How differences among generics might affect your patient's response

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***Savvy Psychopharmacology* presents an evidence-based discussion to guide safe, effective prescribing of psychotropic medications. Developed in collaboration with the College of Psychiatric and Neurologic Pharmacists (CPNP), these articles are intended to help you:**

- Keep current with new developments in psychopharmacology
- Learn more about pharmacodynamics, pharmacokinetics, drug-drug interactions, and prescribing for special populations
- Collaborate with psychiatric pharmacists to solve or prevent problems patients may have with their medications

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Mr. X, age 47, suffers from major depressive disorder, which he developed 1 year ago after experiencing a myocardial infarction. At that time, Mr. X received brand-name fluoxetine (Prozac), 20 mg/d. After 4 weeks, his mood improved, but he experienced delayed ejaculation, which resolved spontaneously after 12 weeks of treatment.

Because Mr. X recently lost his job and health insurance, he inquires about lowering his health care costs. Discontinuing fluoxetine is not advised, so you recommend changing to a generic formulation. Mr. X tolerates this conversion without difficulty; however, 9 months later he reports he is experiencing delayed ejaculation again. He has had no changes in medical history and has not started any new medications. Mr. X claims he has been compliant with his medication, although he mentions that the fluoxetine tablets looked different when he refilled his prescription 2 weeks ago. You call the pharmacy and discover that they started dispensing generic fluoxetine from a different manufacturer around the time Mr. X refilled his prescription. You prescribe Mr. X his old version of generic fluoxetine,

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Practice Points

- For most patients, **using generic medications poses no problems** and offers an appropriate therapeutic option at a lower cost.
- If problems arise during treatment, **consider differences among generic brands.** Although each generic must be tested against the brand-name product for bioequivalence, they do not need to be tested against each other.
- **Different generic formations may have different inert ingredients,** which may cause problems if patients are allergic to a specific inactive ingredient.
- **Consult the 'Orange Book'** for information on approved drugs and their generic interchangeability or the patient's local pharmacist or a board-certified psychiatric pharmacist if you have questions about generic formulations.

Table

Bioequivalence among generic psychotropics: What to know before you switch

Medication	Comments
Amitriptyline/perphenazine	Generic formulations may not be interchangeable*
Anticonvulsants	Because these medications have a narrow therapeutic index when used for seizure disorders, patients are recommended to not switch formulations. When used for psychiatric disorders, the margin of safety is unknown and switching may be appropriate
Chlorpromazine	Generic formulations are not bioequivalent
Clozapine	Generic formulations may not be bioequivalent at all dosages* Dosage adjustments may be needed in patients who need to switch formulations during treatment
Venlafaxine	Some formulations may not be interchangeable*

*Consult the FDA's *Approved drug products with therapeutic equivalence evaluations* to determine if generics are interchangeable

Source: Reference 4

Clinical Point

If a patient switches generic medications, efficacy may be lost or side effects may emerge because of bioequivalence differences

and his sexual dysfunction resolves within 2 weeks.

In the United States, 2.6 billion prescriptions—approximately 70% of all prescriptions—are filled using generic versions of brand-name products.[1] For most patients, generic substitution is acceptable and reduces costs. Although the practice has become routine, certain circumstances may make switching to a generic medication or between generic medication problematic. To understand why, it is important to discuss the FDA's generic drug approval process.[2]

Bioequivalence

Pharmaceutical manufacturers developing a generic drug must create a product that will deliver the same amount of medication at the same rate and in the same form (ie, tablet, capsule, suspension, etc.) as the brand-name product. The FDA requires bioequivalence (BE) studies.[2] These studies usually include fewer than 40 healthy individuals and must show that the generic product has the same pharmacokinetic profile as the brand-name drug (the active ingredient already has been shown to be safe and effective). The generic product can deviate from the brand product's profile by a set amount—currently a 90% confidence interval limit of 80% to 125%.[2] This means that pharmacokinetic parameters such as max concentration (Cmax), time to max concentration (Tmax), mean absorption time, and area under the curve (AUC)—which is a measure of overall drug exposure—are no less than 80% and no more than 125% of the parameters seen with the brand-name product. This may seem like a large deviation, but the FDA reports that generally "small differences in blood levels—<4%—may exist in some cases between a brand and its generic equivalent."[1]

A new generic formulation does not have to be tested against other generic formulations, only against the brand-name drug. Therefore, 2 generic formulations may differ pharmacokinetically by more than a 4% difference if one product is on the low side of the BE limit and the other is on the high side. If a patient starts 1 generic and then switches to another, efficacy may be lost or side effects may emerge because of BE differences. In Mr. X's case, it is possible that the new generic version of fluoxetine resulted in higher plasma drug levels that lead to recurrence of sexual dysfunction.

Exceptions

Generic medications are not recommended for certain medical conditions, such as epilepsy and some hormone replacement therapy, because of lack of satisfactory BE to the

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brand-name drug.[3] For these conditions, generic medications may be used, but should not be substituted for the brand-name product without careful monitoring. Additionally, switching between different generic manufacturers should be avoided.

If you have a question about generic substitution, consult the FDA's *Approved drug products with therapeutic equivalence evaluations*[4]—also known as the "Orange Book," which is available online (see ***Related Resources***). This resource provides guidance about which drugs are interchangeable. The Orange Book is the "gold standard" on approved drug products and their interchangeability.

The ***Table (page 32)*** lists certain psychiatric medications that may have issues with generic substitutions. Most pharmacies stock and dispense only generic drugs that the FDA considers bioequivalent to the brand-name product.

Allergic reactions may occur because of different inert ingredients within each generic or brand-name drug. Generic drug manufacturers are not required to use the same inactive or "filler" ingredients. Some patients may be allergic to 1 version and may require a specific brand or generic version to overcome this potential allergy.[3]

Although most generic substitutions occur without incident, consider BE differences among products and your patient's medical condition before initiating a switch. When switching between generics, carefully monitor your patient as you would when switching from the brand-name product to a generic. If new treatment-related issues arise or lack of efficacy occurs, ask your patient if the pharmacy switched to a new generic formulation.

Clinical Point

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Related Resources

- Food and Drug Administration. www.fda.gov/Drugs/default.htm.
- Generic Pharmaceutical Association. www.gphaonline.org.
- Food and Drug Administration. Orange book: approved drug products with therapeutic equivalence evaluations. www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

Drug Brand Names

Amitriptyline/Perphenazine • Triavil
Chlorpromazine • Thorazine
Clozapine • Clozaril
Fluoxetine • Prozac
Venlafaxine • Effexor

Disclosure

Dr. Ellingrod is a member of an advisory board for Eli Lilly and Company.

References

1. Generic Pharmaceutical Association. Bioequivalence. Available at: http://www.gphaonline.org/issues/bioequivalence. Accessed January 4, 2010.
2. Food and Drug Administration. Guidance for industry. Bioavailability and bioequivalence studies for orally administered drug products—general considerations. Rockville, MD: U.S. Department of Health and Human Services; 2003.
3. Silverman HM. Bioequivalence and interchangeability of generic drugs. In: Merck manual home edition online. 2007. Available at: http://www.merck.com/mmhe/sec02/ch017/ch017b.html. Accessed January 4, 2010.
4. Food and Drug Administration. Orange book: approved drug products with therapeutic equivalence evaluations. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 4, 2010.