New Drugs and Drug News of 2010

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Program Overview:
This knowledge-based program will review the list of FDA-approved drugs and give health care providers an update on their mechanisms of action, significant side effects and drug interactions, and their potential role in therapy.

Objectives:
1. List new prescription and nonprescription medications approved or introduced to the market in 2010.
2. For each new medication, identify pertinent information regarding each, including drug indication(s), usual dosing, contraindications, major warnings/precautions, and major drug interactions.
3. For each new medication, determine the drug's place in therapy based on known efficacy, safety, cost and convenience factors.
4. List drug alerts issued in 2010 by the FDA that are relevant for pharmacy practice, and implications for the pharmacist.
Pitavastatin calcium (Livalo)

- 8th coenzyme A reductase inhibitor (statin)
- Indicated as an adjunctive therapy to diet
  - To reduce elevated total cholesterol, LDL, apolipoprotein B, and triglycerides
  - To elevate HDL
- Pivastatin 4 mg qd (maximum dose)
  - = atorvastatin 20 mg qd, simvastatin 40 mg qd
  - > pravastatin 40 mg qd
  - Max dose for atorvastatin, simvastatin, pravasatin is 80 mg
- Other statins have additional indications
  - Reduce risk of MI, CVA, revascularization procedures in patients with/without clinically evident CHD

Pitavastatin calcium (Livalo)

- Pregnancy category X (all statins)
- Contraindicated in active liver disease
  - Check LFTs baseline, 12 weeks, periodically
- AE – myalgia, myopathy, rhabdomyolysis
- Minimal CYP metabolism
  - Few CYP drug interactions than lovastatin, simvastatin, atorvastatin
- Other drug interactions
  - Cyclosporine – contraindicated
  - Lopinavir/ritonavir (Kaletra), erythromycin, rifampin – increase pitavastatin serum levels

Dalfampridine (Ampyra)

- AKA fampridine or 4-aminopyridine
- Potassium channel blocker
- Shown in animal studies to increase conduction of action potentials in demyelinated axons
- Approved for oral use to improve walking in patients with MS
  - Demonstrated by an increase in walking speed
  - 25 foot walk - < 50% showed improved speed

Dalfampridine (Ampyra)

- Major concern is seizures (dose-related)
  - Contraindicated in patients with seizure history
  - DC if patient has a seizure
  - Drug 90% excreted unchanged in urine
    - Contraindicated in Clcr < 50 ml/min
- Adverse effects include:
  - UTI (12%), insomnia (9%), dizziness (7%), headache (7%), nausea (7%), asthenia (7%), back pain (5%), balance disorder (5%)
- 10 mg LA tablet; Dose 10 mg q12h
- 60 tablets AWP $1056.00

http://healthcare.utah.edu/pharmacy/bulletins/NDB_208.pdf
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Polidocanol (Asclera)

- IV administration to sclerose uncomplicated spider veins and reticular veins in lower extremity.
  - Injection causes vein irritation and scarring, resulting in vein closing off and fading away

Polidocanol (Asclera)

- Compared to sodium tetradecyl sulfate (Sotradecol):
  - Higher percentage of patients satisfied
  - Lower incidence of adverse effects
  - Fewer contraindications (DM, asthma with Sotradecol)

- Contraindicated in acute thromboembolic disease, allergy.
- Adverse effects (injection site) – hematoma (42%), irritation (41%), discoloration (38%), pain (24%), pruritus (19%), warmth (16%)
- About $500/treatment; usually required 3 tx

Denosumab (Prolia)

- Indicated for treatment of postmenopausal women with osteoporosis at high risk of fracture
  - History of osteoporotic fracture, or multiple risk factors for fractures
  - Patients who have filed or are intolerant to other therapies for osteoporosis
  - Does not carry indication for OP prevention

- Unique MOA
  - Human monoclonal antibody
  - Prevents a protein (RANKL) from activating its receptor on osteoclasts (responsible for bone resorption)

Denosumab (Prolia)

