Family Medicine Clinical Pharmacy Forum

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Family Medicine Clinical Pharmacy Forum is a brief bi-monthly publication from the Family Medicine clinical pharmacists distributed to faculty and residents of the Department of Family Medicine. Our intent is to provide timely information on broad-based issues of pharmacotherapy, as well as regulatory and practiced-based issues affecting you as a prescriber. If you have suggestions for things you would like to see, please contact us.

Contents

Pharmacotherapy Issues:

Role of Androgen Therapy in Women

Are androgens effective for the treatment of low sexual desire in women? Results of some studies seem to indicate they might be.

- A Baylor College of Medicine study compared 24 weeks of 300 mcg transdermal testosterone vs. placebo in 533 surgically menopausal women with hypoactive sexual desire disorder on concomitant estrogen. Patients in the treatment group experienced significant improvements in satisfying sexual activity ($p=0.001$) and sexual desire ($p<0.001$). -Obstetrics & Gynecology 2005; 105(5):938-40
- A similar study compared 24 weeks of 150 mcg, 300 mcg, and 450 mcg testosterone patches vs. placebo in 447 surgically menopausal women with hypoactive sexual desire disorder on concomitant estrogen. When compared to placebo, the study found no difference with the 150 mcg patch and similar improvements in sexual desire ($p=0.05$) and satisfying sexual activity ($p=0.049$) with the 300 mcg and 450 mcg patches. -Archives of Internal Medicine 2005; 165(14): 1571-2
- A Columbia University study compared 16 weeks of oral estrogen vs. oral estrogen+methyltestosterone (*Estratest HS*) in 118 postmenopausal women with hypoactive sexual interest or desire. Patients in the combination group experienced significant improvements in sexual desire ($p<0.02$) and frequency of desire ($p<0.01$). -Mayo Clinic Proceedings 2004; 79(suppl): S19-S24

Although these results are promising, some experts question the clinical significance of these findings, and currently, no products are FDA approved for treatment of low libido.

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- **The FDA has postponed approval of Intrinsa**, a 300 mcg testosterone patch due to concerns on long-term safety and the unknown risks of breast cancer and cardiovascular problems, especially since most studies support concomitant estrogen therapy.
  -Pharmacist's Letter/Prescriber's Letter 2005;21(1):210112
- A position statement by the North American Menopause Society supports testosterone use only for hypoactive sexual disorder and recommends transdermal over oral administration. -Menopause 2005; 12(5): 497-511

When considering androgen therapy, don't forget to take the 4 C's into account:

- Cost. #60 Estratest HS tablets $136.99 -www.walgreens.com Accessed 9/12/05
  #30 Androgel 1% packets (2.5 g each) $189.99
- Compounding. NuCara pharmacy makes a testosterone cream at strengths of 1 to 20 mg per 0.5 mL. The cream is applied to the jaw, inner wrists, or inner thighs BID. A 30 day supply costs $36.00. They also make a mini-troche at strengths of 1-4 mg of testosterone taken 1 to 3 times daily. A 30 day supply costs $32.10.
- Concurrent disease states. Testosterone in contraindicated in women with breast or uterine cancer and cardiovascular or liver disease.
- Counseling. All patients should be aware of the potential unknown risks and possible benefits of therapy.

The Squeeze on the Grapefruit Juice Interaction

The study of grapefruit juice and its interaction with certain medications has been a popular research topic in recent years. This effect was discovered coincidentally in a study involving felodipine in 1989, and since that time, various studies have indeed shown that grapefruit juice does increase the bioavailability of certain medications.

How exactly does it do this? Grapefruit contains furanocoumarins, which decrease intestinal CYP3A4 activity through reversible and irreversible inhibition and loss of the enzyme. Less CYP3A4 activity results in decreased metabolism of some drugs metabolized primarily through the CYP3A4 system, most of which also tend to have highly variable oral bioavailability. This drop can occur following consumption of only 8 ounces of grapefruit juice with some medications, but the affect of the interaction may increase when more juice is consumed.

