

## **Prescribing of bisphosphonates and antibiotics in Pakistan: challenges and opportunities for the future**

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### **Abstract**

**Introduction:** The appropriate management of patients with osteoporosis and the rational use of antibiotics are growing concerns in Pakistan. The first step to improve patient care is to understand current prescribing patterns and the rationale behind these patterns. **Aim:** To assesses utilisation patterns, prescribing behaviour and the potential rationale among a range of medicines including bisphosphonates and antibiotics. Subsequently, use the findings to suggest potential future policies for all key stakeholders to improve patient care in the future. **Methodology:** A questionnaire based, cross-sectional study in both private and public health care facilities in Pakistan, conducted between January 2011 and December 2012, involving 438 physicians and 15824 prescriptions. The second study involved 9984 outpatient prescriptions, 127 in-patient cases and over 100 prescribers and dispensers. **Results:** There was adequate history taking and examinations in approximately half of the physicians surveyed, with prescribing typically taking into account issues such as disease severity (84% of respondents) and the socioeconomic status of patients (53%). Prescribing of bisphosphonates was common certainly compared to medicines

to treat cardiovascular diseases and diabetes. However, there are concerns with the low use of generics, high rate of antibiotic prescribing, variable availability of medicines, medical representatives being a key source of information on medicines and typically a limited number of formularies. Discussion: There are considerable opportunities to improve the rational use of medicines in Pakistan including physician education, prescribing guidance and formularies. In addition, educating patients and physicians concerning antibiotics. These should be co-ordinated among key stakeholder groups. There is also a need to ensure low prices for generics and enhance their utilisation.

Keywords: Antibiotics, bisphosphonates, generics, influencing prescribing, Pakistan.

## **Introduction**

The evaluation and assessment of health care quality is receiving worldwide attention (1, 2), with medicines playing an important role to improve the health of patients (3, 4). However in some countries, the costs of medicines can be up to 60% of total healthcare expenditure (5). This includes Pakistan where expenditure on pharmaceuticals accounts for 47% of total healthcare expenditure (6). Private healthcare currently accounts for over two thirds of total healthcare expenditure (7, 8) and over 70% of the total expenditure on pharmaceuticals (6). However, the limited availability of even essential medicines including generics in the public sector forces patients to purchase their medicines in the private sector, where there is a proliferation of originators (brand named medicines) rather than generics (9). This enhances out-of-pocket payments. As a result, up to 64% of total healthcare expenditure is currently borne by households in Pakistan, with medicines accounting for 43% of household expenditure on health (9).

Pharmaceutical expenditure will continue rising across countries unless addressed, driven by well known factors including ageing populations, rising patient expectations and the continued launch of new premium priced technologies (8, 10-13). Potential ways instigated by health authorities to address this include encouraging the prescribing of low-cost generics, especially where generics are priced at 2% to 10% of pre-patent loss prices such as the Netherlands, Sweden and the United Kingdom (14-16). However, this can be a challenge in countries where there are limited availability of generics, a tendency for physicians to prescribe originators (Brand name products) and where prices of generics can be high. This includes Pakistan. Currently there is limited prescribing of generics particularly in the private sector, e.g. over 90% of patients in the private sector typically request originators (Personal communication S Hussain) and prices of generics vary between 0.2 to 7.02 times that of international reference prices among a basket of products (8, 9). However, generic prices tend to be lower in the public sector when procured centrally by provinces, i.e. an average of 0.74 of the international reference price among a basket of products (7). It was estimated in 2010 that even with this range in the pricing of generics, an average of 51% of pharmaceutical costs could be saved among 9 medicines studied with their increased use (17).

Enhancing adherence to the medicines prescribed will help to improve outcomes and reduce long term costs as well as increase physician familiarity with the medicines they prescribe. This can be achieved through the use of formularies and prescribing guidance (18, 19), thereby reducing adverse drug reactions (ADRs) and drug interactions and their associated costs (20-22).

