Session 3:
Critical Caveats for Common Medications

Learning Objectives

1. Effectively manage patients who are on statin therapy with respect to potential drug interactions and muscle-related symptoms.
2. Consider potential adverse effects of proton pump inhibitors, such as impaired absorption of certain nutrients, when prescribing as long-term therapy.
Session 3: Critical Caveats for Common Medications

Faculty

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Frank LoVecchio is one of the founding members of the Center for Toxicology and Pharmacology Education and Research (CTPER). He is the recipient of a multi-site grant in cooperation with UCLA and other universities that examines the clinical management for common skin and soft-tissue infections caused by a treatment resistant bacterium. He completed a public health and outcomes research degree from Harvard Medical School, and is a professor and research scholar at the University of Arizona College of Medicine in Phoenix. Dr LoVecchio is currently an attending physician at Maricopa Integrated Health System, Banner Good Samaritan Medical Center and Phoenix Children’s Hospital, and is co-medical director of the Banner Poison and Drug and Information Center.

Dr LoVecchio is board-certified in medical toxicology, emergency medicine and medical forensics, and practices emergency medicine and critical care in adults and pediatrics. Dr LoVecchio has authored more than twenty-five scholarly publications, numerous book chapters, and actively participates in peer reviews. His wide-ranging interests include ketone levels in the lungs and blood, and pesticide exposures and scorpion stings in young children. He is currently the primary investigator on four National Institute of Health (NIH) grants, including one of the largest emergency medicine grants ever awarded by the NIH.

Dr. LoVecchio has been the invited keynote speaker at several conferences and is recognized internationally for his contributions to the field of emergency medicine.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

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Critical Caveats for Common Medications

Learning Objectives

• Effectively manage patients who are on statin therapy with respect to potential drug interactions and muscle-related symptoms

• Consider potential adverse effects of proton pump inhibitors, such as impaired absorption of certain nutrients, when prescribing as long-term therapy

Recent FDA Drug Warnings

• Proton pump inhibitors (PPI) and Clostridium difficile (moderate worry)

• Statins and cognitive impairment, increased risk of diabetes (low worry level)*

• Incretin-based diabetes drugs and pancreatitis (moderate worry level)

• Azithromycin and cardiac arrhythmias: avoid in patients on QT prolonging drugs or with QT prolongation (low worry level ); conflicting data

Hot off the Presses

• Saxagliptin associated with CHF


• Statins appear to be associated with cataracts


Proton Pump Inhibitors and Infections


  – Meta analysis shows a 65% increase in the incidence of CDAD among PPI users


  – Findings indicate a probable association between PPI use and incident and recurrent CDI

  – Risk further increased by concomitant use of antibiotics and PPI, whereas H2RAs may be less harmful

Potential Problems With PPIs?

- Decreased GI absorption of
  - Calcium
  - Iron
  - Thyroid hormone
  - Magnesium
  - B12
  - Ketoconazole/itraconazole
- Increased fracture risk
- Increased risk of C. diff and recurrent C. diff; more severe C. diff (FDA warning February 2012)
- Minimize risk by stopping PPI when it’s no longer needed


Triptans and SSRIs

Concern for serotonergic syndrome

- Extremely unlikely if only a triptan + SSRI (especially at lower doses of SSRI)
- Beware of patients on multiple drugs that can trigger serotonergic syndrome
  - tramadol, linezolid, meperidine, dextromethorphan, TCA, MAOI, buspirone, trazodone


The Latest on Clopidogrel and PPIs

- Nested case controlled study of clopidogrel users
- Total of 43159 clopidogrel users, with 15415 also using PPI
- No difference in major cardiovascular events between clopidogrel users with or without concurrent PPI use (OR 1.06, CI 0.95-1.18)
- Slight difference in all cause mortality (OR 1.4, CI 1.29-1.53)

Conclusion: combination clopidogrel and PPI appears to have no significant effect on CV outcome


Warfarin Interactions

- Decrease metabolism (increase PT)
- Most Significant
  - TMP/Sulfas
  - Erythromycin
  - Amiodarone
  - Propafenone
  - Ketoconazole/itraconazole
  - Itraconazole
  - Metronidazole
- Possible
  - Quinolones
  - Omeprazole
  - Clarithromycin
  - Azithromycin
- Especially in elderly and with polypharmacy


