**Editorial:**

**Coping with Increasing Medicine Costs through greater Adoption of Generic Prescribing and Dispensing in Pakistan as an Exemplar Country**

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**1. Body of the paper**

Ensuring safe, effective and affordable medicines and vaccines is an integral component of the Sustainable Development Goals (SDGs) to reduce future morbidity and mortality across countries [1,2]. However, currently for more than a quarter of the world's population, essential medicines are either unavailable, inaccessible or of low quality, exacerbated by high rates of co-payment and issues of affordability without universal healthcare [3]. It is crucial to address these challenges, and reduce the financial burden of care and its associated morbidity and mortality, especially as the cost of medicines currently account for an appreciable proportion of the overall cost of care in developing countries [3]. This is currently the situation in Pakistan, which is a lower-middle income country and the fifth most populous country globally with population of over 230 million in 2023 [1,4]. However, approximately 60% of the costs of healthcare in Pakistan is currently borne by patients [1,5]. Despite price controls, the affordability of medicines in Pakistan remains a problem for most due to appreciable prescribing and dispensing of originator brands (OBs) and high-priced branded generics (BGs) as well as substantial price variations in OBs, BGs and low-priced generics (LPGs). Such issues are exacerbated by concerns with the ability of the Drug Regulatory Authority of Pakistan (DRAP) to properly regulate prices [1,5,6].

Currently the price of medicines to treat cardiovascular disease are appreciably higher in Pakistan than other similar countries including Afghanistan, China, Egypt, India, Lebanon and Sudan [1]. Recent studies have also shown that prices of originator acyclovir, atorvastatin, ceftriaxone, ciprofloxacin, diclofenac sodium, omeprazole and simvastatin have been 12 to 18 times higher in Pakistan than international reference prices, with originator fluconazole 60 times higher [5,7,8]. This is not helped by a recent hike of 20% in medicine costs by DRAP equating to a 30% increase in last two years driven by inflation [9]. Despite these rises, there are continuing calls for greater price rises from manufacturers with rising inflation and prices of active ingredients continuing to increase as a result of currency devaluation with Pakistan currently importing 90% of its raw ingredients for medicines [10]. Constraining price rises has resulted in the closure of many small manufacturing plants in recent years despite ongoing requests to increase prices [10].As a result of these multiple economic challenges, the ability of patients to purchase medicines, especially those on low incomes with chronic non-communicable diseases (NCDs), is deteriorating [9,10]. This needs to be urgently addressed.

Most countries currently manage the cost of medicines either directly at the government or national level through formal reimbursement or contracting processes or indirectly through pharmacoeconomic methods coupled with rebates or managed entry agreements [11]. Typically, the availability and affordability of medicines is higher in countries where prices are controlled [8]. A key strategy across countries to improve access to medicines is to encourage greater prescribing and dispensing of multiple sourced generic medicines versus originators, BGs and patented medicines in a class without compromising care [11]. Multiple policies across Europe have resulted in low prices for generics. For instance in the Netherlands, 3-monthly national contracting reduced the prices of generic simvastatin and omeprazole to just 2% of pre-patent loss prices improving access for all patients [11]. In the UK, increased pricing transparency in the pricing of generics, coupled with very high voluntary rates of International Non-Proprietary Name (INN) prescribing, resulted in low prices for generics [11]. Such approaches have led to the consolidation of generic manufacturing companies with economies of scale helping to lower prices. In Lithuania, aggressive policies to lower the prices of generics, coupled with policies to appreciably increase INN prescribing, also resulted in substantial reductions in the prices of generics, e.g., 83% to 87% price reductions for generic simvastatin and atorvastatin respectively in 2009 versus 2000 [12]. Low-cost generics also resulted in appreciable easing of prescribing restrictions for both the proton pump inhibitors and statins in Lithuania, substantially increasing utilisation and resultant patient benefits [13]. Similarly, in the Republic of Srpska, a lower income country, “the need to ensure access to effective, safe and quality medicines, made available in a rational and cost-effective manner to the whole population” resulted in aggressive policies to lower the prices of generics as well as reimbursement restrictions for some medicines [14]. The agressive pricing policies resulted in up to a 82% price reduction for medicines in three high volume classes between 2003 and 2010 in the Republic [11,14]. In addition, in the case of the statins, they became reimbursed following earlier delisting due to cost concerns [14]. Similar experiences with the savings from generics have been seen in Australia, Canada, Japan and the USA as well as developing countries including the Philippines [15]. A key strategy on the Philippines in their goal to improve access to medicines has also been to promote unbranded generics alongside tackling substandard and falsified medicines, similar to a number of other countries [16]. Generic medicines currently account for approximately 90% of prescriptions in the USA, which has been critical to increasing patient access to key medicines [15].

