New Drug Update

Jen Phillips, PharmD

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Conflict of Interest

- There are no conflicts of interest to disclose.

Learning Objectives

- Describe the drug approval process
- Explain the differences between phase I, phase II, and phase III clinical trials
- List at least three new medications that were approved in the previous year

Drug Approval Process

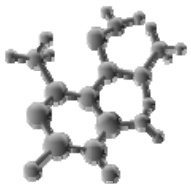
- Steps of the Drug Approval Process
  - Drug Discovery
  - Screening
  - Pre-Clinical Testing
  - Investigational New Drug (IND) Application
  - Phase I Clinical Trials
  - Phase II Clinical Trials
  - Phase III Clinical Trials
  - New Drug Application (NDA) Or Biologics License Application (BLA)
  - Phase IV Clinical Trials

Steps: Drug Discovery

- Identify disease to target
- Develop a hypothetical treatment based on mechanism of disease, mechanism of action of proposed drug
- Use 3-D modeling software to model hypothesis
- Evaluate feasibility of producing and using selected compound

Steps: Screening

- Chemistry
  - Make many potential molecules at one time
  - Test hundreds at a time for activity
  - 1 in 10,000 molecules make it to market!



Steps: Pre-clinical Testing

- Evaluate acute and short-term toxicity in animals
  - One rodent and one non-rodent
  - Give increasingly high doses to induce toxicity and determine lethal dose
  - Give therapeutic doses for short & long time periods
- Determine pharmacokinetic parameters for the drug
  - Absorption
  - Distribution
  - Metabolism/Excretion

IND Application

- IND = Investigational New Drug
  - Submitted to the FDA before any human testing
  - File kept at FDA throughout the testing process
  - Contains information on drug as it passes through the development process

Phase I Clinical Trials

- Determines:
  - Bioavailability
  - Adverse effects (at various doses)
  - Early evidence of efficacy/effectiveness
- Can begin 30 days after IND submitted
- Involves 20-80 healthy subjects
- Usually lasts 1 year
- Cost: $100,000 - $1,000,000

Phase II Clinical Trials

- Assess drug's effectiveness
- Usually involves 100-300 subjects
- Duration is usually 2 years
- Cost: $10-100 million
- Safety and adverse effects are monitored
- Note: less than **1/3** of all INDs survive Phase II testing!

Phase III Clinical Trials

- Confirms safety and effectiveness of the drug
- Requires consultation with the FDA
- Usually involves 1,000-3,000 subjects
- Multiple testing sites
- Duration: 3-3.5 years
- Cost: $10-500 million

The next steps…

- Submit a New Drug Application (NDA) or a Biologics License Application (BLA)
- Obtain Approval from:
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Drug Evaluation and Research (CDER)
- Must prove that drug can be safely produced
  - Test batches
- Must have marketing materials approved

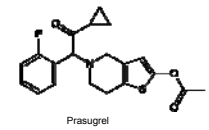
Which of the following is true?

a) Phase III trials involve the most number of subjects
b) An FDA consultation is required before beginning Phase III trials
c) Most drugs do not make it past Phase II trials
✓ d) All of the above

New Drugs of 2009

2009 Statistics

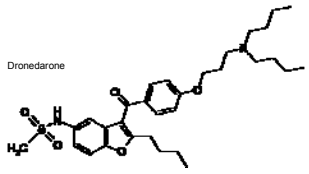
- 19 New Drug Applications Approved
- 33 New Formulations of Existing Drugs
- 5 Drugs Approved that were already marketed
  - Pancrelipase (Creon™ and Zenpep™)
  - Colchicine
  - Capsaicin
  - Codeine Tablets



Prasugrel

Cardiovascular Drugs

Dronedarone



Dronedarone (Multaq™)

- Approved 7/1/09
- Indications
  - Anti-arrhythmic to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter
- Mechanism of Action
  - Anti-arrhythmic with properties of all 4 Vaughan-Williams classes, but contribution to each is unknown.

