulcers
  - Pterygium surgery
  - SLT

Off Label Uses-Topical NSAIDs

- Reducing inflammation associated with DES
- Reduction of pain following surface ablation
  - Ketorolac only one approved
  - Studies with bromfenac
    - Sher NA, Golbin MP, Bond M, Tootller WB, Faulder S, Veirin T. Topical bromfenac 0.09% vs ketorolac 0.4% for the control of pain, photophobia, and discomfort following PK. J Refract Surg. 2006;25:214-220.

Off Label Uses- Topical NSAIDs

- 81 year old AA female
- Medical history: HTN
- Ocular history: unremarkable
- Uncomplicated cataract surgery
- Uncorrected VA @ 3 months: 20/20 OD, 20/60 OS
- Returned two months later
  - BCVA 20/30 OD, 20/60 OS

Cystoid Macular Edema

- Most commonly seen after cataract surgery
- Described in 1953 by Irvine
- Angiographic CME after ICCE: As high as 60%
- Angiographic CME after ECCE: 15% to 30%
- Clinical CME after small incision phaco: 0.1% to 2.35%
- OCT evidence of CME after small incision phaco: 4% to 11%
  - also reported to be as high as 41%

Cystoid Macular Edema

- Topical NSAIDs all approved for post-operative inflammation
  - But not specifically for CME
- Topical NSAIDs for prophylaxis
    - CME in 5 of 279 patients who received perioperative prednisolone, and in 0 of 208 who also received ketorolac
    - 450 patients
      - No cases of CME in patients treated with flunixin and prednisolone
      - 5 cases of CME in group without flunixin treatment
Cystoid Macular Edema

- Treatment
  - Heier et al. (2000) compared the efficacies of topical ketorolac, prednisolone and the combination of the two in 28 patients who developed CME within 21 to 90 days after cataract surgery.
  - Combination therapy resulted in superior visual acuity outcomes compared to monotherapies of either agent.

Zirgan (ganciclovir ophthalmic gel)

- Indication
  - Treatment of acute herpetic keratitis (dendritic ulcers).
- Dosage
  - 1 drop 5x/d (Q3H) until ulcer heals, then TID for 7 d.
  - Limited toxicity, very quick resolution, very comfortable.
- Selectively inhibits synthesis of viral DNA.

Epidemic Keratoconjunctivitis

- Viral conjunctivitis caused by adenoviruses 8, 19.
- Highly contagious.
- Typically unilateral.
- No sore throat / fever.
- Redness.
- Discomfort.
- SEI.
- Chemosis.
- Photophobia.

Off Label Treatments - Zirgan

- Research presented at ARVO 2001 by Tabarra et al.
- 18 patients with EKC
- Compared topical ganciclovir to preservative free tears.

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<thead>
<tr>
<th></th>
<th>Recovery Time</th>
<th>Presence of subepithelial opacities</th>
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</thead>
<tbody>
<tr>
<td>Topical ganciclovir 0.15%</td>
<td>7.7 d</td>
<td>22%</td>
</tr>
<tr>
<td>Preservative free artificial tears</td>
<td>18.5 d</td>
<td>77%</td>
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</tbody>
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Betadine

1. By history, rule out any allergy or sensitivity to iodine.
2. Instill a drop of 0.5% proparacaine.
3. Instill 1-2 drops of a topical NSAID.
4. Instill 4-5 drops of Betadine onto the eye.
5. Ask the patient to gently close the eyes and roll them around to ensure thorough distribution of the Betadine across the ocular surfaces.
6. After one minute, lavage out the Betadine.
7. Instill another drop or two of the NSAID (or even proparacaine if the patient has any discomfort).

Other Off Label Medications

- Avastin
  - Initially approved to treat colo-rectal cancer.
  - Expanded to lung cancer, metastatic breast cancer, glioblastomas, and metastatic renal cell carcinoma.
  - Inhibits VEGF.
  - Study in 2008 at University of Wisconsin.
  - Macular degeneration.
  - Diabetic macular edema.
  - ROP.
  - Pre-surgical treatment for diabetic vitreous hemorrhage.
  - Subconjunctival for corneal neovascularization.
Avastin
- Cystoid Macular Edema

Other Off Label Uses
- Prostaglandins
  - Refractive fluctuations thought to be due to IOP
  - Minimal in intact cornea
  - Once daily dosing may stabilize or maintain IOP

- Alpha-agonists (Alphagan P)
  - Post-surgical glare/halos (RK, LASIK, multi-focal implants)
  - Inhibits sphincter dilator muscle
  - Edwards JD, Burka JM, Bower KS, et al. Effect of brimonidine tartrate 0.15% on night vision difficulty and contrast testing after refractive surgery / Cataract Refract Surg. 2008
  - Dosed 30-60 minutes before night time driving
  - The recommended dosage is 1 drop of ALPHAGAN P 0.1% in the affected eye(s) 3 times daily, approximately 8 hours apart

Off Label Prescribing
- Increases our choices of medications
- Be prudent in decision
- Be aware of potential side effects
- Make patient aware it is an off label treatment
- Consider consent form

SAMPLE CONSENT DOCUMENT TEMPLATES FOR DRUG OR DEVICE
When a drug or device is approved by regulatory use by the Food and Drug Administration (FDA), the manufacturer produces a “label” to explain its use. Once a device/medication is approved by the FDA, physicians may use it “off-label” for other purposes if they are well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use and effects.

I understand that [state drug/device] was approved by the FDA for [state approval purpose/conditions]. Nevertheless, I wish to have [state treatment/procedure] performed on my eye/used in my eye and I am willing to accept the potential risks that my physician has discussed with me. I acknowledge that there may be other, unknown risks and that the long-term effects and risks of [state drug/device] are not known.

Off Label Prescribing
- Increases our choices of medications
- Be prudent in decision
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Thank You.

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