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Generic Drugs for Hypertension: Are They Really Equivalent?

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Abstract

Many antihypertensive drugs are now available in generic formulations at fractions of the cost of their branded counterparts. In the United States, marketing approval for generic medications is usually granted by the Food and Drug Administration on the basis of two simple studies involving dissolution rates and bioavailability in 24–36 healthy people, without data regarding antihypertensive efficacy, safety, or long-term outcomes. This process leaves many true disciples of “Evidence-Based Medicine” in a quandary: prescribe only brand-name medications that have been demonstrated in clinical trials to both lower blood pressure and prevent cardiovascular events, or instead recommend lower-priced generic agents that are usually supported by no such data. This review summarizes the current evidence that generic antihypertensive drugs are likely to be safe and effective, may increase the probability of medication availability and adherence for many patients, but by law, must have a different physical appearance than the original product.

Keywords

Generic medications; hypertension; blood pressure control; bioequivalence; thiazide diuretics; beta-blockers; calcium antagonists; angiotensin converting enzyme inhibitors; angiotensin receptor blockers

Introduction

Recent secular trends regarding causes of death (based on national surveys of death certificates) and age-adjusted incidence of major cardiovascular events in the United States have shown an impressive decline in the risk of myocardial infarction and stroke [1•, 2•]. Much of the desired reductions in cardiovascular disease incidence and prevalence have been attributed to better preventive therapies, including drugs to inhibit platelet aggregation, treat dyslipidemia, and lower blood pressure. Data from recent US National Health and Nutritional Examination Surveys have also documented more widespread treatment of hypertension, with improved control rates in this representative sample of Americans [3, 4]. The most recent estimates of the cost of hypertension in the US (and in Great Britain) have been greatly reduced, presumably by the fact that many antihypertensive drugs are now

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available as generic formulations, at lower prices than their branded predecessors [2, 5•, 6]. While this economic trend is presumably beneficial to society as a whole, questions remain about: 1) the definition of “equivalence” used by the US Food and Drug Administration (FDA) to approve a generic drug, 2) whether generic antihypertensive drugs are effective in lowering blood pressure and reducing adverse cardiovascular outcomes; 3) whether availability of less expensive, generic drugs impact patient adherence; and 4) patient and prescriber preferences regarding generic vs. branded drug formulations. This review brings together some of the recent data about these controversial areas in the interface between federal regulations, economics and medicine within the US healthcare system.

Definition of Generic BioEquivalence

According to US FDA regulations [7], a generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. Applications to the FDA for approval of generic drugs are considered “abbreviated” because they generally do not include preclinical (animal) and clinical (human) data in order to establish safety and efficacy. Rather, generic drug manufacturers must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). In addition to a laboratory study demonstrating that the new formulation dissolves or disintegrates suitably quickly, manufacturers must provide data demonstrating bioequivalence by measuring the drug’s plasma concentration vs. time curve in 24 to 36 healthy volunteers. This provides rate of absorption, and bioavailability, of the generic drug, which can then be compared to that of the innovator drug. To be considered bioequivalent, the generic version must deliver the same amount of active ingredients into the bloodstream in the same amount of time as the innovator drug. The 90% confidence interval for the innovator:generic ratio of area under the curve, maximum concentration and time to reach the maximum concentration must be within 80–125% to achieve bioequivalence.

While some have argued that testing bioequivalence in healthy volunteers may not be sufficient to understand differences in absorption and bioavailability in elderly or other vulnerable populations, current regulations do not require equivalence studies in other populations to obtain generic formulation approval [8]. Additionally, it has been argued that when a generic formulation is manufactured with a different salt form of the innovator drug, as in the case of amlodipine, where amlodipine besylate was the innovator drug while amlodipine maleate is found in one generic formulation, demonstrating bioequivalence may not be sufficient to document long-term differences in blood pressure control or CV outcomes [9].

Importantly, the FDA monitors reported adverse events and lack-of-effects for all approved drugs (whether innovator or generic), and takes action when there is evidence supporting a lack of bioequivalence of an approved generic drug. Recently, the generic formulation of 300 mg extended release bupropion hydrochloride was withdrawn from the market when the FDA conducted its own head-to-head bioequivalence study of the generic and innovator products and observed non-bioequivalence [10•]. Reporting adverse events for all drugs, including generic drugs is important, as the FDA does track all adverse drug events. If a particular generic brand of drug has an increased number of adverse events reported, an investigation would ensue. The investigation would assess whether the generic brand has an increased number of reports compared with the brand product. There could be adverse effects associated with a particular excipient (i.e., filler or dye) included in a generic formulation, and reporting and tracking adverse events is the only way to systematically identify and resolve specific safety issues should they arise.

Once bioequivalence data have been reviewed and accepted, the FDA includes the new generic formulation in its Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book [11]), with about 90% of products being rated “A” (i.e., bioequivalent to an original, innovator formulation), and 10% being rated “B” (not bioequivalent). Using bioequivalence as the basis for approving generic versions of drug products was established by the “Drug Price Competition and Patent Term Restoration Act of 1984,” also known as the Waxman-Hatch Act. This law allows for the expeditious approval of manufacturers’ applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials, ultimately expediting the availability of less costly generic drugs. Simultaneously, the brand-name (innovator) company can apply for up to five additional years of extended patent protection for the innovator drug, to make up for time lost while their product was going through the FDA’s lengthy approval process.