The unnecessary and inappropriate use of antibiotics is also an increasing concern among health authorities worldwide as this can increase antibiotic resistance and associated costs (23-26). Increasing antibiotic resistance will reduce physicians' abilities to treat future infections due to the lack of therapeutic options, adding to medicine and other costs. These concerns have resulted in activities across countries involving all key stakeholder groups to reduce inappropriate antibiotic prescribing in both hospital and ambulatory care (27-31). The prescribing of antibiotics has also been high in Pakistan, i.e. 62% of prescriptions in the private sector include antibiotics and 54% in the public sector (9, 32), with currently few measures to address this. The improper use of medicines including antibiotics reduces the ability of the authorities to manage priority disease areas within available resources (33-38) as well as adversely affect the treatment of future infections.

There is an essential medicines list in Pakistan (Essential Drug List – EDL) which contains 335 medicines (9). However, there are concerns with physician adherence to the EDL with currently few demand-side measures to encourage adherence, over 1100 to 1200 registered molecules and over 50,000 registered drug products currently in Pakistan, appreciable influence of pharmaceutical companies, and variable availability of generic medicines (9, 39). There are also Standard Treatment Guidelines (STGs) for a number of diseases. However, again there are few demand-side measures from the authorities to enhance adherence to STGs (Personal Communication S Hussain). This compares with the Stockholm Metropolitan Healthcare Region in Sweden, where there has been a tradition of selecting evidence-based medicines for common diseases as well as providing treatment guidance (40). Since 2000, approximately 200 medicines have been selected to treat the majority of common diseases in ambulatory care (18), akin to an essential medicines list (41). Respected specialists, working jointly with clinical pharmacologists, pharmacists and general practitioners in over 20 expert groups, suggest which medicines should be selected and included in the list (18, 40). The recommendations subsequently form the 'Wise List' for that year, which is subsequently widely communicated and disseminated (18, 19). There is currently high adherence to the 'Wise List' recommendations at 87% of all prescriptions (18). High physician adherence is enhanced by the use of robust criteria for medicine selection and the use of respected personnel (18, 40). Published studies have shown that care is not compromised with increased adherence to the 'Wise List' recommendations; however, costs are reduced (40, 42, 43). As a result, endorsing this approach in Stockholm.

Enhancing adherence rates to medicines is also important as rates are currently low in patients with chronic asymptomatic diseases (44-46). Potential measures could include quality of care initiatives with this information increasingly being demanded by policy makers, healthcare professionals and the general public (2, 47). Standard setting and assessment of the subsequent quality of care through performance review should be part of everyday clinical practice, although it is recognised that healthcare professionals should not be overloaded (2, 48, 49). However, this is a challenge where there are issues with medicine availability, high out-of-pocket payments, limited adherence to treatment guidelines and no requirements for hospitals to organise and develop Drug and Therapeutic Committees (DTCs). All of which are issues in Pakistan (6, 9).

Osteoporosis is a systemic skeletal illness illustrated by low Bone Mass Density (BMD) and micro architectural weakening of bone tissue. It is more common amongst people older than 50,

with an estimated prevalence of up to one in four women and one in eight men (50-53), and is associated with considerable economic burden (54). Currently, it is estimated approximately 75 million people worldwide are affected by osteoporosis (53). In the US, more than 10 million people currently have osteoporosis (55) and in Europe, twenty-two million women and 5.5 million men are estimated to have osteoporosis (53). This leads to more than 8.9 million fractures annually worldwide (53). Overall, one in two Caucasian women and one in five men will experience an osteoporosis-related fracture at some point in their lifetimes (55). The prevalence of osteoporosis in Pakistan is also high (56, 57). Estimates suggest 97% of women aged 75-84 years and 55% of women aged 45-54 years are prone to osteoporosis (58).

Osteoporosis is responsible for the third highest number of disability life years in Europe after ischaemic heart disease and chronic obstructive pulmonary disease (COPD) (53). The acute and long-term medical care costs linked with osteoporotic fractures were estimated at US\$17 billion in the United States alone in 2005 (55, 59). In addition to direct medical costs, osteoporosis also leads to considerable indirect costs, chiefly due to associated disabilities and early death (53, 60). As a result, improved management of patients with osteoporosis should be a priority among the authorities in Pakistan.

