**PILL PROBLEMS:**

OCULAR COMPLICATIONS FROM SYSTEMIC MEDICATIONS

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**Common Drugs with Ocular Complications**

- Alendronate
- Amiodarone
- Benztrapine
- Diphenhydramine
- Hydroxychloroquine
- Sildenafil
- Tamsulosin
- Tetracycline
- Topiramate
- Warfarin

**NOTE: NOT A COMPLETE LIST!**

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**DIPHENHYDRAMINE**

- Trade: Benadryl®, numerous generic
- Drug class: non-selective histamine blocker
  - Ingredient in numerous cold medications and sleep aids (e.g. Nytol®, TYLENOL® PM)

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**Potential Ocular Side Effects of Select Systemic Drugs**

- Indication(s):
  - Primary: nasal & non-nasal signs and symptoms of seasonal allergy, especially allergic rhinitis
  - Secondary: insomnia, vertigo, motion sickness
- Typical dosage: 25-50 mg, q4h or PRN
Ocular Complications

- Dry Eye

- Due to anticholinergic effects of the medication
  - Diminishes aqueous production via autonomic innervation to the primary lacrimal gland
  - Opposite action of Salagen® (pilocarpine)
  - Can also cause dry mouth, urinary retention and constipation
  - Dose-dependent effect
  - Reversible


... to evaluate the safety of olopatadine 0.2% in a population of patients with both allergic conjunctivitis and dry eye.

32 patients with allergic conjunctivitis and mild-to-moderate dry eye were evaluated.

Randomized to either olopatadine hydrochloride 0.2% or a tear saline once daily for 1 week.

Evaluated TBUT, corneal and conjunctival staining, fluorophotometry, Schirmer’s test, injection, and symptom evaluations.

No significant differences between the treatment groups were observed (p > 0.05).

Conclusion: As there were no significant changes in the signs & symptoms of dry eye, olopatadine 0.2% is safe to use in ocular allergy patients with mild-to-moderate dry eye.

Other Manifestations

- Drowsiness & fatigue
- Anticholinergic effects including dry mouth, urinary retention, and constipation
- Potential for cardiac complications, particularly arrhythmias and tachycardia
- Potential for recreational use/abuse

Similar Medications with Similar Effects

- Chlorpheniramine (Chlor-Trimeton®)
- Brompheniramine (Dimetane®)
- Dimenhydrinate (Dramamine®)
- Meclizine (Bonine®)
- Loratadine (Clarinex®, Alavert®)
- Cetirizine (Zyrtec®)

YES! Non-drowsy does NOT mean non-drying!!


OTC vs. Rx Drugs

- Patients do not always equate items that they buy on store shelves with the terms “drugs” or “medications”. Practitioners and technicians must be SPECIFIC when screening. Checklists on intake forms work well.
**TETRACYCLINE** and derivatives

- **Trade:** Sumycin®, Tetracyn®, numerous generics
- **Includes:** doxycycline and minocycline
- **Drug class:** Macrolide antibiotic

**Indication(s):**
- **Primary:** infection by susceptible bacterial strains
  - Respiratory, skin/soft tissue, UTIs most commonly
  - Rarely a “first-line” antibiotic therapy
- **Secondary:** immunomodulatory agent for sebaceous disorders, including rosacea and MGD
- **Typical dosage:** 250 mg QID ≈ 500 mg BID

**Ocular Complications**

- **Scleral discoloration** (minocycline)

**Pseudotumor cerebri**

- 0.9 per 100,000 people in general population, including children
  - Increased risk in women aged 20–44 who are 20% or more above their ideal body weight
- **Diagnosis** - based on modified Dandy criteria
  - Awake and alert patient
  - Signs and symptoms of increased ICP
  - Absence of localized neuro exam findings, except for CN VI paresis
  - Normal CSF fluid findings except for increased pressure
  - Absence of deformity, displacement, and obstruction of ventricular system
  - No other identifiable cause of ICP

