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Generic drugs: The benefits and risks of making the switch

When is it safe to substitute a generic drug for a brand-name medication, and when should a switch be avoided? Here's a look at the evidence.

PRACTICE RECOMMENDATIONS

› Do not authorize the pharmacy to switch patients from a brand-name antiepileptic drug to a generic without your approval. **(C)**

› Use caution when switching a patient to a generic modified-release formulation, which may not have the same pharmacokinetic profile as its brand-name counterpart. **(C)**

› Consult the FDA's Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> for details on generic substitution. **(C)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

Each year, Americans save an estimated \$8 billion to \$10 billion at retail pharmacies by purchasing generic drugs rather than brand-name medications, the US Food and Drug Administration (FDA) reports.¹ The lower cost, of course, is the key advantage of generics. But the very reason for the cost savings—the fact that generic drugs do not have to undergo the large, expensive clinical trials that are required for approval of brand-name medications—gives rise to questions about the quality and safety of generics.

Are these concerns justified? Under what circumstances is it safe to prescribe generics, or to substitute a generic for a brand-name drug? Are brand-name drugs always better? To answer these questions, we conducted a thorough evidence review, which included numerous randomized controlled trials (RCTs) and case reports, as well as a single meta-analysis that assessed the benefits and risks of generics.

Generics: On the positive side

Safety and efficacy. Our literature search yielded little evidence that generic drugs are less safe or less effective than their brand-name equivalents. The meta-analysis, for example,² included 47 studies (38 of 47 were RCTs) covering 9 subclasses of cardiovascular medications. In trials involving beta-blockers, diuretics, calcium channel blockers, antiplatelet agents, statins, angiotensin-converting enzyme inhibitors, and alpha-blockers, no evidence of superiority of brand-name drugs vs generics was found.²

Cost. Generic drugs typically cost 30% to 60% less than their brand-name counterparts,³ and widespread use of generics has the potential to reduce the price of other brand-name drugs by creating more competition.

Another plus: Patients taking generic drugs appear to be

TABLE

Generic substitution of antiepileptic agents: Where the American Academy of Neurology stands¹⁸

The AAN opposes:
<ul style="list-style-type: none"> • generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval. • generic substitution of anticonvulsants for patients with epilepsy at the point of sale without prior consent of both the physician and the patient. • state and federal legislation that would impede the ability of physicians to determine which anticonvulsant drugs to prescribe for the treatment of patients with epilepsy.
The AAN believes:
<ul style="list-style-type: none"> • formulary policies should recognize and support physician autonomy in prescribing, and patients in accessing, the full range of anticonvulsants for epilepsy.
The AAN supports:
<ul style="list-style-type: none"> • legislation that would require informed consent of physicians and patients before generic substitutions of anticonvulsants are made at the point of sale.
The AAN recognizes:
<ul style="list-style-type: none"> • that different strategies may be appropriate in using anticonvulsants for the treatment of conditions other than epilepsy.

more willing to continue therapy than those taking brand-name medications.⁴ Lower copays are a key factor. In 1 recent study of patients with hypercholesterolemia or diabetes, those taking generics had greater adherence compared with patients receiving brand-name drugs.⁵

Quality. It is important to note that many generic medications are produced under the license of the manufacturer of the original brand-name product, with the lower-cost equivalent often introduced after the drug's patent has expired. Even when different manufacturers produce the branded product and the generic, strict standards exist to guarantee the quality of generic drugs.

The journey to market—the similarities, the differences

Both brand-name and generic medications undergo similar new drug application (NDA) procedures. The manufacturers of both are required to submit detailed evidence of the chemistry, manufacturing, controls, labeling, and testing processes. From there, brand-name and generic products take divergent paths to market.