Dronedarone (Multaq™)

- Contraindications
  - Class IV heart failure or Class II or III symptomatic heart failure with recent decompensation
  - 2nd or 3rd degree AV block
  - Bradycardia (less than 50 bpm)
  - Concomitant use with a strong CYP3A4 inhibitors
  - Concomitant use with drugs that prolong QTc interval
  - Baseline QTc interval ≥ 500 msec
  - Severe hepatic impairment
  - Pregnancy/nursing mothers

Dronedarone (Multaq™)

- Notes
  - Dronedarone produces a moderate (~10 msec) effect on the QTc interval. Stop if QTc is ≥ 500 msec
  - SCr increases by 0.1 mg/dL following initiation of dronedarone. Plateaus after 7 days & reversible upon discontinuation.
    - No effect on glomerular filtration rate
    - Results from inhibition of tubular secretion of creatinine
  - Women of childbearing age ***must*** use contraception with this drug
  - Effects in women are 30% greater than men

Dronedarone (Multaq™)

- Adverse effects
  - Gastrointestinal disorders
  - QTc prolongation
- Dosage
  - 400 mg twice daily with morning & evening meals
- Cost
  - $3.40 each / $6.80 per patient/day

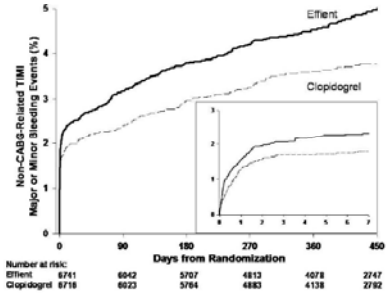
Prasugrel (Effient™)

- Approved 7/10/09
- Indications
  - To reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome managed with PCI
- Mechanism of Action
  - Thienopyridine pro-drug
  - Inhibits platelet activation and aggregation via irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets

Prasugrel (Effient™)

- Contraindications
  - Active bleeding (i.e., peptic ulcer or intracranial hemorrhage)
  - History of prior TIA or stroke
    - TRITON-TIMI 38 trial revealed higher incidence of stroke compared to clopidogrel
- Warnings/Precautions
  - Higher risk of bleeding vs. clopidogrel

Bleeding with Prasugrel



Effient [package insert], Indianapolis, IN; Eli Lilly & Co: 2009

Prasugrel (Effient™)

- Risk factors for bleeding:
  - Age ≥ 75 years
    - Recommended only in high-risk situations
  - CABG or other surgical procedure
    - Discontinue at least 7 days prior (lifetime of platelet)
  - Body weight < 60 kg
    - Consider lowering dose to 5 mg
  - Propensity to bleed
    - Recent trauma/surgery, GI bleed, active peptic ulcer disease, severe hepatic impairment
  - Medications known to increase risk of bleeding
    - Oral anticoagulants, chronic NSAID use, fibrinolytic agents

Prasugrel (Effient™)

- Notes
  - Patients taking prasugrel should also take aspirin (75-325 mg daily)
  - May be administered with or without food
  - Consider decreasing dose to 5 mg for patients < 60 kg
- Dosage
  - 60 mg loading dose
  - 10 mg once daily
- Cost: $4.99 each

Tolvaptan (Samsca™)

- Approved 5/19/09
- Indications
  - Treatment of clinically significant hypervolemic and euvolemic hyopnatremia (sodium < 125 mEq/L)
  - Treatment of less marked hyponatremia that is symptomatic & resistant to fluid restriction
- Mechanism of Action
  - Selective vasopressin V_2-receptor antagonist

Tolvaptan (Samsca™)

- Contraindications
  - Should not be used to acutely raise serum sodium
  - Inability of patient to sense or appropriately respond to thirst
    - Increased risk for overly rapid correction of [Na]
  - Hypovolemic hyponatremia
  - Concomitant use of strong CYP 3A inhibitors
  - Anuric patients
    - No benefit

Tolvaptan (Samsca™)

- Warnings/Precautions
  - Osmotic demyelination syndrome
    - Greater than 12 mEq/L change in 24 hours
    - Dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death
  - Cirrhosis
    - Increased risk of GI bleeding in clinical trials; use only if benefit outweighs risk
  - Dehydration and Hypovolemia
    - Patients should continue ingestion of fluid in response to thirst
  - Concomitant Use of Hypertonic Saline: No data
  - Hyperkalemia
    - Monitor serum potassium during use

Tolvaptan (Samsca™)

- Notes
  - Should be initiated (and re-initiated) in a hospital setting
  - Should not be used to acutely raise serum sodium or to treat serious neurological symptoms
  - No clinical endpoints (i.e., symptoms) have been evaluated

Tolvaptan (Samsca™)