**Other compounds associated with PTC**

- Oral contraceptives
- Vitamin A
- Amiodarone
- Glucocorticoids (withdrawal)
  - e.g., cortisol
- Mineralocorticoids (withdrawal)
  - e.g., aldosterone
Other Manifestations

- Tooth Discoloration
- Photosensitivity

Warfarin

- Trade: Coumadin®, numerous generics
- Drug class: anticoagulant ("blood thinner")

Indication(s):
- Prophylaxis and/or treatment of venous thrombosis and pulmonary embolism
- Thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- To reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
- Hypercoagulable states
- Typical dosage: 5-10 mg daily

OCULAR COMPLICATIONS

Subconjunctival hemorrhage

- 77-year-old female
- Subconjunctival hemorrhage & headache
- Case report showed concurrent therapy with warfarin, levothyroxine, atorvastatin, metoprolol, and paroxetine.
- INR = 9.9

Hyphema

Ocular Complications

- Retinal hemorrhage

Other Manifestations

- Bleeding and bruising - can be potentiated by a variety of drugs & other substances:
  - Antibiotics (e.g. aminoglycosides, macrolides, fluoroquinolones and tetracyclines)
  - Beta-blockers
  - Levothyroxine
  - Atorvastatin
  - Fish oil / Ω-3 / vitamin E
  - Alcoholic beverages
  - Cranberry products
  - Ginseng
  - Garlic
  - Ginkgo biloba
  - St. John’s wort

Management Tips

- Patients on warfarin therapy need to be cognizant of everything they put in their mouths. Medications, food, beverages… EVERYTHING!!
- INR (International Normalized Ratio) should be performed by PCP routinely.
  - Measures the extrinsic pathway of coagulation
  - Normal: 0.8 – 1.2
  - Target range on therapy: 2.0 – 3.0
  - Dangerous: >4.0

AMIODARONE

- Trade: Cordarone®, Pacerone®, numerous generics
- Drug class: anti-arrhythmic agent (Class III)
- Indication: for life-threatening cardiac arrhythmias
  - Hemodynamically unstable ventricular tachycardia
  - Shock-resistant, recurrent ventricular fibrillation
- Typical dosage: 200-400 mg/day

Ocular Complications

- Corneal Verticillata
  - i.e. “vortex keratopathy”, “hurricane keratopathy”

Corneal Verticillata

- Generally asymptomatic
- Rarely may cause haloes or slight decrease in VA
- Seen in ~90% of patients on amiodarone >6 mos, especially those taking >400 mg/day.
- No management required; Self-limiting & reversible
**WARNING:** Vortex keratopathy can also be associated with…?

**FABRY'S DISEASE**
- Hereditary enzyme deficiency
  - α-Galactosidase A
  - Located on the X-chromosome
- Leads to intracellular accumulation of neutral glycosphingolipids in various organs, e.g. skin, eyes, nervous tissue, kidney and heart
- Findings: angiokeratomas, pain in the hands & feet, lesions of the mouth and multiple ocular signs

**Ocular Complications**
- Pseudotumor cerebri or idiopathic intracranial hypertension

**Other Manifestations**
- "Blue skin", "blue man syndrome"
  - Long-term use; more commonly seen with lighter skin tones

**TOPIRAMATE**
- Trade: Topamax®
- Drug class: anticonvulsant
- Indication(s):
  - Primary: treatment of epilepsy and other seizure disorders
  - Secondary: prevention of migraine headaches in adults
  - Off-label: treatment of bipolar disorder, obsessive-compulsive disorder, alcoholism, smoking cessation, cocaine dependence, eating disorders, and neuropathic pain.
- Typical dosage: (adults) 100 – 400 mg daily

**Ocular Complications**
- Acute myopic shift
- Acute angle-closure glaucoma
35-year-old woman presenting to E.D.
- c/o severe eye pain & blurry vision OU
- Hx: Oral topiramate 50 mg BID X 1 week
- IOP: 57 mm Hg OD, 56 mm Hg OS
- B-scan revealed 360° ciliochoroidal detachment OU