Therefore, some researchers recommend that patients taking certain medications avoid drinking grapefruit juice. Table 1 lists medications with which grapefruit juice should be avoided. Major classes involved include some calcium channel blockers, some HMGCoA reductase inhibitors, and some benzodiazepines. Consuming grapefruit juice up to 24 hours before taking these agents could result in increased serum levels and, although rare, serious adverse effects. **Therefore, having patients stagger the timing of their meds will not typically lessen the interaction (e.g. grapefruit juice in the morning and medications at night).**

Overall, the seriousness of this interaction varies from patient to patient. In patients who have been consuming grapefruit juice with medications and have not experienced adverse effects, it is probably not significant. Also, it is important to note that CYP3A4 levels vary among individuals, and patients with lower levels will be less affected by grapefruit juice because there is less CYP3A4 to inhibit.

-European Journal of Clinical Nutrition 2004 Jan; 58(1):1-9.

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-The Medical Letter. 2004 Jan 5; 46(1173):2-4.
-Clinical Pharmacology & Therapeutics 2004 Jan; 75(1):1-12.
-Canadian Medical Association Journal 2002 Aug; 167(3).
-Mayo Clinic Proceedings 2000; 75:933-42.

Table 1 Medications to Avoid with Grapefruit Juice

Medication	Possible Adverse Effect	Medication	Possible Adverse Effect
Amiodarone (*Cordarone*)	Arrhythmias	Nifedipine (*Procardia*)	Tachycardia, hypotension
Amlodipine (*Norvasc*)	Tachycardia, hypotension	Nimodipine (*Nimotop*)	Tachycardia, hypotension
Atorvastatin (*Lipitor*)	Myopathy, rhabdomyolysis	Saquinivir (*Invirase*; *Fortovase*)	Unknown
Buspirone (*BuSpar)*	Increased sedation	Sildenafil (*Viagra*)	Headache, flushing dyspepsia
Carbamazepine (*Tegretol*)	Drowsiness, ataxia, nausea	Simvastatin (*Zocor*)	Myopathy, rhabdomyolysis
Cyclosporine (*Sandimmune*; *Neoral*)	Renal, hepatic dysfunction	Sirolimus (*Rapamune*)	Unknown
Diazepam (*Valium*)	Increased sedation	Tacrolimus (*Prograf*)	Unknown
Felodipine (*Plendil*)	Tachycardia, hypotension	Terfenadine	
Lovastatin (*Mevacor*)	Myopathy, rhabdomyolysis	Triazolam (*Halcion*)	Increased sedation
Midazolam (*Versed*)	Increased sedation		

Hypertension and OTC pain relievers.

A recent article in the journal Hypertension used the Nurses' Health Studies to examine the effect of aspirin, ibuprofen and acetaminophen on hypertension. Previous reports have published similar data from the Nurses' Health Studies, however subjects of this study were not subjects in any of the previous publications. Women who reported taking no analgesics per month were compared to women who took analgesics more than 15 days per month. Subjects were surveyed regarding current use of aspirin, acetaminophen and NSAIDs including frequency of use, number of tablets used, dosage per tablet, brand used and indication for usage.

In NHS1 participants whose daily acetaminophen intake exceeded 500mg, the risk of developing hypertension was 6.9% versus 3.2% in patients who did not take any acetaminophen ($p<0.001$). This is a 93% increased relative risk of developing hypertension after controlling for potential confounders. Those women who used >400mg ibuprofen daily had 78% increased risk for development of hypertension, and those who used >800mg daily had a 2.17-fold higher risk of incident hypertension.

In NHSII, a higher average daily dose of acetaminophen and NSAIDS was also associated with an increased risk of hypertension. Women who used >500mg of acetaminophen/day had a 2-fold increase in incident hypertension. Women who used >400mg or 800mg of ibuprofen daily had relative risks of 1.60 and 1.61 respectively for incident hypertension. This relationship between ibuprofen and incident hypertension did not hold true when controlled for number of physician visits.

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A separate analysis was performed to exclude women who used non-narcotic analgesics for headache. In this subset, acetaminophen and ibuprofen intakes were associated with incident hypertension in both NHSI and NHSII. Older women who consumed more than 500mg/day of acetaminophen had a 2.4-fold increase in incident hypertension and this risk increased to 4.7 in younger women. In those women with ibuprofen intake >400mg/day, the relative risk of incident hypertension was 1.75 in older women and 3.7 in younger women.