New nongeneric drugs must undergo rigorous animal and human studies, includ-

ing large RCTs comparing the efficacy of the new product with that of a placebo and carefully tracking side effects. Bioavailability testing is required, as well. For generic drugs, the process is known as an abbreviated new drug application (ANDA), and bioequivalence studies are sufficient.^{1,6}

The bioequivalence studies required for a new generic are based on pharmacokinetic parameters, most notably, the area under the plasma concentration curve (AUC)—a measure of overall drug exposure—and the maximal plasma concentration (C_{max}). If AUC and C_{max} are within an acceptance range (0.80–1.25 of the brand-name product parameters), the therapeutic equivalence of a generic drug is substantiated.^{7,8}

Concerns about testing, formulation

Opponents of widespread use of generics point out that they are tested on only a few young, healthy individuals, compared with the large numbers of patients who participate in clinical trials of the original drug.

Bioequivalence

According to guidelines from the World Health Organization (WHO), 18 to 24 healthy

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In a study comparing Tegretol with 3 generic formulations of carbamazepine, 1 of the generics was not bioequivalent.

adult volunteers are considered sufficient for a bioequivalence study.⁹ The number of participants may be greater, however, if absorption or clearance of the drug is highly variable. What's more, the people who volunteer for generic drug studies cannot smoke or take concurrent medication. To exclude the possibility that food coadministration affects the generic medication being studied, the FDA further recommends bioequivalence testing of oral formulations on volunteers eating standardized meals.⁸ These criteria help minimize the magnitude of intersubject variability and reduce the possibility of bias—which could be caused by the disease process, concurrent conditions, or medication interaction, rather than by formulation differences.⁸

■ **To further minimize the effects of nondrug-related variation**, bioequivalence studies typically use a crossover design: Half the subjects receive the test drug first, followed by the brand-name product, with a washout period in between. The other half receive the drugs in reverse order.¹⁰ (The study format is altered, as needed, for extended-release products, topical agents, and drugs that are not absorbed systemically. A generic version of cholestyramine, for example, which acts by sequestering bile salts within the intestine, would be approved on the basis of in vitro studies that quantify the binding of the bile salts.¹⁰)

■ **But does this testing mimic the real world?** While possible confounding factors are controlled for in bioequivalence studies of generics, critics point out that this is not the case in the real world. Thus, they worry that when generics are taken by patients with actual illnesses, concurrent use of other medications, medical conditions, and the like may result in differences in treatment that did not occur in the highly controlled environment in which the equivalency studies were conducted.¹¹

Differences in formulation

Another concern centers on formulation differences, which have the potential to affect patients taking generic drugs. A generic copy of a brand-name drug must contain the same active ingredient, in the identical quantity, as the branded product—in the same dose for-

mulation and route of administration. It must also meet standards for strength, purity, quality, and identity.¹¹

However, the inert ingredients in the generic version do not have to be the same as those in the brand-name drug (although the *ratio* of inert to active compound must be similar).¹² Because drugs tested in bioequivalence studies are administered in single doses, many experts wonder whether the inert compounds used in the generics may affect the distribution, metabolism, or absorption of a drug when it is administered in multiple doses, or whether the serum concentration of the generic drug may be elevated when it is taken for long periods.

Proceed with caution in these situations

For most patients taking most medications, generic drugs pose no problems, and provide an opportunity to obtain the same therapeutic benefit at a considerably lower cost. However, making the switch with certain classes of drugs, and with drugs that have a narrow therapeutic range, poses potential problems and must be done with caution—if at all.

