Meds That Don’t Mix With Glaucoma Patients

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Ocular Adverse Effects

- Eye is prone to AE
  - Extensive blood supply
  - Small mass

- Glaucoma
  - Older patients
  - Multiple medications
  - Impaired metabolism and excretion

WHO Causality Assessment of Suspected Adverse Drug Reactions

- Certain
- Probable/Likely
- Possible
- Unlikely
- Conditional/Unclassified
- Unable to assess/Unclassifiable

Clinical Ocular Toxicology

- Fraunfelder F, Fraunfelder W, Chamber W
- 2008

Report it!

- MedWatch
- www.fda.gov/safety/medwatch

Nothing to disclose
**Vigabatrin**

- **Sabril®**
- **IND:** Seizures
- **Bilateral irreversible VF defects**
  - Retinal toxicity
  - Initial <0.1%
  - Now >30%

**Systemic Meds and Glaucoma**

- Angle closure
- Open angle
- Exacerbate
- Potentiate
- Optic Neuropathy
- Visual Field Defects
- Ocular Hypotensive

**WARNING: VISION LOSS**

*See full prescribing information for complete boxed warning*

- **SABRIL** causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity (5.1).
- **Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss (5.1).**
- **Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL (5.1).**
- **Unless a patient is formally exempted, periodic vision assessment is required for patients on SABRIL. However, this assessment cannot always prevent vision damage (5.1).**
- **SABRIL can cause permanent vision loss. SABRIL is available only through a restricted program called the SHARE Program (5.2).**
Acute Angle Closure

- Medications account for 33% of AAC
- Statement is controversial

Risk factors
- Asian ethnicity
- ↑ age
- Female
- Hyperopia
- Anatomical
- Seasonal

Mechanisms

- Pupillary Block

Be Prepared...

- Gonioscopy – not practical
- Some are idiosyncratic
- Educate MDs
Patient Presentation...

- Symptoms
  - Pain
  - Ipsilateral headache
  - Blurry vision
  - "halos"
  - Red eye
  - N/V

Autonomic Nervous System

- Parasympathetic
  - Cholinergic system - acetylcholine (ACh) neurotransmitter

Cholinergic Stimulation in Eye

- Miosis
- Increase aqueous drainage
- Accommodation
- Lacrimation

Tear Stimulation

- Salagen™
  - Oral pilocarpine (5 mg tid-q6h)
  - Approved for xerostomia after radiation and in Sjögren Syndrome
  - Off-labeled for severe, recalcitrant dry eye
- Evoxac™ (cevimiline)
  - Cholinergic agonist
  - Approved for xerostomia in Sjögren Syndrome
  - 30 mg tid

Cholinergic Agonists

- CI: narrow-angle glaucoma
- May precipitate pupillary block angle closure
- Low incidence

Cholinergic Antagonists

- MA: selectivity block muscarinic receptors (postsynaptic site)
- Many drug groups have anticholinergic effects
Cholinergic Antagonists: Effects
- Mydriasis
- Blurred vision (cycloplegia)
- Paralysis of ciliary muscles
- Dry eye

Anticholinergics
- Atropine
  - Systemic use
  - Bradycardia
  - Adjunct – anesthesia
- Scopolamine
- Disopyramide
  - Prevention of cardiac arrhythmias
- Reports of bilateral angle closure after general anesthesia

Antihistamines
- H2 receptor antagonists
  - Tagamet, Zantac
  - Weak anticholinergic properties

Oral H1 Antihistamines
- 1st and 2nd generation drugs
- Formulations include syrups, tablets, capsules, “ready tabs” and extended release
- Often prescribed based on sedative properties (1st gen)

Classification by CNS Sedation
- Nonsedating (Second Generation)
  - Cetirizine (Zyrtec Allergy)
  - Desloratadine (Clarinex)
  - Rx
  - Fexofenadine
    - Allegra Allergy 12 or 24 Hour
    - Loratadine (Claritin)
  - All have a “D” product

What is the “D”?
- Pseudoephedrine as the Decongestant (long acting α1 receptor agonist)
- Avoid phenylephrine (PE)
### Classification by CNS Sedation
- **Mildly sedating**
  - Brompheniramine
  - Chlorpheniramine (Chlor-Trimeton)
- **Moderately sedating**
  - Clemastine (Tavist)
- **Strongly sedating**
  - Diphenhydramine (Benadryl Allergy)
    - 25-50 mg Q4-6H
  - Promethazine