NSAIDs as well as higher average doses of acetaminophen are associated with a greater risk of incident hypertension. In this study, aspirin was not associated with increased incident hypertension. This association may be due to effects on endothelial function or inhibition of vasodilatory prostaglandins. Although study subjects were not directly examined by researchers, all participants were registered nurses and hypertension reporting has been previously shown to be reliable. **These data support the hypothesis that NSAIDs and acetaminophen may independently elevate the risk of hypertension.** As these are the most commonly used medications in the US, the contribution of these to incident hypertension deserves further study.

Forman J, Stampfer M, Curhan G. Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension*. 2005;46:500-507.

Rozerem (ramelteon) is the newest agent on the market approved for insomnia characterized by difficulty with sleep onset. It is a **melatonin receptor agonist** acting on MT1 and MT2 receptors and is not a controlled substance. Agonism of these receptors, as in the case of endogenous melatonin, results in the maintenance of the normal circadian rhythm which regulates the sleep-wake cycle. Peak concentrations occur between 30-90 minutes after administration and T1/2 is 1-2.6 hours. The recommended dose is 8mg 30 minutes prior to bed. This medication should not be taken with a high fat meal as Cmax may be decreased by up to 20%. Clinical trials show ramelteon reduced latency to persistent sleep when compared to placebo and showed no increased residual effect, withdrawal or rebound insomnia compared to placebo. Caution should be used in patients with hepatic impairment, however no adjustment is needed for patients with renal impairment. Ramelteon should not be used in patients with severe COPD or sleep apnea. Ramelteon is primarily metabolized by the CYP1A2 and should not be used in combination with fluvoxamine. Metabolism by the CYP2C family and CYP3A4 also occurs. Possible adverse effects include somnolence, dizziness, nausea, fatigue and headache. Wholesale acquisition cost is $2.25/8mg tablet.
Reference: Rozerem product labeling.

Practice-based issues:

- **Are Cephalosporins safe in patients with Penicillin allergies?**

- The American Academy of Pediatrics (AAP) recently endorsed the use of Cefuroxime, Cefpodoxime, Cefdinir and Ceftriaxone for common pediatric illnesses such as acute bacterial sinusitis and acute otitis media in penicillin-allergic patients as long as the reaction is not

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severe. Severe reactions include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome with multiorgan involvement.

- **The 5-10% chance of cross-sensitivity to cephalosporins in penicillin-allergic patients is no longer held true. As a rule, the cross-allergy risk from first-generation cephalosporins is 0.5% and the risk from second-generation and third-generation cephalosporins is near zero.**
- Approximately 0.004% to 0.015% of treatment courses with penicillin result in anaphylaxis. Anaphylactic reactions from cephalosporins are even rarer, with the risk estimated at 0.0001% to 0.1%.
- The rate of cross-reactivity between penicillin and most second-, third-, and fourth-generation cephalosporins is low and may actually be lower than that between penicillins and other classes of antibiotics. Several studies have suggested that the immune response to cephalosporins depends more on their side chain substituents; that is, cephalosporins with a side chain similar to benzylpenicillin are more likely to cross-react with penicillin and those with side chains like ampicillin are more likely to cross-react with ampicillin and amoxicillin (see table below).
- Likelihood of cross-reactivity between penicillin and cephalosporins based on side chain position and group (cephalosporin generation)

Chemical Structures of 7-position Side Chains of Penicillins and Cephalosporins				
Similar Structure/Possible Cross-Reactivity with Group			**Dissimilar Structures/Unlikely Cross Reactivity**	
Related	**Related**	**Related**	**Not Related**	**Not Related**
Penicillin G	Amoxicillin	Cefotaxime	Cefsulodin	Cefotiam
Cephaloridine	Ampicillin	Ceftizoxime	Cefazolin	Ceftazidime
Cephalothin	Cefaclor	Ceftriaxone	Cefonicid	Cefamandole
Cefoxitin	Cephalexin	Cefpodoxime	Cefotetan	Cephapirin
	Cephradine	Cefpirome	Cefuroxime	Cefixime
	Cefprozil	Cefepime	Cefoperazone	Cefmetazole
	Cefatrizine	Cefetamet	cefdinir	Ceftibuten
	cefadroxil	cefteram		moxalactam

†examples: cephalothin would be a relatively poorer choice to use in a pt with a penicillin allergy; cephalexin would be a poorer choice in a patient with an amoxicillin allergy; cefdinir would appear relatively safe in a patient with an amoxicillin or Pen allergy.