■ **Antiepileptic drugs.** The FDA indicates that many people who are on antiseizure medications re-experience seizures despite continued treatment,¹ and that switching to a generic does not increase the risk of treatment failure.^{1,13} Nonetheless, there are numerous reports of differences between generic and brand-name antiseizure medications (and small studies indicating improper seizure control after switching patients from a brand-name to a generic antiepileptic drug).¹⁴

For example:

- Researchers compared the pharmacokinetic parameters of Tegretol with 3 generic formulations of carbamazepine, and found that 1 of the 3 was not bioequivalent.¹⁵
- In a crossover study of 18 healthy volunteers, 3 generic formulations of carbamazepine were all within the acceptable bioequivalence range, but were absorbed more rapidly than the brand-name drug.¹⁶
- Differences in the bioavailability of brand-name and generic products have also been reported with phenytoin, primi-

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Generic formulations of amitriptyline/perphenazine and venlafaxine may not be interchangeable, according to the FDA.

done, and valproic acid, but the differences were not statistically significant.¹⁷

The American Academy of Neurology has issued a set of recommendations concerning the use of generic antiepileptic drugs (TABLE).¹⁸

■ **Narrow therapeutic ratio.** The potential for complications increases in drugs with a narrow therapeutic ratio, defined by the FDA as <2-fold difference between the median lethal dose and the median effective dose, or between the minimum toxic concentration and minimum effective concentration in the blood.¹⁹ The safe and effective use of such drugs—carbamazepine, divalproex, lithium, phenytoin, and warfarin, to name a few—requires careful dosage titration and patient monitoring.

■ **Water solubility and nonlinear pharmacokinetics may present problems in drugs with a narrow therapeutic ratio,** especially phenytoin.² The drug's serum concentration is allowed to range from 8 to 20 mg/L. A concentration above this range increases the risk for acute cerebellar syndrome, delirium, and coma; a concentration below the range may cause seizures.¹²

Warfarin is also of particular concern, as there is always the possibility that a switch from Coumadin to a generic equivalent could result in under- or overcoagulation. However, studies have shown that the use of generic warfarin in patients previously receiving Coumadin did not affect the international normalized ratio more than continued use of the brand-name anticoagulant.^{20,21}

■ **Psychotropic agents.** There has been a number of case reports of problems occurring following a switch from a brand-name antidepressant to a generic—or from 1 generic antidepressant to another. (See “Did a switch to a generic antidepressant cause relapse?” *J Fam Pract.* 2008;58:109-114.) In fact, the FDA cites some psychotropic drugs for which generic formulations may not be interchangeable—including amitriptyline/perphenazine and venlafaxine—and others for which generic formulations may not be bioequivalent at all doses.²²

■ **Thyroid medication.** There are also concerns about levothyroxine (LT4) administration, and major medical societies debate

the use of generic substitution. According to a recent survey from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society, clinical use of generic LT4 continues to be associated with adverse outcomes.²³ Most of the adverse events (89%) reported by survey respondents were associated with a change, either from a brand-name drug to a generic or from 1 particular generic LT4 to another.

Modified-release formulations may also pose a problem

Problems may also occur with generics in modified-release formulations, which may not have the same pharmacokinetic profiles as their brand-named counterparts. The British National Formulary has advised that prescriptions for modified-release diltiazem hydrochloride, nifedipine, and theophylline be filled with the brand-name drug only.^{24,25} Moreover, a recent study concluded that 2 modified-release products of methylphenidate and nifedipine had concentration profiles that strongly diverged during the period of absorption, although the formulations met the regulatory criteria for bioequivalence.²⁶

■ **The type of salt used to form a compound** is also important. Salt-joining makes a hydrophobic molecule hydrophilic; the result, especially in psychoactive drugs, is improved kinetics, absorption, or physicochemical properties (eg, stability, hygroscopicity, fluidity).²⁷ This may be the reason for differences identified between generic and brand-name amitriptyline, nortriptyline, desipramine, and trimipramine.²⁸ To avoid problems, physicians should prescribe generics containing the same salt as their brand-name counterparts.

When in doubt ...

Brand-name drugs are, and always will be, the best proven therapy, because of the number and extent of clinical trials they go through. In most cases, however, there is no evidence-based reason to avoid generic substitution for patients who cannot afford the brand-name drug. When in doubt, consult the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Eval-*

uations, available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>, before making a switch. **JFP**


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Clinical use of generic LT4 continues to be associated with adverse outcomes.



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