OREGON DUR BOARD NEWSLETTER

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Newsletter Starts Up Again

With this issue, the Oregon Drug Utilization Review Board is launching a newsletter. The goal of the newsletter is to provide useful clinical information to prescribers and pharmacists. It is intended to assist them in providing high quality, cost-effective drug theray for their patients. The Newsletter is also a communication tool to disseminate important information regarding drug utilization of the fee-for-service Medicaid population .

A planned regular feature is *Prescribing Pearls* which reports important trends the DUR Board has noticed in their review. Each newsletter will include a more in-depth article about a current clinical topic, a new drug evaluation, or guidance for prescribers interested in choosing cost-effective therapies.

The Oregon DUR Board is federally mandated through OBRA '90 legislation, and is made up of volunteer members from throughout the state. There are five pharmacists, four physicians and one dentist currently serving on the board. The DUR Board evaluates and makes recommendations on the Prospective and Retrospective DUR programs. The DUR Board also is responsible for overseeing drug therapy educational efforts by the Oregon Medical Assistance Program.

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Clinical Considerations for Generics

By: Ann Hamer, R.Ph. (Pharm.D. Candidate) and Kathy L. Ketchum, R.Ph., MPA:HA; OSU College of Pharmacy at OHSU.

The word generic, meaning "being or having a nonproprietary name," has acquired an undeserved negative connotation often associated with terms such as plain-packaged, cheap or lacking quality. In this context, generic drugs have been misrepresented.

Generic drug products, as they become increasingly available, provide prescribers with an opportunity to reduce drug costs while maintaining quality of care. Although the FDA maintains strict standards and regulations regarding generic substitution, many practitioners have a negative view of generic drugs. The purpose of this article is to present a brief overview of generic bioequivalence standards and definitions, and to discuss clinical issues relevant to generic substitution.

The Food and Drug Administration (FDA) regulates generic drug manufacturing by setting standards for bioequivalence. After patent expiration of the brand drug product, a generic drug product may be developed. The generic product will contain the same amount of the drug in the same type of dosage form. The generic drug product must be bioequivalent, but it may differ from the brand product in physical appearance (i.e., size, color, shape) or in the amount and type of excipients. Before the generic drug product is marketed, the manufacturer must submit an Abbreviated New Drug Application (ANDA) to the FDA for approval. Because pre-clinical

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"This pharmacy may be able to substitute a less expensive drug which is therapeutically equivalent to the one prescribed by your doctor."

Prescribing Pearls

Cisapride Drug Interactions

The RetroDUR and ProDUR programs indicate cisapride is dispensed to patients who are also prescribed drugs that interact dangerously with it. The FDA includes a boxed warning for cisapride which states: "serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, Torsade de Points and QT prolongation have been reported in patients taking cisapride and other drugs that inhibit cytochrome P450 IIIA4. The drugs include ketoconazole, itraconazole, miconazole IV, trolendemycin, erythromycin, fluconazole and clarithromycin. Some of these events have been fatal."

ProDUR alert data from August of 1997 indicates the following rates of cisapride drug interaction alerts for paid cisapride claims submitted (614 Rx's).

Erythromycin	7.5% (46 Rx's)
Fluconazole	6.7% (41 Rx's)
Clarithromycin	5.2% (32 Rx's)
EES/Sulfisoxazole	0.8% (5 Rx's)
Itraconazole	0.3% (2 Rx's)
Ketoconazole	0.2% (1 Rx)
TOTAL	20.7% (127 Rx's)

The incidence of adverse outcome cannot be determined from the available data. However, the manufacturer recommends against the use of cisapride in combination with these drugs. An alternative is to switch to metoclopramide and/or discontinue the cisapride, and allow 40-50 hours (longer if hepatic or renal impairment exists) for washout before starting antibiotic/anti-fungal therapy. Another alternative is to choose an antibiotic/anti-fungal that is not listed.

Opiate/Acetaminophen Combinations

A nuance of the ProDUR alerting system is that opiate/acetaminophen combinations are screened for high dose alerts based only on the opiate component. The alert notifies the pharmacy of excessive opiate dose (i.e. hydrocodone >44 mg). However, the danger is really in the acetaminophen component.