### Antidepressants
- **Selective serotonin reuptake inhibitors (SSRIs)**
  - Prozac, Paxil, etc.
  - MA?
    - Pupillary dilation
    - Serotonin or anticholinergic?
    - ↑ aqueous production
    - Usually within first 6 months

### Antidepressants
- **Tricyclic Antidepressants (TCADs)**
  - Amitryptiline, imipramine
  - Anticholinergic properties
- **Non-TCADs**
  - Celexa, Lexapro
- **Monoamine Oxidate Inhibitors**
  - Phenelzine sulfate (Nardil)
  - Mild anticholinergic

### Anti-Parkinson’s Medications
- **Spasm management**
  - Orphenadrine (Norflex™)
    - anticholinergic
  - Trihexyphenidyl (Artane™, Parkin™)
    - Antimuscarinic
    - Acute and “creeping”

### And the list goes on....
- **Management of COPD/emphysema**
  - Anticholinergic medications
    - Atrovent*
    - Spiriva*
    - 50% with pre-existing narrow angles when receiving nebulized medication → AAC
  - Nebulized form – check mask

### Incontinence Control
- **Overactive bladder**
  - 1/3 >75
    - Urinary incontinence
    - Urgency
  - Manage with muscarinic receptor antagonists
    - Detrol (tolterodine)
    - Ditropan (oxybutynin)
    - Toviaz (fesoterodine)
    - Sanctura, Enblex, VESIcare, etc.
Incontinence Control

- Narrow angle glaucoma exclusion criteria
- OBJECT (OAB: Judging Effective Control)
- OPERA (OAB: Performance of Extended Release Agents)
- ACET: Antimuscarinic Clinical Effective Trial
- PI
  - CI: uncontrolled NAG
  - No evidence of closure or problems with POAG

"Ask to see the patient’s spectacles they wear to see objects in the distance (not their reading glasses). The spectacles of hypermetropic patients will magnify objects and make their own eyes appear very large."

Autonomic Nervous System

- Sympathomimetic
  - adrenergic system - norepinephrine (NE) neurotransmitter at the effector organ

- Sympathetic System
  - ALPHA
    - increase BP
    - in eye:
      - mydriasis (iris dilator)
      - elevation of lid
      - Blood vessel vasoconstriction

Beta Agonists

- Salbutamol (albuterol)
  - β2 agonist
  - Bronchodilation
  - Absorbed through cornea/conj
  - Properly fitted masks and hand-held nebulizers
Adrenergic Agonists

- Epinephrine
- Anaphylaxis
- Severe asthma
- Ephedrine
- URI presenting with AAC
- Majority had used anti-cough mixtures
- Amphetamine
- Narcolepsy, ADHD

Datura wrightii

- Common in SW US
- Jimson weed
- Asthma, motion sickness
- Analgesia
- Atropine, scopolamine

Other Nutraceuticals

- Valerian root
- Anxiety
- Mandrake
- 5-hydroxytryptophan henbane

TABLE 3. World Health Organization (WHO) Classification of Ocular Side Effects Associated With Herbal Medicines and Nutritional Supplements

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxic Reaction</th>
<th>WHO Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Crystalline retinopathy</td>
<td>Certain</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Conjunctivitis</td>
<td>Probable (when applied topically)</td>
</tr>
<tr>
<td>Delux</td>
<td>Mydriasis</td>
<td>Certain</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Conjunctivitis</td>
<td>Possible</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Retinal hemorrhage</td>
<td>Probable</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Hyphema</td>
<td>Possible</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Retinal hemorrhage</td>
<td>Possible</td>
</tr>
<tr>
<td>Licorice</td>
<td>Abnormal vision</td>
<td>Probable (in large doses)</td>
</tr>
<tr>
<td>Nicotin</td>
<td>Cystoid macular edema</td>
<td>Certain</td>
</tr>
<tr>
<td>Nicotin</td>
<td>Blurred vision</td>
<td>Probable</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Intracranial hypertension</td>
<td>Certain (in large doses)</td>
</tr>
</tbody>
</table>

Fraunfelder, Am J Ophth 138(4); 2004.

