



Hot topics in Drug Therapy: New products, new uses, new warning

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Objectives

Upon completion of the program, the participant will be able to:

1. Describe recommendations for the use of new medications.
2. Understand the therapeutic advantage and risks of newer products.

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Objectives (continued)

Upon completion of the program, the participant will be able to:

3. Recognize new indications and cautions for established products.
4. Identify medications that will go off patent to generic status within the next year.

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What is hot? What is not?

- New products
- New warnings
- New indications for established medications
- New generic



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How do medications reach the market? The Process of Drug Approval

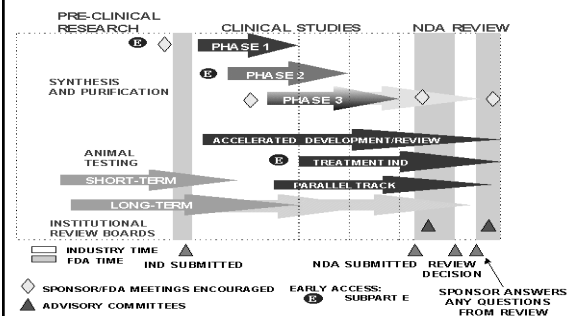
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Source:

www.fda.gov/CDER/HANDBOOK/DEVELOP.HTM



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Development, Testing, Approval of New Medications

- 0-4 years
 - *In vitro* studies
 - What is the mechanism of disease? What molecule might modify this disease? How can this molecule be purified?
 - Includes computer models and animal studies
- Around year 4
 - Investigational New Drug (IND) application to start human studies



Development, Testing, Approval of New Medications (continued)

- Phase 1
 - Is this product safe?
 - Pharmacokinetics (PK, what the body does to the drug) studies also done
 - Subjects = Healthy volunteers, usually taking no other medications, usually 20-80 subjects



Development, Testing, Approval of New Medications Years 4-9

- Phase 2
 - Does it work? Pharmacodynamic studies (PD, what the drug does to the body) expanded
 - Is it still safe? Subjects in patients with the target condition, usually a few hundred in number but might be considerably less with rare condition



Development, Testing, Approval of New Medications (continued)

- Phase 3
 - Does it work in double-blind study in patients with the target condition?
 - One goal is to evaluate the overall benefit-risk relationship of the drug.
 - Usually several hundred to several thousand patients, typically about 1500 subjects unless for a common condition such as HTN, T2DM, dyslipidemia



Phase 4 Postmarketing Surveillance

- Around year 9, the medication comes to market
 - How many subjects at this point?
 - Is it still safe in a large patient group?
- Patent expires at year 20 unless extended



“A wise prescriber avoids using new medications the first 6-12 months the product is on the market.”

Why?
Is that consistently wise advice?



If a significant problem...

- 1/15,000
- 10/150,000
- 100/1,500,000



New OTC PPI with 3 Year Exclusive Patent Extension

- Prevacid 24 hr (lansoprazole)
 - OTC dose= 15 mg
 - Standard Rx dose= 30 mg
 - Medication also recently went off patent



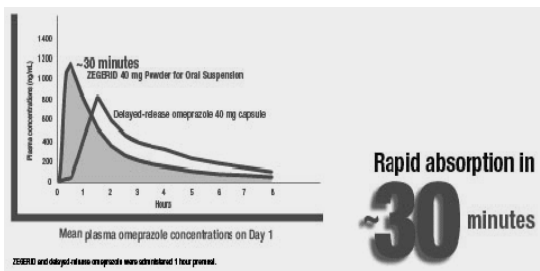
Zegerid OTC: Recent OTC Approval

- Per capsule
 - Omeprazole 20 mg with sodium bicarbonate 1100 mg
- Indication
 - Treatment of heartburn that occurs = >2 days per week
 - Labeled not to be taken for more than 2 weeks



Is this clinically significant?