Bisphosphonates are currently recommended as first-line treatment for patients with osteoporosis following a fracture to reduce the risk of subsequent fractures (53, 55, 61-64). They are potent inhibitors of bone resorption and are widely used in the treatment of osteoporosis and other diseases that cause bone mass loss (53, 65). Despite the demonstrated clinical benefits of bisphosphonates (64), adherence can be poor leading to a higher risk of fractures (51, 61, 65-69). Overall, poor adherence reduces by over 50% the potential benefits of medicines to treat osteoporosis (70). The principal reasons for non-adherence include troublesome side effects such as GI side-effects, out-of-pocket expenses and practical difficulties with their administration, which includes inconvenient dosing regimens (51, 64, 68, 69, 71). GI side-effects are often treated with proton pump inhibitors (PPIs) (72, 73). However, there are increasing concerns with the long-term use of PPIs, including concomitant use with bisphosphonates, and the increasing risk of fractures (73-76).

A first step to improving the rational use of medicines in Pakistan, especially in high priority disease areas including osteoporosis and infections, is to understand current prescribing patterns and the rationale behind these. Subsequently, use the findings to guide future policy initiatives. Consequently, the principal objective of this study is to assess current medicine utilisation patterns including originators versus generics, prescribing behaviour and the potential rationale among a range of medicines including bisphosphonates and antibiotics using indicators and methods described by World Health Organisation (WHO) (77-79).

## Methodology

### *Principal study*

A questionnaire based, cross-sectional study was conducted in both private and public health care facilities among five large cities of two Provinces of Pakistan (Punjab and Khyber Pakhtonkhwa – KPK) from January 2011 to December 2012. These cities and provinces were chosen as they represent approximately half the population of Pakistan. The survey methodology was adapted based on developed WHO guidance (78, 79). To date, it has been implemented in over 13 developing countries (77, 79). The questionnaire was based on indicators for appropriate drug prescribing. The practitioners were informed that the data was being collected for academic purposes from the hospitals or private practice settings and the purpose of the study was not to affect changes in their prescribing behaviour. The principal emphasis of this study was on the management of osteoporosis. However, all medicines prescribed were incorporated into the study, including those to treat hypertension, hyperlipidaemia and diabetes, to provide additional background to the study.

To enhance the robustness of the findings, the survey instruments were developed and pre- tested in another district; however, this data was not included in this study. Data was collected on prescription practices, drug availability at each facility, as well as the attributes and characteristics of the prescribers. Pharmacists and a final year Pharmacy students undertook the surveys with each member trained in administering survey instruments. In case it was not possible to collect adequate prescription histories during the first visit, the same health facilities were re-visited until the required sample size of prescriptions was achieved. The sampling unit was the patient prescriber encounter (P-P encounter). The sample size was estimated using quality of the prescription as the outcome variable. Studies on GPs from Karachi (80) had shown that in cases of diarrhoea in children, the quality of prescription was inadequate in over 50% of P-P encounters. Using this figure as an indicator of the overall quality of prescription with a precision level of  $\pm 5.0\%$  at 95% confidence level, the estimated sample size was 5,000 P-P encounters. Data Processing and Analysis were undertaken through the Statistical Package for the Social Sciences (SPSS-16) and outcome (or dependent) variables, i.e. the quality of prescription and the quality of consultation were computed. Overall, data from 438 physicians was collected involving a total of 15824 prescriptions.

The quality of the prescription, i.e. whether adequate or inadequate, was assessed by a team of interviewers for each patient-provider encounter, especially trained for this purpose. This assessment was based on the likely diagnosis and the standard treatment for the identified health problem and the treatment prescribed i.e. drug(s) group, the mode of administration (type), dosage and the duration of treatment given to the patient. The quality of consultation was also computed based on the quality of the prescription (above), the adequacy of history taking, relevance of physical examination, consultation time, dispensing time and patient's satisfaction with their consultation. In addition, patients were stratified by their income (Pak Rs), self reported health status (3 categories – Good, Fair or Poor) and whether they have had a fracture – Yes or No.

Finally, physicians were also questioned on factors that influenced their prescribing. The themes were subsequently collated into nine categories including the socio-economic status of the patient, severity of the disease, availability of drugs at the facility, and the age of the patient.