However, there are currently concerns with the nature and extent of generic prescribing and dispensing in Pakistan [1], similar to a number of other countries [11,17]. Generic medicines are currently registered in Pakistan as BGs without bioequivalence tests, which results in an appreciable number of multiple sourced medicines being made available from numerous manufacturers. More than 76000 brands of approximately 1600 medicines and combinations are currently registered by DRAP. In 2018, DRAP registered 6440 medicines and Pakistan had 647 actively operating drug manufacturing licenses [18]. This is leading to preference of BGs over unbranded generics due the perception of higher safety and efficacy of branded drugs [19]. The lack of any coherent generic policy in Pakistan, unlike lower income countries including Central and Eastern European countries and the Philippines, is also a factor in driving up the number of manufacturers and prices [11,12,14,16]. The Generic Drug Act was implemented in 1972; however, it was quickly repealed due to significant resistance from the commercial sector and the medical community [20]. In addition, physicians are influenced by gifts, incentives, and inducements from medical sales representatives in return for prescribing their medicines. Having said this, the majority of physicians agree that pharmaceutical companies are involved in unethical drug marketing practices [21].

To improve the situation in Pakistan, pertinent policy measures are needed building on the experiences in other countries. These include measures to increase the prescribing and dispensing of unbranded generic medicines that meet accepted quality standards, i.e., those of the European Medicines Agency and FDA in the US. Alongside this, ensuring sustainable and dependable procurement and financing systems in addition to a robust medicine price monitoring system that strives to increase transparency in the pricing of multiple-sourced medicines. This in addition to ongoing research into medicine pricing systems across countries as additional potential exemplars for Pakistan [1]. Such activities are increasingly needed in Pakistan given the current economic climate, growing concerns with the affordability of medicines coupled with an ageing population increasing NCDs. Stricter measures with the pricing of generics in Pakistan, including BGs, will undoubtedly lead to further consolidation of manufacturing companies in Pakistan. However, this is essential to enhance economies of scale leading to lower prices for generics. Reducing the number of manufacturers will also assist the authorities in Pakistan to monitor their quality, which is currently not happening.

The first stage to enhance the prescribing and dispensing of generics is to reduce concerns regarding their bioequivalence and resultant effectiveness and safety of unbranded generics versus originators and BGs. Consequently, it is essential that the authorities in Pakistan establish proper bioequivalence testing processes via DRAP for future generics including BGs, and working through the backlog of existing generics. Such approaches will be helped by appreciable consolidation in the number of manufacturers. However, whilst this will cause initial problems arising from the consolidation of the local Pharmaceutical Industry in Pakistan, which according to the Pakistan Business Council is estimated to be worth approximately US$3.2 billion, improvements in the quality of multiple sourced medicines will appreciably enhance export opportunities. Only these approved medicines should subsequently be allowed into the healthcare system in Pakistan whether via community pharmacies, drug stores or hospitals, enforced by legislation and subsequent monitoring. As a result, appreciably reduce the availability of medicines through unlawful drug sellers [10]. There should be appreciable financial penalties, as well as prison sentences for outlets selling non-approved generics, to discourage unlawful medicine sellers.