Rapid release



Cost per Drugstore.com

- | | |
|-----------------------------|-----------------------------------|
| • Zegerid OTC | • Prevacid 24 hr |
| – 14 tablets= 14 day supply | – 42 tablets= 42 day supply |
| – Cost= \$11.99 | – Cost= \$26 |
| | • Omeprazole 40 mg |
| | – Generic at \$170 for 30 tablets |



New Warning about an Established Medication

FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury, available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm>, accessed 7.20.10.



Why the new warning?

- The SEARCH trial evaluated over 6.7 years the number of major cardiovascular events (heart attack, revascularization and cardiovascular death) in 6031 patients taking 80 mg of simvastatin compared to 6033 patients taking 20 mg of simvastatin. All patients in the study had previously had a heart attack.

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Why the new warning? (continued)

- Preliminary SEARCH trial results revealed that more patients in the simvastatin 80 mg group developed myopathy compared to patients in the simvastatin 20 mg group (52 [0.9%] cases compared to 1 case [0.02%]).

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Why the new warning? (continued)

- Further, FDA's preliminary analyses of the primary data suggest that 11 (0.02%) of the patients in the simvastatin 80 mg group developed rhabdomyolysis compared to no patients in the simvastatin 20 mg group.

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Caution: DI of Select Statins and Clarithromycin

- "Clarithromycin significantly ($p < 0.001$) increased the AUC and C_{max} of all 3 statins (atorvastatin, lovastatin, simvastatin {CYP 3A4 substrates}), most markedly simvastatin (approximately 10-fold increase in AUC)..."

– Am J Cardiol (2004) 94: 1140-6.

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For All Patients Taking Simvastatin

- Do not take simvastatin with:
 - Itraconazole
 - Ketoconazole
 - Erythromycin
 - Clarithromycin
 - Telithromycin
 - HIV protease inhibitors
 - Nefazodone

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For all Patients Taking Simvastatin

- Do not use more than 40 mg of simvastatin with this medication:
 - Diltiazem
- Do not use more than 20 mg of simvastatin with these medications:
 - Amiodarone
 - Verapamil

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For all Patients Taking Simvastatin (continued)

- Do not use more than 10 mg of simvastatin with these medications:
 - Gemfibrozil (Lopid)
 - No comment on fenofibrate, fenofibric acid
 - Cyclosporine
 - Danazol



What about statin choices if one of
aforementioned meds is needed?



CYP450 Substrates

- CYP450 3A4
 - Atorvastatin
 - Lovastatin
 - Simvastatin
- CYP450 2C9
 - Pitavastatin
 - Rosuvastatin
- Not metabolized by CYP450
 - Pravastatin



- Does the “no statin with grapefruit juice” warning extend to all in the class?



Simvastatin: When compared to Ingestion with Water as Control

- With grapefruit juice
 - C_{max} and AUC increased 12.0-fold ($P < .001$) and 13.5-fold ($P < .001$)
- 24 hours after last grapefruit juice
 - C_{max} and AUC increased 2.4-fold ($P < .01$) and 2.1-fold ($P < .001$)
 - Source- <http://cat.inist.fr/?aModele=afficheN&cpsid=795058>, accessed 7.20.10.



Simvastatin: When compared to Ingestion with Water as Control (continued)

- 7 days after last grapefruit juice dose
 - No change
 - Source- <http://cat.inist.fr/?aModele=afficheN&cpsid=795058>, accessed 7.20.10.