The study was approved by the Ethics committee of the Department of Pharmacy and Board of Studies of Sargodha University, Sargodha, Pakistan.

### ***Secondary study***

A retrospective audit of in- and out-patient prescriptions was carried out in the same two Provinces to evaluate the indicators of drug use pattern including for instance the average number of drugs prescribed per encounter (ANDPE), the average number of antibiotics prescribed per encounter (ANAPE), % encounter with antibiotics (PEA) and % of antibiotic prescriptions based on microbial sensitivity test results (MCST).

A "knowledge, attitude and practice" (KAP) questionnaire survey of hospital prescribers and dispensers was also performed in the two Provinces. Indicators of prescribing and dispensing quality incorporated into the questionnaire included: (i) sources of drug/prescribing information, (ii) availability and use of the hospital formulary, (iii) knowledge of the prescribing process (4 steps) and (iv) the adequacy of the drug supply management system from their perspective.

A total of 9984 outpatient prescriptions and 127 in-patient case notes were audited. The total number of prescribers and dispensers surveyed were 88 and 13 respectively.

The study was also approved by the Ethics committee of the Department of Pharmacy and Board of Studies of Sargodha University, Sargodha, Pakistan.

## **Results**

### ***Principal study***

Table 1 gives the breakdown of the patients receiving prescriptions by gender, age, and income. The socioeconomic parameters of the patients, their self-reported health and history of the fracture are given in Table 2. There are significant differences between Punjab and KPK in a number of parameters including age, income, health (fair and poor) as well as history of fractures.

Table 1: Age/ gender distribution of the patients

Age Group (Yrs)	No. of Patients	Punjab	KPK	p value
Less than 30	248 (1.56%)	202 (2.18%)	46 (0.70%)	<0.001
30-40	2028 (12.82%)	1168 (12.61%)	860 (13.10%)	<0.001
41-50	3006 (18.99%)	1690 (18.25%)	1316 (20.05%)	<0.001
51-60	4012 (25.35%)	2379 (25.69%)	1633 (24.88%)	<0.001
61-70	3888 (24.57%)	2398 (25.89%)	1490 (22.70%)	<0.001
Above 71	1576 (9.96%)	922 (9.96%)	654 (9.96%)	<0.001
Age not mentioned	1066 (6.73%)	502 (5.42%)	564 (8.59%)	Ns
Total Male patients	8044 (51%)	4638 (51.4%)	3406 (51.5%)	
Total Female patients	7780(49%)	4593 (49.6%)	3187 (48.5%)	
Total patients	15824	9261	6563	<0.001

Table 2: Socioeconomic parameters of the patients

Income (Pak Rs)	Total	Punjab	KPK	p value
<10000	4222	2284	1938	<0.05
20000	8004	4448	3556	<0.01
50000	1098	729	349	<0.001
100000	1434	1122	312	<0.001
Above 100000	1066	628	438	<0.001
<b>Self-reported health</b>				
Good	5438	2863	2575	Ns
Fair	4480	3144	1336	<0.001
Poor	5906	3224	2652	<0.01
<b>History of fracture</b>				
Yes	1289	942	347	<0.001
No	14535	8289	6246	<0.001
<b>Gender</b>				
Male	8044 (51%)	4638 (51.4%)	3406 (51.5%)	
Female	7780 (49%)	4593 (49.6%)	3187 (48.5%)	

Table 3 contains details of the consultation indicators across the two provinces, i.e. Punjab and Khyber Pakhtonkhwa (KPK). This includes adequate history taken, relevant physical examination, diagnosis informed to the patient, the number of drugs prescribed by public or private sector as well as the average number of drugs prescribed. Again, there are significant differences between the two provinces in a number of the parameters including informing patients and requesting laboratory tests.

