



# Quality, Safety and Efficacy of Generic Medicines used for Diabetes and Hypertension: A Review of the Literature

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## Abstract

**Background:** Generic medicines procurement and prescribing has become common practice in public sector. Due to high priced branded medicines, prescribers tend to prescribe locally manufactured generic medicines. The aim of this paper is to summarize the perspective of different healthcare professionals on quality, safety and efficacy of generic medicines being used for diabetes mellitus and hypertension in developed and developing world.

**Objective:** The main objective is to systematically identify and review the policies and interventions employed for promoting use of generic medicines in diabetes mellitus and hypertension.

**Methodology:** A total of 52 studies were reviewed from developed countries, developing and Pakistan using the databases such as pubmed, science direct and EBSCO host. **Conclusion:** The review concluded that generic medicines procurement and prescribing has become common practice in public sector. Due to high priced branded medicines, prescribers tend to prescribe locally manufactured generic medicines. Prescribers need to be reassured and educated about the drug regulatory authority approval system of generic medicines with regard to their bioequivalence, quality, price and safety.

**Keywords:** Generics; Safety; Efficacy; Quality; Anti-hypertensives; Anti-diabetics

## Introduction

World Health Organization (WHO) defines the term 'generic drug' or 'generic medicine' as a pharmaceutical product that is usually intended to be interchangeable with an innovator product, is manufactured without a license from the innovator company and is marketed after the expiry date of the patent or other exclusive rights. Introduction of generic medicines can play a crucial role in the effective distribution of financial resources for pharmaceutical medicines. The use of increased amount of generic drugs and the major differences between prices of generic and branded originator medicines have resulted in savings in healthcare costs [1].

The increasing prevalence of diabetes and hypertension is major concern to be addressed at present. The pattern for the treatment of these diseases usually include at least two to three drugs per prescription which has seriously raised

concerns regarding the affordability for the patients. The economic benefits of the use of generic medicines cannot be denied, their use is essential to control healthcare spending especially in treatment of these chronic diseases. If physician is knowledgeable having proper information regarding generics and consumer is well informed about availability of low cost products, the unaffordability issue being the major factor towards patient non-compliance in treatment of diabetes and hypertension can be addressed [2]. The aim of this paper is to summarize the perspective of different healthcare professionals on quality, safety and efficacy of generic medicines being used for diabetes mellitus and hypertension in developed and developing world. The main objective is to systematically identify and review the policies and interventions employed for promoting use of generic medicines in diabetes mellitus and hypertension.

## Methodology

All the related articles and journals were searched through databases such as Science Direct, PubMed and EBSCO host. Few keywords had been used to allocate those particular articles needed such as “generic”, “safety”, “efficacy”, “quality”, and “anti-hypertensives and anti-diabetics”. The inclusion criteria for the articles were that all articles must be in English language. Abstracts that contain one or more of the key search terms were identified. Studies referred were published within the last 10 years from year 2017. A total of 52 studies were reviewed from developed countries, developing and Pakistan.

## Results and Discussion

### Overview of quality, safety and price of generic medicines

The global generics sector reached \$269.8 billion in 2012 and is expected to reach \$518.5 billion in 2018, with a compound annual growth rate of 11.5%. This high penetration of generic medicines is due to various incentives being offered to clinicians, patients and payers; although mandatory INN prescribing in international markets is rare [3]. There are negative perceptions regarding safety and effectiveness of generic medicines in many countries. This can be attributed to the various cultural barriers in the society. In Netherlands, an information campaign with the purpose of improving knowledge of consumers regarding generic medicine alternatives to originator medicines has been run by the government. Generics in the past have been criticized for being substandard or suffering from major quality problems. The major issues highlighted are low compliance to Good manufacturing practice guidelines or identified gaps in site inspections. Good manufacturing practice is a set of principles designed to ensure that licensed medicines are manufactured only by licensed manufacturers, whose premises and processes are regularly inspected, and that the products comply with the latest standards of quality, safety, and efficacy [4].

### Quality, safety and efficacy of available anti-hypertensive medicines

Globally 1 billion people are estimated to be affected by hypertension and 65 million people are affected in USA alone. There is an increased risk of complications such as heart attack, stroke and renal failure with hypertension. The various classes used to treat hypertension include diuretics, beta blockers, calcium-channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). diuretics increase the excretion of water and sodium by acting on kidney, leading to reduction in blood volume as well as reduction in blood pressure. The CCBs and beta blockers both act on the musculature of either the blood vessels and/or the heart. The danger of mortality from cardiovascular disorders in high risk patients can be reduced to half by using aspirin, two blood-pressure drugs, and a statin. The use of this regimen is cost-effective as well as effective. The use of such drugs should

be encouraged that are available for both primary and secondary prevention in developing countries. Some doubts have been made concerning the use of generic preparations versus patent drugs despite of the fact that the efficacy of cardiovascular patent drugs is comparable to generic drugs [5].