- Adverse Effects
  - Thirst, dry mouth, asthenia, constipation, polyuria, hyperglycemia
- Dosage
  - Initially 15 mg once daily
  - Increase at intervals > 24 hrs to 30 mg daily
  - Max dose: 60 mg daily
- Cost
  - $241 each

Pitavastatin (Livalo™)

- Approved 8/3/2009
- Indications
  - Primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total cholesterol, LDL-C, apolipoprotein B, TG, and to increase HDL-C
- Mechanism of Action
  - Similar to other statins, inhibits HMG-CoA reductase

Pitavastatin (Livalo™)

- Contraindications
  - Active liver disease, including unexplained, persistently elevated LFTs
  - Pregnancy/Breastfeeding
  - Concomitant use with cyclosporine
- Warnings/Precautions
  - Myopathy/rhabdomyolysis

Pitavastatin (Livalo™)

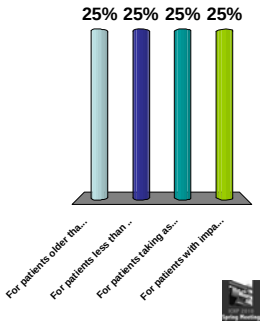
- Notes:
  - No mortality data
  - Undergoes minimal CYP450 metabolism
    - May have less drug interactions (i.e., itraconazole & grapefruit juice)
      - Does not seem to inhibit CYP3A4 to the same degree as other statins
  - Unique cyclopropyl group may confer great potency of LDL reduction compared to other statins
    - This advantage has not been shown in clinical trials

Pitavastatin (Livalo™)

- Dosage
  - 2 mg daily (max of 4 mg daily)
  - Decrease dose by ½ for patients with moderate renal impairment (30-60 mL/min/1.73 m^2)
  - Doses greater than 4 mg increase incidence of myopathy
- Cost
  - Launching June/July 2010

When should the dose of prasugrel (Effient™) be reduced to 5 mg?

- For patients older than 75 years of age
- For patients less than 60 kg
- For patients taking aspirin
- For patients with impaired renal function



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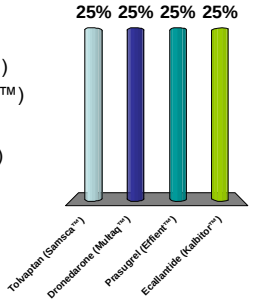
Which of the following drugs causes a small, but reversible increase in SCr?

1. Tolvaptan (Samsca™)
2. Dronedarone (Multaq™)
3. Prasugrel (Effient™)
4. Pitavastatin (Livalo™)



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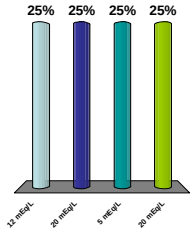
For tolvaptan, changes in serum sodium concentrations greater than ____ mEq/L in 24 hours should be avoided:

1. 12 mEq/L
2. 20 mEq/L
3. 5 mEq/L
4. 20 mEq/L



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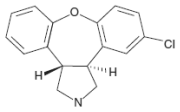
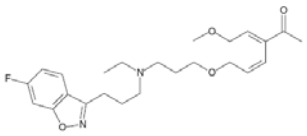
Psych Drugs



Asenapine



Iloperidone

Receptor Binding Profiles

Receptor	Asenapine	Iloperidone	Clozapine	Olanzapine
D_2	+++	++	+	++
5-HT_{2A}	++++	+++	++	+++
5-HT_{2C}	++++	++	+++	++
α	+++	++++	+++	++
M1	-	-	+++	+++

Adapted from *Drugs* 2008;68(16):2269-92

Iloperidone (Fanapt™)

- Approved 5/6/09
- Indications
  - Atypical antipsychotic for the acute treatment of schizophrenia in adult patients
  - 2nd line agent
- Mechanism of action
  - Binds with high affinity to 5-HT_{2A} and Dopamine D_2 and D_3 receptors

Iloperidone (Fanapt™)

- Warnings/Precautions
  - Elderly patients with dementia-related psychosis
    - Increased risk for death from CV events (stroke)
  - QT prolongation
    - Not a first line agent
  - Neuroleptic Malignant Syndrome
  - Tardive Dyskinesia
  - Hyperglycemia and Diabetes Mellitus
  - Orthostatic Hypotension
  - Leukopenia or Neutropenia
  - Suicide
  - Priapism
  - Seizures

Iloperidone (Fanapt™)

