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### INDIAN JOURNAL OF PHARMACY PRACTICE

An Official Publication of Association of Pharmaceutical Teachers of India

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**Printed and Published by:** Prof. B.G. Shivananda, Secretary, on behalf of Association of Pharmaceutical Teachers of India

**Printed at :** Graphic Point, #55/44, 4th 'B' Cross, K.S. Garden, Lalbagh Road, Bangalore - 560 027. Ph: 080-2227310

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## Editorial

*Dear Readers,*

*With the Pharm. D program in full gear, there is ample scope for students to work on various research areas which will benefit the patients.*

*World Health Organization has stated that health is defined not only by the absence of disease but also by the presence of physical, mental, and social well-being. Thus, Quality of Life (QoL), a phrase used to refer to an individual's total well being including all emotional, social, and physical aspects of the individual's life has become the ultimate goal of all health interventions.*

*Quality of life is hugely affected in patients suffering from chronic ailments such as diabetes, hypertension, renal failure, COPD and asthma, psoriasis and so on compared to the general population.*

*In Healthcare, as there is more emphasis on patients now than ever before, quality of life has become an important area to work on.*

*Studies have highlighted the role of pharmacists in improving the adherence and compliance to therapies in patients. Involvement of the pharmacist in the treatment of different chronic conditions by way of patient education and counseling has been noted to improve the outcomes of the treatment, minimizing the complications associated with the disorders and improve the quality of life in patients.*

*Presently the situation in our country is very promising as Pharm. D course has opened up many doors for the aspiring clinical pharmacists to contribute towards improving the patient care, compliance and quality of life.*

*So, hoping for some good contributions by students / researchers in the area of quality of life.*

*Cheers !*

*Shobha Rani*

# Mortality in the developing world- Can pharmacists intervene?

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## ABSTRACT

Submitted: 7/5/2011

Accepted: 10/5/2011

The ever mounting challenge facing global health today is the wide spread gap between the life expectancy observed in the developed and the developing world. War, famine, communicable and non-communicable diseases challenge sustainable development of the human health in the impoverished 3<sup>rd</sup> world nations. Mortality of the population is mainly influenced by the economic, social and technological advances taking place in a nation. In contrast to the healthy lives enjoyed by the inhabitants of Monaco with a highest life expectancy of 90 years, people of Swaziland experience a life expectancy of only 32 years which is the lowest in the world. A majority of the people in the developing nations fall prey to life threatening diseases and infections. This paper provides a comprehensive summary of the causes of mortality among children, adults and older adults across different continents. Independent pharmacies in developing nations can play an important role in reducing mortality, providing continuity of care, improving life expectancy and public health in areas where high health disparity exists. Personalization provided by the pharmacists can improve medication adherence, identify health needs and inspire people to improve their health.

**Keywords:** mortality trends, life expectancy, WHO, global health, developing nations

## INTRODUCTION

Poor medication adherence for chronic conditions can lead to considerable morbidity and mortality in patients.<sup>1,2</sup> The technological and medical advances in healthcare become suboptimal if patients are non adherent to their treatment regimens. In case of hospitalized patients with chronic cardiovascular conditions, medication adherence rates start falling after the patients are discharged. Researchers also found, according to self reports, that only 10% of the discharged patients were completely adherent to their cardiovascular treatment regimens.<sup>3,4,5,6</sup> Sometimes, when a medication is prescribed, the physician might not explain the directions of the medications properly leading to misunderstanding and failure of medication intake on the part of the patient. On the other hand, patients with chronic conditions might miss a dose or take it at the wrong time and

forget to disclose this before their physicians. It is challenging to ensure medication adherence in a particular patients since it cannot be detected by laboratory or blood tests. Physicians and pharmacists can play complementary roles with regards to provision of medication education to the patients for enhancing medication adherence.<sup>7</sup> Complex drug regimens, high drug costs, lack of patient education and adverse drug events are some of the barriers that hinder medication adherence. To overcome these barriers and to motivate the patients to be more adherent to their medications, pharmacists can simplify the patient's treatment therapy. Pharmacists can influence self care behaviors of the patients by playing a key role in assessing, planning and strategically implementing their therapy. Medication adherence might be high in patients who receive counseling compared to patients who do not receive counseling. In the developed nations, pharmacists provide counseling about vaccination, sexual health, smoking cessation and weight management, thereby equipping patients with the healthcare and infrastructure they require to maintain a healthy lifestyle.<sup>8,9,10</sup> Education provided by the pharmacists about complex therapy, side effects of drugs,

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potential adverse events, usage of once daily agents, therapy maintenance can help improve self care and health outcomes in patients.<sup>7</sup>

### Life expectancy

Every nation has a social and economic divide influencing the social and economic status of its residents. Social and economic status combined with the political environment has a great influence on the mortality trends of a nation. The WHO has noted a trend during the past 3-4 decades characterized by a rise in the life expectancy observed in developed nations and most of the developing nations, barring a few nations showing a plateau or a decrease. Here is an overview of some of the nations who have witnessed stagnation or decline in life expectancy.

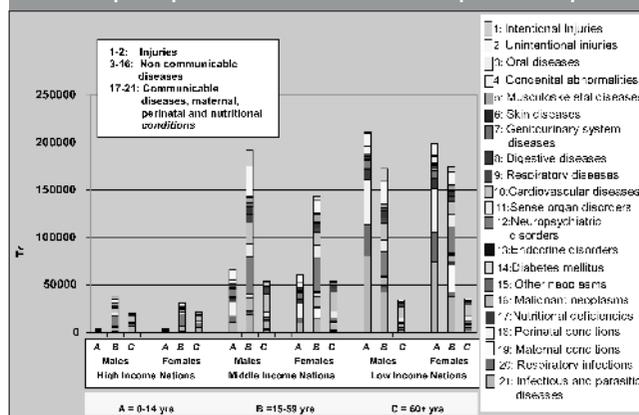
### Mortality in children

Child mortality has gone up in Sub Saharan Africa due to poverty, infectious diseases like HIV/AIDS, rise in malarial mortality, lower respiratory tract infections, diarrhoeal diseases, malnutrition, increase in mother to child transmission of HIV/AIDS, rise in maternal mortality due to HIV/AIDS, stretching away of the resources from child health programs to treat other HIV/AIDS patients, civil unrest and social anarchy. Life expectancy of the children in developing nations of Eastern Mediterranean Region, Latin America and Asia has also declined primarily due to perinatal conditions including birth asphyxia, birth trauma and low birth weight. It has been observed in some South East Asian nations like India, China and Nepal that new born girls have a higher risk of dying due to poor access to health care and the prevalence of stigma that only men are breadwinners in the family. Also, higher rates of child mortality especially female infanticide are witnessed in the rural areas of the developing nations with concentration of poor and illiterate crowd as opposed to educated and informed crowd in the urban areas.<sup>11,13</sup>

### Mortality in adults

Non communicable diseases and injuries (higher prevalence in males) play a major role resulting in adult mortality in many developed nations. The reason for reversal in the adult life expectancy in Africa and some of the developing nations is due to premature adult deaths caused by injuries incurred in war and violence along with the double burden of non communicable and communicable diseases, mainly infectious diseases like HIV/AIDS and parasitic diseases like malaria and tuberculosis which have led to serious

Fig. 1: Total DALYs [Disability adjusted life years (per 1000)] by age group, sex and causes in 192 nations grouped by income per capita across the world: WHO Report- 2004 update.



socioeconomic disparities and political unrest in these regions (figures 1 and 2). On the other hand, even though the life expectancy of adults in developing nations is higher, many poor adults are susceptible to higher disease burden and disabilities. There is an almost 12 fold mortality gap as a result of the improving life expectancy in developed world and deteriorating life expectancy in the developing world.<sup>11,13</sup>

### Mortality in older adults

Emerging epidemic of non communicable diseases marked by the incidence and prevalence of chronic conditions like cardiovascular diseases, cancers of the stomach, liver and colon/rectum, lung cancer caused by smoking, and neuropsychiatric disorders are some of the major contributors augmenting the burden of disease and disability in low-income and middle income nations. The DALYs (Disability adjusted life years)/ YLDs (Years Lived with Disability) that account for reduction in life expectancy rate are defined by WHO as “The sum of years of potential life lost due to

Fig. 2: Number of deaths (in thousands) by age group, sex and cause in 192 nations across the world grouped by income per capita: WHO Report- 2004 update.

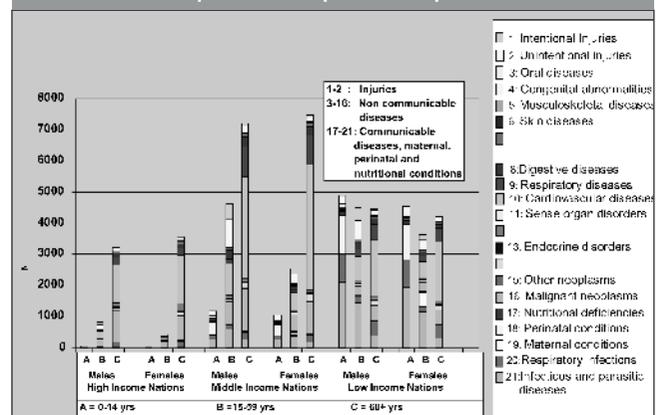


Table 1: Mortality and life expectancy patterns seen in different age groups in various developed and developing nations over the past 2 decades:

Nation	Life expectancy at birth (years)			Healthy Life expectancy (HALE) at birth (in years)	Neo natal mortality rate (per 1000 live births)	Infant mortality rate (ages upto 1) (per 1000 live births)			Under five mortality rate (ages upto 5) (per 1000 live births)			Adult mortality rate (ages 15-60) (per 1000 population)			Reasons for stagnation or decrease in life expectancy
	1990	2000	2008			1900	2000	2008	1900	2000	2008	1990	2000	2008	
China	68	71	74	66	11	37	30	18	46	36	21	172	135	113	War and famine in 1959-1961
Europe	72	72	75	67	7	27	18	12	32	22	14	157	165	149	Industrialization from 1930s – 1950s
USA	75	77	78	70	4	10	7	7	11	9	8	132	114	107	Industrialization from 1930s – 1950s
Russia	69	65	68	60	6	17	16	9	21	20	11	218	309	273	Decline in male life expectancy after 1965 due to heavy alcohol intake, injuries, violence, social unrest, people affected by inadequate government and decades of failures of communism, inefficient Soviet health-care system in 1990s
Sub Saharan Africa	51	50	53	45	40	108	98	85	182	165	142	371	421	392	rapid spread of HIV/AIDS, numerous human losses, many regions are stricken with poverty, illiteracy, war and violence, widespread prevalence of multiple partner induced HIV/AIDS, racial and gender disparities, poor access to medical care systems, rebounding tuberculosis and malaria since 1980s
Uganda	47	45	52	42	31	114	98	84	186	158	135	475	600	436	High prevalence of HIV/AIDS
Rwanda,	50	45	58	43	35	106	112	72	174	186	112	408	547	303	Ongoing war, political upheaval
Angola	42	44	46	45	47	154	141	130	260	238	220	489	460	421	instability
Zimbabwe	61	44	42	39	28	51	62	62	79	102	96	285	711	772	Ongoing economic and social
Kenya	60	51	54	48	33	68	81	81	105	128	128	267	463	371	upheaval affecting child health, development and survival
North Korea	73.2	70.7	67.2	59	29	42	42	42	55	55	55	193	194	196	widespread famine from 1995- 1998, political instability
West African nations like Sierra Leone	41	41	49	35	45	163	151	123	278	252	194	469	530	393	Ongoing serious political conflicts with other nations and within the nation, political and economic instability within the nations
Côte d'Ivoire	54	53	56	47	41	104	96	81	150	138	114	329	399	361	
Liberia	36	50	54	48	44	146	118	100	218	174	144	717	390	340	
Haiti	54	58	62	54	25	105	78	54	151	109	72	336	311	267	reboundng tuberculosis and malaria since 1980s

Source: reference 11,12.

premature mortality and the years of productive life lost due to disability".<sup>15</sup> Even if the prevalence of non fatal conditions like neuropsychiatric disorders is more in developed world, the DALYs/YLDs combined with the severity of the disorder is far higher in high mortality nations (figure 1). As a result, older people in developing nations spend a major portion of their lives in poor health due to insufficient mental health infrastructure, prevalent stigma, lack of policies for mental health care and reduced medication adherence to the existing co morbid chronic conditions, ultimately leading to early death compared to their wealthy peers in developed nations.<sup>13</sup>

### **HALE (Health Adjusted Life Expectancy)**

WHO defines HALE as "Average number of years that a person can expect to live in "full health" by taking into account years lived in less than full health due to disease and/or injury".<sup>16</sup> As stated by Mathers and colleagues<sup>17</sup>, lower levels of compression of morbidity might also be one of the reasons for developing nations to have higher mortality and lower life expectancy compared to developed nations. "Compression of morbidity" is a hypothesis by Dr. James Fries which states that the burden of lifetime morbidity can be compressed if the age of onset of first chronic condition is delayed in a person. Higher compression of morbidity reduces healthcare costs and improves overall health of the patients over time.<sup>18,19,20</sup> Disability also has a greater impact on the HALE of a person living in a developing nation due to lower socioeconomic status, prevalence of high number of co morbidities, poor access of health care, physical and social surroundings, unhealthy behavior/lifestyle and substance abuse.<sup>17</sup>

### **Technological advances**

In the wake of the technological advancements, unequal access to health-care advances, rising poverty, socioeconomic gradient within the nation, vicious cycle of war and injury resulting in death prevent global convergence among the developed and developing nations. Misallocation of resources, rebounding infectious diseases like malaria and tuberculosis, emergence of resistant malarial parasites, impaired health status, improper diet, increase in prevalence of HIV/AIDS, obesity, type 2 diabetes, smoking, alcoholism and environmental health risks have impacted the healthcare systems in the developing nations.<sup>11</sup> Cheap health care technologies can be very beneficial in developing nations where there is a scarcity of healthcare professionals and lack of funds to provide employment to a large healthcare workforce. Modern medical equipments and technology also

prevents medication errors and deaths which mostly occur when patients are treated by untrained and non professional health workers. One of the criticisms of healthcare technology is the fact that most of the modern medical equipments are developed in affluent western nations and the needs of the developing nations are ignored while manufacturing. In order to make healthcare technology accessible and usable in the developing nations, construction of affordable medical equipments developed by local engineers and operated using the technology and infrastructure available in the developing nations is necessary. Even though projects involving the use of healthcare technology are initiated successfully in developing nations by western researchers, some of these projects shut down gradually due to lack of infrastructure and available funds.<sup>21</sup>

### **Retail pharmacies in developing nations:**

In developing nations like India, retail pharmacies are the most valuable resources for procuring cheap pharmaceuticals, obtaining health advice, easy access of pharmaceuticals with minimum waiting time, obtaining pharmaceuticals on credit basis and ease of obtaining desired quantities of pharmaceuticals. The method of distribution of pharmaceuticals for the majority of pharmacies on the other hand is less likely to be standardized or regulated.<sup>22</sup> Pharmacies in poorly developed urban areas or rural areas recruit minimally trained pharmacists or non pharmacists giving rise to establishments housing officially employed but physically absent pharmacists. The existence of investor owned pharmacies lacking professionally trained pharmacists and pharmacist owned pharmacies next to each other not only influence the consumer's choice for purchasing drugs but impact pharmaceutical regulation. Many pharmacists also have biased drug information mostly passed on by medical representatives working for small pharmaceutical companies. In rural areas, the villagers due to social perceptions, on many occasions feel empowered to self prescribe and demand certain types of treatments only.<sup>22,23,24,25</sup> Medical malpractice to gain financial profits is very common both in the public and private hospitals in India.<sup>26</sup> It is necessary to identify and deal with the existent barriers in the healthcare system that impedes the dissemination of quality pharmacy services in developing nations. Considering the contribution of pharmacists towards public health, the Indian government should include them in national public health programs. It should also attempt to promote high standards of care by regulating the practice of pharmacy.<sup>27</sup> Some areas in

retail pharmacy requiring regulation in the developing nations are distribution of pharmaceuticals in the private sector, much needed staff education, appropriate drug substitution, incorrect drug prescribing, self prescribing, mandatory information provision, control on profit margins of pharmacies and unchecked sale of non OTC drugs.<sup>22,28</sup> Due to the human resource crisis in the developing nations, migration of professional healthcare work force including pharmacists to the developed nations is rampant, thereby hampering the provision of adequate and professional healthcare services in the home nation. The Indian government should promote initiatives involving exchange programs whereby the Indian pharmacists travel abroad and pharmacists from the developed nations travel to India in order to gain and exchange professional expertise.<sup>29</sup>