### Quality, safety and efficacy of available anti-diabetic medicines

Diabetes is one of the largest global health emergencies of the twenty-first century. According to International Diabetes Federation, 415 million adults currently have diabetes, and 642 million is the estimated number of people with diabetes worldwide in 2040 [6]. A study conducted in Pakistan reported that majority of the general practitioners agreed that generic medicines are more affordable, and effectiveness of locally manufactured medicines is comparable to brand name medicines. Lack of check on quality during manufacturing of locally produced products was a major concern for majority of respondents [7].

### Overview of quality, safety and price of locally manufactured anti-hypertensive and anti-diabetic drugs in developed countries

Prescription only medicines are crucial for chronic disease management. In the United States, the annual spending is approximately \$325 billion for such drugs. Even less costly and highly effective generic products are available in the market; still prescribers prefer to use expensive brands. In the year 2001, majority of recipients of medicare preferred to use multinational ACEI and CCB instead of available generic products [8]. Pfizer earned approximately more than revenue of \$ 7 billion by introduction of Lipitor (atorvastatin) in the United States in 2010. The total market for prescription lipid-lowering drugs continues to increase; with statins leading the market as this drug class has greater prescription volume than any other class in 2010. The patent for Lipitor's patent expired in June 2011, and the first generic was introduced in the market on November 30 [9]. Healthcare providers as well as consumers should be better informed about generic drugs. To promote educational programs and rational use of generic drugs, health authorities and reimbursement institutes should collaborate with pharmacists and prescribers' medical associations [10].

The generic market share is greater than 40 percent in countries with a mature generic medicines market such as Denmark, Germany, Netherlands, Poland, and UK. The generic market share did not exceeded by 20% in countries with developing generic medicines markets such as Austria, Belgium, France, Italy, Portugal, Spain. The use of generic medicines may be promoted by the use of generic substitution if pharmacist considers it cost-effective to substitute multinational products with local products. Evidence about the price difference between originator and generic medicines needs to be disseminated to relevant people, thus generating an incentive for physicians

to prescribe, pharmacists to dispense and patients to ask for generic medicines. The national medicine regulatory authorities should publish a pricing guide to disseminate information regarding pricing to healthcare providers. Databases of medicines, e-prescription systems and standard treatment guidelines should also include information regarding pricing of medicines [11].

### **Overview of quality, safety and price of locally manufactured anti-hypertensive and anti-diabetic drugs in developing countries**

Majority of the individuals diagnosed with hypertension reside in developing nations which have poor health resources and individuals have poor knowledge and awareness regarding control of hypertension. Globally the prevalence of hypertension is rising and is expected to increase by 500 million by the year 2025. The deaths due to hypertension have risen by 25% in less than 10 years in South Africa. The increasing prevalence of the disease and inadequate control in developing countries are crucial reasons for this high burden of cardiovascular diseases [12]. In less developed countries, accessibility of medicines is a matter of great concern for health services. The four medicines are hydrochlorothiazide, atenolol, enalapril and amlodipine. In developing nations, international guidelines advise use of diuretics and calcium channel blockers. Majority of countries considered diuretic hydrochlorothiazide as the most affordable medicine whereas captopril as the second most affordable drug [13].

According to World Health Organization (WHO) the number of patients in India with diabetes mellitus is estimated to be 79.4 million by 2030. Currently 26% of elderly population has type II DM in India. The first line therapy is oral hypoglycemic agents in India. Target Glycated Hemoglobin (A1C), drug safety and efficacy profile, and therapy cost-effectiveness are few of the factors affecting choice of drugs. Metformin is the most commonly prescribed drug in T2DM. Because of its long t<sub>1/2</sub>, stronger extrapancreatic action, less hyperinsulinaemia, and lower incidence of hypoglycemia, glimepiride is considered an effective choice. Glibenclamide was commonly used as a replacement when glimepiride was out of supply from hospital pharmacy [14].

The National Medicines Policy was introduced in 1996 in South Africa. In public sector the main focus has been to use generic medicines. Generic medicines are being used in the private sector since 2000 due to high medicine prices. In a study conducted in Africa it was concluded that safety and efficacy of medicines was the major factor of concern for consumers and healthcare providers. Majority of respondent's agreed that quality of medicines in South Africa was good. The in vitro tests provided evidence that the products assessed from South Africa met the quality standards [15]. Inaccurate or inadequate knowledge of healthcare professionals about generics causes' hesitation on the utilization of these drugs and chiefly about their

efficacies and this is becoming a major obstacle to a wider use of these products. Studies on consumers' perceptions reported that pharmacists are main determinants in consumers' choice to rational use of generics. According to the study conducted in Ethiopia, the respondents claimed that locally manufactured generics are equal in their quality compared to the imported generics [16].

### **Overview of generic medicines in pakistan**

The system of generic medicines was introduced in 1972 in the country. In 1972, The Pakistani Drugs Act (Generic Names) was implemented. The act stated that any prescription by brand or patent name, and manufacturing and selling of medicines under a proprietary name was prohibited. The purpose of this act was to increase competition between local and multinational manufacturers. The aim was to observe a decrease in prices of medicines. But no decline was observed in prices as the competition focused a shift from price to quality. The strict requirement of manufacturing and marketing pharmaceutical products by generic names was finished as director general of health released orders for another act in the year 1976. After implementation of act stringent requirements were imposed on manufacturing license [7].