CYP450 Substrates

- CYP450 3A4
 - Atorvastatin
 - Lovastatin
 - Simvastatin
- CYP450 2C9
 - Pitavastatin
 - Rosuvastatin
- Not metabolized by CYP450
 - Pravastatin



Statin vs. Statin LDL lowering at various doses (www.prescribersletter.com)

Lova <i>Mevacor</i>		20 mg= 29%	40 mg= 31%	80 mg= 48%
Prava <i>Pravachol</i>	10 mg= 19%	20 mg= 29%	40 mg= 34%	80 mg= 48%
Simva <i>Zocor</i>	10 mg= 28%	20 mg= 35%	40 mg= 40%	80 mg= 48%
Fluva <i>Lescol</i>		20 mg= 17%	40 mg= 23%	80 mg= 33%
Atorva <i>Lipitor</i>	10 mg= 38%	20 mg= 46%	40 mg= 51%	80 mg= 54%
Rosuva <i>Crestor</i>	5 mg= 43%	10 mg= 50%	20 mg= 53%	40 mg= 62%
Pitava <i>Livalo</i>		1 mg= 30%	2 mg= 36%	4 mg= 45%



What about grapefruit juice and drug interactions?
And who first noticed this?



The Grapefruit Juice-DHP

- Initially noted in 1989 during a trial on the interaction of alcohol and DHP CCB where grapefruit juice was used to hide the taste of ethanol

– Source- Drug Interactions with Grapefruit Juice: An Evidence-Based Overview, available at <https://secure.pharmacytimes.com/lessons/200303-02.asp>, accessed 7.1.10.



Questions to ask with Grapefruit Juice-Drug Interactions

- Is the target drug
 - Metabolized by intestinal CYP3A4?
 - Given orally?
 - Low bioavailability?
 - Narrow therapeutic index (TI)?
 - Measure of relative safety of drug
 - LD50-Lethal dose in 50% subjects/
ED50-Effect dose in 50% subjects = TI



Comparing Bioavailability of DPH: Examples of Commonly Used Products

- Amlodipine
 - 64-90%
- Nicardipine
 - 35%
- Verapamil
 - 25-30%
- Felodipine
 - 15%
- Nifedipine
 - 45-56%
- Diltiazem
 - 40%



Statin vs. Statin

McTaggart F, et al.
Am J Cardiol. 2001;87(suppl):28B-32B.

	T 1/2	Bioavailability
Rosuvastatin	20 h	20%
Simvastatin	1-2 h	<5%
Atorvastatin	14 h	14%
Fluvastatin	1-2 h	24%
Pravastatin	1-2 h	17%

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New Option for Treatment of T2DM

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Medication	Mechanism of Action A1c Reduction	Comment
Dipeptidyl peptidase-4 (DPP-4) inhibitor Examples- Sitagliptin (Januvia), saxagliptin (Onglyza)	Increases levels of incretin, increasing synthesis and release of insulin from pancreatic beta cells and decreasing release of glucagon from pancreatic alpha cells. A1c reduction with intensified used =0.6-1.4%	Dose adjustment required in renal impairment. Well tolerated, little hypoglycemia risk, weight neutral. Indicated to improve glycemic control, in combination with metformin or TZD.

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Saxagliptin (Onglyza)

- Dose
 - 2.5-5 mg daily
- With renal impairment
 - No dosage adjustment recommended for creatinine clearance [Cr Cl] >50 mL/min (0.835 mL/s)
 - 2.5 mg dose recommended for Cr Cl <50 mL/min (0.835 mL/s)

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Saxagliptin (Onglyza) (continued)

- Metabolic pathway
 - CYP P450 3A4/5 substrate
- Potential interactions w/use of moderate CYP450 3A4/5 inhibitors
 - Diltiazem, amprenavir, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil
- No dose adjustment recommended

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Saxagliptin (Onglyza) (continued)

- With potent CYP 3A4/5 inhibitor
 - Ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir
- With concomitant use
 - Decrease saxagliptin dose, not to exceed 2.5 mg daily

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Cost per Drugstore.com 4.10

- Sitagliptin (Januvia)
 - 30 tablets= ~\$193
- Saxagliptin (Onglyza)
 - 30 tablets= ~\$189



Where do DDP-4 inhibitors fit?

- Pro
 - Low hypoglycemia risk
 - Little effect on basal insulin, primarily increases insulin in response to carb load
 - Weight gain neutral
 - Theoretical potential of improving or maintaining β -cell function, could alter natural history



Where do DDP-4 inhibitors fit? (continued)

- Con
 - No outcome data for macrovascular or microvascular complications or mortality with DDP-4 inhibitor use
 - Cost!



