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

*Steenland K. J Am geriatr Soc. 2013 Sep;61(9):1449-55

Hot off the Presses

• Saxagliptin associated with CHF

• Statins appear to be associated with cataracts

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 .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 Possible*
    - TMP/Sulfa
    - Erythromycin
    - Amiodarone
    - Clarithromycin
    - Propafenone
    - Ketoconazole/fluconazole
    - Itraconazole
    - Metronidazole
  - * 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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<tbody>
<tr>
<td>Terazosin (control)</td>
<td>20</td>
<td>-1.15</td>
<td>5</td>
</tr>
<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/Sulfa</td>
<td>16</td>
<td>+1.76</td>
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</table>

- 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/Sulfa has the greatest impact of commonly used antibiotics on INR

**Antibiotics and Warfarin: Treatment of Urinary Tract Infection**

- Penicillins/cephalosporins: okay
- Nitrofurantion: 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

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Drug Interactions with Xa Inhibitors

- Xa inhibitors- rivaroxaban apixaban (eliquis)
- Increased risk of bleeding: ketoconazole, itraconazole, clarithromycin, ritonavir
- Decreased efficacy: carbamazepine, phenytoin, St John’s wort, rifampin

Problems with Statins

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

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

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


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**Myalgias and Statins**

- Appears to be dose and, possibly, drug related
- Check TSH level
- More common in patients with low body mass
- More common in Asian patients
- Role of vitamin D?
- Benefit of coenzyme Q10 (low ubiquinone levels)?


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**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


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**Case 5**

- A 60 yo man with CAD returns for follow-up
- Stopped Pravastatin because of myalgias
- Previously had myalgias with simvastatin and lovastatin
- Wary of trying another statin because of myalgias
- He has been taking coenzyme Q10 w/o benefit

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**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


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**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

Other Important Drug Side Effects

Case 6

• 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+

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

Quinolones and Peripheral Neuropathy

• Known since 1990’s
• Can occur within 1st 24 hours on medication, most within 1 week
• Parasthesia most common intitial symptom (81%)
• FDA clarified this concern 8/2013

Ann Pharmacother. 2001 Dec;35(12):1540-7
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 tendinitis 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

**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


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

SSRI and Hyponatremia

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


SSRI Adverse Events

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

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