Table 3: Consultation Indicators

Indicators	No. of Prescriptions n = 15824	Punjab	KPK	p value
Adequate history taken	9060 (50.63%)	6188	2872	<0.001
Relevant physical examination done	8238 (49.68%)	5320	2918	<0.001
Diagnosis informed to patient	10590 (59.18%)	7844	2746	<0.001
Diagnosis written on the prescription	11875 (75.78%)	7020	4855	<0.001
Lab tests ordered	7340 (41.02%)	3914	3426	Ns
Lab tests required	5382 (30.85%)	2884	2498	<0.05
No. of drugs prescribed	77538	42424	35114	<0.01
No. of drugs prescribed by Brand names	59880 (70.67%)	33155	26725	<0.01
No. of generics prescribed	17658 (29.32%)	9244	8414	Ns
No. of drugs prescribed by Public Sector physicians	31586	16543	15043	Ns
No. of drugs prescribed by Private Sector physicians	45952	26262	19690	<0.001
Average no. of drugs prescribed	5.11			
Average no. of drugs prescribed in Punjab	4.90			
Average no. of drugs prescribed in KPK	5.32			

The therapeutic classes of drugs prescribed among all drugs prescribed are included in Table 4, which includes bisphosphonates, vitamins and calcium. Again there are significant differences between the two provinces in some of the drugs prescribed.

Table 4: Categories of Drugs Prescribed (Total population)

<b>Therapeutic class of Drugs</b>	<b>Total no. of Drugs</b>	<b>Punjab</b>	<b>KPK</b>	<b>p-value</b>
Bisphosphonates	12672 (16.34%)	7255	5417	<0.001
NSAIDs	8360 (10.8%)	5342	3018	<0.001
Vitamin D3	8248 (10.6%)	5586	2662	<0.001
General Vitamins and calcium	5060 (6.5%)	2580	2480	Ns
PPIs	6382 (8.2%)	3466	2916	<0.05
Antidiabetic	7280 (9.4%)	3955	3325	<0.05
Antihypertensives	7734 (10%)	4080	3656	Ns
Lipid lowering Drugs	7820 (10.1%)	4490	3330	<0.001
Steroids	4382 (5.6%)	1886	2496	<0.001
Injectables	3582 (4.6%)	1472	2110	<0.001
Tranquilizers or sedatives	3506 (4.5%)	1431	2075	<0.001
Others	5038 (6.5%)	2856	2182	<0.001
Total	77538 (100%)	44424	33139	

Table 5 contains data on the cost of drugs prescribed, broken into 6 groups to aid comparative purposes. These are 0 to 150 (Pak Rs), 151-250, 251 – 350, 351 – 450, 451 – 550, and 551 or above (Table 5). Again, there are significant differences between the two provinces.

Table 5: Cost analysis – total population

<b>Cost (Rs)</b>	<b>Number of prescriptions &amp; (%)</b>	<b>Punjab</b>	<b>KPK</b>	<b>p value</b>
0-150	6684 (42.2)	3660	3024	<0.01
151-250	3674 (23.2)	2186	1488	<0.001
251-350	2018 (12.8)	1328	690	<0.001
351-450	840 (5.3)	524	316	<0.001
451-550	1280 (8.1)	756	524	<0.001
Above 551	1328 (8.4)	777	551	<0.001

Table 6 refers to the factors that influenced physician prescribing among the sampled physicians. Again, there were significant differences between the two provinces. However, formularies or prescribing guidance was not available at most of the facilities.

Table 6: Prioritization of factors that influence prescription among all respondents (No. of responses = 438)

<b>Influencing Factor</b>	<b>Responses % of Punjab</b>	<b>Response % of KPK</b>	<b>p value</b>
Socio-economic status of the patient	53%	35%	<0.001
Previous experience of treating patients	33%	24%	<0.001
Severity of disease	84%	78%	Ns
Patient demand for specific drugs	38%	21%	<0.001
Availability of drugs at facility	53%	34%	<0.001
Placebo effect of drugs	7%	8.5%	<0.01
Age of the patient	74%	54%	<0.001
Concern of losing patients to others practitioners	34%	56%	<0.001
Others	12%	9%	<0.001

Finally, Table 7 describes the current sources of information used by physicians when making their prescribing choices. This principally centres on medical representatives, with again significant differences between the two provinces.