### Regulation of pharmaceuticals

The high disease burden seen in the developing nations promises many financial gains for pharmaceutical manufacturers, drug sellers and medical practitioners. However, irrationality in the distribution and prescription of pharmaceuticals is witnessed in the developing nations. People in most need of pharmaceuticals don't have access to it and if they do have access, then inappropriate or unnecessary pharmaceuticals are prescribed for them<sup>30</sup>. This paradox calls in attention for drug regulation in the developing world. The pharmaceutical companies dump their expired pharmaceuticals in many African nations or they sell pharmaceuticals in one nation but they do not sell in another nation. Some companies also sell pharmaceuticals to developing nations for indications that are different than that used for in their own nation. This occurs because the recipient nation does not have efficient healthcare systems to protect their citizens. Primary healthcare systems should be suited to the local lifestyles and characterized by timely access to healthcare, drugs and vaccines. India spends more on tobacco compared to healthcare.<sup>31</sup> Allocating sufficient resources for adequate research on endemic diseases, preventing drug dumping, preventing sale of expired pharmaceuticals, preventing over the counter sale of prescription drugs and ensuring that drug labels are fair, accurate and consistent with the manufacturing nation, are some of the measures that can ensure drug regulation.<sup>31,32</sup> The International Code of Pharmaceutical Marketing Practice (IFPMA) states that "The pharmaceutical industry, conscious of its special position arising from its involvement in public health, and justifiably eager to fulfill its obligations in a free and fully responsible manner, undertakes to ensure that all products it makes

available for prescription purposes, have full regard to the needs of public health".<sup>32</sup> Evidence based promotional drug communication, regulating drug pricing, encouraging people to actively promote and safeguard their own health, building of successful pharmacist and healthcare provider partnerships, more use of generics instead of brand drugs and prescription of essential pharmaceuticals only can help control healthcare costs and narrow high profit margins of the pharmaceutical companies.<sup>30,31,32</sup> Absence of drug regulation in developing nations endangers their public health, encourages drug misuse and improper resource utilization and weakens their healthcare system by increasing the healthcare disparities among their rich and poor populations.<sup>30,32</sup>

### Care in inaccessible areas:

For the purpose of providing care to the poor and under deserved populations residing in inaccessible areas in developing nations, medical mission teams travel from urban areas or from other developed nations. These teams have a demand far greater than availability and consist of physicians, surgeons, dentists, nurses, pharmacists and others. Pharmacists fill an important niche in this mission field work by providing their high quality services and knowledge about drug products, drug usage, storage, labeling, dispensing, therapeutic substitution, patient consultation, drug regulation and organized workflow and maintenance of medication.<sup>33,34</sup> Unlike shopkeepers and tradesmen, pharmacists have high education and are more driven by professional values rather than commercialism. In many developing nations, pharmacists adapt their role to meet the needs of the local people. At times, in rural areas, amidst a shortage of physicians, pharmacists use their skills to make independent diagnosis and prescribe drugs in serious situations.<sup>35,36,37</sup> Advancement of good health, prevention of ill-health and the attainment of health objectives and maintenance of medication quality are some of the important elements of Good Pharmacy Practice (GPP). In order to achieve the important elements of GPP, it is important that pharmacists have licensure to practice pharmacy and regulate drug quality. Drug quality should be controlled by storing and selling it in properly marked containers, having information about its importer and producer, monitoring its expiration and avoiding its mixing.<sup>38</sup> Rural areas in developing nations are characterized by shortage of licensed professionals including pharmacists. Better public health and regulated drug supply can be achieved in rural areas by educating non licensed drug sellers who are the main sources for obtaining

pharmaceuticals.<sup>39</sup> Successful interventions have been facilitated to augment GPP by enforcing educational and regulatory reforms among pharmacists in Laos and Vietnam.<sup>38,40</sup> The success of many vertically designed disease control programs depends on strong and sustainable healthcare systems characterized by availability of trained healthcare workforce and equal and consistent access to pharmaceuticals.<sup>41</sup>

### Social pharmacy

Successful implementation of healthcare interventions requires patient support along with professional expertise. India is the largest democracy in the world and has several castes, communities, ethnicities and tribes. It is important for pharmacists as professionals to socially abide by and consider peoples' opinions, views and perceptions about health and medication usage while designing and implementing treatment regimens.<sup>42</sup> In conjunction with social beliefs, educational level is found to be directly correlated with higher life expectancy.<sup>43</sup> A study assessing the impact of social and cultural beliefs held by patients on their healthcare decision making found that child mortality was very low in the state of Kerala in India. The authors found that social service network, family planning, high literacy among the population and special techniques employed for child care were some of the main factors contributing to lower child mortality in that region.<sup>44</sup> On the other hand, recognition is a bidirectional need. In a system where it is important to recognize the needs of the patients coming from varied backgrounds, recognition of pharmacists by other professionals is also equally important. Pharmacists are integral part of communities they serve and many patients go to them for healthcare advice in India in order to save costs associated with physician visits. In spite of this, they are viewed as mere product suppliers.<sup>45,46</sup> Nevertheless, one of the major issues facing the Indian pharmacists and pharmacists in other developing nations is the lack of recognition as professionals by other healthcare professionals like doctors and nurses.<sup>45,47,48</sup> There are many people in developing nations that practice self medication and lay people who consider their physician's prescription as blue print without ever questioning it.<sup>46</sup> In India, the positionality of pharmacists is being questioned with regards to management of chronic conditions and so far their expertise has been under utilized in designing national public health campaigns, interventions and promotions. Ghana, a third world nation in Africa now uses the pharmacist services for management of STIs and HIV/AIDS.<sup>42</sup>

### Use of electronic care and telecommunication:

In developed nations like USA and Canada, usage of electronic media and telemedicine by physicians and pharmacists have led to reduction in the overall health costs incurred by patients, time spend by physicians and emergency department visits as well as an improvement in therapeutic outcomes, medication adherence, healthcare quality, post-surgical medical support, treatment of patients in rural areas and chronic disease management for mood disorders, diabetes mellitus and mental disorders.<sup>49</sup> A meta-analysis study assessing the impact of mobile phones to improve health outcomes globally illustrates that unlike developed nations, developing nations need sufficient evidence about the cost effectiveness of value based telecommunication and improvement in the medication adherence of patients suffering from TB, HIV and non communicable chronic conditions. One of the reasons that could be the fact that ownership of mobile phones is shared in many developing nations as opposed to individualized in developed nations.<sup>50</sup> A study conducted in 10 primary health centers located in East India provides evidence that healthcare professionals are eager to use e-health and information communication technology (ICT) to deliver healthcare services more efficiently. However, system failures comprising of the lack of ICT infrastructure, absence of broadband network 24/7, power shutdowns and lack of funds to purchase computers and related accessories hinder this process.<sup>51</sup> Pharmacists in India are less likely to use ICT compared to physicians and nurses. Gour et al. (2010) studied the knowledge of computers among pharmacists and found that they used computers mostly for internet, email or for entertainment purposes due to lack of orientation towards using technology for healthcare delivery services. The Ministry of health in India has planned initiatives for launching nationwide telemedicine and e-health tools as part of their 11<sup>th</sup> 5 year plan, most of these initiatives are mere pilot programs.<sup>52</sup>

### CONCLUSION

HIV/AIDS, rebounding malaria, tuberculosis, the double burden of other communicable and non communicable diseases and injuries causing disability are the major causes of premature deaths of children, adults and the elderly population. Halting or reversing the spread of HIV/AIDS, malaria and TB in every nation across the globe are some of the major health related initiatives started by the WHO as part of the Millennium Development Goals (MDGs). Barring a few nations with a stagnant or negative progress, most of the developing nations are progressing towards the fulfillment of



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# A systematic review of risks and benefits of sitagliptin and saxagliptin monotherapies and metformin combination therapies

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## ABSTRACT

Submitted: 25/4/2011

Accepted: 12/5/2011

India has the highest prevalence of diabetes (50.8 million people). Sitagliptin and saxagliptin are the two newer drugs approved for the treatment of type 2 diabetes mellitus. The purpose of this paper is to conduct a systematic literature review of the pharmacological and pharmaco-economical profiles of sitagliptin and saxagliptin. Using the MeSH terms in PubMed, a total of four searches were conducted: only sitagliptin, only saxagliptin, and sitagliptin and saxagliptin combined with economics, separately. Various articles were found and analyzed: only sitagliptin (n=125), only saxagliptin (n=34), sitagliptin+economics (n=11), and saxagliptin+economics (n=3). These searches were then narrowed down using the inclusion and exclusion criteria: only sitagliptin (n=26), only saxagliptin (n=9), sitagliptin+economics (n=0), and saxagliptin+economics (n=0). The pooled results of clinical trials show that sitagliptin and saxagliptin have a good general safety profile. However, no formal economic evaluation of sitagliptin and saxagliptin in India were found during the search. Formal economic evaluations of sitagliptin and saxagliptin costs and consequences are required.

## INTRODUCTION AND BACKGROUND

According to the latest report by the International Diabetes Federation, India has the largest number of diabetes patients (50.8 million people) in the world. Following India on the diabetes prevalence are China (with 43.2 million people) and United States. According to the World Health Organization, between the years 2006 to 2015, the predicted loss of national income from diabetes is International Dollars (ID) 336.6 billion in India and ID 557.7 billion in China. Studies have demonstrated that the prevalence of diabetes in India are rising with the progression of time.

About 90-95% of all the diabetes patients are of the type 2 diabetes mellitus (T2DM). T2DM is a progressive disorder with an insidious onset. The most common precipitating cause of T2DM is the beta-cell dysfunction. The other metabolic disorders associated with T2DM are: chronic hyperglycemia, hepatic glucose production in the prandial state, and insulin insensitivity in fat and muscle cells. The common risk factors of T2DM are: impaired glucose intolerance, age over 45 years, family history of diabetes, polycystic ovarian syndrome, high blood pressure, obesity,

physical inactivity, low high-density lipids or high triglycerides levels, being of certain racial and ethnic groups, and women who had gestational diabetes. T2DM also has various vascular complications associated with it, i.e. macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).

A range of classes of oral therapeutic agents exists for the treatment of T2DM. Among these are biguanides (e.g. metformin), sulfonylureas (e.g., glipizide), alpha-glucosidase inhibitors (e.g., acarbose), thiazolidinediones (rosiglitazone), glinides (e.g., repaglinide), glucagon-like peptides-1 (GLP-1) (e.g. exenatide), and Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin, saxagliptin, and vildagliptin). All of these classes of drugs have different mechanisms of actions, courses of treatments, safety profiles, and associated costs. Among these classes, the latest approved drug therapeutic class by US FDA is that of DPP-4 inhibitors in which FDA approved sitagliptin and saxagliptin.

Sitagliptin and saxagliptin have demonstrated to offer substantial glycemic control in T2DM patients and offer substantial benefits when used. However, sitagliptin and saxagliptin come at increased costs. Thus, to inform healthcare providers about these two new drugs, a systematic review of their pharmacological and economic profiles is

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required. Therefore, the purpose of this paper is to conduct a literature review of the pharmacological and economic profiles of saxagliptin and sitagliptin monotherapies and combination therapy with metformin.

## RESEARCH DESIGN AND METHOD

### Literature review of saxagliptin:

In an attempt to identify the current literature on the saxagliptin, especially the literature on the cost-effectiveness analysis and clinical trials, a search was carried out in Medline by querying PubMed search engine using the MeSH terms. The MeSH term “saxagliptin” was first searched alone by activating the following limits: clinical trial, randomized controlled trial, review, and English. “Saxagliptin” was then combined with the MeSH term “economics” using the Boolean combiner “AND” without activating any limits to obtain the query results. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

### Literature review of sitagliptin:

Similar to the objectives of the literature search for the saxagliptin, to identify the current literature on the sitagliptin, a search was carried out in Medline by querying PubMed search engine using the MeSH terms. The MeSH term “sitagliptin” was first searched alone using the following limits in the PubMed: clinical trials, meta-analysis, randomized control trial, review, English language, and humans. “Sitagliptin” was then combined with the MeSH term “economics” using the Boolean combiner “AND” without any limits to obtain the query results. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

## RESULTS AND DISCUSSION

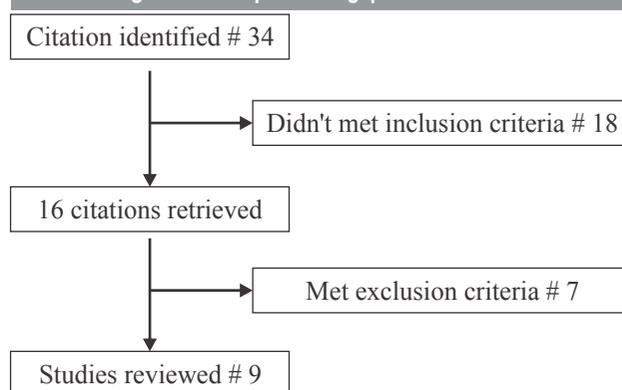
### Literature review of saxagliptin:

A total of 34 studies and 3 studies were obtained when the PubMed was searched for saxagliptin only and for saxagliptin and economics combined. These searched were examined in the following manner: For the first search which extracted 34 studies, these 34 studies were shortlisted to 16 studies (figure 1) on applying the following inclusion criteria to the abstracts of the 34 studies: studies describing the pharmacology, efficacy, safety, and dosage and administration of saxagliptin and/or saxagliptin combination therapy with metformin. Next, the following exclusion criteria were applied and the number of studies were shortlisted to 9: all clinical trials,

presence of full-text, excluding reviews in which saxagliptin was not an area of primary discussion. The full text articles of these 9 studies were then retrieved and reviewed.

From the results of second PubMed search, which consisted of 3 studies, abstracts were reviewed for cost-effectiveness analysis of saxagliptin, especially studies describing the economic analysis of sitagliptin in India. However, all three studies were rejected as none of them met the above described inclusion criteria. This indicates that no economic evaluation of saxagliptin has been conducted till now.

Fig. 1: Roadmap for saxagliptin PubMed search



**Pharmacology:** saxagliptin is a selective and reversible DPP-4 enzyme inhibitor. DPP-4 enzymes cause enzymatic degradation of the GLP-1 into inactive metabolites. GLP-1 is required for the stimulation of glucose-dependent insulin secretion and reduction of glucagon secretion from the pancreas. The DPP-4 inhibitors (sitagliptin and saxagliptin), by acting on the beta-cells, inhibits the DPP-4 enzymes and prevents the deactivation of GLP-1. This in turn helps in secretion of insulin and reduction of glucagon levels in the body. This insulin then helps in maintaining the proper metabolic levels of glucose in the body.

**Pharmacodynamics, dosage and administration, and clinical efficacy:** currently, the saxagliptin is approved at once a daily dosage of 2.5 mg and 5 mg in individuals with normal renal functioning and at 2.5 mg in individuals with moderate-to-severe renal insufficiency or end stage renal disease (ESRD). Several clinical trials have shown the effectiveness of saxagliptin monotherapy and saxagliptin+metformin combination therapies: in a 12-week, multicentre, randomized, parallel-group, double-blind, placebo-controlled trial conducted at 152 out-patient US study centres, 338 (low-dose cohort) and 85 (high-dose cohort) drug-naive patients with T2DM and inadequate glycaemic control, saxagliptin resulted in a placebo-

subtracted statistically significant reduction in the HbA<sub>1c</sub> levels ranging from 0.7%-0.9% and a placebo-subtracted statistically significant reduction in fasting serum glucose of range 14-25mg/dl.

In another 23 week randomized control trial with 401 patients (HbA<sub>1c</sub> > or = 7% and < or =10%), participants were randomized and treated with oral saxagliptin 2.5, 5, or 10 mg once daily or placebo for 24 weeks and a separate open-label cohort with 66 patients (HbA<sub>1c</sub> > 10% and < or =12%) who received saxagliptin 10 mg once daily for 24 weeks. It was found that saxagliptin demonstrated statistically significant decreases in adjusted mean HbA<sub>1c</sub> changes from baseline (mean, 7.9%) to week 24 (-0.43%, -0.46%, -0.54%) for saxagliptin 2.5, 5, and 10 mg, respectively, vs. +0.19% for placebo (all p < 0.0001).