Pediatrics 2005; 115: 1048-1057

● Cross-reactivity between Sulfonamide antibiotics and Sulfonamide non-antibiotics.

- There is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide non-antibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs (a history of penicillin allergy is at least as strong as a risk factor.)
- If sulfonamide-based nonantibiotics were to be avoided in those with a prior sulfa allergy, they would also have to be avoided in those with a prior penicillin allergy.
- Sulfur-containing medications include amoxicillin, captopril, omeprazole, ranitidine, spironolactone, sulindac, rofecoxib; sulfites (used as antioxidants in food and drugs: sodium sulfite, sodium bisulfite, and sodium/potassium metabisulfite) and sulfates (sulfate salts used to

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stabilize drugs: ferrous sulfate) do not contain a sulfonamide group and therefore do not carry the risk of cross-sensitivity with sulfonamides.

- Sulfonamide nonantibiotic drugs:

Drug Class	Sulfonamide drugs	Alternatives
Antibiotics	Sulfadiazine, sulfapyridine, Sulfamethoxazole, sulfisoxazole, sulfacetamide	Cephalosporins, Clindamycin, macrolides Penicillin
Anti-inflammatory agents	Celecoxib, Valdecoxib	Rofecoxib, non-selective NSAIDs
Anti-glaucoma agents	Acetazolamide, Brinzolomide	Beta-blockers, Prostaglandin analogues
Diuretics	Bumetanide, Chlorthalidone Furosemide, HCTZ, Metolazone, Torsemide Indapamide	Amiloride, Spironolactone, Triamterene
Hypoglycemics	Glyburide, Glimepiride, Tolbutamide, Glipizide	Metformin, thiazolidinediones

NEJM 2003; 349: 1628-1635

Medicare Part D

Medicare prescription drug coverage begins Jan 1, 2006 and will be available to all Medicare recipients who are enrolled. **Enrollment begins Nov 15, 2005** and patients can enroll by either calling the company offering the plan, or by calling 1-800-MEDICARE. Patients have a choice of which plan they would like to enroll in. Patients who do not enroll by May 15, 2006 will have to pay additional fees to join later. If your patient receives a letter and 4-page application from Social Security, they should fill it out and mail it back.

Both brand and generic prescriptions will be covered and there is additional assistance available for those with limited income. With the average plan, once a patient has enrolled, he/she will pay a monthly premium (about $37) and will pay a portion of the cost of their medications. Individuals with yearly incomes less than $14,355 and couples with yearly incomes less than $19,245 may be eligible for additional assistance and lower copays. Patients should be referred to the Medicare information line, 1-800-MEDICARE, the state information line, 1-800-351-4664, or www.medicare.gov. Patients who are eligible for additional assistance can call the SSA at 1-800-772-1213 or visit www.socialsecurity.gov.

Prescription Price Update

- Ouch! Check out the prices below for a **30 day supply** of long-acting narcotics. These prices are current retail costs from a local community pharmacy in Waterloo. **Generic MS Contin appears to be the least expensive alternative at low to moderate doses**. Duragesic patches are available generically, but it still remains rather expensive.

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Drug	Strength/Qty	Price ($)
Duragesic/generic	25mcg Q72H #10	149.59/135.09
Duragesic/generic	50mcg #10	269.09/242.09
Duragesic/generic	75mcg #10	407.69/367.39
Duragesic/generic	100mcg #10	652.89/485.99
Oxycontin	10mg BID #60	99.84
Oxycontin	20mg BID #60	190.12
Oxycontin	40mg BID #60	336.58
Oxycontin	80mg BID #60	632.07
MS Contin (generic)	**15mg BID #60**	**64.40**
MS Contin (generic)	**30mg BID #60**	**96.69**
MS Contin (generic)	100mg BID #60	269.59

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