Table 7: Source of Information on medicines (n = 438)

Source	Percentage% Practitioners of Punjab	Percentage% Practitioners of KPK	p value
Medical Representative	68%	86%	<0.01
Textbooks on pharmacology	26%	14%	<0.001
Therapeutic Indices	12.0%	18%	<0.001
Charts and Guidelines	28%	12%	<0.001
Scientific Journals	29%	8.0%	<0.001
News Letters	28%	14%	<0.001
Other Sources (i.e. doctors prescriptions)	12%	14%	<0.05

### **Secondary study**

The average number of drugs prescribed per encounter (ANDPE) was 3.16 for out-patients and 9.7 for in-patients. The average number of antibiotics prescribed per encounter (ANAPE) were 1.1 and 2.4 for out-patients and inpatients respectively.

The percentage encounter with antibiotics (PEA) was 50.3% for out-patients and 96.7% for in-patients. Only 4.2% of in-patient antibiotic prescriptions were based on microbial sensitivity test results (MCST). The percent encounter with switches in antimicrobial therapy was 52.1%, whilst the average number of switches per encounter was 1.35. In 18.5% of the in-patient encounters, there was evidence of drug incompatibilities.

The knowledge, attitude and practice (KAP) survey revealed that prescribers and dispensers in the hospital rely on different sources for their drug information needs (MIMS vs Martindale Extra Pharmacopoeia). None of the prescribers surveyed was able to correctly enumerate all the 4 steps involved in the prescribing process, approximately 25% of dispensers got at least 2 steps correctly, and only 9.1% of the dispensers surveyed could accurately define a hospital formulary. The drug supply management system was also found to be inadequate.

### **Discussion**

There were a number of positive findings that arose from these two studies as well as a number of areas of concern. Areas of concern that need to be addressed to enhance the rational use of medicines in in Pakistan in the future include measures to improve history taking an diagnosis in some provinces, enhance the prescribing of low cost generics and reducing inappropriate prescribing including antibiotics and potentiall polypharmacy.

There appeared to be adequate history taking and relevant physical examinations in approximately half the physicians surveyed (Table 3). However, this was significantly higher in the Punjab versus KPK, which suggests educational activities should be undertaken among physicians in the KPK region to improve history taking and examinations. 59% of physicians also informed their patients about their diagnosis and 76% wrote the diagnosis on the prescription. Again, this was significantly higher in the Punjab province (Table 3) suggesting the need for educational activities in the KPK region. The statistically higher occurrence of these four indicators in the Punjab compared with the KPK province may reflect differences in the communicative approaches in the two provinces. Practitioners in the Punjab typically have better communication and rapport with their patients, which needs to be addressed in the KPK region. There appeared to be limited differences in the number of tests ordered versus those required. This is encouraging, although there were again concerns in the KPK province (Table 3).

It was also encouraging to see that disease severity and socioeconomic factors were important influencers of prescribing (Table 5), especially given the typical low income of most patients (Table 2).

There appeared to be appreciable prescribing of bisphosphonates (Table 4) compared to other drug classes including the PPIs as well as medicines for diabetes, hypertension and dyslipidaemia. This included a trend in the prescribing of bisphosphonates along with vitamins, including vitamin D, and calcium supplements in accordance with current recommendations (81). This would suggest that osteoporosis is currently seen as a more serious disease than cardiovascular disease as there appeared to be lower use of antihypertensives and lipid-lowering drugs despite most hospital formularies, where they exist, not including bisphosphonates. However, this needs to be confirmed before any definitive statements can be made.

The lack of bisphosphonates in hospital formularies means 100% patient co-payment. High patient co-payments can be an issue, especially with the low income level of most patients (Table 2), similar to other publications (6, 7, 9). This resulted in the majority of prescriptions being below 250 Pak Rs for both regions, although there are again differences between them (Table 5). Increasing the availability and prescribing of low cost generics may help to address this, and increase the availability and utilisation of bisphosphonates.

We acknowledge that we have not looked at current adherence rates with the bisphosphonates which, as mentioned earlier, can be a concern, augmented if co-payments are an issue. In addition, we did not specifically look at the concomitant use of PPIs and bisphosphonates given, as mentioned, increasing concerns with the long term use of PPIs and the development of fractures and infections (74, 75, 82). These areas will be the subject of future research projects given the growing prevalence of osteoporosis in Pakistan and the need to adequately treat these patients to prevent future fractures.