- Has not been directly compared with other agents
- Greater risk of serious infection
- Must be given parenterally (SQ twice a year)
- Contraindicated in hypocalecmia
- Adverse effects
  - Back pain (35%), pain in extremity (12%), musculoskeletal pain (8%), cystitis (6%), hypercholesterolemia (7%)
  - Rarely dermatologic reactions (dermatitis, eczema), osteonecrosis of the jaw
- $$$$

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Tocilizumab (Actemra)

- IV treatment for adult patients with moderately-to-severe rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies (not first line treatment)
- May be used as monotherapy or with MTX or other nonbiological DMARD
- Unique MOA – interleukin-6 antagonist
  - Pro-inflammatory cytokine overproduced in RA
  - Leads to joint destruction
- Not compared to other agents directly
- Administered every 4 weeks as a 60 minute IV drip

Tocilizumab (Actemra)

- Adverse Effects
  - Infusion reactions (7%), URI (7%), nasopharyngitis (7%), headache (7%), hypertension (6%), elevated ALT (6%)
  - May cause serious infections or gastrointestinal perforation
  - Do not use in patients with active hepatic disease or active serious infection (screen for TB prior to therapy)
  - Do not administer with ANC < 2,000/mm³, platelet count < 100,000/mm³, or who have ALT or AST about 1.5 times ULN
- Modestly effective for RA pts who have not responded adequately to TNF inhibitors

Dabigatran etexilate mesylate (Pradaxa)

- Indicated to reduce the risk of stroke and systemic embolism in patients with NVAF
- MOA – thrombin inhibitor (different from warfarin)
- More effective in reducing stroke and systemic embolism
  - Prevents 5 more strokes than warfarin per 1000 Afib pts
- Monitor of blood tests not necessary
- Interacts with fewer medications
- Not likely to interact with herbal products and dietary items
- Not likely to require dosage adjustment

Dabigatran etexilate mesylate (Pradaxa)

- Usual dosage – 150 mg twice a day
  - 75 mg twice a day with Clcr 15-30 ml/min
  - Missing doses may cause problems (increase CVA risk)
- Risks
  - Contraindicated in active pathological bleeding
  - Concurrent rifampin may reduce effectiveness
  - Reduce dose in severe renal impairment
- Adverse effects
  - Bleeding events (same as warfarin, but higher in patients > 75 yo, and more GI bleeding with dabigatran), GI adverse effects (35%, includes GI like symptoms such as GERD, esophagitis, ulcer, dyspepsia)
Dienogest/estradiol valerate (Natazia)

- New progestin used with estradiol valerate as an oral contraceptive formulation
  - Also has antiandrogenic activity similar to drospirenone (progestin component of Yaz)
- Four phase dosage regimen may reduce occurrence of breakthrough bleeding
  - 2 dark-yellow tablets (3 mg EV)
  - 5 medium-red tablets (2 mg EV/2 mg D)
  - 17 light-yellow tablets (2 mg EV/3 mg D)
  - 2 dark-red tablets (1 mg EV)
  - 2 white tablets (insert)
- 1 month - $86.00 (Yaz is $93.00)

Dienogest/estradiol valerate (Natazia)

- Risks
- Adverse effects:
  - Headache (13%), menorrhagia and irregular menstruation (8%), breast pain, discomfort or tenderness (7%), nausea or vomiting (7%), acne (4%), increased weight (3%)
- Start on day 1 of menstrual cycle, use backup for 9 days

Fentanyl SL tablet (Abstral)

- Opioid tolerant patients:
  - Initial dose is 100 mcg
- If adequate analgesia is not obtained after 30 minutes a second Abstral 100 mcg dose may be taken.
- No more than two doses of Abstral may be used to treat an episode of BTP.
- Patients must wait at least 2 hours before treating another episode of BTP with Abstral.
- Strengths: 100, 200, 300, 400, 600 and 800 mcg

Abstral Proposed REMS Strategy

- Goals of the REMS Program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:
  - Prescribing and dispensing Abstral only to appropriate patients, which includes use only in opioid-tolerant patients
  - Preventing inappropriate conversion between fentanyl products
  - Preventing accidental exposure to children and others for whom it was not prescribed
  - Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction and overdose.