Essential Blepharospasm

- Neuropathologic disorder

SENSORY

CENTRAL

MOTOR
Essential Blepharospasm

- ↑ blinking and lid spasms → disabling condition with pain and functional blindness
- F>M
- Usually >60

Essential Blepharospasm: S/S

- Increased blinking
- Maybe photophobia and ocular irritation
- Progressive
- May report disability
- Relieving factors:
  - Sleep
  - Relaxation
  - Inferior gaze

Management

- ± MRI
- Tinted SpRx
- Lubricants / punctal plugs
- Pharmacotherapy
  - TCAD
  - Benzodiazepines
  - Anti-spasmodics
- BOTOX
- myectomy

Botox

- Botulinum toxin
- Periocular
- Likely MA
  - Diffuse to ciliary ganglion
  - Sphincter inhibition

Patient Presentation...

- Symptoms
  - Pain
    - Ipsilateral headache
  - Blurry vision
    - "halos"
  - Red eye
  - N/V

Management

- Lower IOP
  - Topical agents
Beta-Adrenergic Antagonists
- β Blockers
- MA: blocks β2 receptors at the ciliary body
  - Probably cAMP mediated
- Reduces aqueous production
- Onset 30-60 min
- Peak effect ~ 2 hours

OSE
- Allergic blepharoconjunctivitis
- ↓ corneal sensitivity
  - Varies by specific drug
- Dry eye / ↓ TBUT
- SPK
- Blur
  - Transient
  - Mild
  - Only with GFS

Systemic Side Effects
- Bradycardia
- Arrhythmias
- Hypotension
- CHF
- Heart block
- Raynaud’s phenomenon

Systemic Side Effects
- Bronchospasm
- Dyspnea
- Inability to achieve exercise-induced tachycardia

Systemic Side Effects
- CNS effects
  - BLAH...
- Impotence
- Alopecia
- Mask symptoms
  - Hypoglycemia
  - Graves disease
- May worsen MG
- ↓ HDLs

Contraindications
- Severe heart disease
- Asthma
- COPD
- Bradycardia
  - < 60 bpm
- Hypersensitivity
- Pregnancy?
Drug Interactions

- Calcium channel blockers
- Caution
- Cardiac glycosides
- Use epocrates or other reference!

Timolol maleate

- Timoptic™
  - 0.25%, 0.5%
- Timoptic XE™ / Timolol GFS
  - 0.25%, 0.5%
- Istalol™
  - 0.5%

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>Concentration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol maleate</td>
<td>Timoptic</td>
<td>0.25%, 0.5%</td>
</tr>
<tr>
<td></td>
<td>Timoptic-XE / Timolol GFS</td>
<td>0.25%, 0.5%</td>
</tr>
<tr>
<td></td>
<td>Timoptic in Ocudose</td>
<td>0.25%, 0.5%</td>
</tr>
<tr>
<td></td>
<td>Istalol</td>
<td>0.5%</td>
</tr>
<tr>
<td>Timolol hemihydate</td>
<td>Betimol</td>
<td>0.25%, 0.5%</td>
</tr>
<tr>
<td></td>
<td>Betagan</td>
<td>0.25%, 0.5%</td>
</tr>
<tr>
<td></td>
<td>Optipranolol</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Ocupress</td>
<td>1%</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Betoptic S</td>
<td>0.25%</td>
</tr>
<tr>
<td></td>
<td>Betoptic</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Iopidine

- 0.5%
- 1%
- Used for:
  - Prevention of IOP spikes associated with laser procedures
  - ↓ IOP associated with laser procedures
  - Angle closure attack (glaucoma)

Brimonidine

- 0.15%, 0.2%
- BAK preserved

Alphagan P

- Purite®
CI
- Allergic to clonidine
- Use of MAOI
- Caution
  - Severe CV disease

Combination
- Brimonidine 0.2%
- Timolol maleate 0.5%

Direct Acting Cholinergic Agonists
- Pilocarpine
  - 1, 2 and 4%
  - When IOP <40 mmHg

Management
- Lower IOP
  - Topical agents
  - Beta blocker
  - Alpha agonist
  - Pilocarpine
  - Usually when IOP < 40 mmHg
- Oral carbonic anhydrase inhibitor
  - Acetazolamide 500 mg

CAIs
- Unsubstituted aromatic sulfonamides
- Very different structurally from antibacterial sulfonamides
- OK to use?