- Notes
  - Previously deemed "not approvable" in July 2008
    - Earlier trials compared to risperidone and haloperidol
    - More recent trials compared to ziprasidone
    - Favorable akathisia profile?
  - Unlike ziprasidone, no need to take with meals
  - Long-term data lacking (6 weeks is longest trial)
  - Must be titrated slowly (control of symptoms may be delayed)
    - Alpha-adrenergic blocking effects (orthostatic hypotension)

Iloperidone (Fanapt™)

- Drug Interactions
  - CYP2D6 Inhibitors: reduce dose by ½
    - Fluoxetine or paroxetine
  - CYP3A4 Inhibitors: reduce dose by ½
    - Ketoconazole or clarithromycin

Iloperidone (Fanapt™)

- Dosage
  - Target dose: 12-24 mg/day administered twice daily
  - Start at 1 mg twice daily and titrate up:
    - 2 mg (day 2)
    - 4 mg (day 3)
    - 6 mg (day 4)
    - 8 mg (day 5)
    - 10 mg (day 6)
    - 12 mg (day 7)
- Cost
  - $10/each

Asenapine maleate (Saphris™)

- Approved: 8/13/2009
- Indications
  - Treatment of schizophrenia in adults
  - Treatment of bipolar disorder
- Mechanism of action
  - Similar to other atypical antipsychotics
  - Antagonist activity at D_2 and 5-HT_{2A} receptors

Asenapine maleate (Saphris™)

- Contraindications
  - None
- Warnings/Precautions
  - Not recommended in severe hepatic impairment
  - Increased risk of death for elderly patients with dementia
  - Tardive Dyskinesia
  - Neuroleptic Malignant Syndrome
  - Hyperglycemia and Diabetes Mellitus
  - Orthostatic hypotension
  - QT prolongation
  - Leukopenia, neutropenia, agranulocytosis

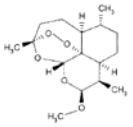
Asenapine maleate (Saphris™)

- Notes
  - Useful options for patients with predominant or resistant negative symptoms
  - Different receptor profile
  - Limited extrapyramidal, antimuscarinic, and metabolic adverse effects

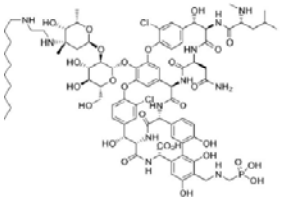
Asenapine maleate (Saphris™)

- Dosage:
  - 5 mg SL BID
  - Usual maintenance dose is 10 mg BID
- Cost
  - ~$10/each

Anti-Infectives



Artemether/
Lumefantrine



Telavancin

Telavancin (Vibativ™)

- Approved: 9/11/2009
- Indications
  - Treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following gram-positive *organisms:*
    - *S. aureus, S. pyogenes, S. agalactiae, S. anginosus,* or *E. Faecalis*
- Mechanism of Action
  - Structurally similar to vancomycin
  - Concentration dependent, rapidly bactericidal
  - (1) Similar to vancomycin, inhibits late stages of bacterial cell wall synthesis
  - (2) Also reduces membrane barrier potential

Telavancin (Vibativ™)

- Contraindications
  - None
- Warnings/Precautions
  - Nephrotoxicity
  - Decreased efficacy in patients with $Cl_{Cr} \leq 50$ mL/min
  - Red-man Syndrome
  - *C. difficile*
  - QTc prolongation
  - Coagulation test interference
    - PT, INR, APTT, ACT, Factor Xa
      - Should collect blood samples for these tests prior to telavancin dose

Telavancin (Vibativ™)

- Notes
  - Dual mechanism of action may confer more activity against resistance strains
  - Interferes with some anticoagulation tests when drawn 0-18 hours after administration
    - PT, INR, aPTT, ACT, Anti-factor Xa
  - Avoid use in pregnancy
    - 3 animal studies showed adverse outcomes
    - REMS
      - Pregnancy test prior to initiation
      - Pregnancy prevention during use
      - Medication guide

Telavancin (Vibativ™)

- Dosage
  - 10 mg/kg IV daily x 7-14 days
  - Infuse over 60 minutes
  - Dose adjust for $Cl_{Cr} \leq 50$ mL/min
  - Stable 4 hours at RT, 72 hours refrigerated
- Cost
  - 250 mg vial: $60 (AWP)
  - 750 mg vial: $180 (AWP)

Artemether/Lumefantrine (Coartem™)