FDA Advisory: Sitagliptin

- Eighty-eight post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported to the agency between October 2006 and February 2009.

– Source- <http://www.fda.gov/Safety/MedWatch>, 4.1.10.

Medication	Mechanism of action A1C reduction	Comment
Incretin mimetics	Stimulates insulin production in response to increase plasma glucose, inhibits of glucagon release postprandial.	Major adverse effect = N/V, usually better with dose adjustment, continued use.
Example- Exenatide (Byetta)	Slows gastric emptying, often leading to appetite suppression and weight loss. Reported weight loss varies.	Contraindicated in gastroparesis.
Liraglutide (Victoza) Injection only	Anticipated A1C reduction with intensified use= 1-2%	Adjunct to improve glycemic control in T2DM when not adequately controlled with biguanide and/or sulfonylurea.



Liraglutide (Victoza)

- Glucagon-like peptide-1 (GLP-1) receptor agonist (AKA incretin mimetic)
 - Same class as exenatide (Byetta)
- Dosing
 - Subcutaneous, once a day, abdomen, thigh, upper arm, 0.6 mg once a day



Liraglutide (Victoza) (continued)

- Adverse effects liraglutide vs. glyburide
 - Which are potentially consistent with medication's MOA?
 - Nausea= 28.4% vs 8.5%
 - Diarrhea= 17.1% vs 4.8%
 - Vomiting= 10.9% vs 8.5%
 - Constipation= 9.9% vs 4.8%

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PK Implications with Medications that Slow Gastric Emptying

- Pharmacokinetics (PK)
 - Liraglutide use does not affect absorption of most medications
 - Where peak concentrations necessary for clinical efficacy, medication should be taken at least 1 h prior to liraglutide injection
 - Examples = Oral contraceptives, most antimicrobials

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Victoza (Liraglutide)

- Dose
 - 0.6-1.8 mg daily as a single injection
- Supplied
 - 18 mg/3 ml pens, a 10-30 day supply, depending on dose
 - 1 box with 2 pens= \$279.97 at drugstore.com

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Recent FDA Announcement about Byetta (Exenatide)

- FDA has approved revisions to the drug label for Byetta (exenatide) to include information on post-marketing reports of altered kidney function, including acute renal failure and insufficiency.

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Recent FDA Announcement about Byetta (Exenatide) (continued)

- Nearly 7 million prescriptions for Byetta were dispensed between April 2005 and September 2008. The 78 cases represent a small percentage of the total number of patients using the drug to control blood sugar (glucose) levels

– Source:
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm188708.htm>, accessed 4.9.10.

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Recent FDA Announcement about Byetta (Exenatide) (continued)

- The revisions to the drug label allow healthcare professionals to better weigh the known benefits of Byetta with the potential risks that exist for certain patients.

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Byetta (Exenatide) Labeling Update

- Do not prescribe with severe renal impairment (Cr Cl < 30 ml/min {0.50 mL/s}) or end-stage renal disease
- Use caution when initiating or increasing doses from 5 mcg to 10 mcg in patients with moderate renal impairment (Cr Cl = 30 to 50 ml/min {0.50-0.835 mL/s})

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Byetta (Exenatide) Labeling Update (continued)

- Monitor patients carefully for the development of kidney dysfunction, and evaluate the continued need for Byetta if kidney dysfunction is suspected while using the product.
- Advise patients about risk.
- Mechanism of problem is unclear.

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Recent FDA Advisory: Byetta

- "Byetta has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis."

– Source-
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm>, accessed 4.9.10.

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Recent FDA Advisory: Byetta (continued)

- "After initiation of Byetta, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Byetta should promptly be discontinued and appropriate management should be initiated."

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Recent FDA Advisory: Byetta (continued)

- Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.