Public Citizen Petition to FDA
February 28, 2006

- Basis for Public Citizen petition:
  - These products [propoxyphene-containing] have a high level of cardiotoxicity.
  - A substantial number of deaths, both accidental and intentional, are associated with use of the products.
  - The products are over-prescribed in the elderly.
  - The products have addiction-causing properties and a related potential for abuse.
  - The products are relatively ineffective as pain medications, the purpose for which they are indicated.

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

- What is the evidence that propoxyphene contributes to the efficacy of propoxyphene and acetaminophen combination products?
- What is the evidence that propoxyphene is cardiotoxic in the therapeutic range, and whether additional data are needed to adequately assess the potential for cardiac effects, and if so, what data?
- What are the potential risks associated with the replacement of propoxyphene with alternative products should propoxyphene-containing products be removed from the market?
- Whether the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain?

FDA Action – Nov 19, 2010

- FDA called for a halt in the prescribing and dispensing of propoxyphene-containing products
- FDA requested prescribers contact patients do discontinue taking propoxyphene, inform patients of the risks associated with continued therapy, and discuss alternative pain management strategies.
- MAD Study Review
  - 18 healthy subjects, propoxyphene 600 mg or 900 mg for 11 days
  - 600 mg largest mean change QTc = 29.8 ms
  - 900 mg largest mean change QTc = 38.2 ms
  - Change in QTc > 20 ms “substantially increases likelihood of being proarrhythmic”

Exalgo (Once Daily Hydromorphone)

- Indicated for management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time (at least one week):
  - 60 mg oral morphine per day
  - 25 mg TDF every three days
  - 30 mg oral oxycodone per day
  - 8 mg oral hydromorphone per day
  - 25 mg oral oxymorphone per day
- Tablets – 8 mg, 12 mg, 16 mg ($250, $370, $495)
- Dosed once a day
Butrans (BU-tranz)
- Transdermal buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time
  - Osteoarthritis, low back pain
- Available as 5 mcg/h, 10 mcg/h, 20 mcg/h
- Schedule III

Butrans
- Each patch is meant to be worn for 7 days
- In opioid-naive patients the initial dose should always be 5 mcg/h
- Converting to Butrans:
  - Apply to upper outer arm, upper chest, upper back or the side of the chest. Do not re-use site for 21 days.

Advantages over TDF:
- Lower abuse potential
- Less dangerous in an overdose
- Causes fewer withdrawal symptoms

Butrans (BU-tranz)

Contraindications and Precautions
- Significant respiratory depression, asthma, paralytic ileus
- Acute post-op, mild, or intermittent pain

Cost for 4 patches (1 month) AWP
- 5 mcg/hour - $151.20
- 10 mcg/hour - $226.80
- 20 mcg/hour - $401.52

Dextromethorphan/Quinidine (Nuedexta)
- Approved by FDA as first line treatment for uncontrolled laughing or crying, known as pseudobulbar affect (PBA).
  - AKA pathologic laughing and crying or emotional incontinence
- See in patients with MS, ALS, traumatic brain injury, stroke, and other neurologic conditions
- PBA episodes occur out of proportion to the individuals underlying emotional state
- Acts on sigma-1 and NMDA brain receptors

www.butrans.com; Prescribing Information
New Drugs and Drug News of 2010

Dextromethorphan/Quinidine (Nuedexta)
- Dextromethorphan hydrobromide (20 mg) is the active ingredient
- Quinidine sulfate (10 mg) is a metabolic inhibitor that increases dextromethorphan bioavailability 20 fold, prolonging half life from 2 to 13 hours
- Prolongs QTc
- AE – diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, UTI, influenza, flatulence
- One capsule daily for 7 days, then one capsule q12h
- 60 capsules AWP $586.60