Acetaminophen is hepatotoxic. The maximum, adult daily dose of acetaminophen is 4000 mg. Liver damage has occurred with a single dose of 5850 mg.

Routinely, opiate/acetaminophen combinations are prescribed at greater than the maximum daily acetaminophen dose. For example, Darvocet-N-100 is often prescribed at 1-2 tabs q4-6h prn pain and could result in 7800mg of acetaminophen taken by a patient in one day.

The acetaminophen content of commonly prescribed combinations is listed in Table 1.

Table 1:
OPIATE/ACETAMINOPHEN COMBINATION PRODUCTS

Drug	Opiate	Acetaminophen	No. Tabs to Max Dose
Tylenol #3	30mg	325mg	12/d
Vicodin/Lortab	5mg	500mg	8/d
Vicodin ES	7.5mg	750mg	5/d
Darvocet-N-100	100mg	650mg	6/d
Percocet-5	5mg	325mg	12/d

The ProDUR alert report indicates potentially excessive acetaminophen doses at the following rates for the federal fiscal year of 1997 ending in October. The accuracy of the data is dependent on reliable entry of the "days supply" field by the pharmacist and may be skewed. However, it does indicate a trend. Again, the actual incidence of adverse outcome is not able to be determined.

Table 2:
Alert Rates for Excessive Acetaminophen Dose

DRUG	Alert Rate	# of Alerts	# Pd. Claims
Hydrocodone with APAP	18.8%	6,679	35,452
Propoxyphene N/APAP	18.7%	2,658	14,314

The DUR Board recommended to continue screening for excessive acetaminophen doses because of the serious nature of the toxicity and the apparent wide spread overdosing of it in combination with opiates. ■

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safety and efficacy studies have already been performed for the brand product, only bioequivalence studies are required for the ANDA. In addition, the FDA monitors the generic makers' production sites and blocks the marketing of any drugs that are produced in substandard facilities. (See "Definitions and Standards" box below.)

FDA bioequivalence standards allow for 20% variation from product to product. In practice, the great majority of products fall within 3% variation. These numbers warrant some perspective. In randomized control trials of drugs vying for FDA approval, a 50% increase in dose rarely causes a statistically different therapeutic effect.

"The word generic, meaning 'being or having a nonproprietary name,' has acquired an undeserved negative connotation often associated with terms such as plain-packaged, cheap or lacking quality. In this context, generic drugs have been misrepresented."

The vast majority of generic drugs will not cause a detectable clinical effect except in rare cases of drugs that have extremely variable bioequivalency coupled with narrow therapeutic index. In these cases, a patient should be stabilized on a single source of drug. A patient may be stabilized on a generic or brand drug, but switching indiscriminately is not recommended. Examples of drugs with narrow therapeutic indexes and highly variable bioequivalence are: digoxin, phenytoin, and carbamazepine.

Extended release dosage forms can be substituted with caution. The rate of absorption is the most difficult to control. However, in most cases, the rate of absorption is not clinically relevant but the extent of absorption and peak levels are. Theophylline products are an example of this phenomenon. Patients should be stabilized on a particular product.

There are not reliable bioequivalency standards yet for the biotechnologically produced peptides and proteins and they should not be substituted.

Pharmacists should routinely notify the prescriber when generic substitutions are made. They need to monitor patients for untoward effects (e.g. the rare allergy to an excipient). They also are responsible for counseling patients about characteristics of the substituted product that may be different (shape, packaging or color). This counseling is a crucial element of a successful substitution. It makes the patient more comfortable with the product and improves their compliance.