- Approved 4/7/09
- Indications
  - Treatment of acute, uncomplicated malaria due to *Plasmodium falciparum* in patients 5 kg or above
- Mechanism of Action
  - 1:6 part mixture or artemether and lumefantrine
  - Both shown to inhibit nucleic acid and protein synthesis

Artemether/Lumefantrine (Coartem™)

- Warnings/Precautions
  - QTc prolongation potential
    - Avoid if history of congenital QT prolongation, known electrolyte abnormalities, other QT prolonging drugs (including other anti-malarial drugs with QT prolongation properties)
  - Drugs that inhibit CYP3A4
    - Increased potential for toxicity (QT prolongation)
    - Ketoconazole
  - Anti-retrovirals
    - Potential for toxicity and variable response of both agents

Artemether/Lumefantrine (Coartem™)

- Notes
  - Not approved for ***prevention***; only approved for ***treatment***
  - Should be taken with food (increases absorption)
    - Patients with malaria usually have decreased appetite
    - Give a repeat dose in the event of vomiting
  - Can crush tablets and mix with 2 tsp of water (for children)

Artemether/Lumefantrine (Coartem™)

- Dosage
  - Each tablet contains: 20 mg artemether and 120 mg lumefantrine
  - Administered over 3 days as follows:
    - Initial dose (4 tablets): immediately
    - Second dose (4 tablets): 8 hours later
    - Doses 3-6 (4 tablets): Twice daily for next 2 days

Artemether/Lumefantrine (Coartem™)

- Pediatric Dosing
  - 5-15 kg: 1 tablet
  - 15-25 kg: 2 tablets
  - 25-35 kg: 3 tablets
  - > 35 kg: same as adult
- Cost: $2.79/each

Additional Anti-Infectives

- Benzyl Alcohol lotion (Ulesfia™)
  - For the treatment of head lice infestation
  - Suffocates lice vs. paralyzing them
  - $30 per bottle
    - May need multiple bottles for longer hair
  - Needs to be applied twice

Additional Anti-Infectives

- Besifloxacin ophthalmic (Besivance™)
  - Quinolone antimicrobial
  - Treatment of bacterial conjunctivitis
  - Suspension vs. Solution
    - Higher concentrations in the tear film for a longer period of time
  - ~ $75 per bottle

Vaccines

Vaccines

- Human papillomavirus vaccine (Cervarix™)

HPV Type	Manifestation	Gardasil™	Cervarix™
6, 11	Most common cause of genital warts	x	
16, 18	Most common cause of cervical cancer	x	x
31	High-risk cancer causing strain	x	x
33, 45	High-risk cancer causing strains		x

Vaccines

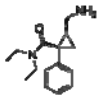
- Human papillomavirus vaccine (Cervarix™)
  - Contains a different adjuvant that may extend the duration of immunization compared to Gardasil™
    - 6.4 years vs. 5 years
  - Age indication differs
    - Cervarix™: 10-25 years
    - Gardasil™: 9-26 years
  - Cost: $150

Vaccines

- Japanese encephalitis Vaccine (Ixiaro™)
  - Japanese encephalitis (JE) caused by a virus endemic in Asian countries
    - Transmitted by mosquito
  - Indicated for individuals who travel to or live in areas where disease occurs
  - IM injection given as 2 doses on days 0, 28
    - $195 per package

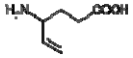
Which of the following is false?

1. Use of telavancin should be avoided in pregnant women
2. Telavancin may interfere with coagulation test assays
3. Coartem™ is indicated for the prevention of malaria
4. Cervarix™ may offer a longer duration of protection against HPV virus compared to Gardasil™



Milnacipran

CNS Drugs



Vigabatrin

Milnacipran (Savella™)

- Approved 1/14/09
- Indications
  - Management of patients with fibromyalgia
- Mechanism of Action
  - Selective serotonin and norepinephrine reuptake inhibitor (SNRI)

Milnacipran (Savella™)

- Contraindications
  - Use of monoamine oxidase inhibitors (MAOI)
  - Uncontrolled narrow-angle glaucoma
    - Mydriasis has been reported
- Warnings/Precautions
  - Suicidality
  - Serotonin Syndrome
  - Increased blood pressure, heart rate
  - Seizures
  - Hepatotoxicity
  - Abrupt discontinuation
  - Bleeding

Milnacipran (Savella™)

- Notes
  - No clinically significant drug interactions
  - No need to take with food, but may increase tolerability
  - Reduce dose by 50% for patients with severe renal impairment
  - Norepinephrine:Serotonin ratio is 3:1
    - Competitor (duloxetine, Cymbalta™) ratio is 1:9
    - More potent pain modulation agent?