Antibiotics and Warfarin

<table>
<thead>
<tr>
<th>Drug name</th>
<th>n</th>
<th>Mean INR change</th>
<th>% w/ INR &gt;4</th>
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<tr>
<td>Terazosin (ctl)</td>
<td>20</td>
<td>-1.15</td>
<td>5</td>
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<tr>
<td>Azithromycin</td>
<td>32</td>
<td>+0.51</td>
<td>31</td>
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<tr>
<td>Levofloxacin</td>
<td>27</td>
<td>+0.85</td>
<td>33</td>
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<tr>
<td>TMP/Sulfas</td>
<td>16</td>
<td>+1.76</td>
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- Retrospective cohort study 104 patients on stable warfarin therapy to determine effect on INR
- Mean INR change and % increase over therapeutic range were statistically significant for the antibiotics compared to control
- Conclusion: TMP/Sulfas has the greatest impact of commonly used antibiotics on INR

Antibiotics and Warfarin: Treatment of Urinary Tract Infection

- Penicillins/cephalosporins: okay
- Nitrofurantoin: okay
- Quinolones: be very cautious
- TMP/Sulfa: don’t use

Case 2

- A 39 yo woman with a prosthetic aortic valve presents with bruising
- Her last INR 6 weeks ago = 2.4; today’s INR = 6.5
- She has not taken any extra warfarin

Warfarin and Acetaminophen

Several studies suggest increased INR with acetaminophen (APAP) + warfarin

- APAP: >9100 mg/week led to 10x risk for INR>6
- APAP: 4 g/d; INR increase 1.2 vs .37 in control (p<.001)
- APAP: 2 gm or 4 gm vs placebo; 54% on APAP overshot INR goal vs 17% on placebo

Problems with Statins

- Fibrates: gemfibrozil 15X > fenofibrate
- Azole antifungals
- Amiodarone
- Macrolides: erythromycin, clarithromycin (NOT azithromycin)
- Protease inhibitors
- CCBs: verapamil, diltiazem
- Least drug interactions with pravastatin, most with simvastatin and lovastatin

Case 3

- A 65 yo man presents with cough and fever
- Severe diarrhea for 2 days; was on a cruise with a friend who was diagnosed with Legionella yesterday
- PMH: diabetes, hyperlipidemia, hypertension
- Meds: lisinopril, simvastatin, amlodipine, gemfibrozil, Metformin
- Chest x-ray shows patchy bilateral infiltrates
- WBC 17,000
- Na 125 mEq/L

Drugs That Increase Risk of Statin Induced Rhabdomyolysis

- Fibrates: gemfibrozil 15X > fenofibrate
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**Side Effects of Statins**

- Liver failure: 0.0001%
- Rhabdomyolysis: 0.01%
- Liver failure: exceedingly rare
  - Elevated hepatic enzymes: 0.5% to 2%
- Myalgias: 5% to 18%
- Cataracts

References:

**Case 4**

- 55 yo man with type 2 diabetes started having myalgia
- Three months ago when atorvastatin was started for high LDL-C
- Symptoms stopped shortly after discontinuing the drug
- He was switched to pravastatin 3 weeks ago and myalgia started again

**Myalgias and Statins**

PRIMO study: 10.5% had muscle symptoms on statins

- For those receiving the highest doses of statins, rates of myalgias were
  - Fluvastatin XL: 5.1%
  - Pravastatin: 10.9%
  - Atorvastatin: 14.9%
  - Simvastatin: 18.2%

**Conclusion:** Statin myalgias are common and seem to differ in frequency among statins

References:

**The Latest on Coenzyme Q10**

To assess the benefit of coenzyme Q10 in the treatment of Statin induced myalgias

- Patients who recently started a statin or had a statin with dose increase and development of myalgias in two or more extremities
- Randomized to coenzyme Q10 60 mg BID (n=40) or placebo (n=36), while still taking the statin
- No difference in visual analog pain scores at one month (p=.34)

**Clinical pearl:** The jury is out on coenzyme Q10, this study is one of two negative studies

References:
Twice Weekly Rosuvastatin for Patients with Statin Myalgias

- Retrospective chart review of previously statin intolerant patients in a lipid lowering clinic
- 40 total patients; received Rosuvastatin 5mg twice a week (30) or rosuvastatin 10 mg twice a week (10)
- Mean LDL reduction was 43, with 54% reaching NCEP goal
- 8 patients (20%) discontinued rosuvastatin due to side effects