In another 24 week multicentre, randomized, double-blind, active-controlled phase 3 trial, 1306 treatment-naïve patients with T2DM and glycosylated haemoglobin (HbA<sub>1c</sub>) > or = 8 to < or = 12% were randomized to receive saxagliptin 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo or metformin 500 mg + placebo for 24 weeks. At week 24, the saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin demonstrated statistically significant adjusted mean decreases vs. saxagliptin 10 mg and metformin monotherapies in HbA<sub>1c</sub> (-2.5 and -2.5% vs. -1.7 and -2.0%, all p < 0.0001 vs. monotherapy).

Overall, saxagliptin monotherapy as well as the saxagliptin+metformin combination therapy demonstrated clinical efficacy in terms of HbA<sub>1c</sub>, FPG, and PPG reductions. Other benefits of saxagliptin include weigh-neutrality and fewer gastrointestinal-related adverse events. However, as saxagliptin was approved recently in the year 2009, currently no long-term clinical trials data are available for it.

**Adverse effects and tolerability:** pooled data from various randomized clinical trials has shown that monotherapy and combination therapies of saxagliptin are generally well tolerated. In one of the trials, adverse events in the treatment group occurred with a similar frequency to that of the placebo group and no significant dose-related adverse events were identified at the tested dosage levels of saxagliptin. In a trial conducted by Jadzinsky and colleagues, skin-related adverse events were reported in 4.2% of the patients receiving 10mg saxagliptin monotherapy and 3.4-4.3% in patients receiving the combination therapy of saxagliptin with 5 or 10 mg metformin. Chen and colleagues conducted a literature review of clinical trials outcomes of the hypoglycemic events

due to saxagliptin and found that the overall incidence of hypoglycemia was less than 2.5%. In a dose-ranging study, there were no cases of confirmed hypoglycemia with a dose of ≤ 40 mg. In another dose-ranging study, hypoglycemia was reported in 6.3% of the patients receiving 2.5-4.0 mg daily dose versus 1.5% receiving placebo. In another trial, after 102 weeks of treatment, 9-11% of patients receiving saxagliptin reported hypoglycemia versus 10% of those receiving metformin plus placebo. Furthermore, the cardiovascular safety (death, myocardial infarction, stroke, revascularization procedures, and cardiac ischemia) of saxagliptin was assessed using the post hoc analysis of eight trials, which included a total of 4607 patients. No increased risk of increased cardiovascular disorders saxagliptin monotherapy or combination therapy with metformin was found.

#### Literature review of sitagliptin:

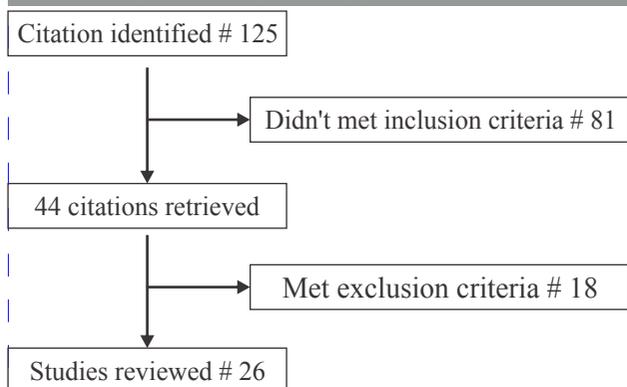
A total of 125 studies and 11 studies were obtained when the PubMed was searched for sitagliptin only and for sitagliptin and economics combined. These searches were examined as follows: the abstracts of 125 studies obtained from the first search were reviewed by applying the following inclusion criteria: pharmacology, efficacy, safety, and dosage and administration of sitagliptin and/or sitagliptin combination therapy with metformin. Based on this inclusion criteria, 44 studies were shortlisted (figure 2). On these 44 studies, the following exclusion criteria was applied: all clinical trials, presence of full-text, excluding reviews in which saxagliptin was not an area of primary discussion (figure 2). Based on this exclusion criteria, the number of studies shortlisted was 26. The full-text of these 26 studies was carefully examined.

From the results of second search, which consisted of 11 studies, abstracts were reviewed for cost-effectiveness analysis of sitagliptin, especially studies describing the economic analysis of sitagliptin in India. Based on this criteria, I found no studies.

**Pharmacology:** Belonging to the same class of oral hypoglycemic agents, i.e. DPP-4 inhibitors, both sitagliptin and saxagliptin has same mechanism of action; prevents the enzymatic degradation of GLP-1 proteins which in turn helps in increase in the secretion of insulin and decrease in the secretion of glucagon in the body to help maintain the appropriate metabolic levels of glucose in the body.

**Pharmacodynamics, dosage and administration, and clinical efficacy:** The recommended daily dosage of sitagliptin in the US is 100 mg once daily which may be taken

Fig. 2: Roadmap for sitagliptin PubMed search



without regard to food. Several clinical trials have shown the effectiveness of sitagliptin monotherapy and combination therapy with insulin secretagogues, like metformin.

The efficacy of sitagliptin monotherapy was well established in three large ( $n = 363$ ,  $555$  or  $743$ ) well designed, dose-ranging studies, which showed that treatment with sitagliptin improved glycaemic control in patients with inadequately controlled type 2 diabetes ( $HbA_{1c}$  levels of  $6.5$ – $10.0\%$ ). In these trials,  $HbA_{1c}$  levels were significantly ( $p < 0.001$ ) reduced with sitagliptin  $25$ – $100$  mg once daily or  $50$  mg twice daily (placebo-subtracted differences  $-0.39\%$  to  $-0.56\%$ ) sitagliptin  $25$ – $200$  mg once daily ( $-0.69\%$  to  $-1.04\%$ ) or sitagliptin  $5$ – $50$  mg twice daily ( $-0.38\%$  to  $-0.77\%$  versus  $-1.0\%$  with glipizide  $5$ – $20$  mg/day) relative to placebo after 12 weeks of therapy.

The efficacy of sitagliptin was also evaluated in several,  $\leq 24$  week, randomized, double-blind, clinical trials. Oral sitagliptin  $100$ mg once daily as monotherapy significantly improved glycaemic control relative to placebo in adult patients with inadequately controlled type 2 diabetes. The efficacy of sitagliptin was sustained in a 30-week extension of a 24-week double-blind trial.

The efficacy of sitagliptin as initial combination therapy with metformin was evaluated in a 24-week, randomized, double-blind, placebo controlled trial and a double blind 30-week, followed by a 50-week extension in patients with inadequately controlled type 2 diabetes. Oral sitagliptin as initial combination therapy with metformin significantly improved glycaemic control in adult patients with inadequately controlled type 2 diabetes; after 24 weeks of treatment,  $HbA_{1c}$ , FPG and 2-hour PPG levels were significantly reduced with sitagliptin plus metformin compared with sitagliptin or metformin monotherapy or placebo. Furthermore, the efficacy of sitagliptin as add-on

therapy to ongoing treatment with metformin was evaluated in several 12- to 52-week, randomized, double blind, placebo and active comparator, controlled trials. After up to 30 weeks of treatment, the  $HbA_{1c}$ , FPG and 2-hour PPG levels were significantly reduced with sitagliptin add-on treatment relative to existing treatment.

**Adverse effects and tolerability:** pooled data from clinical trials show that sitagliptin is generally well tolerated. Overall, the most common (incidence  $>6\%$  in either group) treatment-emergent adverse events in the sitagliptin or comparator groups were upper respiratory tract infection ( $7.8\%$  vs  $8.4\%$ ), nasopharyngitis ( $7.1\%$  vs  $5.9\%$ ) and hypoglycaemia ( $3.4\%$  vs  $10.9\%$ ). Among patients receiving sitagliptin as add-on treatment to metformin, no adverse events occurred with an incidence  $\geq 5\%$  and more frequently than with existing metformin therapy. In addition, the individual trials showed that sitagliptin monotherapy or combination therapy with metformin was associated with a low ( $0.3\%$ ) incidence of hypoglycaemia and gastrointestinal events. Sitagliptin was also found to be weight neutral in these clinical trials.

## CONCLUSION

This literature review demonstrates that the new DPP-4 inhibitors, sitagliptin and saxagliptin, have a good general safety and efficacy profile. These drugs have been approved worldwide including in places such as India, USA, and Europe. However, from this literature review, it was found that no formal economic evaluation of sitagliptin and saxagliptin has been conducted till date in India. And, for saxagliptin, it was found that no economic evaluation has been conducted anywhere in the world, till date. Therefore, a systematic economic evaluation for accessing the costs and consequences of using sitagliptin and saxagliptin in the treatment of T2DM patients is required.

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# Colesevelam a bile acid sequestrant use in type 2 diabetes mellitus as glucose and lipid lowering agent

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## ABSTRACT

Submitted: 9/3/2011

Accepted: 18/3/2011

The bile acid sequestrants are the group of medications utilized to bind certain components of bile in the gastrointestinal tract. Enterohepatic circulation of bile acids is disrupted by sequestering bile acids and preventing their reabsorption from the gut. They are generally considered as hypolipidemic agents, although may be used for purposes other than cholesterol lowering. In diabetes lipid abnormality occur leading to various other cardiovascular complications. Studies have demonstrated that changes in enterohepatic circulation modulate FXR- and TGR5-mediated pathways may regulate glucose homeostasis. This review discusses the major findings of clinical studies which have investigated the glucose and lipid lowering effects of Colesevelam for the treatment of Type 2 Diabetes Mellitus (Type 2 DM) and the mechanism involved in regulating lipid and glucose metabolism through bile acid mediated activation of FXR and TGR 5 signaling pathways.

**Keywords:** Colesevelam, Type 2 DM, FXR, TGR5

## INTRODUCTION

Bile acids are the potent digestive surfactants that promote/boost the lipid absorption including fat soluble vitamins and act as emulsifiers.<sup>1,2</sup> They form the primary pathway for the catabolism of cholesterol and account for 50% of the daily cholesterol turnover<sup>1</sup>. The synthesis of bile acid occurs exclusively in liver. In a series of enzymatic reactions, the hepatocytes convert the hydrophobic cholesterol into more water-soluble amphiphatic compounds.<sup>2</sup> The production of bile acids is localized primarily in the perivenous hepatocytes which are the cells surrounding the central hepatic vein.<sup>3</sup> The primary bile acids, the cholic and chenodeoxycholic acids are the immediate products of the bile acid synthetic pathways in humans. The action of intestinal bacterial flora on primary bile acids forms the secondary bile acid species, the deoxycholic and lithocholic acids which are the derivatives of cholic and chenodeoxycholic acids.<sup>4</sup>

Recently, in-vitro and in-vivo data showed that bile acids also modulate gluconeogenesis by regulating the expression of the rate-controlling enzyme of the lyase family, the phosphoenolpyruvate carboxykinase (PEPCK) employed in

the metabolic pathway of gluconeogenesis, glucose-6-phosphatase (G6Pase) and that of the Fructose-1, 6-bisphosphatase (FBP1).<sup>4,5</sup>

Colesevelam hydrochloride is a bile acid sequestrant that has been approved by the United States Food and Drug Administration (FDA) in January 18, 2008. It improves glycemic control (measured as hemoglobin A1C) in adults with type 2 diabetes mellitus (Type 2 DM). It is given in combination with metformin, sulfonylureas, or insulin either alone or in combination with other anti-diabetic agents.<sup>6</sup>

### Mechanism of action

#### Primary hyperlipidemia:

Bile acid sequestrants (cholestyramine, colestipol, colestimide, and colesevelam) are positively charged non-digestible resins that become attached to the bile acids in the intestine and form an insoluble complex that is excreted in the feces. This decreases the level of bile acids in liver and increases bile acid synthesis from cholesterol and thus decreases hepatic cholesterol levels.<sup>7</sup>

#### Farnesoid X receptor (FXR) and Synthesis of bile acid:

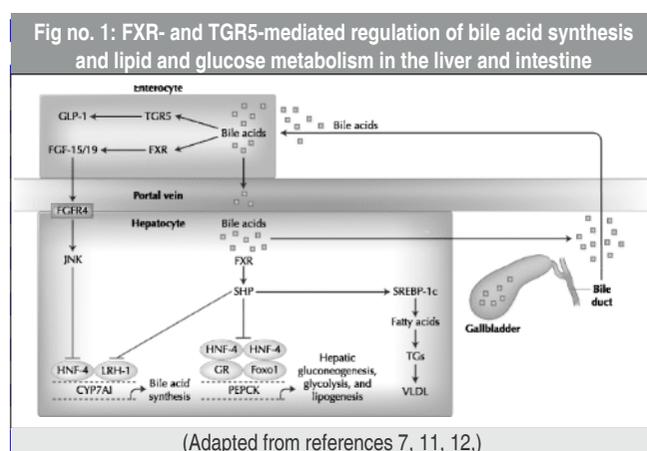
FXR is member of the nuclear receptor super family of ligand-activated transcription factors. It occurs in the liver and intestine and gets activated under the influence of primary bile acid chenodeoxycholic acid.<sup>8</sup> In response to increase in size of the bile acid pool in liver, bile acid activation of FXR

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up-regulates expression of the gene encoding the inhibitory nuclear receptor's small heterodimer partner (SHP)<sup>8</sup>. Activation of several transcription factors including liver X receptor, liver receptor homologue-1 (LRH-1) and the hepatocyte nuclear factor-4 $\alpha$  (HNF-4 $\alpha$ ) is repressed by SHP, subsequently suppressing the LRH-1 mediated activation of cytochrome P450 7A1 (CYP7A1) in humans, thereby inhibiting the first step in cholesterol catabolism (Fig. 1). Bile acid-mediated repression of HNF-4 $\alpha$  inhibits the transcription of CYP7A1 as well.<sup>9</sup> FXR-mediated initiation of fibroblast growth factor-19 (FGF-19; [FGF-15 in mice]) in the intestine is a second pathway of bile acid-mediated repression of its own synthesis. In response to the presence of meal in the intestine, trans-intestinal transport of bile acids is done in the intestine inducing the activation of intestinal FXR thus resulting in the expression of FGF-19.<sup>10</sup> Binding of FGF-19 to surface hepatocyte fibroblast growth factor receptor 4 results in a c-Jun N-terminal kinase-mediated repression of CYP7A1 transcription which is a potent SHP-independent alternative pathway of CYP7A1 repression (Fig. 1).<sup>10</sup>



{FXR- and TGR5-mediated regulation of bile acid synthesis and lipid and glucose metabolism in the liver and intestine. Bile acid synthesis and lipid and glucose metabolism are regulated in the liver and intestine via pathways involving the bile acid receptors FXR and TGR5. In the liver, bile acids activate FXR resulting in upregulation of SHP, an inhibitor of bile acid synthesis, gluconeogenesis, and fatty acid synthesis. In the intestine, bile acid activation of FXR upregulates FGF-15/19 and ultimately inhibits bile acid synthesis<sup>7</sup>}.