Milnacipran (Savella™)

- Adverse Effects
  - Nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, hypertension
- Dosage
  - Day 1: 12.5 mg
  - Day 2-3: 12.5 mg twice daily
  - Days 4-7: 25 mg twice daily
  - After Day 7: 50 mg twice daily
  - Max recommended dose: 200 mg/day

Milnacipran (Savella™)

- Cost
  - 12.5 mg: $1.58/each
  - 25 mg: $1.58/each
  - 50 mg: $1.58/each
  - 100 mg: $1.58/each

Vigabatrin (Sabril™)

- Approved 8/21/09
- Indications
  - Adjunctive therapy of refractory complex partial seizures in adults (2nd line)
  - Treatment of infantile spasms in children 1 month to 2 years of age
- Mechanism of Action
  - Hypothesized to irreversibly inhibit GABA-T, the enzyme responsible for GABA metabolism, resulting in increased levels of GABA in the CNS

Vigabatrin (Sabril™)

- Contraindications: None
- Major Warnings/Precautions
  - Irreversible vision loss (black box warning)
    - Risk proportional to dose and duration of therapy
    - Patients who fail to show benefit in 3 months should be withdrawn from treatment
  - MRI abnormalities
  - Neurotoxicity (rodents, dogs)
  - Suicidal ideation/behavior

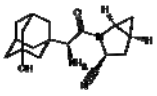
Vigabatrin (Sabril™)

- Notes
  - Withdraw treatment gradually
  - Stop therapy if patients do not respond in 3 months
  - Only available through the **SHARE** program
  - Vision testing required at baseline, every 3 months (while on therapy) and 3-6 months after stopping therapy
  - If also taking phenytoin, monitor levels
    - 16-20% average reduction in levels

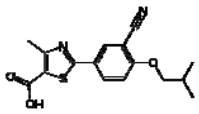
Vigabatrin (Sabril™)

- Dosage
  - Seizures:
    - 500 mg BID
    - Titrate up to 1500 mg daily (increase by 500 mg/week)
  - Infantile Spasms:
    - 50 mg/kg BID
    - Increase to a max of 150 mg/kg BID
  - Dose adjustment in renal impairment
    - 25% mild (50-80 mL/min)
    - 50% moderate (30-50 mL/min)
    - 75% (10-30 mL/min)

More New Drugs



Saxagliptin



Febuxostat

Febuxostat (Uloric™)

- Approved 2/13/09
- Indications
  - Chronic management of hyperuricemia in patients with gout
- Mechanism of Action
  - Inhibition of the enzyme xanthine oxidase, which leads to a decrease in serum uric acid
    - More selective inhibition than allopurinol

Febuxostat (Uloric™)

- Contraindications
  - Patients treated with azathioprine, mercaptopurine, or theophylline
    - These drugs are substrates for xanthine oxidase
- Warnings/Precautions
  - Like other anti-hyperuricemic agents, may increase gout flares upon initiation
    - Use NSAIDs or colchicine to manage flares
    - Do not discontinue drug
  - Liver Enzyme Elevation
    - Monitor LFTs periodically

Febuxostat (Uloric™)

- Notes
  - No renal dose adjustment needed
  - Effects on uric acid level reduction
    - 40 mg febuxostat ~ 300 mg allopurinol
    - 80 mg febuxostat better than 300 mg allopurinol
  - No trials evaluating clinical outcomes
- Adverse Effects
  - LFT elevations, nausea, arthralgia, rash

Febuxostat (Uloric™)

- Dosage
  - 40-80 mg once daily
  - 80 mg is for patients who do not achieve a serum uric acid level <6 mg/dL after 2 weeks
- Cost
  - 40 mg: $4.30/each
  - 80 mg: $4.30/each

Saxagliptin (Onglyza™)

- Approved: 7/31/2009
- Indications
  - As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Mechanism of Action
  - Inhibits dipeptidyl peptidase-4 (DPP4), which slows the inactivation of incretin hormones and results in reduced fasting and postprandial glucose concentrations in patients with type 2 diabetes

Saxagliptin (Onglyza™)