Pathological Mechanism
- Appears to be a sulfa-allergic response
  - Swelling/congestion and forward rotation of the ciliary body
  - Ciliochoroidal effusion with forward shifting of lens-iris diaphragm
  - Induces extreme anterior chamber shallowing and angle-closure
- Congestion of ciliary body allows lens zonules to go slack
  - Results in lens thickening; this, in addition to the forward rotation of the lens-iris diaphragm induces a myopic shift
  - Lens thickening generally does not contribute to angle closure
- NO pupil block; NO iris bombé!

Other Manifestations
- Dysgeusia (taste perversion)
- Parasthesias (numbness & tingling)
- Fatigue
- Difficulty with concentration, attention and memory
- Weight loss

TAMSULOSIN
- Trade: Flomax®
- Drug class: alpha-adrenergic antagonist
- Indication(s):
  - Primary: signs and symptoms of benign prostatic hyperplasia (BPH)
  - Off label: urinary retention in women and those with multiple sclerosis; facilitated passage of kidney stones
- Typical dosage: 0.4 mg once daily

Mechanism: works by relaxing smooth muscle at the distal portion of the urethra
Ocular Complications

- **IFIS - Intra-operative Floppy Iris Syndrome**

IFIS

- Clinical manifestations:
  - Poor preoperative dilation
  - Iris billowing and prolapse
  - Progressive intraoperative miosis

- Management:
  - Identify patients at risk and discontinue medication if possible
  - Use of stronger dilating agents, e.g. epinephrine and/or atropine
  - Use of Malyugin or Marcus ring

Other Manifestations

Sulfa Allergy

- Pustular, erythematous skin eruptions with urticaria
  - Can affect any part of the body
  - May progress to Stevens-Johnson syndrome in severe cases

Other Manifestations

- Fever, chills, body aches, or flu symptoms
- Light headedness, dizziness, weakness, drowsiness
- Headache
- Nausea, diarrhea
- Runny nose
- Diminished ejaculate
- Decreased sex drive, which leads us to...

Sildenafil

- Trade: Viagra®
  - Similar medications: tadalfil (Cialis®), vardenafl (Levitra®, Staxyn®)
- Drug class: phosphodiesterase enzyme inhibitor (PDEI)
  - Originally studied as an anti-angina medication!
- Indication(s):
  - Primary: treatment of erectile dysfunction
  - Secondary: symptoms of benign prostatic hyperplasia
  - Off-label: pulmonary hypertension, Raynaud’s phenomenon (Revatio®)
- Typical dosage: 50 mg (not to exceed 100 mg)
Mechanism of action

1. By affecting PDE6 in the retina, sildenafil can lead to altered color vision perception (usually a blue or green “tinge” to vision).
2. 4 out of 5 men without vascular risk factors reported this problem after taking sildenafil.

Cyanopsia (“blue vision”)

Nonarteritic anterior ischemic optic neuropathy

60-year-old diabetic man
c/o sudden decrease of vision OU, 16 hours after his 3rd consecutive 50 mg daily sildenafil ingestion.

In patients with a predisposing diabetic condition, sildenafil intake can cause changes in NO balance altering the normal vascular autoregulation so that the ocular circulation may not be able to compensate for a drop in systemic blood pressure.

Other Manifestations

- Headache
- Stuffy nose
- Facial flushing

And of course…
### Other Manifestations

#### HYDROXYCHLOROQUINE

- **Trade:** Plaquinil®, numerous generic
- **Drug class:** aminoquinoline
  - anti-malarial drug
  - DMARD
- **Indication(s):**
  - treatment of malaria
  - treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis
- **Typical dosage:**
  - 400-800 mg/day (malaria)
  - 200-400 mg/day (lupus & RA)

### Ocular Manifestations

- **Corneal deposits**

  - Fig. 4: Gibb's-Nels deposit in the central cornea after hydroxychloroquine medication. Slit-lamp examination


- **“Bulls-eye” maculopathy**

  - Ocular Manifestations

  - “Bulls-eye” maculopathy

  - Ocular Manifestations

  - “Bulls-eye” maculopathy

  - Ocular Manifestations

  - “Bulls-eye” maculopathy
66 visual fields from patients with HCQ retinal toxicity.
- HVF changes preceded fundus changes in 60% of patients.
- Abnormalities were more obvious on pattern deviation than the grey scale.
- Authors recommend white stimulus 10-2 fields (vs. red-stimulus), as per AAO guidelines.