Fingolimod (Gilenya)
- First oral agent for relapsing forms of multiple sclerosis (250,000-300,000 Americans have MS; current treatment includes Avonex, Betaseron, Rebif, Copaxone, Tysabri, Extavia – all SQ or IM treatments)
- MOA – unknown
  - May involve reduction of lymphocyte migration into the CNS
  - Reduces amount of circulating lymphocytes available to mount an autoimmune reaction to the myelin sheath surrounding axons in the patient with MS
- Dosage – 0.5 mg once daily, with/without food
- Study vs. weekly injections of IM interferon beta
  - Equivalent clinical outcomes
  - Fingolimod showed fewer lesions on MRI
**Fingolimod (Gilenya) Safety Concerns**

- Bradycardia (baseline EKG; observe patient for 6 hours after first dose to monitor bradycardia)
- Infections (drug causes dose-dependent reduction in peripheral lymphocyte count by 20-30%; increase infection risk). Check CBC within 6 months and suspend therapy if a serious infection develops
- Macular edema (increased risk for patients with h/o uveitis; baseline ophthalmologic exam and q3-4months into tx)
- Decrease in pulmonary function tests (PFT as appropriate)
- Increased LFTs (baseline and monitor as appropriate)
- Fetal harm in animals (avoid pregnancy during and 2 months after therapy)

**Place in therapy?**

**Fingolimod (Gilenya) Safety Concerns**

- Cost of treating MS:
  - Avonex, Rebif, Betaseron, Extavia, Copaxone, Tysabri
    - $35,000-40,000/year
  - Fingolimod
    - $58,000/year
- Medical Letter positions this agent:
  - Until more safety data becomes available, limit to patients unable to tolerate injections or breakthrough disease with other therapies

**Pegloticase (Krystexxa)**

- Gout results from an excess of uric acid, which eventually deposits as crystals in the joints or soft tissues (causes swelling, redness, heat, pain, stiffness)
- A PEGylated uric acid specific enzyme (urate oxidase)
- MOA – catalyzes the oxidation of uric acid to alantoin, an inert and water soluble purine metabolite that is renally excreted
- Indicated to treat gout unresponsive to conventional therapy; given as an IV infusion every 2 weeks
- After six months of therapy, 45% of patients achieved complete resolution of tophi.

**Pegloticase (Krystexxa)**

- 25% of patients experience a severe allergic reaction when receiving Krystexxa infusion
  - Corticosteroid and antihistamine are given before infusion
- 80% of treated patients have a gout flare within the first few months, but this tapers off with continued therapy in responders
- Other AE – nausea, vomiting, contusion or ecchymosis, nasopharyngitis, constipation, and chest pain
- Cost - $20,000/year
  - Allopurinol $100/year, Febuxostat (Uloric) $2,000/year
IV Formulation of Acetaminophen

- IV acetaminophen (Ofirmev) indicated for the management of mild to moderate pain, moderate to severe pain with opioids, and reduction of fever
- May be used for postoperative pain
  - 1000 mg q6h superior to placebo after hip/knee replacement surgery
  - 1000 mg q6h or 650 mg q4h superior to placebo for post-abdominal laparoscopy surgical pain
  - 1000mg q6h superior to placebo for fever reduction
- Given as a 15 minute infusion
- 100 ml vial, 10 mg/ml (AWP about $10.50)

Acetaminophen (Ofirmev)

Dosing of OFIRMEV for adults, adolescents, and children >2 years old

<table>
<thead>
<tr>
<th>Age group</th>
<th>Dosing interval</th>
<th>Maximum single dose</th>
<th>Maximum total daily dose of acetaminophen (by any route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥13 years old) ≥50 kg</td>
<td>Q6h</td>
<td>1000mg (100 mL)^2</td>
<td>4000 mg</td>
</tr>
<tr>
<td>Adults and adolescents (≥13 years old) &lt;50 kg</td>
<td>Q6h</td>
<td>Weight-based dose: 75 mg/kg</td>
<td>75 mg/kg</td>
</tr>
<tr>
<td>Children ≥2 to 12 years old</td>
<td>Q6h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA Action on Acetaminophen