Generic drugs provide a viable avenue to reduce the cost of drug therapy. The FDA has set and maintains standards for the production and evaluation of generic drug products. While there are precautions that limit the indiscriminate use of generic substitution, in many cases prescribers have the ability to limit drug costs by choosing a therapeutically equivalent, less expensive product. ■

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DEFINITIONS AND STANDARDS

- **Pharmaceutical Equivalents**: Drugs that have the same active ingredient(s), are of the same dosage form, same route of administration and are identical in strength or concentration. They may differ in shape, packaging, excipients (i.e. color, flavor) and expiration time.
- **Pharmaceutical Alternatives**: Drugs that contain the same therapeutic moiety, but may be different salts (i.e. erythromycin stearate vs. erythromycin ethosuccinate). Different dosage forms and strengths of the same moiety are also considered pharmaceutical alternatives.
- **Therapeutic Equivalents**: Pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Only therapeutic equivalents are considered safe for generic substitution. One of the five criteria that must be met in order to be considered therapeutic equivalents is the requirement for bioequivalence.
- **Bioequivalent**: Pharmaceutical equivalents or pharmaceutical alternatives that display comparable bioavailability when studied under similar experimental conditions.
- **Bioavailability**: The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

The FDA publishes the standards and definitions it uses to judge drug bioequivalency and a list of the approved drug products with therapeutic equivalence evaluations in *The Orange Book*. This is available on the Internet at **http://www.fda.gov.cder.**

Cost-Effective Prescribing:
Specific Cases Where Generics Save Money and Maintain Quality

By: Dean Haxby, Pharm.D.

NSAIDS

Non-steroidal anti-inflammatory drugs (NSAIDs) are a commonly prescribed class of drugs. Table 3 lists the top ten NSAIDs by dollar cost for the fee-for-service Oregon Medicaid Program. This utilization data indicates considerable opportunity to reduce costs and maintain quality.

Table 3: TOP TEN NSAIDs PAID FOR BY OMAP

Drug Name	Dollars Paid by OMAP from Aug. 97-Jan. 98	No. Of Claims Paid by OMAP Aug. 97-Jan. 98	Average Amt. Paid per Rx by OMAP
NABUMETONE	$165,605.83	2685	$61.68
ETODOLAC	$63,681.06	1060	$30.08
IBUPROFEN	$55,512.43	6999	$7.93
DICLOFENAC SODIUM	$44,907.81	856	$52.46
NAPROXEN	$42,137.05	2724	$15.47
KETOPROFEN	$36,271.73	637	$56.94
SALSALATE	$18,225.88	937	$19.45
NAPROXEN SODIUM	$15,057.58	598	$25.18
BROMFENAC SODIUM	$14,259.52	447	$31.90

Relafen® (nabumetone) has been promoted as an NSAID that causes fewer GI side effects. In recent comparison studies, however, the rate of GI bleeding associated with nabumetone was found to be similar to other NSAIDs. According to FDA spontaneous reports, nabumetone had three times the number of reported GI incidents compared to naproxen.[1]

NSAID Prescribing Recommendations

- Ibuprofen is a good first choice for NSAID therapy due to its relatively low toxicity profile and low cost.
- For non-inflammatory conditions like osteoarthritis, consider acetaminophen as first line therapy, or if using an NSAID, use lower doses.
- Before switching NSAIDS, make sure full doses at regularly scheduled intervals have been taken for at least 2 weeks.
- If an adequate trial of three NSAIDS does not produce the desired effect, additional NSAID trials are probably not going to be useful.
- Keep expectations for therapy realistic.
- Toradol® or Duracet® are not more effective than ibuprofen or naproxen, but are significantly more expensive and may have higher toxicity.

Table 4: INDIVIDUALIZING NSAID THERAPY

Clinical Situation	Recommended Drug
osteoarthritis	*acetaminophen or ibuprofen*
ankylosing spondylitis	*indomethacin*
warfarin/increased bleeding risk	*salsalate*
acute gout	*indomethacin*
acute athletic injury	*ibuprofen*
mild renal impairment	*salsalate or sulindac*
elderly	*avoid indomethacin and piroxicam*
gastropathy risk	*acetaminophen or salsalate*

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Table 5: NSAID COST COMPARISON

