Editorial

Does generic substitution always make sense?

Paul E Greenberg

Introduction

Over the past 25 years, as healthcare payers and providers have attempted to rein in increasing drug costs, generic medications have gone from 19 to 65% of all prescriptions filled in the US[1]. Generics are now available in nearly every therapeutic class, including the most widely selling – statins and antidepressants. The savings associated with generics can be dramatic. According to a recent FDA analysis, the cost of a generic can be as little as 5% that of a brand-name drug (though the precise amount of the discount, which can vary widely, is typically a function of several factors including the number of generic products in the marketplace)[2]. Furthermore, the move toward greater utilisation of generics shows no sign of slowing down. Over the next few years, drugs with current annual sales of about $50 billion are losing their patent protection, meaning that a whole new set of generics is about to be launched[3]. Next year, blockbusters such as the heartburn medication Prevacid®* and the anti-obesity agent Xenical®† will also face generic competition.

Across the US, health insurance companies and pharmacy benefit managers actively promote the use of generics to both doctors and patients. Over the last few years, tiered-drug co-pays have become the norm; and with the co-pay for generics much less than that for brand-name drugs, patients have a financial incentive to choose generics. In addition, many states mandate that prescriptions automatically default to the generic version of a drug compound when it is dispensed at the pharmacy unless the prescribing physician specifically designates the brand[4]. And many insurers now circulate software packages to remind doctors of generic equivalents every time they are about to prescribe a brand-name drug. Thus, there is considerable pressure from many sources for physicians to prescribe and pharmacists to dispense generics.

Although generics clearly offer a significant opportunity for prescription drug cost savings, substituting generics for brand-name drugs may not be cost effective

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* Prevacid is a registered trademark of TAP Pharmaceuticals.
† Xenical is a registered trademark of Roche.

10.3111/13696990802371075

in the long run in every instance. That is, while generics are generally cheaper than brand-name drugs, to the extent that they compromise patient safety and efficacy, their use can lead to additional costs down the line from added hospitalisations, doctor visits, or the use of other medications and medical services. Therefore, determination of whether to use a particular generic medication should start with a thorough understanding of the trade-off between drug safety and efficacy on the one hand, and cost on the other. According to a growing body of research, the risk posed to the patient by a generic may sometimes offset any cost advantage. Recognising when and why it can make sense to depart from the default preference for generics warrants attention.

What is generic equivalence?

Many people assume that generics are exactly the same as brand-name drugs, but this is not always true. According to the FDA definition, "a generic drug is identical, or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use." In addition to bioequivalence, which refers to the equivalent release of the drug substance, the FDA measures bioavailablity, the rate and extent to which the active ingredient is absorbed and becomes available at the site of action. Bioavailability may vary because the FDA gives generic manufacturers some leeway; according to its stipulation, the bioavailability of the generic can range anywhere from 4/5 to 5/4 (i.e. 80–125%) that of the comparator brand-name drug. Furthermore, not all forms of a generic medication are identical, as bioavailability can vary from one generic to the next up to as much as 45%. This is of concern especially when pharmacies don't substitute with the same generic version.

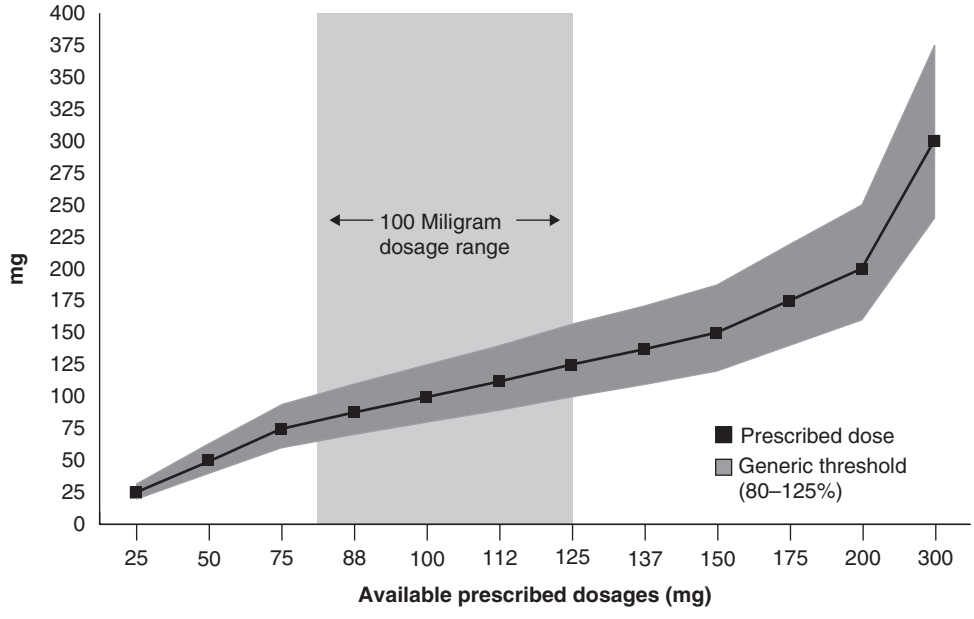
Switch to generics – same compound

Because of these differences in bioavailablity, when a doctor substitutes a generic for a brand-name drug, the patient in effect may not end up receiving the exact same medication. As a result, generic substitution can sometimes compromise both safety and efficacy. For example, with Narrow Therapeutic Index (NTI) drugs, where a consistent dosage is absolutely critical for efficacy, even a small variation can induce an undesirable reaction. Consider the case of Synthroid®‡, a hypothyroidism drug which can be prescribed in 12 different dosages so as to pinpoint the precise amount delivered to the patient (see Figure 1).

