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AN EVIDENCE BASED DRUG THERAPY RESOURCE

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Generic Psychotropic Drugs Offer Quality and Affordability

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Generic psychotropic drugs offer an opportunity to provide consumers with safe and effective alternatives to branded drugs and reduce healthcare costs. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies.[1] Generic drugs are considered by the U.S. Food and Drug Administration (FDA) to be equal to brand name products in terms of dosage, safety, strength, how it is taken, quality, performance and intended use. However, the prices of these "copycat" drugs are typically 35%, and as much as 80%, less than their brand name counterparts.

The FDA requires generic products to undergo tests and procedures as rigorous as those for brand products prior to drug approval.[2] An abbreviated new drug application (ANDA) must be submitted to the FDA for review in order to market a generic product. To gain FDA approval under the Drug Price Competition and Patent Term Restoration Act of 1984, a generic drug must:[1]

- contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have the same indications
- be bioequivalent to the innovator drug product (equal in the rate and extent to which the active ingredients are absorbed and become available at the site of drug action)[3]
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products

A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent and, therefore, interchangeable. Therapeutic equivalency is defined as having the same clinical effect and safety profile as the innovator drug and behaving in the body the same way.[3] The FDA provides "equivalency" ratings (Table 1) for brand name and generic drugs in an annual compendium, *Approved Drug Products with Therapeutic Evaluations*,[3] more commonly referred to as the Orange Book. For a generic to be interchangeable with the brand or another generic, it must be "A" rated.

TABLE 1 – FDA THERAPEUTIC EQUIVALENCE CODES[3]

Therapeutic Equivalence Code	Definition	Sub-codes
A(X)	Drug products considered to be **Therapeutic Equivalents** therapeutically equivalent to other pharmaceutically equivalent product s; there are no known or suspected bioequivalence problems	(1) **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form; or (2) actual or potential bioequiva -lence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequiva -lence. These are designated **AB**.
B(X)	Drug products considered NOT to be therapeutically equivalent to other pharmaceutically equivalent products; potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence	(1) **BC**, **BD**, **BE**, **BN**, **BP**, **BR**, **BS**, **BT**, **BX,** or **B***.depending on dosage form (2). Often the problem is with specific dosage forms rather than with the active ingredients

Despite stringent guidelines and the FDA's assurance of product quality, misconceptions and controversy still exist regarding the safety and efficacy of generic drug products. Generating doubt in consumers and health care professionals regarding the quality of generic drugs is one of many strategies that the pharmaceutical industry uses to maintain market share for their products after patent protection expires.[10,13-18]

CLOZAPINE CONTROVERSY

Recently, attention has been given to clozapine, an atypical antipsychotic indicated for patients with refractory schizophrenia. The patent for Novartis' brand name, Clozaril, expired in 1998. A generic form of clozapine manufactured by Zenith Goldline Pharmaceuticals (ZGP) received FDA approval in 1997.

Anecdotal reports provided by Novartis illustrate the decompensation of patients switched to ZGP's clozapine after being stabilized on Clozaril. In response, the Minnesota State Psychiatric System conducted a comparison study to evaluate the clinical effects of patients switched from Clozaril to generic ZGP-clozapine.[4] Results indicated that clinicians should monitor more closely stable Clozaril-treated patients who are being switched to generic clozapine.

Zenith's bioequivalence study, submitted in its ANDA, compared 12.5mg (1/2 of a 25mg tablet) of clozapine (ZGP) to the same dose of Clozaril. A waiver to use the lower dose was requested due to concerns of potential serious side effects that higher doses of clozapine can cause in healthy volunteers. The FDA granted the waiver based on acceptable *in vivo* and *in vitro* dissolution data and proportionality of formulations.[5]

Ereshefsky, et. al[6]., at the University of Texas, questioned the accuracy of ZGP's bioequivalence study results for the FDA and conducted a 21-patient, open-label study sponsored by Novartis. The study assessed the relative bioavailability and interchangeability of 100mg tablets of generic ZGP-clozapine at steady state in patients with chronic psychotic disorders who had previously been stable on Clozaril 100mg tablets. Results indicated a significantly lower peak plasma concentration (C_{max}), a small difference in mean area under the concentration-time curve (AUC), and overall lower plasma concentrations for 100mg ZGP-clozapine than for 100mg Clozaril. Significant differences in the absorption rate constant (K_a), and time to peak plasma concentration (T_{max}) were also reported. These values were confirmed in a post-hoc analysis by Tooney, et.al.[7] The authors theorized that differences in C_{max} may be important for drugs with "loose" Dopamine-2 binding, such as clozapine and may account for the perceived difference in clinical effect of Clozaril and ZGP-clozapine.[6,7]

ZPG claims the Texas bioavailability study has "serious design flaws and draws erroneous conclusions" noting that "26,000 patients are successfully treated using clozapine, of which 21,000 hav e switched from brand to generic".[8] The FDA's review found that the cited studies were not conducted in a manner that could evaluate whether the generic version is unsafe or ineffective. In addition, FDA's inspection of the Texas study site uncovered "irregularities", "casting doubt on the results".[9] It also concluded that the Texas study was "not actually designed to evaluate whether patients responded to the generic version as well as they did to Clozaril, nor could the results be interpreted to provide a basis for FDA

regulatory action".[9] Similar conclusions were drawn from the Minnesota study. However, according to established FDA guidelines and testing requirements, the bioavailability, pharmacokinetics and therapeutic effect of Clozaril and ZGP's generic clozapine are equivalent.