Whilst not the principal subject of this research paper, the apparent limited prescribing of lipid lowering treatments in Pakistan is a concern (Table 5). This is despite non-communicable diseases such as diabetes being a high priority alongside communicable disease (7, 34). A separate analysis has shown that the limited prescribing of lipid lowering drugs is not helped by

these medicines currently being unavailable in most public health care facilities (34). In addition, osteoporosis may currently be seen by patients as having greater importance, and hence a higher priority when co-payments are required. However, this is speculation at this stage. This again will be the subject of future research projects.

There were a number of areas of concern. These include the number of medicines prescribed by originator (brand name) rather than generic (INN) name. This may well be enhanced by physicians believing generic medicines are less safe than brand name medicines (8), augmented by currently concerns with the low quality threshold for registration of medicines in Pakistan (9), and their variable availability (9), and the average number of medicines prescribed per encounter (Table 3) including antibiotics (second study). In addition, the lack of formularies, the lack of knowledge about the prescribing process and steps involved with developing formularies (study 2), patient demand influencing prescribing (both studies especially in the Punjab region – Table 6), availability of medicines at the various facilities (Table 6) as well as medical representatives being the key source of prescribing information especially in the KPK region (Table 7). The latter finding mirrors other studies which have shown the influence of medical representatives in Pakistan (8).

The average number of drugs per prescription at 4.9 and 5.32 respectively in the Punjab and KPK regions (Table 3) appeared high compared with the Attock District of Pakistan at 4.1 drugs per prescription (4.5 private and 2.77 public) as well as the average of 2 to 3 in lower and middle income countries (9, 32). This level of prescribing may not always be appropriate since polypharmacy, which is generally described as 5 or more medications (83-86), can cause problems to patients. Problems include negative health outcomes, which incorporate adverse drug reactions and potentially harmful drug interactions, poor adherence and geriatric syndromes, which include urinary incontinence, cognitive impairment and impaired balance leading to falls (83, 84, 87), as well as contributing to hospitalizations (88). However, we cannot comment further without analyzing the rationale behind the prescribing of the different medicines to individual patients and over time. This will also be the subject of further research, especially among private sector facilities where individual motivation and incentives appear important, including patient demands and fear of losing patients (Table 6).

We believe the lack of formularies among the various facilities in Pakistan, as well as the variable availability of generic medicines, resulted in more than 70% drugs being prescribed by their originator (brand name) rather than INN name (Table 3). This may be enhanced by the promotional strategies of pharmaceutical companies leading to concerns with generics (8, 89, 90), which were a major source of information regarding medicines (Table 7). In addition, brand name medicines may well be a potential income source for private practitioners especially with previous research showing that private practitioners in Pakistan are more likely to prescribe originator drugs, antibiotics and injectables than physicians in other countries (32). The low percentage of prescriptions by their generic (INN) name adds to high cost of drugs to patients (91), especially as good quality generics, e.g. generic omeprazole and simvastatin, are priced as low as 2% to 4% of pre-patent loss prices in the Netherlands, Sweden and the UK (14, 15, 40). Generic prices in Pakistan can be as low as 10% to 30% of originator (brand name) prices especially in the public sector; however, generic prices are very variable (7, 92). Methods to

enhance INN prescribing include educational and other initiatives as seen in the UK (15); alternatively, compulsory INN prescribing as seen in Abu Dhabi and Lithuania (93, 94).

Patient demand can be a concern when it comes to prescribing behaviour (Table 6), especially if it enhances the inappropriate prescribing of antibiotics (95-97). The considerable frequency of prescriptions for antibiotics in each physician: patient encounter, which is similar to other studies (9), the low use of microbial sensitivity test results (Study 2), coupled with patient demand generally for medicines (Table 6), suggests that multiple interventions will be needed among all key stakeholder groups in Pakistan to enhance future rational use of antibiotics.. This also applies to dentists in Pakistan (98). Potential strategies for antibiotics could be based on campaigns successfully undertaken in Europe (24, 30, 99-102). For example in France, the government launched a nationwide campaign to reduce the antibiotic use in the community, which reduced unnecessary antibiotics by 26.5% over 5 years (24). In Italy, a community-based educational intervention campaign including posters, brochures, and advertisements in the local media, coupled with a newsletter on antibiotic resistance targeting pharmacists and physicians, significantly improved antibiotic prescribing (100). A ten year multi-faceted programme in Slovenia involving physicians and the health insurance agency, and targeting both physicians and patients, also successfully reversed a growing trend in antibiotic prescribing (27).