Variations between the brand and the generic version could result in markedly reduced effectiveness or even potentially serious side effects. The same concerns can arise with other NTI drugs such as

‡ Synthroid is a registered trademark of Abbott Laboratories.

Figure 1. Potential range of variation between prescribed dose and generic threshold for Synthroid.



Coumadin®§, a blood thinner, and certain antiepileptic drugs.

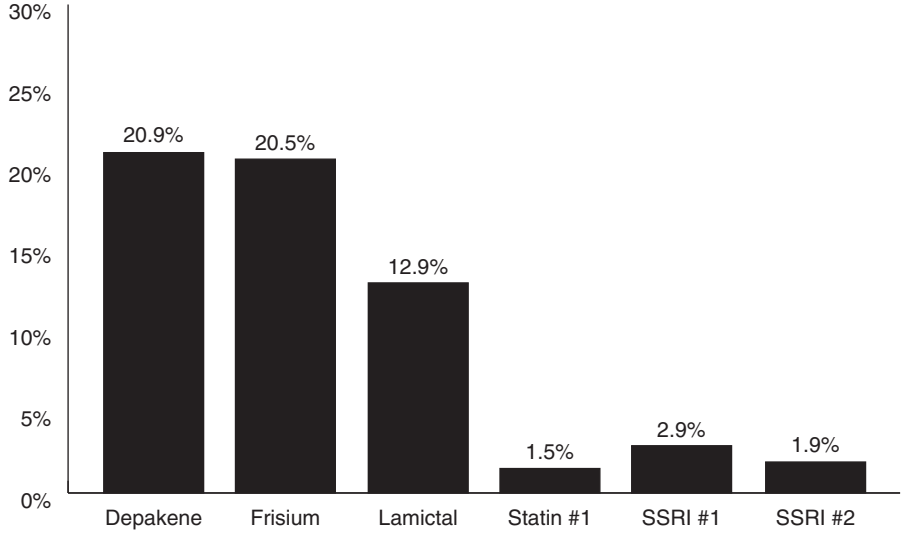
Similarly, since not all generics are exactly the same, switching patients from one generic to another can impair safety or efficacy. This type of switching may not be deliberate, but could result, for example, when a patient changes pharmacies and receives a generic version made by a different manufacturer.

Recent research results suggest another reason why brand-name drugs may sometimes work better than their generic counterparts: patient perceptions. In the case of prescription drugs used for pain relief, for instance, the lower price of a generic medication may lead some patients to be less confident about its efficacy. In a 2006 study at the Massachusetts Institute of Technology, researchers found that patients experienced a greater reduction in pain from a regularly priced drug than from a discounted one (both of which were, in fact, the same placebo). Regarding this finding, one of the researchers concluded, "It is possible that the therapeutic efficacy of medications is affected by commercial features such as lower prices"[5]. Such placebo responses to commercial features have many significant clinical implications.

Thus, for many reasons, patients who are switched to generics do not always elect to remain on generics despite the allure of potential cost savings. Extensive research has been conducted looking at the rates at which patients switch back to brand-name drugs, and have found that switchback rates can

§ Coumadin was originally patented by DuPont.

Figure 2. Switchback rates associated with antiepileptic therapies (depakene, frisium, Lamictal) are high compared to those of drugs in other therapeutic areas (statins and SSRI antidepressives).



SSRI, selective serotonin reuptake inhibitor.

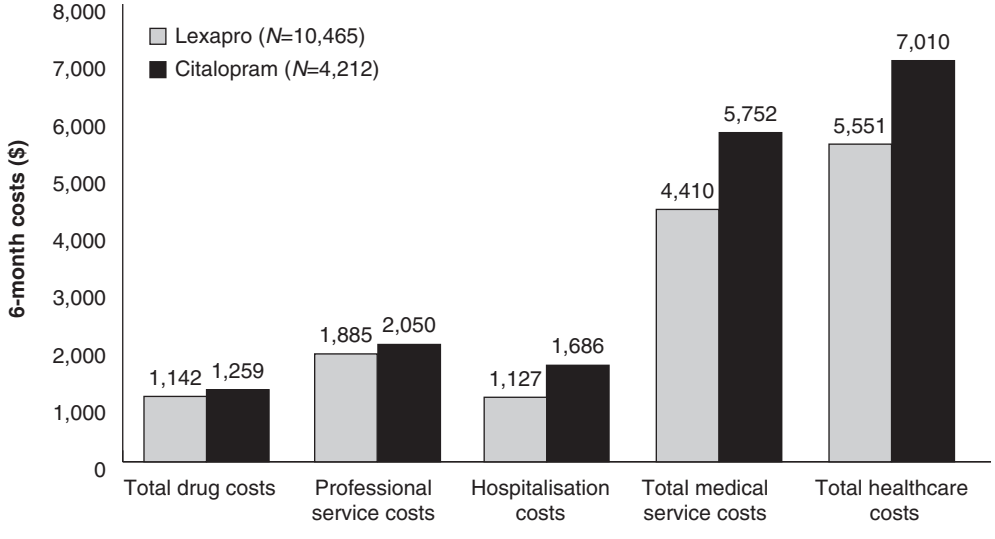
be especially high with antiepileptic drugs such as lamotrigine (Lamictal®¶) (Figure 2)[6]. Moreover, the supposed cost savings associated with generic lamotrigine disappears when all healthcare costs, not just drug costs, are considered[7].