MOST Cost-Effective Drugs	Dose	Cost/ 10 Days Tx (1)	Cost Per Year (1)
piroxicam (generic FELDENE®)	20mg QD	$1.00	$30
indomethacin (generic INDOCIN®)	25mg TID	$1.00	$33
ibuprofen (generic MOTRIN®)	600mg TID	$1.00	$44
aspirin	650mg QID	$1.00	$51
naproxen (generic NAPROSYN®)	375mg BID	$3.00	$111
sulindac (generic CLINORIL®)	150mg BID	$4.00	$128
naproxen sodium (generic ANAPROX®)	275mg TID	$4.00	$154
flurbiprofen (generic ANSAID®)	100mg BID	$7.00	$254
salsalate (generic DISALCID®)	1500mg BID	$10	$364
LESS Cost-Effective Drugs	**Dose**	**Cost/ 10 Days Tx**	**Cost Per Year**
choline magnesium trisalisylate (generic TRILISATE®)	1500mg BID	$12	$434
diflunisal (generic DOLOBID®)	500mg BID	$17	$636
RELAFEN®★ (nabumetone)	500mg BID	$21	$750
LODINE XL®★ (etodolac ER)	400mg BID	$22	$816
DAYPRO®★ (oxaprozon)	600mg BID	$24	$894
ORUVAIL®★ (ketoprofen ER)	200mg QD	$25	$899
diclofenac sodium EC (generic VOLTAREN®)	50mg TID	$25	$907
ketoprofen (generic ORUDIS®)	50mg QID	$33	$1,194
DURACET®★ (bromfenac)	25mg QID	$37	$1,348
ORUDIS® (ketoprofen)	50mg QID	$40	$1,449
CATAFLAM®★ (diclofenac potassium IR)	50mg TID	$44	$1,614
TORADOL®★ (ketorolac)	10mg QID	$47	$1,714

BETA-BLOCKERS

Beta-blockers are useful therapeutic agents in a variety of cardiovascular conditions. Regular release atenolol, metoprolol and propranolol are extensively studied beta-blockers with proven outcome data to support their use. Fortunately, they are also the least expensive beta-blockers available. Thus they are the preferred agents.

One opportunity to lower cost is to reduce the use of sustained release beta-blockers. For example, Toprol XL is a sustained release form of metoprolol that is over four times as expensive as regular release metoprolol (See table 6).

Toprol XL offers no real advantage over normal release beta-blockers. In fact, in a study evaluating ambulatory blood pressure monitoring, "long acting" beta blockers did not control blood pressure throughout the entire day.[2,3]

Prescribing Recommendations for Beta-Blockers:

- Atenolol is a good choice in most circumstances because it is cardioselective, well tolerated, inexpensive and can be dosed once daily.
- Beta-blockers are proven to reduce the risk of hypertensive complications and are recommended as preferred first line anti-hypertensives along with thiazide diuretics.
- Beta-blockers are first line agents along with nitrates in the management of stable and unstable angina.
- They also significantly reduce the risk of re-infarction and death post MI.
- Brand name and extended release beta-blockers do not offer any advantages over generic regular release beta-blockers, but they are much more expensive.
- When discontinuing therapy, beta-blockers should generally be tapered.

Table 6: BETA-BLOCKER COST COMPARISON

MOST Cost-Effective Drugs	Dose	Cost Per Year (1)
atenolol (generic TENORMIN®)	50mg QD	$16
propranolol (generic INDERAL®)	80mg BID	$18
metoprolol (generic LOPRESSOR®)	50mg BID	$56
LESS Cost-Effective Drugs		
pindolol (generic VISKIN®)	10mg BID	$159
nadolol (generic CORGARD®)	80mg QD	$241
TOPROL XL®★ (metoprolol ext. rel.)	100mg QD	$259
ZEBETA®★ (bisoprolol)	10mg QD	$264
KERLONE®★ (betaxolol)	10mg QD	$270
acebutolol (generic SECTRAL®)	400mg QD	$391
propranolol LA (generic INDERAL LA®)	160mg QD	$425
NORMODYNE®★ (labetalol)	200mg BID	$492

★ Brand name available only
(1) Cost to Oregon Medicaid Program excluding dispensing fees

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We hope you found this issue of the
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useful as well as thought-provoking and interesting.
If you have any questions, concerns, comments or ideas regarding this newsletter,
please forward them to the managing editor:

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