Use of generics can be crucial for reducing the treatment cost and healthcare expenses as 77% of the population of the country spends out of pocket on healthcare and the income is less than 2 US \$ per day [17]. The major barrier hindering use of generic medicines by community pharmacists was cited to be safety of such products. Poor financial status of patients was considered to be factor for dispensing generic medicines. The use of generic medicines can be promoted if satisfactory bioequivalence, safety and toxicity reports are disseminated to community pharmacists. Generic substitution is a continuing phenomenon in community pharmacy practice in Pakistan. Generic substitution is not allowed by law in the country, but still pharmacists and illegal drug sellers are by passing doctors' prescriptions in this regard without doctors' consent. Proprietary products have been currently included in National Essential Drug List (NEDL) which are costly for majority of the population [18].

### **Overview of quality, safety and price of locally manufactured anti-hypertensive and anti-diabetic drugs in pakistan**

The burden of cardiovascular diseases and hypertension is high in the country. Pakistan with a total population of approximately 150 million people has poor health indicators in the region. The National Health Survey of Pakistan (NHSP) 1990-1994 reported that one in five people aged 15 or older in the country is diagnosed with hypertension. Majority of the population remain undiagnosed and approximately 3% of the population has well controlled blood pressure [19]. A study was conducted in Pakistan to evaluate the benefit and risks of the side effects from the thiazide diuretics concluded that thiazide

Diuretics should not be considered as the first-choice drug but should be included amongst first-choice drugs. The benefit of diuretics as antihypertensive drugs should be weighed against the risk of unwanted side effects in the long term; they could have a major impact on cost-benefit analyses, especially in country like Pakistan where the cost of medicine is incurred by patients from their pockets. Thiazide Diuretics have been formed as an essential part of the drug treatment for hypertension since decades and used in major randomized trials conducted in western countries, as a result it was established that they are effective in 50% of hypertensive patients as a monotherapy and reduces the cardiovascular morbidity and mortality [20].

ACEIs are considered preferred drug treatment in hypertensive patients with diabetes according to guidelines of ADA. In the study conducted in Lahore, Pakistan reported majority of patients were prescribed ACEI in two, three, and four drug combinations. Monotherapy with ACEI is equally effective in reducing BP. Other drugs such as CCB, ARB's, and Diuretics were also found to be equally effective in reducing blood pressure, both in monotherapy as well as in combination therapy [21]. One of the most prevalent metabolic disorders in the country is diabetes mellitus. According to the National Diabetes Action Plan of Pakistan 2015, approximately 7 million of the population is suffering from the disease. The prevalence of diabetes in 2014 was 7% according to a report published by International Diabetes Federation (IDF) [22].

According to a study conducted at outdoor patient department (OPD) of various public and private sector hospitals of Lahore, Pakistan showed high prevalence of type 2 diabetes especially among females. The initial therapy was started with a monotherapy of metformin, Sulfonylureas and lifestyle modification, followed by combination of oral hypoglycemic agents [23]. According to the study conducted in Peshawar, Pakistan insulin was highly prescribed drug followed by metformin and glimepiride. Most frequently prescribed anti-diabetic two drug combination was sitagliptin + metformin [24]. Another study conducted in Pakistan, on assessment of pharmacokinetics of different generics of tablet gliclazide 80 mg reported that formulations manufactured in different manufacturing units of Pakistan are near to the standard formulation and produce comparable results. Although this data assures the ultimate quality of gliclazide tablet manufactured in Pakistan but every formulation should be studied for assurance of safety and efficacy because life of patient is a matter of concern [25].

### Conclusion

The review concluded that generic medicines procurement and prescribing has become common practice in public sector. Due to high priced branded medicines, prescribers tend to prescribe locally manufactured generic medicines. Many prescribers believe that generic medicines are of low efficacy and not aesthetically good in packaging. Prescribers

need to be reassured and educated about the drug regulatory authority approval system of generic medicines with regard to their bioequivalence, quality, price and safety. There is lack of generic policy for promoting generics and improving consumer awareness along with introducing incentives for prescribers and pharmacists for prescribing and procuring generics. Pharmacist should be included in pharmacy and therapeutic committee so they can play a professional role in procurement of locally manufactured generic medicines. Pricing policy of generic medicines needs to be formulated and implemented according to the needs of healthcare system of Pakistan. There is lack of quality control testing and pre-clinical trials at the time of registration of generic medicines. Safety and efficacy of locally manufactured drugs needs to be ensured through proper quality control testing and stability studies.

Future research should involve designing qualitative studies exploring the factors involved in prescribing local and multinational manufactured medicines. Studies aimed at assessing the quality, safe and price of locally manufactured medicines for other chronic diseases prevalent in the country should be designed. Interventional studies aimed at improving knowledge of healthcare professionals as well as final year students of healthcare professions can be designed to promote use of locally manufactured medicines.

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