Clinical pearl: Rosuvastatin twice weekly effective and well tolerated; long term studies needed

Approach to Management of Myalgias on Statins

- Check CK and TSH
- Stop statin: when symptoms disappear, restart statin at lower dose or change statin
- If recurrent symptoms, consider
  - Fluvastatin 80mg XL QD
  - Atorvastatin 10 mg alternate day or 2X weekly
  - Low-dose rosuvastatin daily, QOD or weekly
- If symptoms continue, could try ezetimibe


Statin Interactions

Interaction risk largely dependent upon degree that statin is metabolized by cytochrome P450 enzymes

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
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</thead>
<tbody>
<tr>
<td>Atorvastin</td>
<td>Pitavastatin</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Simvastatin*</td>
<td>Rosuvastatin</td>
</tr>
</tbody>
</table>

Common Statin Interactions
- Amiodarone
- Azole antifungals
- Macrolides (clarithromycin, erythromycin)
- Fibrates, avoid ALL statins

Management: Avoid or use lower dose high-risk statin, or switch to low-risk statin

* June 2011 FDA advisory to not put new patients on 80 mg of simvastatin

Beware of Clarithromycin

- Major statin interaction (especially simvastatin/lovastatin)
- Major interaction with CCB
- Increase levels of glypizide/glyburide (hypoglycemia)
- Major interaction with colchicine
- 82 major drug interactions reported!


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Other Important Drug Side Effects

- A 55 yo man has had increasing diarrhea and foul smelling stool for the past six months
- Lost 15lbs during that time
- PMH: depression, GERD, hyperlipidemia, and hypertension
- Meds: sertraline, omeprazole, ezetimibe, rosuvastatin and olmesartan

Olmesartan and Sprue-like Enteropathy

• 22 patients seen at Mayo Clinic with sprue-like symptoms while taking Olmesartan over a three year period
• Celiac disease ruled out in all
• Most patients on 40 mg of olmesartan. All had villous atrophy (15) or sub-mucosal collagen deposition
• All recovered when olmesartan was stopped
• FDA warning issued July 2013


Case 7

• A 78 yo man presents to his physician for evaluation of edema
• Reports three month history of bilateral peripheral edema. No pain or SOB
• PMH: HTN, Parkinson’s disease, depression, T2DM
• Meds: lisinopril, diltiazem, atorvastatin, pramipexole, escitalopram, and metformin
• Exam
  – BP: 110/70
  – P: 70, no increased JVP
  – Chest: clear
  – Ext bilateral edema: 2+

Case 8

• 60 yo man presents with acute visual changes in right eye
• Noticed wavy lines initially, then decreased vision
• Diagnosed with a retinal detachment
• Severe COPD, recent exacerbation
• Meds (oral): prednisone, levofloxacin, codeine, albuterol, fluoxetine, and omeprazole

Drug-induced Edema

• Dihydropyridines (nifedipine, felodipine, amlodipine)
• TZDs (pioglitazone, rosiglitazone)
• NSAIDS
• Estrogen and testosterone
• Pramipexole – in 17/300 patients; resolved with drug discontinuation
• Gabapentin and pregabalin (7%-8%)
• Omeprazole


Oral Fluoroquinolones and Risk of Retinal Detachment

• Nested case control study: cases of retinal detachment in a cohort of patients visiting an ophthalmologist in Canada 2000 to 2007
• Patients with retinal detachment were matched with 10 controls each. Cohort of 989591 patients, 4384 cases of retinal detachment, and 43840 controls
• OR 4.5 for retinal detachment in quinolone users, with average time from use to detachment of 4.5 days
• Patients taking oral fluoroquinolones were at a higher risk of retinal detachment, although the absolute risk for was small1
• Recent negative JAMA study. RR was 1.29 (95% CI, 0.53 to 3.13) for current use2


Risk of Tendinopathy with Quinolones

• Large healthcare database of Achilles tendonitis and rupture dx; charts were reviewed for antibiotic use in the previous 30 days, compared to control patients
  – Quinolone antibiotics were associated with OR of 4.3 for Achilles tendonitis and OR 2.0 for Achilles rupture
  – Risk was 48/100,000 new quinolone prescriptions for Achilles tendonitis, 6/100,000 for Achilles tendon rupture
  – Risk of Achilles tendonitis was higher in patients
    – >60 years of age (OR 8.3 vs 1.6 in patients <60 years)
    – BMI <30 (OR 7.7 vs 2.4 for BMI >30)
    – On glucocorticoids (OR 9.1 vs 3.2)