- January 13, 2011 – FDA asked manufacturers of prescription combination products that contain acetaminophen to limit acetaminophen to no more than 325 mg per tablet or capsule
- Three year phase in
- Update all labels of prescriptions containing acetaminophen to warn of potential risk for severe liver injury (boxed warning)
- Maximum daily dose remains at 4,000 mg

Duloxetine (Cymbalta)

Chronic Musculoskeletal Pain

- Indications: depression, anxiety, PDN, fibromyalgia
- Sustained-release once daily Cymbalta approved for treatment of chronic musculoskeletal pain (chronic low back pain and osteoarthritis, 60 mg/day)
- Efficacy questioned (noninferiority vs. superiority)
- One of every 5-8 patients on duloxetine for 13 weeks have a 30% reduction in pain
- One of every 8-12 patients DC therapy due to adverse effects
- Adverse effects > 5%: Nausea, dry mouth, insomnia, sleepiness, constipation, dizziness, fatigue
- Adverse effects < 1%: Hepatotoxicity, allergic/hypersensitivity reactions, pneumonia, suicidality
- Start with 30 mg po qd for a week (due to nausea); up to 60 mg po qd

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239894.htm
www.fda.gov/acetaminophen

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OxyContin Reformulation

- New OxyContin tablets are “bioequivalent” to the original formulation from Purdue Pharma
- New formulation contains polyethylene oxide
  - Nonionic hydrophilic polymer that is insoluble in alcohols
  - Forms a viscous gel on contact with water
  - Harder to abuse, crush or chew to release all the drug at once, or to get powder to snort
- Takes longer to reach peak serum levels
  - Some patients complain not as “effective”
  - Ask for “OC” tablets (old) vs. “OP” tablets (new)
- AWP 40 mg tablets, #60 - $375.00

Aldosterone Antagonists for Systolic Heart Failure

- Aldosterone antagonists (spironolactone, eplerenone)
  - Already recommended for moderately severe to severe systolic failure
- EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure)
  - NYHA Class II patients, LVEF ≤ 30%, on ACEI/ARB and BB, and diuretics if needed
  - Composite endpoint of CV mortality or hospitalization for worsening HF
  - 37% ↓ in composite of CV death or hospitalization due to HF (24% ↓ CV death; 42% ↓ HF hospitalization)

Aldosterone Antagonists for Systolic Heart Failure

- Eplerenone 25 mg po qd x 4 weeks; then 50 mg qd
- Study ended early because efficacy endpoint met
- Adverse effects – hyperkalemia and kidney dysfunction
  - Do not use if K > 5 mEq/L, Scr > 2 (2.5 men) mg/dl
- Role of spironolactone?
  - $21.99/month (vs. $141.94 for Inspra)
  - Anti-androgen effects (gynecomastia, impotence, decreased libido)
New Dosage Formulations

- Dulera – combination inhaler for asthma
  - Mometasone (Asmanex) and formoterol (Foradil) - inhaler
  - Comparable to Advair (fluticasone/salmeterol) - powder
  - Comparable to Symbicort (budesonide/formoterol) - inhaler
- Doxepin (Silenor) for insomnia
  - 3 or 6 mg at bedtime; increases sleep by 30 minutes
- Trazodone (Oleptro) for depression – 150 or 300 mg qd
- New generic formulations of venlafaxine
  - Effexor XR capsules
  - Venlafaxine Extended Release Tablets

Medical Marijuana

- Allowed in 14 states and DC
- Still scheduled as a C-I in the US (federal offense)
- Helps with chronic and neuropathic pain, nausea, appetite stimulation, MS-related spasticity and tremor, incontinence
  - Migraines, epilepsy, stress
- Adverse effects include dizziness, tachycardia, cognitive impairment, depression, psychosis, chronic bronchitis

Naproxen/Esomeprazole (Vimovo)