{CYP7A1—cytochrome P450 enzyme cholesterol 7  $\alpha$ -hydroxylase, FGF-15/19—fibroblast growth factor 15/19, FGFR4—fibroblast growth factor receptor 4, FXR—farnesoid X receptor, GLP-1—glucagon-like

peptide-1, GR—glucocorticoid receptor, HNF-4—hepatocyte nuclear factor-4, JNK—c-jun N-terminal kinase; LRH-1—liver receptor homologue-1, PEPCK—phosphoenolpyruvate carboxykinase, SHP—small heterodimer partner, SREBP-1c—sterol regulatory element-binding protein-1c, TGs—triglycerides, VLDL—very low density lipoprotein.}

Cholesterol 7  $\alpha$ -hydroxylase also known as cholesterol 7  $\alpha$ -monooxygenase or cytochrome P450 7A1 (CYP7A1):

Cholesterol 7  $\alpha$ -hydroxylase in humans is encoded by the CYP7A1 gene. During the bile synthesis from cholesterol, this enzyme (Cholesterol 7  $\alpha$ -hydroxylase) functions as a rate-limiting enzyme.<sup>13</sup>

Fibroblast growth factor 15/19 (FGF-15/19), fibroblast growth factor receptor 4 (FGFR4):

FGFs are multifunctional proteins that act as a mitogens and also have various regulatory, morphological, and endocrine effects. It is synthesized in the intestinal cells but acts on FGFR4-expressing liver cells to down regulate key genes in the bile acid synthesis pathway. Its synthesis occurs in bone but acts on FGFR1-expressing kidney cells to regulate the synthesis of vitamin D and in turn affect calcium homeostasis.<sup>14</sup>

Farnesoid X receptor:

Farnesoid X receptor (FXR/bile acid receptor), occurs in the liver and intestine. Chenodeoxycholic acid and other bile acids are natural ligands for FXR. Similar other nuclear receptors, when activated, FXR translocates to the cell nucleus, forms a dimer (in this case a heterodimer with RXR) and binds to hormone response elements on DNA which up- or down-regulates the expression of certain genes. One of the primary functions of FXR are to beat down cholesterol 7  $\alpha$ -hydroxylase (CYP7A1), that is rate limiting in bile acid synthesis from cholesterol. FXR induces expression of small heterodimer partner (SHP) which then functions to inhibit transcription of the CYP7A1 gene. In this way a negative feedback pathway is established in which synthesis of bile acids is inhibited when cellular levels are already high.<sup>15,16</sup>

Glucagon-like peptide-1 (GLP-1):

The incretins are peptide hormones. Peptides are short polymers formed by the linking, in a defined order, of  $\alpha$ -amino acids. They are secreted into the circulation, in response to luminal nutrients, within minutes of eating. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide

(GIP). GLP-1 is secreted by the L cells in the ileum and colon whereas GIP is secreted by enteroendocrine cells (called K cells) in the duodenum.<sup>17, 18, 19, 20, 21</sup>

Glucocorticoid receptor (GR):

Glucocorticoids exert their physiological functions by the GR and have their important role in the regulation of carbohydrate, protein, and fat metabolism. Gluconeogenesis and glycogen synthesis is stimulated by the different mechanisms by glucocorticoids in fasting state. These include increase in the synthesis of essential enzymes for gluconeogenesis, increase in the secretion of amino acids from muscles, enhanced insulin resistance in the peripheral tissues, and inhibition of adipokines such as adiponectin. These processes defend glucose-dependent tissues (e.g. brain and heart) during starvation.<sup>22, 23</sup>

Hepatocyte nuclear factor-4:

Hepatocyte nuclear factor (HNF)-4a is a transcription factor which has critical role in the transcriptional regulation of genes involved in glucose metabolism in both hepatocytes and pancreatic b-cells. Recent evidence has implicated AMP-activated protein kinase (AMPK) in the modulation of both insulin secretion by pancreatic b-cells and the control of glucose-dependent gene expression in both hepatocytes and b-cells.<sup>24</sup>

C-Jun N-terminal kinases (JNKs):

JNK is the kinase that attaches and phosphorylates c-Jun on Ser63 and Ser 73 within its transcriptional activation domain.<sup>25</sup> Kinase is also known as a phosphotransferase. It is a type of that transfers phosphate groups from high-energy donor molecules, such as ATP to specific substrates. The process is known as phosphorylation and should not to be confused with phosphorolysis which takes place by phosphorylases. Phosphorylation is the transfer of a phosphate group to a molecule, not the reverse, i.e., phosphorolysis, the transfer of a molecular to a phosphate group. An enzyme that removes phosphate groups is known as a phosphatase.<sup>26</sup>

The c-Jun N-terminal kinases (JNKs) regulate the essential physiological and pathological processes which are involved in several diseases including diabetes, atherosclerosis, stroke, Parkinson's and Alzheimer's diseases. Inhibition of JNKs suppresses pathological features of these diseases but the many physiological functions of these enzymes argue against the use of sustained, systemic, nonspecific inhibition in the treatment of these diseases. For example, loss or absence of

the gene that encodes JNK1 prevents insulin resistance, disrupts neuronal cytoarchitecture and initiates the pathology of Alzheimer's disease. Thus, it is not enough to inhibit selectively either JNKs or individual isoforms of JNK. Instead, the aim is to inhibit the damaging actions of JNK. This can be achieved using peptides that selectively block molecular domains of individual JNK signaling complexes (exclusively) that form under pathological conditions. Peptide inhibitors of JNK are useful in preventing ischemia-induced brain damage and insulin resistance following obesity.<sup>27</sup>

Liver receptor homolog-1:

LRH-1 is a member of the nuclear receptor family of intracellular transcription factors. Liver receptor homolog 1 (LRH-1), an orphan nuclear receptor, is abundant in liver and intestine, where it regulates the cholesterol, bile acid, and steroid hormone homeostasis. Among the proposed LRH-1 target genes in liver are those encoding cholesterol 7 $\alpha$ -hydroxylase (CYP7A1) and sterol 12 $\alpha$ -hydroxylase (CYP8B1), which catalyze key steps in bile acidsynthesis.<sup>28</sup>

Phosphoenolpyruvate carboxykinase:

Phosphoenolpyruvate carboxykinase (PEPCK) of lyase family participates in metabolic pathway of gluconeogenesis converts oxaloacetate into phosphoenolpyruvate and carbon dioxide. When dietary carbohydrate is unavailable, glucose required to support metabolism in vital tissues is generated via gluconeogenesis in the liver. Expression of phosphoenolpyruvate carboxykinase (PEPCK), commonly considered the control point for liver gluconeogenesis, is normally regulated by circulating hormones to match systemic glucose demand. However, this regulation fails in diabetes.<sup>29</sup>

Small Heterodimer Partner:

Small heterodimer partner (SHP) is an atypical orphan nuclear receptor that prohibits transcriptional activation by several other nuclear receptors. It has been reported recently that mutations in the SHP gene are associated with insulin resistance. A reporter gene assay showed that a gene product of SHP increased the transcriptional activation of peroxisome proliferator-activated receptor (PPAR) gamma.<sup>30, 31</sup>

Sterol regulatory element-binding protein-1c:

Sterol Regulatory Element Binding Proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are

encoded by the genes SREBF1 and SREBF2. SREBP-1 expression produces two different isoforms, SREBP-1a and -1c.

Sterol regulatory element-binding protein 1 (SREBP-1) also known as sterol regulatory element-binding transcription factor 1 (SREBF1) is a protein that in humans is encoded by the SREBF1.

Sterol regulatory element-binding protein 2 (SREBP-2) also termed as sterol regulatory element binding transcription factor 2 (SREBF2) is a protein which is encoded by the SREBF2 gene in case of humans.<sup>32</sup>

Forkhead box protein O1 (FOXO1): a protein which is encoded by the FOXO1 gene in human. In rhabdomyosarcoma, it is recognized as forkhead. In pancreatic alpha-cells FOXO1 is important in regulating prepro-glucagon expression. In pancreatic beta cells it mediates glucagon-like peptide-1 effects on pancreatic beta-cell mass<sup>33</sup>.

### **Type 2 Diabetes Mellitus:**

The mechanism by which Colesevelam lowers glucose levels in patients with Type 2 DM is not yet clearly understood. However, evidences point towards the fact that the glycemic effects of bile acid sequestrants occur through farnesoid X receptor (FXR/bile acid receptor), liver X receptor, fibroblast growth factor-19 and TGR5-mediated effects on intestinal glucose absorption, and through hepatic glucose metabolism in addition to influences on peripheral insulin sensitivity, incretin effects and energy homeostasis<sup>7,34</sup>.

{TGR5 is a G protein-coupled receptor found in brown adipose tissues and muscles where its activation by bile acids triggers an increase in energy expenditure and attenuates diet-induced obesity. Using a combination of pharmacological and genetic gain- and loss-of-function studies in vivo, TGR5 signaling activates intestinal glucagon-like peptide-1 (GLP-1) release, leading to improved liver and pancreatic function and enhanced glucose tolerance in obese mice. In addition, the induction of GLP-1 release in enteroendocrine cells by 6alpha-ethyl-23(S)-methyl-cholic acid (EMCA, INT-777), a specific TGR5 agonist, is linked to an increase of the intracellular ATP/ADP ratio and a subsequent rise in intracellular calcium mobilization<sup>34</sup> }.

It has been shown that the bile acid induced activation of FXR reduces expression of genes involved in gluconeogenesis including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. In addition, hepatic glucose production

during fasting and postprandial hepatic glucose utilization may be modulated by FXR.<sup>35,36</sup> However, alterations in the bile acid pool in Type 2 DM and its subsequent effects on FXR activation are still under investigation. Emerging data suggest a partial regulatory role for FXR modulators in peripheral insulin sensitivity suggesting a future role for FXR for treating insulin resistance and Type 2 DM.<sup>37,38</sup> The incretin release and the induction of glucagon-like peptide-1 (GLP-1) secretion through activation of the G-protein coupled receptor TGR5 is also influenced by the bile acids.<sup>39,40</sup> Colestimide, a bile acid sequestrant causes an increased secretion of GLP-1 in patients with Type 2 DM, although the functional consequences are still unclear.<sup>41</sup> Bile acids have also been implicated in metabolic regulations through FXR-mediated regulation of energy substrate mobilization and storage.<sup>42</sup> These glycemic effects are unique to bile acid sequestrants and among these only colesevelam have been approved for improving glycemic control in adults with Type 2 DM. Cholesterol absorption inhibitor, the ezetimibe does not show these effects. Further study, however, is needed to determine the precise mechanism involved in the effect of bile acid sequestrants on glucose metabolism in patients with Type 2 DM.

### **FXR receptor and its role in hepatic Glucose Metabolism:**

Liver asserts a balance between glucose production and utilization and thus plays a central role in controlling blood glucose homeostasis (Fig. 1). Moreover, various studies have emphasized the role of bile acids in glucose metabolism and have shown that the composition and pool size of the bile acid gets altered in diabetic animals and humans.<sup>43,44</sup> A link between FXR and glucose metabolism has been proved by the observation that hepatic expression of the gene encoding FXR was decreased following quantitative analysis of hepatic FXR mRNA expression in a rat model of type 1 diabetes. This was also accompanied by increased expression of CYP7A1 which contributes to the enlarged bile acid pool that is also characteristic of such diabetic animals.<sup>44</sup> Moreover, hepatic expression of FXR also decreased with age in a rat model of Type 2 DM<sup>45</sup>. When the hepatocytes from nondiabetic rats were incubated with glucose and insulin to assess the effects of these two on hepatic FXR expression, the groups of hepatocytes incubated with insulin repressed the expression of FXR, an effect that is reduced by glucose. These results suggested that diabetes impairs the normal regulation of FXR expression<sup>45</sup>. However, a precise mechanism of FXR regulation of glucose metabolism is unclear.

### Pharmacodynamics:

The maximum therapeutic lipid-lowering response of colesevelam was achieved within 2-weeks and was maintained during long-term therapy. In the diabetes clinical studies, a therapeutic response to colesevelam, as reflected by a reduction in hemoglobin A1C was initially noted following 4-6 weeks of treatment and reached maximal or near-maximal effect after 12-18 weeks of treatment.<sup>6,46</sup>

### Pharmacokinetics:

*Absorption:* Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

*Distribution:* Colesevelam hydrochloride is not absorbed and, therefore, its distribution is limited to the gastrointestinal tract.

*Metabolism:* Colesevelam hydrochloride is not metabolized systemically and hence does not interfere with systemic drug-metabolizing enzymes such as cytochrome P-450.

*Excretion:* In 16 healthy volunteers an average of 0.05% of administered radioactivity from a single <sup>14</sup>C-labeled colesevelam hydrochloride dose was excreted in the urine.<sup>6,46</sup>

**Pregnancy Category** -Colesevelam is Pregnancy Category B.<sup>6,46,47</sup>

### CONCLUSION

Bile acid sequestrants change the bile acid pools thus affecting lipid and glucose metabolism. Studies have demonstrated that changes in enterohepatic circulation modulate FXR- and TGR5-mediated pathways may regulate glucose homeostasis. However, further studies are required to assess the role of FXR- and TGR5-mediated signaling pathways on lipid and glucose metabolism in animal and human models of Type 2 DM and obesity. Studies are also required to understand how these signals become united to mediate the lipid- and glucose-lowering effects of bile acid sequestrants.

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# Initiation and evaluation of patient counseling centre services to out patients in a tertiary care hospital

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## ABSTRACT

Submitted: 24/2/2011

Accepted: 9/5/2011

Patient counseling is a critical component of the dispensing process, in order to ensure that the patient receives and understands important information such as the name of the drug and the purpose of the medication. Clinical pharmacists are the most qualified health professional to provide counseling to the patients. Physicians due to their heavy patient load, lack of time are unable to spend enough time with the patients and so the pharmacists should take this as their primary responsibility and counsel the patients. The objectives of the study were to initiate a patient counseling centre and to assess the medication adherence and disease knowledge of the patients before and after educating by clinical pharmacist. The study was conducted for a period of 8 months after obtaining Ethics Committee approval. A survey was conducted for health care professionals and a patient counseling centre was initiated in a semi-private room for patient counseling. 104 patients were enrolled as per the inclusion and exclusion criteria. Medication adherence and disease knowledge questionnaires were administered before and after Clinical Pharmacist intervention. 94 patients completed the follow up of the study out of 104 enrolled patients. There was statistically significant improvement ( $P < 0.001$ ) in knowledge level from baseline (7.298) to the follow up (13.691). Comparison of various demographic factors like age, gender, diagnosis and education status showed impact of patient counseling on improvement of overall medication and disease knowledge score. The non-compliance reasons to stop/miss medication as told by patients were 09(30.0%) patients forgetfulness, while 7(23.33%) patients mentioned their fear of side effects, 1(3.33%) patient had confusion in the schedule of taking drugs and 1(3.33%) patient mentioned high cost of drugs as reason for non-adherence. The findings showed of this study showed that a well-structured patient counseling by clinical pharmacist will result in better knowledge of disease and medications which in turn improves their medication adherence.

**Keywords:** Medication knowledge, Medication adherence, Patient counseling centre, Patient counseling.

## INTRODUCTION

Patient counseling is a critical component of the dispensing process, in order to ensure that the patient receives and understands important information related to disease, drugs and other necessary details.<sup>1</sup>

Patient counseling is therefore defined as “The process of providing information, advice and assistance to help patients to use their medications appropriately.” The information is given by pharmacist to patient or representative.<sup>2</sup>

Patient counseling is an important task for achieving pharmaceutical care by providing medication related information orally or in written form on the topics like direction of use, advice on side effects, precautions, storage, diet and life style modifications.<sup>3</sup>

Patients often fail to adhere to their medications due to lack of proper information which often leads to failure of achieving therapeutic goals and decreased quality of life. Effective communication by pharmacists is essential to improve the use of medications by patients and ensure optimal therapeutic outcomes.<sup>3</sup> It is important for pharmacists to provide appropriate, understandable and relevant information to patients about their medication. The pharmacist is in a highly visible and readily available position to answer patient concerns and enquiries about their medications and alternate treatments they may read about or hear from others.<sup>4</sup> The pharmacist is in a highly visible and readily available position to answer patient concerns and enquiries about their medications and alternate treatments they may read about or hear from others.<sup>5</sup>

Effective communication by pharmacists is essential to improve the use of medications by patients and ensure optimal therapeutic outcomes. Pharmacists can improve patient adherence to drug therapy through appropriate strategies, including patient counseling and education. In

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addition to verbal communication, appropriately written recommendations to physicians to resolve drug therapy problems can be an effective strategy for drug therapy changes.<sup>6</sup>

#### **National scenario:**

In India the first masters in pharmacy practice was developed in 1996 but from then more emphasis was given on attending ward rounds, drug information, drug therapy review but importance given for patient counseling was not up to the mark. In India 95% of pharmacists do not offer counseling services to patients. This is because of provider based, patient based and system based barriers.<sup>7</sup>

#### **International scenario:**

In developed countries pharmacist take the responsibility of patient counseling. In America the pharmacist counseling patients on the correct use of their medication was started from 1964 and the use of private offices for patient pharmacist interactions, counseling the patients was started from 1965.<sup>8</sup>

#### **Patient Counseling Environment:**

Pharmacy counseling environment plays an important role in counseling. Patients were not comfortable receiving advice about their medications over a window.<sup>8</sup> Education and counseling should take place in an environment conducive to patient involvement, learning, and acceptance one that supports pharmacists' efforts to establish caring relationships with patients. The counseling environment should be comfortable, confidential, and safe. Counseling is most effective when conducted in a private room that ensures privacy. Patient should be counseled in a semi-private, or private, area away from other people and distractions, depending on the medication(s). Distractions and interruptions should be few, so that patients and pharmacists can have each other's undivided attention and the patient will be able to ask questions that he/she may be hesitant to ask in public.<sup>5</sup>

For the above mentioned facts, it is assumed that there is need for patient counseling for better health care outcomes i.e; improved quality of life and achieving the therapeutic goals. Physicians due to their heavy patient load, lack of time are unable to spend enough time with the patients and so the pharmacists should take this as their primary responsibility and counsel the patients.<sup>3</sup> The pharmacokinetic profile of a drug may vary with paediatric, geriatric patients, so special counseling to them is important. Drug use at the time of pregnancy and lactation should be taken care of as they may cause teratogenicity, so constant counseling to them is also

important.<sup>7</sup> In multidisciplinary (multispeciality) hospitals where patient pool is more, initiation of a patient counseling centre with the support of physicians may be necessary. So the purpose of the study was to initiate a patient counseling centre at the hospital.