Clinical pearl: Age and corticosteroid treatment are risk factors for tendinopathy with quinolones

**Quinolones and Tendon Rupture**

- Reports of shoulder, hand, and Achilles tendon ruptures in patients on quinolones
- Achilles tendon: most common site
- Can occur anytime during the course of treatment and even after treatment
- Risk is greatest if corticosteroids are being used and in older patients

**Quinolones and Arrhythmias, Neuropathies**

**Arrhythmias**
- Canadian retrospective review, 1990-2005
- Of 605127 patients, 1838 cases of serious arrhythmia, 4.7/10000 person years; RR 1.76 in non-hospitalized patients
- Moxifloxacin probably carries the highest risk for available quinolones

**Peripheral neuropathy**
- August 2013: Required label warning of risk for possibly permanent nerve damage
- Can occur within days of starting IV or oral quinolone
- No risk factors identified

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**Case 9**

- 66 yo woman presents with fatigue
- PMH: bipolar disorder and reflux disease
- Felt well the past few months until the last few weeks
- Meds: rabeprazole, lithium, paroxetine, calcium
- PE: normal
- Labs:
  - Na: 120
  - K: 3.6
  - BUN: 3
  - Cr: 0.7
  - Li: therapeutic

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**SSRI and Hyponatremia**

- Older age
- Female
- Concomitant diuretic use
- Low body weight

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**SSRI Adverse Events**

- Probable increased risk of UGI bleed
- Often overlooked cause of hyponatremia
- Sexual dysfunction (20%-50%)
- QT prolongation with citalopram

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**Citalopram and QT Prolongation**

- Dose dependent QT prolongation
- Maximum dose recommended for citalopram 40 mg (maximum dose 20 mg for age >65)
- Escitalopram also can prolong QT, but less so; other SSRIs do not (maximum dose 10 mg for age > 65)
- Contraindicated in patients with congenital long QT syndrome
- Important interaction with CYP2C19 inhibitors (fluvoxamine, fluoxetine, PPIs, cimetidine, clopidogrel)
- Avoid use with other QT prolonging drugs

NOTE: Data lacking re other SSRIs and QT prolongation

http://www.fda.gov/drugs/drugsafety/ucm297391.htm.
Zolpidem and Morning-after Impairment

- FDA warning May 2013 about impaired functioning including driving in the morning after using zolpidem
- Problem is greatest with using sustained release formulation
- Also, dose for women was recommended to be reduced from 10 mg to a maximum of 5 mg for zolpidem, maximum 6.25 mg for sustained release

FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem


Case 10

- 62 yo man with a hx of MI 4 years ago
- Presents with right hip pain
- Discomfort with walking for the past 6 months
  - X-ray reveals moderate osteoarthritis
- Labs
  - Bun: 6
  - Cr: 0.8
  - Gluc: 100

Risk of MI With NSAID Use

- Nationwide cohort study in Denmark. 99187 patients with a mean age of 69
- Studied pharmacy and medical records for all patients age >30 with a first time admission for myocardial infarction between 1997 and 2009
  - Subsequent NSAID use was tracked
- HR for death with NSAID use was 1.59 at one year, 1.63 at five years. Risk for recurrent MI was 1.3 at one year, 1.41 at five years.

Clinical pearl: Avoid NSAID use in patients with CAD


NSAIDS and CHF in the Elderly

- 365 cases of patients admitted with CHF compared to 658 control patients admitted without CHF
- NSAID users had an odds ratio of 2.1 for admission for CHF
- Odds ratio of 10.5 for first admit for CHF if patient had heart disease and used NSAIDS
- Risk of admission for CHF correlates with dose of NSAID and long acting drug

Clinical pearl: Avoid NSAID in patients with CHF


What To Remember From This Talk

- Watch carefully for interactions with TMP/Sulfa, simvastatin, and clarithromycin
- Statin myalgias are common but can often be effectively managed
- Consider the potential for side effects when prescribing quinolones

Always weigh the potential risks versus benefits of drug therapy

Questions?