- Warnings/Precautions
  - Hypoglycemia
    - May need lower doses of sulfonylureas if used in combination
- Notes
  - Minor benefits over Sitagliptin (Januvia™)
    - Smaller pill
    - Combination pill with metformin is dosed once-daily vs. BID

Saxagliptin (Onglyza™)

- Dosage
  - 2.5-5 mg once daily (without regard to meals)
  - Use 2.5 mg dose for patients with renal impairment
  - Use 2.5 mg dose with strong CYP450 3A4/5 inhibitors
- Cost
  - AWP ~ $6 each

Hereditary Angioedema

- Approved for the treatment of acute attacks of hereditary angioedema
  - C1 esterase inhibitor (Berinert™)
    - 20 units/kg via slow IV Push
    - Hypersensitivity reactions reported
    - Thrombotic events reported
  - Ecallantide (Kalbitor™) injection
    - 30 mg (3 mL) in three SQ injections
    - Black box warning for anaphylaxis

Additional Biologics

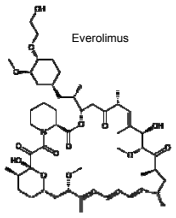
- Golimumab (Simponi™)
  - TNF-α blocker for rheumatoid arthritis, psoriatic arthritis, and anklosing spondylitis
  - Once monthly 50 mg SQ injection
  - Black Box Warning
    - Risk of serious infections
    - Must dispense Medication guide
  - ~$1500/month

Additional Biologics

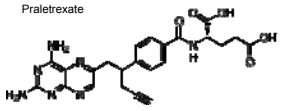
- Ustekinumab (Stelara™)
  - Monoclonal antibody for moderate-to-severe psoriasis
  - SQ injection every 12 weeks
    - 45 mg for patients weighing ≤ 100 kg
    - 90 mg for patients weighing > 100 kg
  - REMS
    - Medication guide describing risk of infection
  - Cost: ~$6,000 per vial
    - Comparable to annual cost of Humira™ and Enbrel™

Chemo Drugs

Everolimus



Praletrexate



New Agents for Renal Cell Carcinoma

	Everolimus (Afinitor™)	**Pazopanib (Votrient™)**
Indications	Advanced renal cell carcinoma after failure of sunitinib or sorafenib	Advanced renal cell carcinoma
Mechanism of Action	Inhibits mTOR kinase activity	Multi tyrosine-kinase inhibitor
Dosing	10 mg every day •Do not crush or chew	800 mg once daily •At least 1 hr pre or 2 hr post meals •Do not crush or chew
Drug Interactions	*CYP 3A4 & PgP inhibitors*: Avoid co-administration with strong/moderate inhibitors *CYP 3A4 inducers*: Increase dose to 20 mg *Hepatic impairment*: Reduce dose to 5 mg for moderate hepatic impairment (Child-Pugh Class B)	*Hepatic impairment*: 200 mg daily for moderate impairment *Strong CYP 3A4 inhibitors*: Avoid or reduce dose to 400 mg *Strong CYP 3A4 Inducers*: Avoid
Major Adverse Effects	Infections, non-infectious pneumonitis, oral ulcerations	Severe or fatal hepatotoxicity (black box warning) -Monitor LFTs at baseline and monthly for 1st 4 months
Notes	Avoid live vaccines Monitor renal function, blood glucose, lipids, hemoglobin, neutrophils, and platelets at baseline & periodically	Avoid if any of the following occurred in the past 6 months: hemoptysis, cerebral, or GI hemorrhage, MI, angina, ischemic stroke or TIA May impair wound healing; hold for 7 days prior to surgery

New Oncology Drugs

- Ofatumumab (Arzerra™)
  - Chronic lymphocytic leukemia (CLL)
    - 2nd line treatment for patients refractory to fludarabine and alemtuzumab
    - Binds to portion of the CD20 molecule on B-lymphocytes, resulting in cell lysis
  - Do not administer IV push
  - Pre-medicate 30 minutes to 2 hours before each infusion
    - Acetaminophen 1000 mg
    - Oral/IV antihistamine (cetirizine 10 mg or equivalent)
    - IV corticosteroid (prednisolone100 mg or equivalent)
  - Administer with in-line filter

New Oncology Drugs

- Ofatumumab (Arzerra™)
  - Dosing:
    - 300 mg initially
    - 2,000 mg weekly x 7 doses
    - 2,000 mg every 4 weeks x 4 doses
  - Prepare all doses in 1 L of 0.9% NS
    - Titrate up on the rate based on appearance of infusional toxicities