#### **OBJECTIVE**

To initiate a patient counseling centre and evaluate the counseling services provided by a pharmacist.

#### **METHODOLOGY**

##### **Study setting:**

The study was conducted in Patient counseling centre which was initiated near out patient department in a tertiary care hospital of northern Karnataka.

##### **Study Duration:**

The study was conducted for a period of 8 months.

##### **Ethics Committee Approval:**

The study protocol was prepared and submitted to the Institutional ethics committee on human subject research for ethical clearance. The study was approved by Institutional ethics committee and issued ethical clearance certificate for the same.

##### **Study design:**

The study was a prospective, questionnaire based hospital study.

##### **Study Materials:**

The study materials include:

- a. Patient profile form
- b. Knowledge assessment questionnaire(Baseline)
- c. Knowledge assessment questionnaire(Follow up)
- d. Patient counselling documentation form

##### **Study procedure:**

A survey was conducted for the hospital physicians, surgeons and PG students regarding their opinion about the initiation of patient counseling centre and according to the results obtained Patient Counseling Centre (PCC) was initiated in hospital. Once the patient comes to the counseling centre if he/she is willing to participate in the study, consent is obtained. The initial patient information was collected like demographic details, past medical and medication history, current diagnosis and treatment regimen and then baseline knowledge assessment questionnaire for the patient will be

filled up. The counselling session was then initiated and the patient is counseled. During the patient's next hospital visit the follow up questionnaire is filled in. Medication adherence was assessed using Morisky scale of adherence score 0-4 having 4 questions each question counts for score 1 if patient's answer is no. The maximum the score, the better the adherence to prescribed medication therapies. Statistical analysis of the same is done Wilcoxon signed-ranks test was used for the analysis. All the attributes are significant between baseline and follow up.

## RESULTS

104 patients were enrolled in this study and 94 patients completed the study. 10 patients did not come for follow up who were considered drop outs. Among the total patients, male patients 27(28.72%) were less compared to female patients 67(71.28%). The age distribution of enrolled patients is as follows 43(45.75%) patients were between the age group of 18-35 years of age and 11(11.70%) were between the age group of 36 to 49 years of age. The remaining 40(42.55%) patients were  $\geq$  50 years of age. Among the participants of the study, 5(5.32%) of the patients were having formal education and were graduates; 19(20.21%) had a formal education up to 12<sup>th</sup> std; 31(32.98%) were having education between first to 10<sup>th</sup> standard and 39(41.49%) patients were illiterate patients who have not received any formal education. Out of 94 patients assessed for the smoking habit 6(6.39) belonged to smoking category, 88(93.61%) patients belonged to non-smoking category. The time for counseling for 64 patients is 15-30 minutes. For 22 patients it took about 36-45 minutes. For the remaining 8 patients it took between 46-60 minutes. The total average time taken for counseling the patients irrespective of their disease is about 30.37 minutes. Out of 94 patients who completed the study, 64 patients were house wives, 14 were farmers, 9 were having their own business, 4 were employed and 3 were students. Out of 94 patients who completed the study, maximum included the pregnancy cases followed by diabetes and hypertension cases. The other are COPD and Anaemia cases followed by Gastro Enteritis and Osteo Arthritis, IHD, infectious diseases (2 cases of viral fever, 1 case of malaria and 1 case of UTI), 3 cases of Peptic Ulcer Disease, 2 cases of Rheumatoid Arthritis and 2 cases of Asthma. The time for counseling for 64 patients is 15-30 minutes. For 22 patients it took about 36-45 minutes. For the remaining 8 patients it took between 46-60 minutes. The total average time taken for counseling the patients irrespective of their disease is about 30.37 minutes.

All the 94 participants of the study were initially provided knowledge assessment questionnaires at the time of

enrollment and subsequent follow up. Mean knowledge score was assessed at baseline and follow up. It was observed that there was significant improvement in the mean knowledge score of patients. Out of 94 patients who completed the study, mean medication knowledge score at baseline was 7.298 and at follow up it was 13.691. Baseline to follow up showed a mean increase in knowledge 6.393 and ( $P < 0.001$ ) which is statistically significant.

Demographic details of all patients were analysed to assess the knowledge scores in each group at visit. Knowledge scores were compared to gender, age and educational wise to check the impact of demographic factors on knowledge scores. Mean adherence score was assessed pre and post counseling. It was observed that at baseline it was 3.2 and post counseling it improved to 3.9. Various barriers for medication adherence were identified by pharmacist. The maximum number of patients i.e., 9 complained of forgetfulness in daily schedules, while 7 patients mentioned their fear of side effects, 1 patient had confusion in schedule for taking drugs and 1 patient mentioned high cost of drugs as reason for non-adherence.

## DISCUSSION

Physicians due to their heavy patient load, lack of time are unable to spend enough time with the patients and so the pharmacists should take this as their primary responsibility and counsel the patients. Pharmacists can improve patient adherence to drug therapy through appropriate strategies, including patient counseling and education. In addition to verbal communication, appropriately written recommendations to physicians to resolve drug therapy problems can be an effective strategy for drug therapy changes.

Medication regimens for patients particularly for chronic illnesses like diabetes, cardiovascular complications and pregnant females are vulnerable to adherence problems because of their duration, the use of multiple medications. A survey was conducted for the health care professionals out of which many of the professionals felt a necessity for counseling the patient in a private room for counseling. Thus patient counseling centre was initiated. The centre was a semi-private room made for counselling the patients from the free pharmacy of the hospital. The aim was to counsel the patients who visit the counseling centre.

The purpose of the study was to assess and improve their knowledge and thereby medication adherence. Also to identify various contributing factors for non adherence and employing strategies of counseling regarding medication,

disease, and interviewing the patient to enhance medication adherence. The patients were assessed for medication and disease knowledge at the baseline by structured interviews and at subsequent follow up visits. A total of 94 patients were assessed for medication adherence and their knowledge regarding disease and medication, during the study out of which, 27(28.72%) were males and 67(71.28%) were females. More number of female patients were enrolled may be because the results show that more pregnant females visited the counseling centre.

Out of 94 patients who completed the study 43(45.75%) patients were in the age group of 18-35years, 11(11.70%) were in the age group of 36-49 years and 40(42.55%) patients who were equal to and above 50 years. Maximum numbers of patients enrolled in the study were from the age group of 18-35 years who constitute to about 45.75% of the total population which mainly included pregnant females. The remaining were from the age group of years  $\geq 50$  which constitute 42.55% which mainly included diabetic, hypertensive and cardiovascular risk patients. Limited patients were there in age group 36-49 years of age. A total of 94 patients were assessed during the study. Educational background of the individuals was found to be maximum for illiterate 39(41.49%). Secondly 31(32.98%) number of patients were having educational levels  $\leq 10^{\text{th}}$  std. while 19(20.21%) patients were educated till 12<sup>th</sup> std where as only 5(5.32%) patients were graduates/diploma holders. Adepu R et al. in their study said that low educated patients had 40% excess cause of mortality compared with educated subjects.

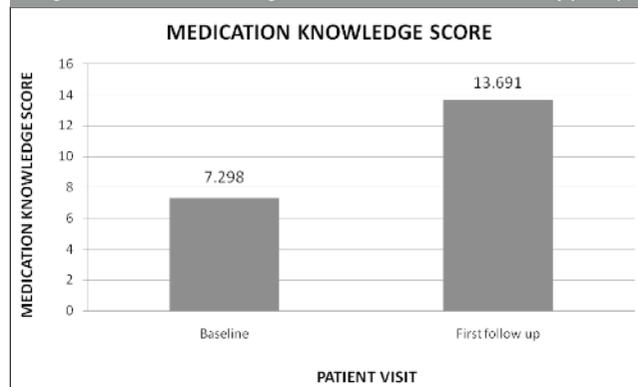
Out of 94 patients assessed for the smoking habit 6(06.39) belonged to smoking category, 88(93.61%) patients belonged to non-smoking category. All women patients were non smokers. A total of 94 patients were assessed during the study out of which 89 (94.68%) patients were married and 05(05.32%) were unmarried. In India people get married early at the age of 18years. The counseling aid patient information leaflet was provided to 61 patients out of 94 who completed the study. So, the PIL was provided to 64.89% of patients which help them in reading and reminding the information whenever they want. Out of 94, in 71 cases counseling was provided to patient and patient's representative. So, in 75.53% of cases counseling was also provided to patient's representatives which mainly included geriatric patients and pregnant females.

Baseline results of our study too indicated the necessity of counseling to patients as their knowledge assessment score was low 7.298. After counseling there is significant improvement in the knowledge score i.e, 13.691. There is

Table 1: Demographic characteristics of enrolled patients

Characteristics		Number (n=94)
Gender	Male	27(28.72%)
	Female	67(71.28%)
Age Group (years)	18-35 yrs	43(45.75%)
	36-49 yrs	11(11.70%)
	$\geq 50$ yrs	40(42.55%)
Education Background	Graduates	5(5.32%)
	PUC	19(20.21%)
	Up to 10th std	31(32.98%)
	Illiterate	39(41.49%)
Occupation	Employed	4(04.25%)
	Agriculture	14(14.89%)
	Businessman	09(09.57%)
	Housewife	64(68.08%)
	Student	3(3.19%)
Life Style Habits (Alcohol and Smoking)	Smokers	6(6.39%)
	Non- Smokers	88( 93.61%)
Marital status	Married	89(94.68%)
	Unmarried	5(5.32%)

Fig.1: Medication knowledge score at baseline and follow up(n=94):



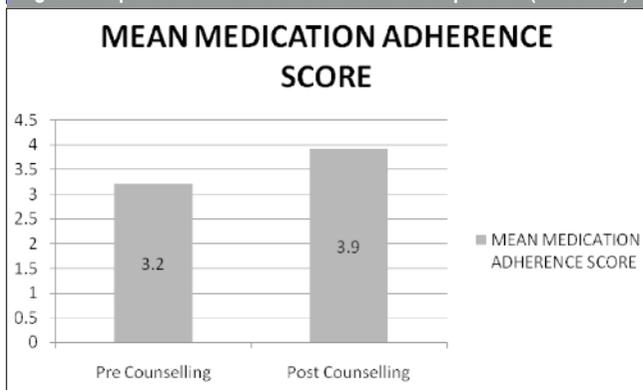
direct correlation of medication knowledge with medication adherence in the patients. This shows that pharmacist is an important part of health care system and play a vital role in patient counseling. Ponnusankar S et al. had shown that pharmaceutical care improves medication knowledge and in turn medication adherence.<sup>9</sup>

In this study, comparison for medication knowledge improvement was done by using various demographic factors like age, gender and education. The study showed significant difference in medication knowledge at first follow up scores between literate and illiterates, and male and female patients (P < 0.001), this may be due to significant difference in baseline scores in literate and illiterate patients and in male and female patients.

**Table 2: Comparison of the mean knowledge assessment score of patients at baseline and follow up:**

Mean baseline score ± SD	Mean Follow up score ± SD	Difference of Mean	P-Value
7.298	13.691	6.393	P<0.001

**Fig. 2: Comparison of mean adherence scores of patients (score=0-4) :**



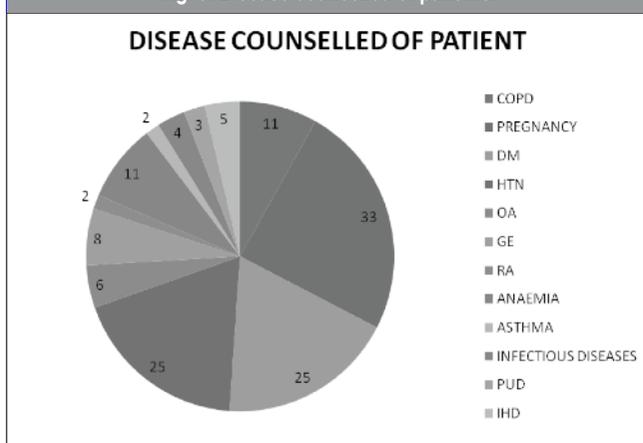
**Barriers to medication adherence (n=30) :**

Various barriers for medication adherence were identified by pharmacist. The maximum number of patients ie, 9 complained of forgetfulness in daily schedules, while 7 patients mentioned their fear of side effects, 1 patient had confusion in schedule for taking drugs and 1 patient mentioned high cost of drugs as reason for non-adherence.

**Table 3: Barriers for medication adherence:**

Barriers for Medication Adherence	Reported by No. of Patients	Percentage
Forgetfulness	9	30
Fear of side effects	7	23.33
Confusion in schedule	1	3.33
Cost of drugs	1	3.33

**Fig. 3: Disease counselled of patients:**



**CONCLUSION**

The study highlights on the important and vital role that a pharmacist has to play as they are the most accessible healthcare professionals, important liason between referral and the patient and they have got opportunity to remind, reinforce and extend the education of the patient, evaluate the patient's knowledge and facilitate the patient. The results of this study reveal the importance of patient counseling centre and also demonstrate the need for a pharmacist in providing patient counselling services to the patients. The finding of this study suggests that a well-structured patient counseling by clinical pharmacist regarding their disease and medications will be effective to change their attitude and behaviour. This can further lead to a better understanding about their disease and medications being used.

**ACKNOWLEDGEMENTS**

We would like to thank the Principal, Vice-Principal, Staff and Postgraduate students of Department of Pharmacy Practice, KLEU's College of Pharmacy, Belgaum for their support and encouragement.

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# Status of spontaneous reporting of adverse drug reaction by physicians in Delhi

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## ABSTRACT

Submitted: 14/2/2011

Accepted: 8/4/2011

Adverse drug reaction (ADR) monitoring and reporting activity is in its infancy in India. Physicians being frontline caregivers, a study was conducted to determine the level of awareness of physicians about ADR reporting and the extent of their involvement in pharmacovigilance activities. A study of physicians was conducted among various government hospitals, private hospitals and private clinics of Delhi (INDIA) from Dec 2009 to July 2010. A questionnaire containing 19 questions was distributed to 200 physicians. Only 124 physicians completed the questionnaire giving response rate of 62%. Out of these, only 70.97% physicians were aware of the term Pharmacovigilance. Majority of the respondents (99.19%) consider ADR monitoring to be essential. However, 96.77% physicians noticed ADRs in patients but only 34.68% physicians reported them. Only 8.87% of the physicians knew the pharmacovigilance centers of Delhi. Out of these only 2.42% had phone number and address of these centers and they reported ADRs at these centers. The major reasons for not reporting ADR were: not aware of reporting centers (97.58%), non-availability of ADR reporting form (90.32%), adverse drug reaction already well known (57.26%), uncertainty about drug causing it (47.58%) and lack of set procedure of ADR reporting in their organization (42.74%). Most of physicians (87.90%) consider ADR monitoring should be made mandatory on doctors. Despite good observation and knowledge of ADR among doctors the rate of reporting to ADR monitoring centers is very low.

**Keywords:** ADR, ADR reporting, Pharmacovigilance, Physicians.

## INTRODUCTION

Adverse drug reaction is a response to a medicine which is noxious and unintended and which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions.<sup>1</sup> ADRs are global problem of major concern.