– Source-
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm194556.htm>, accessed 2.10.10.

- Mechanism of disease
 – Unclear

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Liraglutide (Victoza): Pancreatitis Rate in Clinical Trial

- Pancreatitis rate
 – 2.2 cases per 1000 patient-years vs. 0.6 cases 1000 patient-years in individuals treated with other DM drugs

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Boxed Warning

- "Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise."



On the Horizon...

- Exenatide LAR (long-acting release)
 - Byetta in a once a week injection
- Price for the BID formulation
 - \$270 at drugstore.com (60 doses/30 days)
- Projected to double the use of the medication in USA



Emergency Contraception: Why is there a need?

After single coital act, women who do not use contraception have 7.2% chance of becoming pregnant. Emergency contraception helps to reduce pregnancy risk.



New Options for Emergency Hormonal Contraception

- Plan B One-Step
 - A single dose emergency contraceptive containing levonorgestrel 1.5 mg in a single tablet
 - Contains same total dose as Plan B in two tablet dose
- <http://www.planbonestep.com/>



New Options for Emergency Hormonal Contraception (continued)

- Next Choice
 - Identical to standard Plan B, a two-pill option
 - The first "branded generic" of HD levonorgestrel to be used as emergency contraception
- <http://www.mynextchoice.com>



Cost

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • Plan B One Step <ul style="list-style-type: none"> – \$49.99 per drugstore.com – \$10 off coupon at www.planbonestep.com | <ul style="list-style-type: none"> • Next Step <ul style="list-style-type: none"> – \$44.99 per walgreens.com – For additional information, see http://www.mynextchoice.com |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



"Make Your Own" Plan B

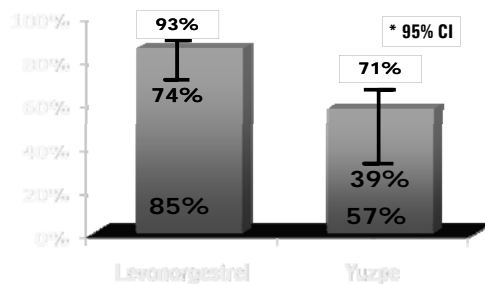
- Progestin-only pill such as Ovrette
 - 0.075 mg levonorgestrel per tablet
 - 20 tablets in two doses or 40 tablets as a one-time dose
 - Same timing rules as with Plan B
- Cost per drugstore.com
 - \$40 per 28-pill pack, will need two packs= \$80

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Proportion of Pregnancies Prevented by Levonorgestrel vs. Yuzpe Regimen



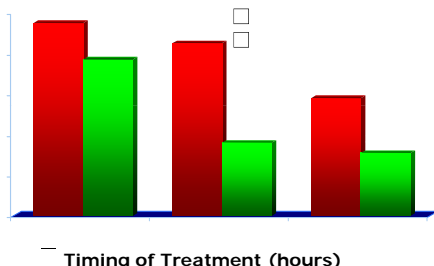
Task Force on Postovulatory Methods of Fertility Regulation. Lancet. 1998;352:428-433.

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Proportion of Pregnancies Prevented by Levonorgestrel vs. Yuzpe, by Timing of Treatment



Task Force on Postovulatory Methods of Fertility Regulation. Lancet. 1998;352:428-433.

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Getting Around the Limitations of Most Health Insurance Plans

Women who opt not to menstruate or who simply want to have fewer periods while using OC, ring, patch, and follow typical prescribing advise need to purchase extra contraception, often not covered by insurance.

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From Contraceptive Pearls 3.10

- "Cost-conscious hint: The ring contains 35 days' worth of hormones, so it can be changed every calendar month rather than every 4 weeks. The patch can be changed every 9 days rather than every week. The ring and patch are expensive, so these extra days of protection are worth a lot!"