Alongside these pricing measures, a plethora of other initiatives should be introduced in Pakistan to appreciably enhance the prescribing and dispensing of generics at affordable prices to patients. Potential measures, building on examples in other countries, include compulsory INN prescribing, with pharmacies and drug stores obliged to inform patients of the differences in prices for different generics. This can be facilitated by prominently displaying a list of the cheapest generics in pharmacies to reduce patient co-pays, authorised through a growing role for DRAP [8]. In this way, reduce the dispensing of more expensive BGs with affordability implications for an appreciable number of patients in Pakistan [1]. Compulsory INN prescribing, apart from a small agreed list of medicines where substitution can cause concerns including lithium and certain anti-epileptic medicines, has worked well when properly thought through in lower-income countries [11]. In the UK, there are extremely high voluntary INN prescribing rates, typically around 99% for multiple sourced medicines unless concerns. However, such practices will take time to develop in Pakistan especially with BG and originator companies offering incentives to physicians and pharmacists to prescribe and dispense their particular brands, and physicians not used to INN prescribing [1,11,21]. However, effective communication and education programmes can help in this situation especially if this leads to lower prices and increased affordability for patients. Additional benefits of INN prescribing include reduced confusion among patients if they are dispensed different named-medicines on each occasion without a full explanation [11]. Remuneration for community pharmacies and drug stores could subsequently be based principally on items dispensed so they do not lose out financially for dispensing low-cost INN generics as opposed to BGs or originators with associated incentives. Pharmacists and Technicians could also be incentivised for giving advice to patients regarding their medicines especially if they are taking multiple medications for their NCDs to enhance adherence. This builds on their growing role in healthcare systems post COVID-19 including Pakistan [22,23].

Whilst not related to this subject, pharmacists could also be incentivised to offer advice to patients regarding appropriate treatment of self-limiting conditions, including acute respiratory infections, to appreciably reduce current high rates of dispensing of antibiotics without a prescription for such conditions, especially ‘Watch’ and ‘Reserve’ antibiotics, driving up antimicrobial resistance (AMR) [22]. AMR in Pakistan is a critical and growing issue [22]. However, any activities with pharmacists regarding generics need to be well thought through and co-ordinated. Otherwise, the objectives will not be met as seen in Abu Dhabi with community pharmacists and physicians in South Korea [11].

In addition, in both public and private sector hospitals, an active procurement system based on INNs that are part of national guidelines/ essential medicine lists should be introduced. Alongside this, suitable educational activities along with incentives with physicians to enhance INN prescribing and reduce their reliance on incentives from manufacturers of BG or originators. Such activities should be combined with educational activities among patients on the efficacy and safety of generics to reduce current fears. These co-ordinated activities among all key stakeholder groups should subsequently be regularly monitored via mobile and other technologies to help patients, especially those with NCDs, afford and trust prescribed generic medicines. This is essential given the growing burden of NCDs in Pakistan and their subsequent impact on morbidity and mortality.

**2. Expert Opinion**

The authorities in Pakistan have a real opportunity to implement multiple reforms and initiatives to benefit of patients facing real difficulties with access and affordability of medicines, especially those with chronic NCDs. Removing the concept of BGs which have ultimately resulted in appreciably higher costs of medicines to patients is a key target along with strengthening the licensing process for multiple sourced medicines in Pakistan. Strengthening the licensing system with mandatory bioequivalence data is essential to build trust in compulsory INN prescribing initiatives. Alongside this, greater involvement of DRAP with encouraging greater transparency in the pricing of generics. Whilst this will result in the closure of companies in Pakistan, this can be compensated by appreciably greater export opportunities. Alongside this, there also needs to be a complete overhaul of the remuneration system for pharmacists with the drive towards low-cost generics. Future remuneration must include financial compensation for their potentially great role in discussing diagnosis and dosing schedules with patients to improve future compliance. This is especially important among patients with NCDs. Pharmacists’ efforts will be wasted unless patients can afford their prescribed medicines, and these are of acceptable quality. Overall, multiple combined measures are essential for the future in Pakistan. Alongside this, there needs to be constant monitoring and adjusting of the multiple initiatives to benefit patients since without such reforms patients will continue to suffer. Competent academic researchers will be vital for robust monitoring and debate long into the future.

**Declaration of Interests**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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