Clozapine requires frequent monitoring of white blood cell (WBC) counts because of the significant risk of agranulocytosis, a potentially life-threatening adverse event.[11] For this reason, and the sake of monitoring drug performance, careful patient monitoring is required irrespective of whether the drug is brand or generic.[2]

Conclusion

The FDA has concluded it is not necessary for the health care provider to approach generic drugs differently from branded drugs when there has been a determination of therapeutic equivalence by the FDA.[2] Generic drug use provides consumers with a unique opportunity to reduce soaring health care costs. The myth that there is not interchangeability between branded and generic drug products is probably related more to monetary issues than quality. The FDA's Office of Generic drugs assures the public that generic drug products can be used with absolute confidence.[12]

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Dispelling Marketing Myths

By Ann Hamer, Pharm.D., OSU College of Pharmacy

Generic fluoxetine versus Prozac Weekly. Prozac has always been known as the SSRI for the noncompliant. With an 84-hour half-life, the original Prozac is adequately dosed when taken every few days. The higher the dose, the longer it lasts. While the retail price of 4 capsules of Prozac Weekly is $76, generic fluoxetine costs as little as $3 per month.

Celexa and Lexapro—is there a difference? Forest Pharmaceuticals, the makers of Celexa (citalopram), are launching a new antidepressant called Lexapro. Lexapro (escitalopram) is the s-enantiomer of Celexa. Here are some facts:

- Celexa is expected to go off patent next year. Generic drug manufacturers may be able to produce generic citalopram as soon as January 2004.
- Much of the evidence used to gain approval for Lexapro was based on earlier Celexa studies rather than conducting new research. Studies have not been done comparing Lexapro to other antidepressants, including Celexa.

Seroquel—the cataract debate. In pre-marketing studies, Seroquel was linked to cataract formation in beagles. The animals received doses in excess of 4 times the recommended amount for human patients. There are no known case reports of Seroquel-induced cataracts in humans. Allegations to the contrary are unsubstantiated. The manufacturer includes the following warning in the package insert:

"The development of cataracts was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term Seroquel treatment, but a causal relationship to Seroquel use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment."

Depakote ER—Depakote ER is designed to extend the release of divalproex sodium allowing for once daily dosing. It is indicated only for prophylaxis of migraine headaches in adults. **This product should not be confused with the original Depakote, which is a delayed-release product and designed to improve the tolerability of the active ingredient by delaying its release.** Currently, there are no published studies looking at the use of Depakote ER in bipolar mania. It is not recommend that patients who are stable on Depakote be switched to Depakote ER. Retail price for 30 days of Depakote 500mg twice daily is $96 and for 30 days of Depakote ER 1000mg daily is approximately $101.

Paxil versus Paxil CR. The difference in formulation between Paxil and Paxil CR is a degradable polymeric matrix called Geomatrix. Due to this matrix formulation, Paxil CR is released more slowly into the body than the immediate release formulation. Here are the facts:

- Time to maximum drug concentration is extended by 0.8 hours to 4.8 hours.
- The half-life of Paxil is equivalent to, if not longer than Paxil CR. (21 hrs vs. 15-20 hrs)
- Immediate release Paxil appears to reach steady state concentration at the same time, if not sooner than Paxil CR.
- Although the main selling point of Paxil CR is improved tolerability, a review of the side effect profiles of each drug compared to placebo, reveals similar rates of adverse effects.

Side-Effect	Paxil CR	Placebo	Paxil	Placebo
Headache	27%	20%	18%	17%
Asthenia	14%	9%	15%	6%
Nausea	22%	10%	26%	9%
Diarrhea	18%	7%	12%	8%
Constipation	10%	4%	14%	9%
Somnolence	22%	8%	23%	9%
Insomnia	17%	9%	13%	6%
Decreased Libido	**7%**	3%	**3%**	0%
Abnormal Ejaculation	**26%**	1%	**13%**	0%
Female Genital Disorder	**10%**	<1%	**2%**	0%

- Cost is the one true differentiating factor between these two formulations. Retail price for 30 days of Paxil 20mg is $41 if ½ tablets of a 40mg are used and for 30 days of Paxil CR 25mg is $80. Paxil CR cannot be split because the tablet integrity is lost.

Last but not least, Zyprexa Zydis—cost. Zyprexa Zydis is an orally disintegrating formulation of Zyprexa designed to limit "cheeking". This is the only difference between the products. Retail price for 30 days of Zyprexa Zydis 15mg is $453 for 30 days of Zyprexa 15mg is $419.

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