Acetazolamide and Sulfonamide Allergy: A Not So Simple Story

Acetazolamide
- 250 mg tablet
- Diamox Sequels®
  - 500 mg ER capsule
- Don't use Sequels...

Systemic SE
- Paresthesias
- Metallic taste
- Symptom complex
- Diuresis
- Metabolic acidosis
- Hypokalemia
- Renal calculi
- Blood dyscrasias
- Electrolyte imbalance

Contraindications
- Severe liver disease
- Severe COPD
- Renal disease
- Sickle cell

Use with Caution If...
- Using K⁺ depleting drugs
- Sulfonamide allergy

Acetazolamide

"Allergy" to Sulfonamide

Consider Other Strategies...
Dorzolamide
- Topical CAI
- Trusopt®
- 2% sol’t
- ↓ IOP 20-25%
- pH = 5.6

Brinzolamide
- Topical CAI
- Azopt®
- 1% suspension
- pH = 7.5
- ↓ IOP 20-25%

Combo Drug
- Dorzolamide 2% + Timolol maleate 0.5%
- Cosopt
  - Ocumeter Plus Dispenser
  - BAK
  - Generic
  - BAK
  - Also - PF

Simbrinza™
- April 2013
- Brimonidine 0.2% + Brinzolamide 1%
- Suspension
- only combination without a topical beta-blocker

Management
- Topical steroid
- Compression gonioscopy
- Clear the cornea
- Consult with Prescriber

Management
- Peripheral Iridotomy
  - If pupillary block
- Eventual lens extraction?
  - 67-72% cases managed without medications
The Procedure
- Argon or YAG
- PI at least 200 microns
- Verify patency
  - plume
  - transillumination
  - angle deepens
  - zonules

Anticoagulants
- Warfarin
- Angle closure
  - Spontaneous choroidal or subretinal hemorrhage

Idiosyncratic Angle Closure
- Allergic rxn to sulfa moiety?
- Ciliary body edema \(\rightarrow\) zonule relaxation \(\rightarrow\) anterior-posterior lens thickening \(\rightarrow\) ciliary body/lens/iris shift forward narrowing anterior chambe
- Choroidal effusion likely contributing factor
- Non-pupillary block

Sulfonamides
- Topiramate
- Hydrochlorothiazide
- Acetazolamide
- Trimethoprim/Sulfamethoxazole

- Also seen with Mefanamic Acid (NSAID)

Topamax™
- Topiramate
  - FDA Category D
  - Safety not established < 2 YO

- Indications:
  - Epilepsy
  - Migraines
  - Off-label
    - Bipolar disorder, depression, neuropathic pain, smoking cessation, idiopathic intracranial HTN
Qsymia®
- Approved 7/17/2012
- Phentermine
  - Sympathomimetic anorectic
- Topiramate ER
  - Capsules contain 23, 46, 69 or 92 mg!
- Obese (BMI ≥30)
- Overweight (BMI ≥ 27) with at least one weight-related comorbidity

Topamax™
- Precise Mechanism of Action: not known
- Thought to block voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV
- ???

Topamax™
- Ocular side effects (2001)
  - Acute myopia and 2° angle closure
  - May be associated with supraciliary effusion resulting in anterior displacement of the lens and iris
  - ± mydriasis
  - Usually within first month
  - Pediatric population too!
  - First line treatment is d/c Topamax

Topamax™
- Ocular side effects
  - Conjunctivitis
  - Diplopia
  - Nystagmus

Topamax™
- Ocular Changes Associated with Topiramate
  - Ozturk et al
  - Current Eye Research, 36(1), 47–52, 2011
  - N = 76 eyes
  - 3 month f/u
  - Significant myopic shift and an increase in RNFLT were observed
  - Further studies are warranted

Topiramate
- Ocular Changes Associated with Topiramate
  - Ozturk et al
  - Current Eye Research, 36(1), 47–52, 2011
  - N = 76 eyes
  - 3 month f/u
  - Significant myopic shift and an increase in RNFLT were observed
Adverse Events
- 20,402 (2004 – 2012)
- VF Defects: 43 (0.2%)