Default to generics – different compounds

Just as doctors are now routinely switching patients within a compound from a brand-name drug to its generic, so too are they often switching patients across compounds, from brand name to generic within the same therapeutic class. Not surprisingly, in some instances these substitutions are not optimal in managing the patient's symptoms. Consider the class of selective serotonin reuptake inhibitor (SSRI) antidepressants. Most of the popular brand-name drugs in this therapeutic class such as Prozac®**, Zoloft®††, Paxil®‡‡ and Celexa®§§ have lost patent protection, such that generic equivalents are now available for each. However, that is not the case for the newer brand-name SSRI, Lexapro®¶¶. Nevertheless, at present, patients who are responding well to Lexapro are sometimes switched by their doctor to one of the

¶ Lamictal is a registered trademark of GlaxoSmithKline.
** Prozac is a registered trademark of Eli Lilly.
†† Zoloft is a registered trademark of Pfizer.
‡‡ Paxil is a registered trademark of SmithKlineBeecham.
§§ Celexa is a registered trademark of Forest Laboratories.
¶¶ Lexapro is a registered trademark of Forest Pharmaceuticals.

Figure 3. Total medical and healthcare costs associated with the generic citalopram are significantly higher than those related to the brand-name Lexapro.



NOTE: Multivariate analysis (adjusted for differences in demographic characteristics, comorbidity frequency and severity, and baseline period healthcare resource utilisation) confirmed studies results. P-value <0.001.

generic medications in this class. But numerous studies have shown that such generic substitution away from Lexapro can actually increase rather than reduce healthcare costs. For example, studies comparing Lexapro with generic citalopram (known as Celexa in its branded form) have repeatedly demonstrated the higher long-term costs of using the generic. In one study comparing results over a 6-month period, the patients taking Lexapro incurred total medical costs of $5,551, as opposed to $7,010 for the patients taking citalopram[7] (Figure 3). In a similar study focusing exclusively on elderly patients, those taking Lexapro incurred total healthcare costs of $11,498, as opposed to $18,907 for the comparison group[8]. Furthermore, Lexapro has been shown to be not only more effective than Celexa, but also more effective than all the other generic equivalents in its therapeutic class.

Conclusion: looking at the whole picture

Although generics tend to be much less expensive than brand-name drugs in terms of acquisition costs, stakeholders need to consider more than just the cost of the prescription itself. If the generic is associated with decreased safety or efficacy, paying more upfront for the brand-name drug may turn out to be cost effective. Analyses comparing the effectiveness of brand-name drugs to that of generics are already available for some drugs, but for others, definitive answers await further research. Such research, although costly, might prove to be a case of money well spent,

as millions of patients face important prescription decisions every day, and a sound cost–benefit analysis could potentially save billions of dollars in unnecessary healthcare costs. Consider Pfizer's blockbuster Lipitor®, the cholesterol-lowering agent with current sales of $12 billion a year that does not go off patent until 2011[9]. Lipitor now faces competition from various generic statins including, most recently, simvastatin (sold exclusively as Zocor® by Merck until 2006). The cost effectiveness of Lipitor relative to that of generic statins remains to be studied. However, given the potentially huge volume of patients who will likely be switched from Lipitor to a generic statin (i.e. either across compounds or within the simvastatin compound when generic entry eventually occurs), such research is no doubt worthwhile.

Impending scientific advances in the biopharmaceutical industry may also provide assistance. For example, the emerging science of biogenomics may one day enable us to pinpoint how a given patient might respond to a particular drug based on his or her genetic make-up. Unfortunately, biogenomics is just in its infancy, and the customised delivery of medications is still far off. But even before all the evidence comes in, all stakeholders (payers, providers, pharmacists and patients) need to keep in mind that automatically substituting generics for brand-name drugs, either in a first prescription or in a refill, can at times prove more costly on a number of important dimensions.

Acknowledgements

Declaration of interest: Analysis Group has consulted to manufacturers of NTI drugs in the antiepileptic area, and to manufacturers of antidepressants as noted in the references. The author has received no payment in the preparation of this manuscript.

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