### *Impact of ADR on Health:*

ADRs are the cause of hospital admission in 3% to 6% of patients of all ages.<sup>2,3</sup> While the incidence of hospital admissions due to ADR in elderly patients is 3% to 24%.<sup>4</sup> ADR incidence has been reported to range from 5.9 to 22.3% of all emergency department admissions.<sup>5</sup> According to a study carried out in a tertiary referral center in South India the admissions due to ADRs accounted for 0.7% of total admissions and deaths due to ADRs accounted for 1.8% of total ADRs.<sup>6</sup> The study of Bord et al indicated that, in patients who experience ADRs, death rates were 19.18% higher and

the length of hospital stay is 8.25% higher.<sup>7</sup> ADRs are 4<sup>th</sup>-6<sup>th</sup> largest cause of death in USA. ADRs have been estimated to account for up to 106,000 deaths annually in the United States.<sup>8,9</sup>

### *Impact of ADR on Healthcare Cost:*

ADRs have a considerable negative impact on both health and healthcare costs.<sup>10</sup> In a study at Taiwan teaching hospital, the mean cost of an ADR associated with extended hospitalization was US \$3489.<sup>11</sup>

Bordet's study shows that increase in the cost of hospitalization attributable to ADR was US \$3200. He identified that longer hospital stays were directly contributing to increased ADR related costs.<sup>12</sup> Dormann's study found that the mean additional cost of hospitalization for an ADR was US \$1400.<sup>13</sup>

### *Need of ADR Reporting and Scenario of ADR Reporting in India:*

India is a developing country with large drug consuming population, with per capita income of only \$ 1031.<sup>14</sup> It is fourth largest producer of pharmaceuticals in the world with more than 6,000 licensed drug manufacturers and over 60,000

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branded formulations.<sup>15</sup> It is also emerging as a clinical trial hub exposing larger population to newer drug treatments. Thus it is essential that the drug treatment should be safe, efficacious and cost effective. It is the need of the hour to identify adverse drug reactions as early as possible and to prevent them if possible, to ensure the well-being of the patient at reasonable cost.

Spontaneous reporting of ADRs would enhance monitoring and evaluation activities related to drug safety.

To improve the pharmacovigilance activities in India, the Ministry of Health and Family Welfare had initiated the National Pharmacovigilance Program (NPP) on 1 January 2005 which was further revived in July 2010.<sup>15,16</sup> This program is overseen by Central Drugs Standard Control Organization (CDSCO), New Delhi. The program is envisaged to be rolled out in three phases:

- Phase I plans to include 40 ADR monitoring centers (AMCs).
- Phase II plans to include 140 MCI recognized medical colleges by end of 2011.
- Phase III would ultimately cover the total healthcare system by 2013.

ADR reports will be collected at the AMCs which will then be dispatched to the coordinating centre as per the standard operating procedures. The coordinating centre will conduct causality assessment and upload the reports into the pharmacovigilance software. Lastly, the integrated ADR data will be transmitted through vigiflow software interface into the Uppsala Monitoring Center's ADR database where signal processing can be carried out.<sup>16</sup>

#### **Physicians and Pharmacovigilance:**

In India, physicians are frontline healthcare givers in a community. They play a pivotal role in maintaining the well being of society. Preventing ADRs is an integral part of routine clinical work of any physician. Their active involvement in spontaneous reporting of ADRs is essential for the effective implementation of National Pharmacovigilance Program.

#### **Objectives:**

The primary objectives of this study were:

1. To assess the knowledge, attitude and skills of physicians regarding pharmacovigilance and spontaneous reporting of ADR.

2. To identify the reasons for under-reporting.
3. To suggest methods for improvement in the current spontaneous ADR reporting system.

#### **METHODOLOGY**

**Research Design:** This was a questionnaire based study involving physicians, who were surveyed with a questionnaire. The study was conducted in Delhi, the National capital of India, over a period of 8 months from December 2009 to July 2010. Entire area of Delhi was covered which included North, East, West, South and Central zones of Delhi. We visited the physicians personally, distributed the questionnaire and collected the duly filled questionnaire on same day.

**Material used:** A questionnaire containing 19 questions was prepared. First four questions were designed to generate demographic information about the name, qualification, specialization, sector and experience. The remaining questions were designed to evaluate knowledge (3 questions), to assess their attitude (3 questions) and to judge their skills (9 questions) about pharmacovigilance and ADR reporting.

▶ Questions on knowledge revealed information regarding their knowledge about pharmacovigilance, awareness about ADR reporting, phone number and address of pharmacovigilance centers in Delhi. Further they were asked to choose the place of ADR reporting from given multiple choice of - hospital pharmacy, senior/fellow physician, manufacturing industry, regional monitoring centre and national monitoring centre.

▶ Questions on attitude regarding pharmacovigilance helps to know their opinion on essentiality of ADR monitoring and possible reasons for non-reporting of an encountered ADR such as ADR is well known, not sure about the drug causing ADR. Further their perception about 'whether ADR monitoring should be made mandatory' was probed.

▶ Questions on skills covered various activities or inputs given by physicians to strengthen pharmacovigilance and ADR reporting like – informing patients about possible side effects, noticing ADRs in patients, getting feedback of discomfort experienced by patient after drug treatment, availability of ADR form, reporting/non-reporting of observed ADR, existence of set procedure of reporting ADR in their organization.

**Subjects:** The study included 200 physicians practicing in government or private sector hospitals/clinics of Delhi.

**Study setting:** The study covered 10 government hospitals, 3 private hospitals and 6 private clinics of Delhi. Following hospitals were included in the study.

#### Government sector hospitals

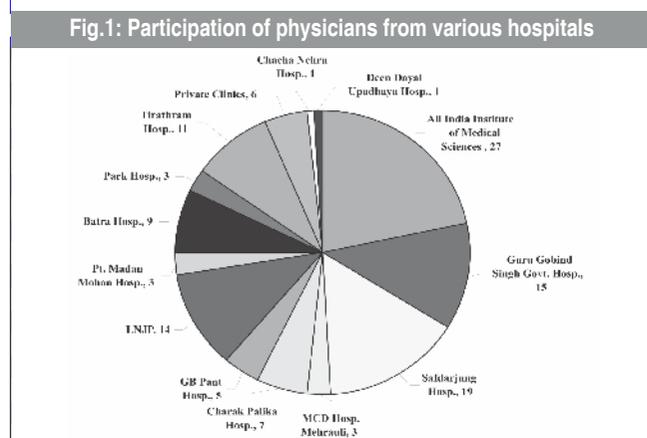
1. All India Institute of Medical Sciences and Research (AIIMS)
2. Guru Gobind Singh Government Hospital (GGSGH)
3. Safdarjung Hospital (SJH)
4. Deen Dayal Upadhaya Government Hospital (DDU)
5. Charak Palika Hospital (CPH)
6. Govind Ballabh Pant Hospital (G B Pant)
7. Lok Nayak Jaiprakash Hospital (LNJP)
8. Primary Health Centre (PHC), Mehrauli.
9. Pt. Madan Mohan Malaviya Hospital
10. Chacha Nehru Bal Chikitsalaya

#### Private sector hospitals

1. Park Hospital
2. Batra Hospital and Medical Research Centre
3. Tirathram Shah Hospital

## RESULTS

Out of 200 physicians approached to participate in study, 124 physicians completed and returned the questionnaire, giving response rate of 62%. The participation of physicians from various hospitals is represented in Fig.1. The demographic profile of respondents is represented in Table No.1. Maximum participants (27, 21.77%) were from All India Institute of Medical Sciences and Research, New Delhi.



**Table 1: Demographic profile of respondents**

Demographics	Number	Percentage
Qualification		
Post graduate	92	74.19
Under graduate	32	25.81
Gender		
Male	95	76.61
Female	29	23.39
Sector		
Government	95	76.61
Private	29	23.39
Experience		
0-5 yrs.	52	41.93
5-15yrs.	53	42.74
15-25yrs.	12	9.68
25 or more	7	5.64

#### Knowledge of physicians:

Out of the total (124) physicians, 88 (70.97%) reported that they were aware of the term pharmacovigilance, 29 (23.39%) physicians did not know the term pharmacovigilance and 7 (5.64%) physicians did not respond indicating that total 29+7=36 (29.03%) physicians, did not know the term pharmacovigilance. The results show considerable variability regarding physicians' knowledge about the possible reporting centers in India. Six (4.84%) physicians had faint idea that reporting can be done at National Monitoring Center (NMC) and/or Regional monitoring centers (RMC) because NMC and RMC were one of the many options chosen by them for place of ADR reporting. The percentage response to other options was senior/fellow physicians (16.93%), hospital pharmacy (11.29%) and manufacturing industry (3.22%). Two (1.61%) physicians gave mixed response. Physician's responses for reporting centers other than those provided in the multiple choices were Medical Superintendent, Hospital pharmacy, Hospital laboratory, Hospital committee, Journal, OPD card, Director Health Services and Drugs controller. Eleven (8.87%) physicians knew that AIIMS and LHMC are the reporting centers of Delhi but Surprisingly only 3 (2.42%) physicians had the phone number, address of the reporting centers. It indicates that 97.58% physicians report ADRs at places other than NMC and RMC.

#### Skills of physicians:

Majority of physicians (120, 96.77%) reported that they inform the patients about the possible side effects of the prescribed drug and thereafter notice ADRs in patients. One hundred twenty two (98.39%) physicians said that patients

inform them about the discomfort /side effects/adverse effects experienced by them during or after the drug treatment. One (0.81%) physician said that patients do not interact with them about discomfort /side effects/adverse effects observed after and during the drug treatment. One (0.81%) physician did not respond. Only 43 (34.68%) physicians said that they report observed ADR while 73 (58.87%) do not report ADR and 8 (6.45%) did not respond. Thus, 73+8= 81 (65.32%) physicians did not report the ADRs which they had come across. Only 23 (18.55%) physicians said to have set procedure of reporting ADR in their organization. Most respondents 53 (42.74%) agreed that their organization do not have set procedure of reporting ADR while other 23 (18.55%) physicians said that they did not know answer to this question and 25 (20.16%) physicians did not respond. So we can state that 23+25=48 (38.71%) physicians were doubtful about the existence of set procedure for ADR reporting in their organization. The hospital wise response of physicians towards existence of set procedure in their organization is given in Table No.2. Twenty eight (22.58%) physicians did not report ADRs because they were not sure of the drug causing the ADR while 31 (25.0%) physicians did not respond to this query. So, total 28+31=59 (47.58%) physicians were uncertain about drug causing ADR. Half of the physicians did not report the observed ADR because they did not know the center of reporting. Surprisingly only 12 (9.68%) physicians had ADR reporting form while 98 (79.03%) physicians said they do not have this form and 14 (11.29%) physicians did not respond. Thus total, 112 (90.32%) physicians did not have ADR reporting form.

Table 2: Response for existence of set procedure of ADR reporting in different hospitals

Hospitals	Total Physician	Yes	No	Don't Know	No Response
AIIMS	27	7	7	12	1
GGSGH	15	1	11	2	1
SJH	19	1	13	2	3
PHC	3	0	3	0	0
CPH	7	1	4	0	2
GB Pant	5	2	0	2	1
LNJP	14	1	5	4	4
Pt. Madan Mohan	3	1	2	0	0
Batra	9	5	0	1	3
Park	3	1	2	0	0
Tirathram	11	0	2	0	9
Chacha Nehru	1	1	0	0	0
DDU	1	1	0	0	0
Pvt. clinics	6	1	4	0	1

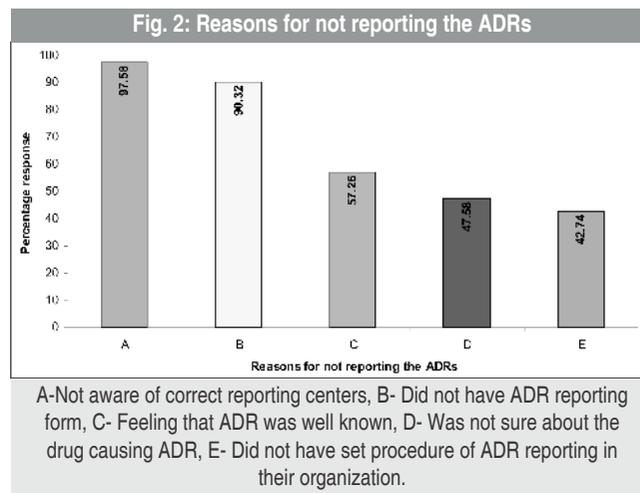
**Attitude of physicians:**

One hundred twenty three (99.19%) physicians felt that the ADR monitoring is essential. One (0.81%) physician did not respond. It may be possible that he did not understand the meaning of ADR monitoring.

Forty two (33.87%) physicians felt that there is no need to report the ADR as it is well known. Fifty three (42.74%) physicians responded negatively while 29 (23.39%) physicians did not respond. So, total 42+29=71 (57.26%) physicians do not report the ADR with the feeling that it is well known. Good number of physicians (109 , 87.90%) were of the opinion that ADR reporting should be mandatory on doctors while 8 (6.45%) physicians considered that ADR reporting should not be mandatory and 7 (5.64%) physicians did not respond.

**Summary of results:**

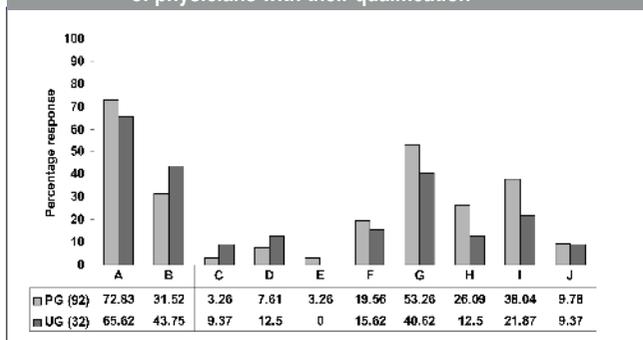
Fig.2 represents the major reasons for not reporting of ADR by physicians. They were - unawareness of reporting centers (97.58%), non-availability of ADR reporting form (90.32%), do not have set procedure of reporting in their organization (42.74%), adverse drug reaction already well known (57.26%) and uncertainty about drug causing ADR (22.58%).



**Correlation between knowledge, attitude and skills of physicians with their qualification (Fig.3):**

The physicians were grouped as per their qualification as: post graduate (PG) physicians (74.19%), undergraduate (UG) physicians (25.81%). The awareness of UG physicians (65.62%) about pharmacovigilance was less than PG physicians (72.83%). Involvement of undergraduates in ADR reporting was more (43.75%) as compared to that of 31.52% of PG physicians but none of the UG physician had phone

**Fig. 3: Correlation between knowledge, attitude and skills of physicians with their qualification**



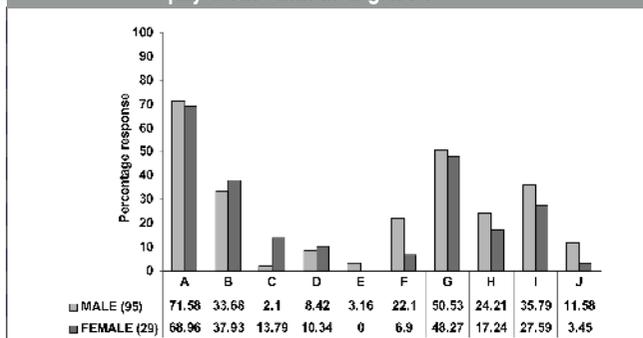
A - Aware of pharmacovigilance, B - Report observed ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone number and address of NPP reporting center, F - Have set procedure of ADR reporting in their organization, G - Non-reporting due to lack of knowledge about center, H - Uncertain of drug causing ADR, I - Feel all ADRs are well known, J - Have ADR reporting form

number and address of pharmacovigilance centers in Delhi while 3.26% of PG physicians had this information. It seems that undergraduates report ADRs to senior physicians and not to ADR monitoring centers. Uncertainty about the drug causing ADR was more among PG physicians (26.09%). The feeling that ADRs are well known and thus need not be reported was also more in PG physicians (38.04%).