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References

- Abrams LS, Skee D, Natarajan J, Wong FA. Pharmacokinetic overview of ortho Evra/Evra. Fertil Steril. 2002;77(2 Suppl 2):S3-12.
- Abrams LS, Skee DM, Wong FA, Anderson NJ, Leese PT. Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. J Clin Pharmacol. 2001;41(11):1232-1237.

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References (continued)

- Timmer CJ, Mulders TM.
Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. Clin Pharmacokinet. 2000;39(3):233-242.



To Sign Up for Contraceptive Pearls

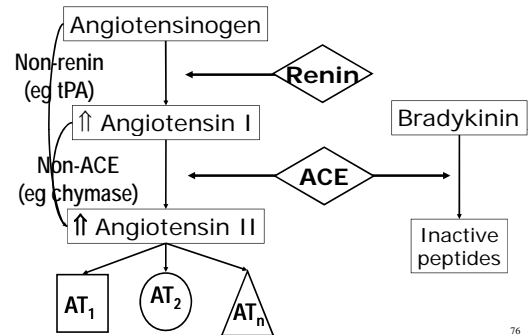
- A periodic email newsletter sponsored by Reproductive Health Access Organization
– <http://org2.democracyinaction.org/o/5854/t/6008/signUp.jsp?key=1434>



The First Drug in a Class to Become Available in Generic Form



Renin-angiotensin Cascade: What works where?



First Generic ARB Available in 2010

- Losartan (Cozaar)
 - Currently labeled for QD or BID use
 - Duration of activity likely lends best to BID dosing when renal function intact
 - As of 4.20.10, 30, 100 mg tablets= ~\$100 on drugstore.com
 - When will cost drop?



Converting from 1 ARB to Another

- Equipotent doses
 - Losartan (Cozaar) 50 mg/day
 - Candesartan (Atacand) 8 mg
 - Irbesartan (Avapro) 150 mg
 - Valsartan (Diovan) 80 mg
 - Telmisartan (Micardis) 20 mg
 - Olmesartan (Benicar) 10 mg



New Vaccine Approval for Males



Recent FDA Announcement

- HPV quadrivalent vaccine (Gardasil) approved for the prevention of genital warts (condyloma acuminata) due to human papillomavirus (HPV) types 6 and 11 in boys and men, ages 9 through 26.

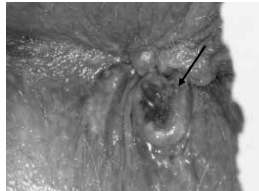
– Source-
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187003.htm>, accessed 4.20.10.



Malignant HPV-associated Disease

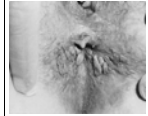
Highest risk = HPV 16, 18,
 Significant risk = HPV types 31, 33, 52, 56

- CIN and invasive cervical cancer



- Anogenital cancer



Condition	Causative Organism	Clinical Findings	Treatment
Genital warts (<i>Condyloma acuminata</i>)	Human papilloma virus, most commonly HPV - 6, -11 causing genital warts (HPV - 16, -18, -31, -33 most commonly associated with GU malignancies. Infection with multiple HPV types common)	Verruca-form lesions or may be subclinical or unrecognized 	Location of lesion can guide choice of treatment. Podofilox, liquid nitrogen, cryoprobe, trichloroacetic acid, podophyllin resin, surgical removal or imiquimod.



Gardasil ®

(Quadrivalent Human Papillomavirus {HPV} Types 6, 11, 16, 18 Recombinant Vaccine)

- Human papillomavirus (HPV) Types 6, 11
 - Cause of ~90% genital warts
- Human papillomavirus (HPV) Types 16, 18
 - Cause of ~70% cervical cancers
 - 50% vulvar/vaginal intraepithelial neoplasias as well as anal, male genital neoplasias



Gardasil ®

(Quadrivalent Human Papillomavirus {HPV} Types 6, 11, 16, 18 Recombinant Vaccine)
 (continued)

- Efficacy with all 3 vaccine doses given by schedule development in males via development of humoral immune response
 - 89% efficacy in prevention of HPV 16/18-related disease



Gardasil ®

(Quadrivalent Human Papillomavirus {HPV}
Types 6, 11, 16, 18 Recombinant Vaccine)
(continued)

- No therapeutic impact
 - On existing HPV-related disease
- No indication yet in males for malignancy prevention



True or false?