Anderson C, Blaha GR, Marx JL. Humphrey visual field findings in hydroxychloroquine toxicity. Eye (Lond) 2011 December; 25(12): 1535-45.

OCT: The New Standard

Flying Saucer Sign

ERG: The Emerging Standard
- Normal mERG
- mERG in HCQ toxicity

Risk factors for maculopathy
- Maintenance dose greater than 6.5 mg/kg/d
  - 120 lb. woman: >400 mg/d
  - 200 lb. man: >600 mg/d
- Duration of treatment: >10 years
- Evidence of renal insufficiency or hepatic disease
- Obesity
- Advanced age
- Presence of macular degeneration or dystrophy

Other Manifestations
- Vertigo, tinnitus, headache
- Skin rashes and dermatitis
- GI disturbances
- Muscle weakness

ALENDRONATE
- Trade: Fosamax®, numerous generic
- Drug class: aminobiphosphonate
  - anti-resorptive agent (strengthens bones)
  - similar drugs include Actonel®, Boniva®
- Indication(s):
  - Primary: treatment or prevention of osteoporosis, treatment of Paget’s disease
  - Off label: Metastatic bone cancer, hypercalcemia, vitamin D overdose
- Typical dosage: 5-10 mg/day (osteoporosis) 40 mg/day (Paget’s disease) X 6 months

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Ocular Manifestations

- Non-specific conjunctivitis and/or keratitis

Other Manifestations

- Nausea, dyspepsia, acid regurgitation
- Abdominal pain, constipation, diarrhea
- Musculoskeletal pain
- Hypocalcemia
- Osteonecrosis of the jaw

Parkinsonian Tremor

- Anticholinergic effects [think atropine]:
  - Mydriasis
  - Cycloplegia
  - Impaired accommodation
  - Transient refractive shift
  - Dry eyes

BENZTROPINE

- Trade: Cogentin® (discontinued in US); numerous generics
- Drug class: anti-parkinsonian medication
  - Possesses both anticholinergic and antihistaminic effects
- Indication(s):
  - As an adjunct in the therapy of all forms of parkinsonism
  - For control of medication-induced movement disorders due to antipsychotic agents, e.g.
    - Chlorpromazine (Thorazine®), haloperidol (Haldol®), risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®)
- Typical dosage: 1-2 mg/day

Episcleritis, scleritis, anterior uveitis
Ocular Manifestations

- Esotropia / diplopia
  - Proposed mechanism: The ratio of convergence to accommodation may increase with anticholinergics due to partial block of accommodation. To see a near target in the setting of blocked accommodation, children would increase accommodative effort, resulting in increased convergence. Too much convergence may cause esotropia.

Other Manifestations

- MORE anticholinergic effects
  - PERIPHERAL
    - Dry mouth
    - Hot, dry skin
    - Tachycardia
    - Constipation
    - Urinary retention
  - CENTRAL
    - Sedation
    - Confusion
    - Delirium
    - Slowed cognitive function
    - Risk of falls

CONCLUSIONS:

- Optometric PHYSICIANS must realize that the eye is impacted by numerous systemic diseases and drugs.
- A working knowledge of pharmacology and common drugs is essential (especially when dealing with an adult or geriatric population).
- Even if you don’t (or can’t) prescribe them, you have the responsibility to recognize the potential ocular impact of commonly prescribed medications.

ARE THERE ANY QUESTIONS?

THANK YOU...