**Correlation between knowledge, attitude and skills of physicians with their gender (Fig.4):**

The participation of male physicians and female physicians in the study was 76.61% and 23.39% respectively. Awareness about pharmacovigilance of male physicians (71.58%) was better than female physicians (68.96%). The knowledge of NMC/RMC as reporting centers was better of female physicians (13.79%) as compared to 2.10% of males. Male

**Fig. 4: Correlation between knowledge, attitude and skills of physicians with their gender**



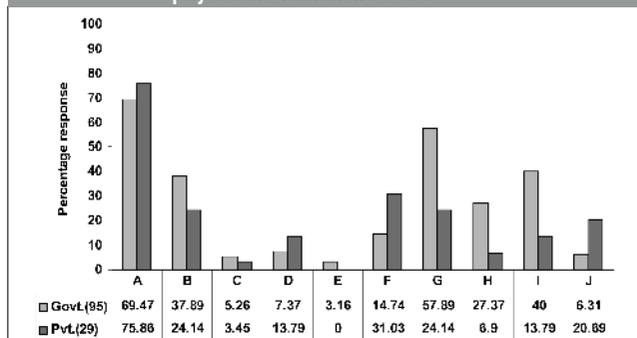
A - Aware of pharmacovigilance, B - Report observed ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone number and address of NPP reporting center, F - Have set procedure of ADR reporting in their organization, G - Non-reporting due to lack of knowledge about center, H - Uncertain of drug causing ADR, I - Feel all ADRs are well known, J - Have ADR reporting form.

physicians were more aware about phone number and address of pharmacovigilance centre of Delhi (3.16%) and set procedure of ADR reporting in their organization (22.10%). Availability of ADR reporting forms was more with male physicians (11.58%). Reporting of ADR by female physicians (37.93%) was more than male physicians (33.68%). Uncertainty about drug causing ADR was more in males (24.21%) as compared to 17.24% of females. The feeling that ADRs are well known and thus need not be reported was more in males (35.79%).

**Correlation between knowledge, attitude and skills of physicians with their sector (Fig.5):**

The physicians were grouped as per their sector of working as: Government sector physician (76.61%), Private sector physician (23.39%). Awareness about pharmacovigilance of

**Fig. 5: Correlation between knowledge, attitude and skills of physicians with their sector**



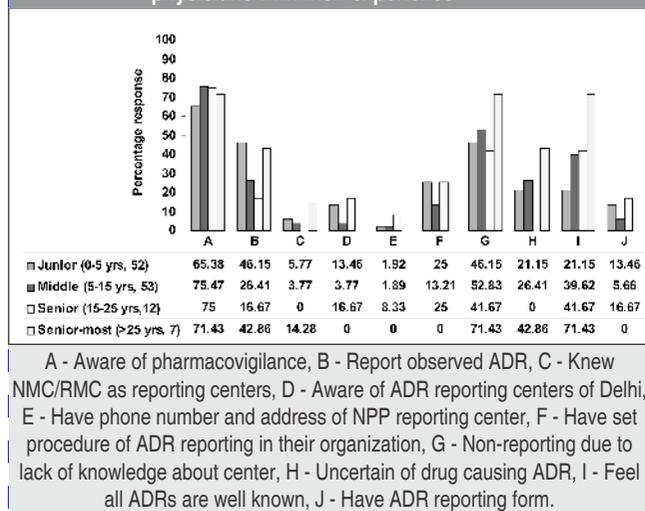
A - Aware of pharmacovigilance, B - Report observed ADR, C - Knew NMC/RMC as reporting centers, D - Aware of ADR reporting centers of Delhi, E - Have phone number and address of NPP reporting center, F - Have set procedure of ADR reporting in their organization, G - Non-reporting due to lack of knowledge about center, H - Uncertain of drug causing ADR, I - Feel all ADRs are well known, J - Have ADR reporting form.

physicians from private sector (75.86%) was better than government sector (69.47%). Knowledge of phone number and address of pharmacovigilance centre of Delhi was better of government sector physicians (3.16%). Actual reporting by physicians from government sector was better than private sector physicians. The reason may be that hierarchy is observed in reporting from Junior doctors to Senior doctors to Consultants within private organization but further communication to ADR monitoring centers does not occur. Major reasons for underreporting in government sector were – Lack of knowledge about centre (57.89%); uncertainty about the drug causing ADR (27.37%); feeling that ADRs are well known hence need not be reported (40.0%). Major reason for underreporting in private sector was non availability of reporting form (79.31%).

### Correlation between knowledge, attitude and skills of physicians with their experience (Fig.6):

The physicians were grouped as per their experience as: Juniors (0-5 years, 41.93%), Middle (5-15years, 42.74%), Senior (15-25years, 9.68%) and Senior most (more than 25 years, 5.64%). Juniors were found to be least aware of pharmacovigilance (65.38%). However, no significant difference was found regarding awareness of pharmacovigilance among physicians having experience

Fig. 6: Correlation between knowledge, attitude and skills of physicians with their experience



more than 5 years. Senior-most physicians were most aware about NMC/RMC as reporting centers (14.28%) followed by junior (5.77%) and senior physicians (3.77%) while none of the middle physicians had this information. The availability of ADR reporting forms was maximum (16.67%) with senior doctors. Senior physicians were most aware about reporting centers in Delhi (16.67%) and their phone number and address (8.33%). Reporting of observed ADRs was best by junior doctors (46.15%). But the availability of ADR reporting forms was low, it seems that junior doctors are reporting to senior doctors and senior most doctors are discussing ADRs in physician forums. Non-reporting of ADRs due to lack of knowledge of reporting centers (71.43%) as well as the uncertainty about the drug causing the ADR (42.86%) was maximum in senior-most doctors. The feeling that ADR is well known and thus need not be reported went on increasing with experience.

## DISCUSSION

The countries like Australia, Brazil have well established spontaneous ADR reporting systems with participation from

all healthcare professionals.<sup>17</sup> In India, very few studies have looked at ADRs as the cause of hospital admissions and fewer still have looked at costs associated with ADRs.<sup>18</sup> ADR monitoring and reporting activity is in its nascent stage in India.<sup>19</sup> This survey helps in knowing the actual participation of physicians of Delhi in spontaneous reporting to ADR monitoring centers. The overall response rate of this survey was (62.0%) which is somewhat higher than the 50% response rate reported by Hasford et al in his study.<sup>20</sup> Physician's expertise in informing patient about expected side effects and noticing ADRs in patient was very good (96.77%). Physicians have extended their role beyond diagnosing and prescribing. The physicians are informing patients about the expected therapeutic effects, dosage regimen, directions for use and possible side effects. Patient's feedback to doctors about experienced discomfort was also good (98.39%). Such data indicates that physicians have good communication skills and they have been successful in developing healthy relationship with patients which is essential for patient safety. Significant percentage (90.32%) of physicians was devoid of ADR reporting form. This is against the finding of Cosentino M that only 16% of physicians of Northern Italian district were devoid of ADR reporting form.<sup>21</sup> As per NPP, adverse drug reactions should be reported to national or regional centers,<sup>15,16</sup> but in our study fellow physicians (16.93%) and hospital pharmacy (11.29%) were found to be the most common recipients of ADR reports. Surprisingly 65.32% physicians did not report the ADRs which they had come across which is almost similar with the study of J. Hasford et al., which found that 68.2% physicians did not report the suspected adverse drug reaction.<sup>20</sup> But our percentage is much higher than the finding of Cosentino M that 50% medical practitioners did not report observed ADRs.<sup>21</sup>

In a study conducted by J. Hasford et al. in 2002, 66.3% physicians were found to be uncertain of definite causality thereby not reporting it<sup>20</sup> while in our study 47.58% physicians were found to be uncertain about drug causing the ADR. The reason for such finding can be enhancement in physician's ADR assessment ability over the period of 8 years. Although the NPP states that all suspected reactions to any drug in the market must be reported, 57.26% physicians felt that the observed ADR need not be reported as it is well known. This is lower than the findings of J. Hasford et al. which state that 75.6% of suspected ADR went unreported by physicians as they were considered to be well known.<sup>20</sup> The set procedure of reporting ADR in their organization was

known to only 18.54% physicians. Remaining physicians were either doubtful or were of the opinion that such procedure does not exist in their organization. Further when the physicians responses were studied hospital wise (Table No.2), a clear fact came forward that; there is no dissemination of the information regarding existence of a set procedure for reporting of ADRs in their organizations. There was a mixed response from the physicians of the same hospital setting. For example, in prime hospital of Delhi like AIIMS, where pharmacovigilance centre exists, out of 27 physicians who participated in the study, 7 physicians were of the opinion that they have set procedure of ADR reporting while 7 other physicians totally disagreed and 12 physicians said that they did not know answer to this question. One physician did not respond to this query. So, conclusive results could not be drawn whether the said hospital setting has a set procedure for reporting ADR. This may be due to:

1. Lack of importance given to the ADR reporting and Pharmacovigilance.
2. Inappropriate dissemination of information and inadequate co-ordination.
3. Communication gap between the NPP representatives, hospital administration and physicians.

Similar pattern was observed in other hospitals of Delhi.

Almost all physicians felt that the ADR monitoring is essential which is in alliance with study of Consentino M that, no doctor seemed to believe that ADR reporting is useless.<sup>21</sup> Though Physicians (99.19%) felt ADR monitoring is essential only 34.68% reported them, indicating that the attitude of physician's is not in sync with their skills. Sixty two (50.0%) physicians felt that they did not report ADR because they did not know where to report. This indirectly indicates that remaining 62 physicians knew where to report ADR but this is contradictory to the fact that only 9.68% physicians had ADR reporting forms and merely 2.42 % had phone number and address of reporting centers of Delhi. Thus we can say that majority of the physicians were ignorant about the existence of ADR monitoring centers, their phone number and address as well as the guidelines of NPP that ADRs should be reported in the ADR reporting form to the monitoring centers. Possibly these 34.68% reported ADRs are discussed in physician's forums or the junior doctors are reporting them to senior doctors. This is in congruence with study of J.Hasford, conducted in Germany, where only few physicians report directly to the German drug authority.<sup>21</sup> In addition, the ADRs reported by physicians may die silent death without

any action for benefit of the society as the reporting is scattered and it does not reach the NMC. Thus we can say that the reporting by physicians of Delhi to ADR monitoring centers is extremely low. This is in congruence with study of Janaje et.al., with estimates of only around one in 20 serious ADRs are reported.<sup>22</sup> ADR reporting should be mandatory on doctors was of the opinion of 87.90% physicians. This shows their willingness to contribute in the pharmacovigilance program.

#### ***Suggestions for Improvement in ADR Reporting:***

1. Each hospital should build local 'Pharmacovigilance Unit' for disbursement and collection of ADR reporting forms.
2. The NPP should periodically collect ADR forms from hospitals by sending representatives.
3. Periodical meetings of experts from NPP with doctors should be arranged to boost reporting.
4. ADR drop boxes should be introduced at strategic sites in hospitals.
5. Pharmacovigilance workshops for health care professionals should be initiated.
6. Facilitate ADR reporting by e-mail, fax and phone.
7. Incorporation of pharmacovigilance in the syllabus of UG and PG courses of medicine.
8. Associating ADR reporting with rewards.
9. Felicitation of physicians for maximum ADR reporting in a year.
10. Assurance of non-involvement in legal matters, if they arise.
11. Positively changing the mindset, so that ADR reporting becomes an accepted and understood routine.
12. The Government of India may pass a law for making ADR reporting mandatory for physicians.

#### **CONCLUSION**

Despite good observation and knowledge of ADR among doctors, the rate of reporting to AMC was low. The overall awareness of doctors about ADR reporting centers of Delhi, their phone number, address and availability of ADR reporting forms was very low. The actual reporting of ADRs by physicians to monitoring centers designated by national pharmacovigilance program was very low. Sensitization and orientation of physicians towards reporting of ADRs to

monitoring centers is essential to improve reporting rate. Implementing the suggestions would significantly improve ADR reporting. Proactive participation of physicians is a key to enhance spontaneous reporting.

#### ACKNOWLEDGEMENT

The authors wish to thank all the physicians who participated in the study.

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# A Study of medication administration errors in a tertiary care hospital

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## ABSTRACT

Submitted: 23/2/2011

Accepted: 25/3/2011

Medication administration errors account for 34% of all medication errors and identified as one of the important reasons for patients' morbidity and mortality. NPSA statistics show that 59.3% of medication errors occur during the administration stage. Thus identifying and resolving the administration errors will improve the patient care and decreases the health care costs. National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy was used to analyse the frequency, types, severity and factors responsible for medication administration errors. The findings of the study reveal that the frequency of medication administration errors is 15.34%, omission errors (33.02%), improper dose (17.43%) and wrong time (12.84%) errors were the major types of errors occurred and the majority administration errors belonged to category C (112), B (46) and D (35). Frequent interruptions and distractions, lack of communication between health care professionals, performance deficit and work stress on duty nurses are identified as major factors responsible for administration errors.

**Keywords:** Medication Administration Errors (MAEs), National Coordinating Council for Medication Error Reporting (NCC MERP) taxonomy, National Patient Safety Agency (NPSA) and Patient Care.

## INTRODUCTION

Medication use in hospitals is a complex process and depends on successful interaction among health care professionals functioning at different areas. Medication errors may occur at any stage of prescribing, documenting, dispensing, preparation, or administration.<sup>1</sup> Medication errors may contribute to morbidity, mortality and increased health care costs.<sup>2</sup> In 2007, National Patient Safety Agency (NPSA) statistics shows that 59.3% of medication errors occur during the administration stage.<sup>3</sup> Medication administration errors are defined as any deviation from the physician's medication order as written on patient's treatment chart during medication administration to patient.<sup>2</sup> The plan for administering a medication begins with identifying the patient, the drug, the dose, the route, and the time.<sup>4</sup> In 1995, the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) classified administration errors in to wrong drug, wrong route, wrong dose, wrong patient, wrong timing of drug administration, contra-indicated drug, wrong site, wrong dosage form, wrong infusion rate and expired medication. Such errors may occur intentionally or

unintentionally.<sup>2</sup> The elderly, and mentally ill patients are particularly more susceptible as they may be confused, resist medication administration, physically weak and require complex medication regimens.<sup>5</sup> In a study conducted over a period of three and half years in UK at a psychiatric hospital, the most frequent types of errors observed were the improper dose, wrong drug, and dose omission.<sup>6</sup> The drugs often associated with harmful events of medication errors in pediatric patients include morphine, insulin, vancomycin, potassium chloride, gentamicin, ceftriaxone, and heparin.<sup>4</sup>

In addition to the morbidity and mortality, medication errors also contribute to increased health care costs. The department of health in UK, estimated the direct and indirect health care expenditure due to medication errors as 2£ billion.<sup>1</sup> In US, an American health care system estimated the medication errors related expenditure as \$37 billion per year.<sup>7</sup>

Medication administration has become more complex as a result of the increasing number of medications available and new routes of administration. Nurse is considered as vital in medication administration process and the literature review states that poor calculation competency of nurses, poor adherence to protocols and poor knowledge of medications are the important reasons leading to medication administration errors.<sup>4</sup>

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An observational research study conducted in Newzealand conclude that, poor knowledge of nurses about medicines, dose calculations, and route of administration were the key elements contributing for medication administration errors.<sup>2</sup> The other contributing factors for MAE were identified as frequent distractions from work, peak work load, and inadequate communication between health care professionals. An observational multinational study conducted in 27 countries of five continents by Valentin A et al suggest that, increased work load, stress, and fatigue are the contributing factors for medication administration errors. In addition to the above, poor hand writing in prescriptions, drugs with similar packing are the system errors leading to medication administration errors.<sup>8</sup> Therefore medication errors may compromise patient confidence in the health-care system.<sup>9</sup> Worldwide intensive research was conducted to find the types, categories, contributing factors, and cost implications of medication administration errors in various health care settings however very little research was conducted in this area in India. Thus the present study was conducted to assess the frequency, types, severity and factors responsible for medication administration errors in a tertiary care teaching hospital.

## MATERIALS AND METHODS

### Study Setting

The present study was conducted at a South Indian 1200 bed multi specialty tertiary care teaching hospital for a period of nine months during November 2009 and August 2010 in inpatient wards of general medicine and surgery departments. Every day 200 patients are admitted either from the outpatient, emergency and casualty departments or transferred from the wards of other clinical specialties to the above departments. The present study was approved by the Institutional Human Ethics Committee.

### Study procedure

A suitably designed documentation form was used to analyse the types, frequency and factors responsible for medication administration errors and the data was collected from the case notes, treatment charts, medication administration records and interviewing the in-patients admitted to surgery and general medicine wards. Demographic details of the patients, diagnosis and treatment recommended were documented. Medication administration of the in-patients was followed up on daily basis to identify the administration errors. Frequency

of medication administration errors was analysed by using the following formula.<sup>10</sup>

$$\text{Frequency of MAE} = \frac{\text{Number of Significant + Non significant MAEs}}{\text{Doses given + doses ordered but not given}} \times 100$$

NCC MERP taxonomy was applied to analyse the frequency and types of medication administration errors. The types of medication administration errors were classified in to omission error, improper dose, wrong medication, wrong strength, wrong dosage form, wrong technique, wrong route of administration, wrong rate, wrong time, wrong patient errors and other types.<sup>11</sup>

Medication administration errors were categorised in to various categories as A, B, C, D, E, F, G, H and I categories based on NCC MERP. Current NCC MERP categorizes medication administration errors in to the 9 following categories.