It is only after multiple generic versions of an innovator product are approved and enter the marketplace that consumers realize substantial cost savings. Table 1 lists available single agent antihypertensive drugs, and all but five of them are available in an FDA-approved, bioequivalent, generic formulation. Table 2 includes two- and three-drug antihypertensive drug combination products, many of which are also available in generic formulations.

Generic Antihypertensive Drugs and Outcomes

With the demonstration of bioequivalence of generic drugs comes the presumption of similar efficacy. For the case of antihypertensive drugs, efficacy is assessed by blood pressure lowering and CV event reduction. While the vast majority of outcome-based clinical trials of antihypertensive drugs were performed using an innovator, brand-name, product, rather than a generic formulation, some have included both generic and brand name drugs. Kesselheim et al. conducted a large, systematic review and meta-analysis of generic and brand-name drugs used to treat CV diseases which included 47 publications. A total of 38 (81%) of the articles were randomized clinical trials (RCTs) that compared generic and innovator drugs using clinical efficacy and safety endpoints [12]. Among the RCTs, they observed no evidence of superiority of innovator to generic drugs. Importantly, this analysis included drugs from classes including beta-blockers, diuretics, calcium antagonists, antiplatelet, angiotensin converting enzyme inhibitors, statins, α -blockers as well as the narrow therapeutic index drug, warfarin. Conclusions from this review were that it is reasonable for physicians and patients to rely on FDA bioequivalency rating as a proxy for clinical equivalence.

Additionally, in hypertensive patients specifically, large RCTs that utilized both innovator and generic drug formulations have been conducted. In the Controlled-ONset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) hypertensive patients were randomized to either an innovative formulation of verapamil or the physician’s choice of generic atenolol or hydrochlorothiazide [13]. In the International Verapamil-trandolapril Study (INVEST), patients with hypertension and coronary artery disease were randomized to receive a different innovator version of verapamil or generic atenolol, with the addition an innovator ACE inhibitor and or generic hydrochlorothiazide (HCTZ) as needed for blood pressure lowering [14]. In both CONVINCE and INVEST, blood pressure lowering was not statistically different comparing the two treatment groups, one led by innovator drugs, and the other led by generic drugs. Because CONVINCE was stopped early for non-study related reasons, the numbers of outcomes accrued at the time of study closure were less than what the prespecified power calculations estimated were necessary to establish “equivalence” of the two treatment regimens. Nevertheless, major CV outcomes were not significantly different comparing the groups.[13] In INVEST, where prespecified power

assumptions were met, adverse CV outcomes were equivalent comparing the treatment groups [14].

Both CONVINCE and INVEST were designed to compare newer antihypertensive agents to generic formulations of older antihypertensive agents. It could be argued that comparing newer, innovator agents with generic formulations of older agents from other drug classes may introduce potential confounders into the interpretation of the trial's results. However, both of these studies, which together studied more than 39,000 hypertensive patients, demonstrated equivalent blood pressure lowering.

Some have interpreted the Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack (ALLHAT) trial to be a comparison of four generic agents, but in fact, amlodipine, doxazosin, and lisinopril were not generically available until the study was nearly completed [15]; therefore, branded products were obtained, as "in-kind" contributions from their manufacturers during this trial, while the fourth agent, chlorthalidone was used in the generic form [16, 17]. ALLHAT demonstrated that generic chlorthalidone was associated with significantly greater blood pressure reductions than the other branded drugs, and the risk of at least one subtype of adverse CV outcomes was significantly lower with generic chlorthalidone, compared to each of the other branded drugs [15].

When differences in blood pressure response or CV outcomes are observed at the individual patient level, other clinical factors, including race [18], and patient adherence with prescribed therapy, or compliance with refilling prescriptions in a timely manner [19,20], are more likely than generic *versus* branded status of a drug, to predict drug class response. Recently, the relationship between access to generic medications among Caucasian and African American diabetic hypertensive subjects and blood pressure control was evaluated [21•]. While access to generic medications significantly increased from 66% in 2003 to 81% in 2007, and the odds of achieving blood pressure control (< 130/80 mmHg) were 66% higher in 2007, there was no significant relationship between access to generic antihypertensive drugs and blood pressure control when other demographic factors were considered. Taken together, these large RCTs and other important studies, which evaluated both innovator and generic formulations, provide compelling evidence that blood pressure lowering and CV outcomes are similar, regardless of drug status, and other important factors contribute to the level of blood pressure lowering and CV outcomes observed.