- Cervarix (HPV type 16, 18 bivalent vaccine) can be substituted for Gardasil in providing HPV protection against genital warts.



True or false?

- The use of HPV vaccine (Gardasil, Cervarix) has been associated with an increase of early onset sexual activity in preadolescents and adolescents who receive the immunization.



You are asked about giving acetaminophen prior to immunizations...

- By the parents of a healthy 6 month-old who was a "bit fussy and warm" for a day after her 4 month-old immunizations.
- Is this a helpful or harmless practice?

– Source- *Detail-Document*; Prescriber's Letter 2009; 16(11):251105.



Antipyretics: After, but not before, Vaccine, and then only if Needed

- Giving acetaminophen prior to vaccine might impact immunologic response
 - Studied in diphtheria, tetanus, acellular pertussis, *H. influenzae* type B, pneumococcal vaccines
- Proposed mechanism
 - Effect on cell-mediated response by selectively inhibiting cyclo-oxygenase-2



New Warning About Existing Sleeping Aid; New Option in Sleeping Aid



Recent FDA Warning in Patient Drug Information

- "...sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving."



Recent FDA Warning in Patient Drug Information (continued)

- "Sleep driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event."



Silenor (Doxepin)

- Recently FDA approved as sleep aid
- Recommended dose
 - 3 mg (elder) or 6 mg (adult)
 - Take within 30 mins of going to bed
 - Do not take within 3 h of a meal
 - Alters PK



Silenor (Doxepin) (continued)

- CYP450
 - 2C9, 2C19 substrate
- Potential drug interaction
 - Cimetidine-concomitant use nearly doubles doxepin exposure
 - Only SSRI mentioned in PI is sertraline (Zoloft) with minimal PK effect



Silenor (Doxepin) (continued)

- PK parameters
 - T_{max} = 3.5 h post dose when taken on an empty stomach
 - Doubled when taken with a high fat meal, labeled warning
 - T_{1/2} = 15.3 h



CYP450 Isozyme Inhibition by the SSRIs

	CYP Isoenzymes				
	1A2	2C9	2C19	2D6	3A4
Escitalopram	0	0	0	0	0
Citalopram	+	0	0	+	0
Fluoxetine	+	++	+ to ++	+++	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition*.
von Moltke et al., 2001; Greenblatt et al., 2002; Greenblatt et al., 1998



Silenor (Doxepin) (continued)

- Pharmacogenomic warning
 - Poor CYP2C9, 2C19 metabolizers will likely have greater doxepin exposure



Silenor (Doxepin) (continued)

- Cost
 - TBD
- Generic doxepin at drugstore.com
 - 90, 10 mg capsule= \$19
 - 10 mg/ 1ml liquid= 120 ml= \$16



References (continued)

- Fitzgerald, M., Miller, S. Comprehensive Clinical Pharmacology Course, Available at <http://www.fhea.biz/pharmlive.aspx?BC=home>, accessed 8.05.10.
- Fitzgerald, M., Miller, S. Pathophysiology for Advanced Practice Course, Available at <http://www.fhea.biz/nprpharmdetail.aspx?ID=3849&Column=NPR>, accessed 8.05.10.



References (continued)

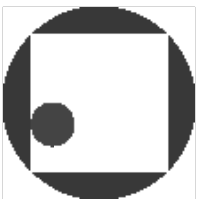
- Fitzgerald, M.A. (2010) Nurse Practitioner Certification Examination and Practice Preparation, 3rd Edition, Philadelphia: F. A. Davis. Available at www.fhea.biz



End of Presentation!

Thank you for your time and attention.

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