Management
- No acetazolamide
- No pilocarpine
- No PGs
- No PI

Management
- Ocular hypotensive
- Cycloplegic agent
  - Atropine
  - Homatropine
  - Topical steroid

Gonioplasty
- Pre-treat with 1% pilocarpine
- Argon laser
  - 500 micron spot size
  - 0.5 sec
  - 200-300 mW
  - ~20 burns
  - Contraction without scarring

ACE Inhibitors?
- ACE Inhibitors
- Angiotensin II Receptor Blockers (ARB)
- SE: angioedema
- Report of choroidal effusion precipitating malignant glaucoma

Open Angle Glaucoma
- ↑ IOP
- Oral Steroids
  - Less likely than with topicals
  - Onset
    - Several weeks with more potent
    - Months with weaker
  - One study...
    - 1.4 mmHg increase per 10 mg increase in daily dose
Open Angle Glaucoma

- Steroid Responder Risk Factors
  - (Tripathi et al)
  - DM
  - >40
  - High Myopia
  - FHx of POAG
  - Any route

Retinal Drugs

Intravitreal Injections

- >50% of non-glaucomatous eyes ↑ IOP

Ozurdex®

- 70% dexamethasone + 30% polymer delivery system (Allergan)
- Bioerodible (Novadur)
- Delivers drug for ~ 6 weeks

Ozurdex®

- IND
  - Macular edema after RVO
  - Chronic noninfectious posterior uveitis (6/2010)
  - Diabetic macular edema (9/26/14)

Ozurdex®

- MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) Study
  - Demonstrated long-term efficacy without the need for monthly injections
  - two multi-center 3-year sham-controlled, masked, randomized clinical studies
Side Effects

- ↑ IOP
  - Peak at week 8
- Cataract
  - 68% vs 21% (sham)

Iluvien®

- Fluocinolone acetonide
- Alimera Sciences
- Intravitreal Implant
  - Non-bioerodible
- 0.19 mg
  - 0.25 microgram/day (initial rate)
  - 36 months
- Approved 9/26/2014

Table 2: Summary of Elevated IOP Related Adverse Reactions

<table>
<thead>
<tr>
<th>Event</th>
<th>ILUVIEN (N=375)</th>
<th>Sham (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥ 5 mmHg from Baseline</td>
<td>157 (42%)</td>
<td>18 (10%)</td>
</tr>
<tr>
<td>IOP elevation ≥ 10 mmHg</td>
<td>75 (20%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Any IOP-lowering medication</td>
<td>144 (38%)</td>
<td>58 (31%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated intracocular pressure</td>
<td>18 (5%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
Steroid Responder
- ↓ TMW outflow
  - Interference with phagocytosis in Schlemm’s canal
  - Increased accumulation of glycosaminoglycans (GAGS) in TM
- Genetic susceptibility
  - Myocilin gene – highly expressed when TMW cells exposed to steroids
  - Future testing to predict?

Open-Angle Glaucoma
- Cancer drugs
  - Docetaxel, paclitaxel
  - Microtubule inhibitors
- MA?
  - May be related to fluid retention

Caffeine
- Large amounts may slightly ↑ IOP
  - >180 mg/day → small IOP spike
  - Blue Mountains Eye Study
    - POAG 19.6 mmHg vs 16.8 mmHg

Miscellaneous
- Smoking
  - Possible ↑ risk of OAG
- Fat Intake
  - Certain ratios of fats ↑ risk of OAG

Anticholinergics and POAG?
- 23% POAG ↑IOP
- 2% normals ↑IOP
- MA?
  - Possibly ↓ aqueous outflow
- Clinical Implications...
Gilenya®
- fingolimod
- Novartis Pharmaceuticals
- sphingosine 1-phosphate receptor modulator
- Blocks lymphocyte leakage from lymph nodes
- MA?

Systemic Beta-Blockers
- Metoprolol (Lopressor, Toprol-XL)
- Atenolol (Tenormin)
- Carvedilol (Coreg)
- Propranolol (Inderal)
- ETC...
- Addition
- Change in dosage
- Discontinuation

Meds that Don’t Mix with Glaucoma
- Drug History
  - High Index of Suspicion
- Communicate
- Report