Generic Drugs and Medication Adherence

Medication nonadherence is a common and costly healthcare concern. An estimated 50% of patients worldwide were not taking medications as prescribed [22], leading to an estimated \$100 billion spent each year in avoidable hospitalizations [23]. Reduced out-of-pocket expenses have been associated with improved medication adherence [24•]. Whether use of generic drugs, which have lower copayments, can improve medication adherence has been the subject of some investigation. An analysis of healthcare claims data from 45 large employers showed that generic prescribing was associated with increases in medication adherence in patients with hypercholesterolemia and diabetes, while in patients with hypertension, use of generic drugs was associated with lower medication adherence. Copayments of \$0 were a more consistent predictor of increased adherence [25].

Lastly, in a study of generic pill appearance and medication adherence amongst users of antiepileptic drugs, changes in pill color was associated with a significant 53% increase in nonpersistence of therapy [26•]. This finding lead the authors to conclude that current FDA regulations, which require a difference in color and shape for generic drugs, should be reevaluated in light of the negative impact on patient adherence. In fact, the FDA's Office of

Generic Drugs has started to include in its reviews the visual dimensions of product presentations that could have an impact on patient adherence and persistence [27].

Patient and Prescriber Preferences Regarding Generic Drugs

A national survey of 1891 physicians in 7 specialty areas indicated that approximately 4 of 10 physicians sometimes or often prescribe a brand-name drug to a patient when a generic drug is available because the patient requested it. This was more common among physicians in practice more than 30 years compared with those in practice less than 10 years. Additionally, this was more common among those physicians who received industry provided food or beverages in the workplace, and those physicians who received industry provided drug samples [28•]. Clearly, prescribing innovator drugs when bioequivalent generic formulations are available generates higher healthcare expenditures.

Conclusions

Generic drugs are bioequivalent to their corresponding innovator brand in dosage form, strength, route of administration, quality, performance characteristics and intended use. While they are usually chemically identical to their branded counterparts, they appear different in size, shape and color, in accordance with current regulations. They are also sold at substantial discounts from the branded version. Despite the documented similar efficacy with regard to blood pressure lowering and CV outcomes for various generic antihypertensive agents, they are not always prescribed, and when they are prescribed, significantly improved adherence and outcomes has not been observed. While cost of, and access to, medications is an important factor in medication adherence and overall efficacy, it is not the only factor, and there remain other important factors that contribute to the continued prevalence of under- or uncontrolled hypertension, both in the US and worldwide.

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Table 1

FDA-Approved Single-Agent Drugs for the Treatment of Hypertension

Diuretics	Beta-blockers	Calcium Antagonists	ACE inhibitors	ARBs	Others
amiloride	acebutolol	amlodipine	benazepril	azilsartan *	aliskiren *
bumetanide	atenolol	diltiazem	captopril	candesartan *	clonidine
chlorothiazide	bisoprolol	felodipine	enalapril	eprosartan	doxazosin
chlorthalidone	carvedilol	isradipine	fosinopril	irbesartan	guanabenz
epplerenone	labetalol	nicardipine	lisinopril	losartan	guanethidine
ethacrynic acid	metoprolol	nifedipine	moexipril	olmesartan *	guanfacine
furosemide	nadolol	nimodipine	perindopril	telmisartan *	methyl dopa
indapamide	nebivolol *	nitrendipine	quinapril	valsartan	minoxidil
HCTZ	pindolol	verapamil	ramipril		prazosin
metolazone	propranolol		trandolapril		reserpine
spironolactone	timolol				terazosin
torsemide					
triamterene					

ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, HCTZ hydrochlorothiazide,

* not currently available in a generic formulation

Table 2

FDA-Approved Two- and Three-Agent Drug Products for the Treatment of Hypertension

Diuretic + Beta-blocker	Diuretic + ACE inhibitor	Diuretic + ARB	Diuretic + Diuretic	Diuretic + Other	ACE inhibitor + Calcium Antagonist	ARB + Calcium Antagonist	Renin Inhibitor + Other	3-Drug Combinations
chlorthalidone + atenolol	HCTZ + benazepril	chlorthalidone + azilsartan *	HCTZ + amiloride	chlorthalidone + clonidine	benazepril + amlodipine	olmesartan + amlodipine *	aliskiren + amlodipine *	HCTZ + amlodipine + aliskiren *
HCTZ + bisoprolol	HCTZ + captopril	HCTZ + candesartan *	HCTZ + spironolactone	HCTZ + hydralazine	trandolapril + verapamil SR	telmisartan + amlodipine *	aliskiren + HCTZ *	HCTZ + amlodipine + olmesartan *
HCTZ + metoprolol	HCTZ + enalapril	HCTZ + eprosartan *	HCTZ + triamterene	HCTZ + methyl/dopa		valsartan + amlodipine *	aliskiren + valsartan *	HCTZ + amlodipine + valsartan *
HCTZ + propranolol	HCTZ + fosinopril	HCTZ + irbesartan						
HCTZ + timolol	HCTZ + lisinopril	HCTZ + losartan						
	HCTZ + moexipril	HCTZ + olmesartan *						
	HCTZ + quinapril	HCTZ + telmisartan *						
		HCTZ + valsartan						

ACE angiotensin converting enzyme. ARB angiotensin receptor blocker, HCTZ hydrochlorothiazide,

* not currently available in a generic formulation