New Oncology Drugs

- Pralatrexate (Folotyn™)
  - Peripheral T-cell lymphoma
    - 2nd line treatment for relapsed or refractory disease
  - Dihydrofolate reductase inhibitor
  - Need supplementation with folic acid and vitamin B12
  - Dose: 30 mg/m^2 once weekly x 6 weeks
  - IV push over 3-5 minutes
  - Do not Dilute!!!
  - Infuse via the side port of a free flowing IV line with 0.9% sodium chloride

New Oncology Drugs

- Pralatrexate (Folotyn™)
  - Warnings & Precautions
    - Thrombocytopenia, neutropenia, anemia
    - Mucositis
      - Don't start unless Grade 1 or lower
      - Stop or modify dose if Grade 2 or higher
    - Can cause fetal harm
      - Avoid pregnancy
    - Can cause elevated LFTs
      - Stop or modify dose if Grade 3 or higher
  - Drug Interactions
    - Avoid concomitant use with NSAIDs or tirmethoprim/sulfamethoxazole due to delayed clearance

New Oncology Drugs

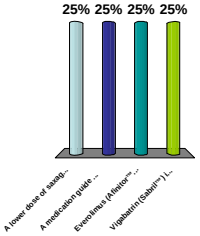
- Romidepsin (Istodax™)
  - Histone deacetylase inhibitor
  - Cutaneous T-cell lymphoma
    - 2nd line therapy
  - 14 mg/m^2 infused over a 4 hour period on days 1, 8, and 15 of a 28 day cycle
  - Reconstitute with supplied 2 mL diluent & further dilute in 500 mL 0.9% sodium chloride

New Oncology Drugs

- Romidepsin (Istodax™)
  - Effects on QTc interval
    - K and Mg should be within normal limits prior to starting infusion
    - Consider EKG monitoring if history of QT prolongation or taking other drugs known to prolong QT interval
  - CYP 3A4 substrate
    - Avoid concomitant use with strong CYP450 inhibitors and inducers

Which of the following is false:

1. A lower dose of saxagliptin (Onglyza™) may be needed for patients on a sulfonylurea.
2. A medication guide must be dispensed with golimumab (Simponi™).
3. Everolimus (Afinitor™) and pazopanib (Votrient™) both have significant CYP 3A4 drug interactions.
4. Vigabatrin (Sabril™) is a safer alternative to other anti-epileptics on the market.



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Questions?

CYP 3A4 Inhibitors/Inducers

	Moderate Inhibitors	Strong Inhibitors	Inducers
CYP 3A4	Amprenavir Aprepitant Diltiazem Dronedarone Erythromycin Fluconazole Fosamprenavir Grapefruit Verapamil	Atazanavir Clarithromycin Darunavir/ritonavir Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telithromycin tipranavir/ritonavir Voriconazole	Amprenavir Aprepitant Carbamazepine Dexamethasone Efavirenz,ethosuximide Etravine Garlic Modafinil Nevirapine Oxcarbazepine Phenobarbital, phenytoin Primodone, rifabutin Rifampin, ritonavir St. John's wort

Adapted from *Cytochrome P450 drug interactions. Pharmacist's Letter/Prescriber's Letter 2006;22(2):220233. [Full update October 2009].*

ICHP Spring Meeting 2010
Phillips – New Drugs
121-000-10-016-L01-P & T

Post Test Questions

1. Which of the following is true:
    a. Phase III trials involve the most number of subjects
    b. Must have an FDA consultation before beginning Phase III trials
    c. Most drugs do not make it past Phase II trials
    d. All of the above

2. Which of the following drugs was not approved in 2009?
    a. Milnacipran (Savella)
    b. Dronedarone (Multaq)
    c. Prasugrel (Effient)
    d. Tolvaptan (Samsca)
    e. All of the above were approved in 2009

3. Which of the following is not a step in the drug approval process?
    a. Submitting an IND
    b. Consulting with the FDA
    c. Phase I clinical trials
    d. Phase V clinical trials

4. Which agency approves biological agents?
    a. CDER
    b. CBER
    c. DEA
    d. Department of Agriculture

5. Of the drugs approved in 2009, which is not yet commercially available?
    a. Milnacipran (Savella)
    b. Tolvaptan (Samsca)
    c. Pitavastatin (Livalo)
    d. Febuxostat (Uloric)
    e. Artemether/Lumefantrine (Coartem)