- Combination product – dosed twice daily 30 min before meals
  - Oval, yellow, multi-layer, delayed-release tablet
  - Enteric-coated naproxen core with an immediate-release esomeprazole magnesium layer surrounding the core
  - 375 mg naproxen/20 mg esomeprazole
  - 500 mg naproxen and 20 mg esomeprazole
- Indicated for symptomatic relief of OA, RA, and ankylosing spondylitis, and to decrease the risk of developing gastric ulcers in patients at risk for NSAID-associated ulcers
- Reduced risk of developing NSAID-associated endoscopically detected gastric ulcers vs. naproxen alone
  - 4.1% vs. 33.1% at six month
- $140/month (cost same for both strengths)
  - $62/mo for naproxen; $200/mo Nexium (esomeprazole)
  - $25/mo for generic naproxen 500 + omeprazole

NSAIDs and Risk

- Danish study over nine years
- Compared to those who did not take a NSAID
  - Ibuprofen → 29% greater risk fatal/non-fatal CVA
  - Diclofenac → 91% greater risk CV death
  - Rofecoxib → 66% increased risk CV death
  - Naproxen → not associated with increases in CV problems

Fosbol et al. Circ Cardiovasc Qual Outcomes; July 2010; http://circoutcomes.ahajournals.org
Warning! Tramadol

- Strengthened warnings regarding risk of suicide for patients who are "addiction-prone" or taking tranquilizers or antidepressants
- Additive effects with alcohol, other opioids, or illicit drugs

Donepezil (Aricept) 23 mg

- Indicated for moderate to severe Alzheimer's dementia
- Start at 5 mg once daily at bedtime
  - After 4-6 weeks, increase to 10 mg once daily
  - After 3 months, increase to 23 mg once daily if needed
  - Re-titrate if ≥2 doses missed
- Increasing from 10 to 23 mg/day improved cognitive functioning by 2 points on a 100-point scale
  - Severe Impairment Battery (100 point measure of cognition)
  - SIB improved 2.2 with higher dose
  - Memantine added to donepezil improved SIB 3.4
  - No accepted clinically important change in SIB
- Increased anticholinergic effects (bradycardia, fainting)
  - 19% patients DC due to adverse effects
- 23 mg tabs cost ~ $260/month (AWP)
- 10 mg generic tabs cost ~ 170/month

OTC News

- Zegerid OTC (omeprazole 20 mg and sodium bicarbonate 1,100 mg per capsule) for GERD
- CryoSTAT – drug-free cold therapy pack; six disposable soft-cloth cold packs for hemorrhoid relief
- Baby Orajel SmartDose Teething Gel – topical local anesthetic agent (benzocaine) for relief of teething pain in infants
- Kank-A Soothing Beads – oral anesthetic (benzocaine) for relief of minor mouth and gum pain (indicated for 2 years and older)

Other New Drug Approvals

- Carglumic acid (Carbaglu)
- Hexaminolevulinate (Cysview)
- Tesmorelin (Egrifla)
- Eribulin (Halaven)
- Cabazitaxel (Jevtana)
- Alcaftadine (Lastacaft)
- Cefaroline (Taflaro)
- Velaglucerase alfa (VPRIV)
- Everolimus (Zortress)
- Alpha1-proteinase inhibitor (Glassia)
- Alglosidase alfa (Lumizyme)
- Sipuleucel-T (Provenge)
- Incobotulinum-toxin A (Xeomin)
- Denosumab (Xgeva)
- Collagenase clostridium histolyticum (Xiaflex)
## Top Ten Most-Read News Stories by Pharmacists in 2010

1. Propoxyphene withdrawn from US market
2. Abbott withdraws sibutramine from market
3. Gemtuzumab voluntarily withdrawn from US market
4. FDA restricts rosiglitazone: EMA pulls the plug
5. FDA issues second warning against treating leg cramps with quinine
6. Fingolimod receives FDA approval as first oral MS treatment
7. FDA approves oral contraceptive containing folate
8. FDA again warns about IV administration of nimodipine
9. FDA adds femur fracture warning to bisphosphonate label
10. FDA temporarily suspends use of rotarix vaccine