The last major challenge to address will be to introduce regulations that lead to active DTCs in all healthcare facilities. This will enhance appropriate prescribing as well as prescribers' and dispensers' knowledge of the prescribing process and formulary management. Alongside this, the development, distribution and monitoring of physician adherence to standard treatment guidelines for high priority disease areas (33). The WHO provides good guidance on how to establish DTCs (41), and the experience in Stockholm, Sweden, and other countries suggests that trusted physicians should be a key element in the development of formularies and prescribing guidance to enhance subsequent adherence (18, 19). Such activities should be undertaken alongside instigating continuous medical education and continuous professional development (CPD) for physicians surrounding an agreed list of prescribed drugs. Such activities will help reduce the reliance on medical representatives to provide information on medicines (Table 7). Concerns that pharmaceutical company activities appreciably influence prescribing behaviour, including the prescribing of more expensive brand medicines (89, 95, 103-105), has resulted in a number of countries introducing measures to reduce their activities alongside measures to enhance the rational use of medicines. This includes limiting pharmaceutical company contacts with physicians and gifts, with the potential for fines for inappropriate activities (106, 107). This provides exemplars for the authorities in Pakistan.

The development of appropriate formularies and STGs should be seen as part of a long-term campaign in Pakistan to enhance the appropriate management of patients with chronic diseases. The Pakistan Medical and Dental Council, pharmacy groups, the Federal Ministry of Health and the provincial departments of Health should play a key role with developing these formularies, guidelines and indicators, to improve future patient care. Part of the rationale of involving all key stakeholder groups should be to ensure that all identified medicines in the formularies are available and affordable at each facility. These activities should improve medicine use (33) as this is influenced by the medicines on the formulary and their availability at each facility (Table 6).

Other major areas to address including strategies to enhance the quality of locally produced generics at prices that enhance their affordability for all citizens in Pakistan (7).

Limitations of this study include the fact that the studies were conducted in only five large cities in two Provinces and involved representative samples rather than the total physician population. However, as stated, these two Provinces comprise approximately half of the population in Pakistan. In addition, we believe in view of the number of physicians included in the two studies, coupled the total number prescriptions analysed, that the findings are robust and generalizable to the whole of Pakistan. We are also aware that we did not correlate diagnosis, treatment and outcomes in our analysis. However, Pakistan currently does not have a comprehensive drug utilization system that can link drug use by patients to outcomes (such as improved patient health and reduced hospitalizations) and link drug use and outcomes across payers (public and private) and across sectors (primary care, acute care and continuing care, including long-term care). This is an area for the future. Having said this, we believe that there were interesting findings emanating from this research to provide guidance to all key stakeholder groups in Pakistan to improve the care of patients.

## **Conclusion**

The study suggests that the prescribing of bisphosphonates is common in Pakistan along with increased prescribing of Vitamin D, certainly compared to medicines for other NCDs such as cardiovascular disease and diabetes. There was also adequate history taking and examinations in approximately half of the physicians surveyed as well as prescribing taking into account issues such as disease severity and the socioeconomic status of patients, which is encouraging.

However, there are concerns with the availability of bisphosphonates and other medicines to treat patients in high priority disease areas. There is also a need to enhance the prescribing of generics versus originators as well as ensure low prices for generics to enhance access to priority medicines. These include generic bisphosphonates, antihypertensives and statins as well as drugs to treat diabetes. There is also a need to develop and instigate robust formularies in each facility in Pakistan alongside continuing medical education to reduce physicians' reliance on medical representatives for information regarding medicines. Such activities will improve prescribers and dispensers knowledge of the process surrounding the generation and management of hospital formularies. There is also a need for educational initiatives among both patients and physicians to enhance the appropriate use of antibiotics given current high rates of prescribing and limited testing.

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