**Category A:** Circumstances or events that have the capacity to cause an error

**Category B:** An error has occurred but the error did not reach the patient

**Category C:** An error has occurred that reached the patient, but did not cause harm to patient

**Category D:** An error has occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

**Category E:** An error has occurred that may have contributed to or resulted in temporary harm the patient and required intervention

**Category F:** An error has occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization

**Category G:** An error has occurred that may have contributed to or resulted in permanent patient harm

**Category H:** An error has occurred that required intervention necessary to sustain life

**Category I:** An error has occurred that may have contributed to or resulted in the patient's death.

## RESULTS

Medication records of 286 patients were reviewed and 218 medication administration errors were observed in 167 patients who received 1430 doses. The frequency rate of medication administration errors was found as 15.24%.

Among the 167 patients, 115 were male patients and 52 were female patients. Out of 218 medication administration errors, 112 errors (51.37%) were observed in surgery department and 106 errors (48.62%) were observed in medicine department.

According to the NCC MERP taxonomy, the medication administration error types were analysed. The most common types of errors observed were omission errors (failure to administer or failure to record the administration, (n=72) and improper dose (over dosage (n=38), followed by wrong time (n=28), wrong strength (e.g. dose was given in noon instead of morning dose (n=21), wrong rate ( IV infusion rate was too fast, ( n=18), wrong drug (drug other than the prescribed one, (n=12), and others (Patients refusal to take medication/not bought the medication, (n=14). The details of types of medication administration errors are given in Table No 1.

**Table 1: Types of Medication Administration Errors**

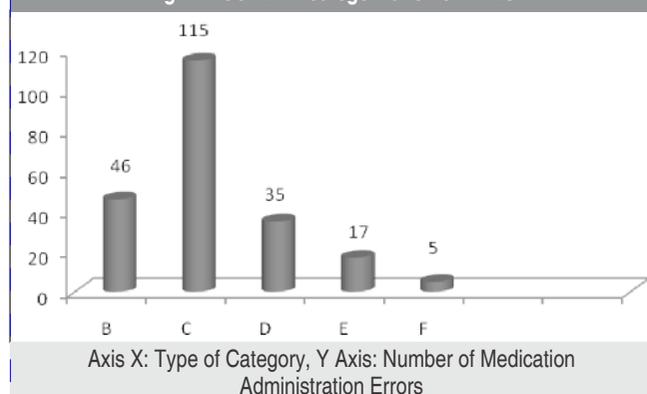
S.No	Types of errors	Percentage (%)
1.	Omission error	33.02
2.	Improper dose/quantity	17.43
3.	Wrong strength	09.63
4.	Wrong drug	05.50
5.	Wrong dosage form	01.83
6.	Wrong route	01.83
7.	Wrong rate: too fast	08.25
8.	Wrong duration	03.21
9.	Wrong time	12.84
10.	Others	06.42

Note: Others include (Patient refusal to take medication/ Unable to purchase/swallow medication etc)

Majority administration errors were belonged to the Category C (52.75%), Category B (21.10%) and Category D (16.05%) followed by the category E; (07.79) and category F; (02.29).

Details of categories of the medication administration errors according NCC MERP categorisation are presented in Fig. 1.

**Fig. 1: NCCMERP Categorization of MAEs**



The system related factors responsible for medication administration errors identified as prequent interruptions and distractions (33%), poor communication among health care professionals (23%), inadequate training (8%) and inadequate staff(8%) and others (14%). The details of factors responsible for MAE are presented in Table No 2.

Human factors responsible for medication administration errors were studied. Predominant human factors responsible for MAE were identified as performance deficit (42.20%), stress (21.10%) and fatigue and lack of sleep (8.71%) and the list of human contributing factors causing medication administration errors are presented in Table No 3. Types of dosage forms highly involved in medication administration errors were injectable drugs (49.54%) and tablets (33.94%). The types of dosage forms involved in MAE are presented in Fig. 2.

**Table 2: System related factors responsible for MAEs**

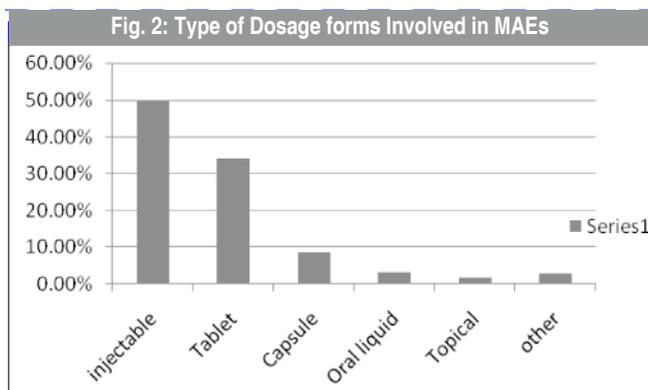
Sl. No.	Contributing factors	Percentage (%)
1	Lack of Lighting	6.0
2	High Noise level	8.0
3	Frequent interruptions & distractions	33.0
4	Lack of training	8.0
5	Lack of staffing	8.0
6	Lack of Communication between HCPs	23.0
7	Others*	14.0

\*Others = Patient refusal to take medication/ Unable to purchase/swallow medication etc

**Table 3: Human Factors responsible for MAEs**

S.No	Human factors	Percentage (%)
1	Knowledge deficit	05.50
2	Performance deficit	42.20
3	Miscalculation of dosage or infusion rate	05.96
4	Stress	21.10
5	Fatigue/ lack of sleep	08.71
6	Poor communication among health care professionals	01.83
7	Others*	14.67

\* Others include (Patient refusal to take medication/ Unable to purchase/swallow medication etc).



## DISCUSSION

Medication use is a complex process that involves coordination among various health care professionals. Medication errors may happen at any stage of patient care like prescribing, transcribing, dispensing, and administration.<sup>1</sup> Studies have corroborated that medication administration errors may contribute to morbidity, mortality and increased health care expenditures.<sup>1,7</sup> A study has calculated a medication error cost as USD 5000.<sup>12</sup> Medication administration errors may take place at the time of administration due to prescriber's medication order deviation. As per National Health Service (NHS) of UK statistics, medication errors may affect 850,000 people each year and incur the health care expenditure up to £2 billion.<sup>1</sup> In USA, American Health System calculated the morbidity, mortality and health care expenditure associated with medication errors. The statistics reveal that medication errors had caused 88,000 deaths and incurred \$37 billion as health care expenditure annually.<sup>7</sup> In a US based study, it was estimated that medication administration errors have accounted for 34% of medication errors.<sup>5</sup> National Patient Safety Agency (NPSA) shows that 59.3% of medication errors occur at administration stage having high potential for morbidity and mortality and increased health care costs.<sup>3</sup> Administration errors are one of the most common types of medication errors affecting approximately 5 percent of all administered doses.<sup>6</sup>

In the health care team, nurse is responsible for medication administration to the patients and is therefore considered as the key faulty component for medication administration errors.<sup>3</sup> The findings of many international studies showed that, performance deficit, poor calculation competency, poor adherence to protocols, poor knowledge of medications and complacent behaviour of the nurses are the main reasons for medication administration errors.<sup>13</sup> Other system related causes for administration errors include physicians poor handwriting, similar packing of medications.

As medication errors are resulting in damage to patient's health and influence the health care budgets, it is worth studying the types, frequency, impact of medication errors and the factors responsible for administration errors. The literature review suggests limited research has been carried out in India in this area. The present study focuses on scientific understanding the medication administrations errors in a tertiary care teaching hospital and to suggest initiatives to improve the patient safety.

During the study period, frequency of medication administration errors was calculated as 15.24%. In many overseas studies, the frequency of medication administration errors range from 14 to 59%. In two observational studies conducted in an acute settings have found the medication administration error frequency rates as 14.9% and 32.4%.<sup>2</sup> In a prospective cohort study, the frequency of medication administration errors was found as 38%. Analysis of MEDMARX data base suggests the frequency of medication administration errors as 59.5%. The error frequency rate in the present study closely matches with the findings of the international studies. The higher the frequency of medication administration errors occur results in higher chances of morbidity and mortality in the patients.

NCC MERP taxonomy was used to analyse the categories of the medication administration errors. The medication administration errors of the present findings were analyzed and classified in to various categories. In our study the most common types of errors observed were omission errors (failure to administer or failure to record the administration, n=72) and improper dose (over dosage, n=38), followed by wrong time (n=28), wrong strength (e.g. dose was given in noon instead of morning dose. n=21), wrong rate (IV infusion rate was too fast, n=18), wrong drug (drug other than the prescribed one, n=12), and others (Patients refusal to take medication/not bought the medication, n=14). Our observations are in consistent with the findings of previous studies.<sup>8</sup>

In a prospective observational multinational study involving 113 ICUs from 27 countries across five continents, including Australia the most common administration errors include wrong time of administration (n = 386), missed medication (n = 259), followed by wrong dose (n = 118), wrong drug (n = 61) and wrong route (n = 37).<sup>8</sup> Similarly in another observational study of MAEs conducted by Camilla Haw et.al. in old-age psychiatric inpatient wards at St. Andrew's Hospital, UK identified 148 administration errors through

treatment chart review. The most common types of errors detected were belong to omissions errors (133), Improper dose errors (over doses, 9), wrong time errors (5) and administration of a discontinued medication (1). The MAEs detected were reported using hospital's medication error reporting system.<sup>5</sup>

In the present study NCC MERP taxonomy was used to assess the severity of the medication administration errors on patient outcomes. As per the taxonomy, Category A to D is considered as mild, E and F is moderate and G to I is severe in nature. The medication administration errors were analyzed and classified in to various categories. Most of the errors were belonged to the Category C (52.75%), Category B (21.10%) and Category D (16.05%) followed by the category E; (07.79) and category F; (02.29). In a descriptive and retrospective study conducted over a period of 5 years to assess the administration errors made by nursing students, categorized the medication administration errors using NCC MERP taxonomy. Most of the administration errors belonged to the Category C (70.57%) and Category D (23.29%).<sup>13</sup>

Frequent interruptions and distractions (32.56%), lack of communication between the health care professionals (HCPs) (23.39%), other factors (13.76%), lack of staffing and noise level (08.25%) and lack of training (7.79%) are identified as the system related factors responsible for medication administration errors in our study.

An observational multinational study identified heavy workload, stress and fatigue are the contributing factors causing 32% ( $n = 272$ ) of the administration errors followed by lack of knowledge ( $n = 81$ , 9%), violation in protocols ( $n = 76$ , 9%) and problems with handover processes ( $n = 53$ , 65%).<sup>8</sup>

Zane Robinson et al, in their study identified performance deficit (51.01%) and knowledge deficit (26.52%) as the common contributing factors responsible for medication administration errors. The common human factors responsible for medication administration errors were also studied. They were identified as performance deficit (42.20%), stress (high work load etc) (21.10%), others (14.67%), and fatigue (08.71%) are the commonest human factors responsible for medication administration errors.<sup>12</sup>

In our study, the dosage forms which are involved in most MAEs include injectable drugs (49.54%) and tablets (33.94%). In a study conducted by Fanak Fahimi et al. in ICU and medical wards of a large hospital in Tehran observed that the majority of administration errors occurred during bolus

administration (43.4%), followed by wrong infusion rate (23%).<sup>13</sup> The increased frequency of the medication administration errors is may be due to various contributing factors. The findings of our study were also similar to that of the findings of Tehran study.

Adequate training and motivation to nurses, computerized physician order entry system (CPOE) and medication administration record system will help in preventing the medication administration errors by nurse. Introduction of Medication Error reporting system in the hospital will help in preventing the medication errors.

## CONCLUSION

The findings of the present study concludes that, omission of the dose, improper dose, wrong time, and wrong strength were identified as common medication administration errors. Majority errors belong to NCCMERP category C and interruption and distractions during the work, performances deficit, and stress are the common risk factors contributing for medication administration errors.

## ACKNOWLEDGEMENTS

We extend our sincere thanks to JSS University, Dr. H.G.Shivakumar, Principal, JSS College of Pharmacy, Dr. G. Parthasarathi, Head, Department of Pharmacy Practice, Dr. K.A.S Murthy, Head, Department of Medicine, Dr. Siddesh, Head, Department of Surgery, JSS Medical College and Hospital, Mysore for their support in carrying out the research work.

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# A study of self medication pattern in Punjab

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## ABSTRACT

Submitted: 28/1/2011

Accepted: 30/4/2011

The objective of this study was to describe and examine the self medication pattern in the state of Punjab. A sample of 300 nuclear families from 5 different districts of Punjab were randomly selected for the study. The study showed that the prevalence of self medication was high in the educated group rather than uneducated group. Self medication was mostly employed for pain, cough, fever, and cold. After analgesic there was priority for food supplements, as 73% of population used to go for self medication of food supplements. Chemists/ Pharmacists were the major source of information for self medication, followed by friends and advertisement. From the study it was concluded that majority of the persons go for self medication without proper knowledge of dose, Adverse drug reactions, Drug interactions. Hence, the issue needs to be addressed by the responsible authorities of State Pharmacy Council/Ministry of Health.

**Keywords:** Self medication, Punjab.

## INTRODUCTION

Self-medication can be defined as obtaining and consuming drugs without the advice of physician either for diagnosis, prescription or surveillance of treatment.<sup>1</sup> This includes acquiring medicines without a prescription, resubmitting old prescriptions to purchase medicines, sharing medicines with relatives or members of one's social circle or using leftover medicines stored at home.<sup>2</sup> There is a lot of public and professional concern about the irrational use of drugs. In developing countries like India, easy availability of wide range of drugs coupled with inadequate health services result in increased proportions of drugs used as self-medication compared to prescribed drugs.<sup>3</sup> Although, OTC (over the counter) drugs are meant for self-medication and are of proved efficacy and safety, their improper use due to lack of knowledge of their side effects and interactions could have serious implications, especially in extremes of ages (children and old age) and special physiological conditions like pregnancy and lactation.<sup>4,5</sup> There is always risk of interaction between active ingredients of OTC drugs and that of prescription medicines, as well as increased risk of worsening of existing disease pathology.

Rational use of drugs has drawn public health attention globally with the aim of maintaining quality health care at lower cost.<sup>6</sup> As dispensing medication in an appropriate way is a cornerstone of rational use, the dispenser should be regularly updated with information, tools and skills.<sup>7</sup> Internationally, self-medication has been reported as being on the rise.<sup>8-10</sup> Various studies have shown that the use of self-medication is twice as common as that of prescribed medication, and that self-medication is often used together with prescribed medication.<sup>11</sup>

## METHOD

Five different districts of Punjab were selected for the study. These include (Moga, Ludhiana, Jalandhar, Ferozepur, Barnala). From these districts 50 nuclear families were selected randomly by stratified sampling. A self administered questionnaire was distributed among the families and also that interview was conducted in local language. Participants' were informed regarding the purpose of the study. The study questionnaire was adapted from similar study conducted previously.<sup>12</sup> In case the families were not well educated, questionnaires were filled by qualified assistants. The questionnaires include the questions pertaining to identification of data (name of the head of the family, no. of children, no. of adults, address, qualification, employment, income), practice of self medication by the family, commonly used medicines as self medication, knowledge of the family

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regarding the dose of a drug, source of information regarding the drug, Knowledge regarding allopathic, homeopathic, and ayurvedic system of medicines.

## RESULT

A trend towards self medication was observed, which was high in educated population as compared to uneducated population. Conditions which were treated by the self medication include fever, cough, cold, headache, nutritional loss etc. Ongoing trend was observed towards use of Ayurvedic and Homeopathic system of medicines. From the study it was observed that the most frequently class of drug used for self medication is NSAIDs. As shown in Table 1, about 78% of the study population uses this class of drug for

Category	Percent	Drug	Percent n=300, N=%
Analgesic and antipyretics	78	PCM	59
		Ibuprofen	11
		Diclofenac	5
		Others	3
Food Supplements & Tonics	73	Becasule	56
		Calcium	10
		Multivitamin	07
Drug for cold and cough	39	D'Cold	27
		Benedrayl	7
		chericof	5
Antimicrobials/	11	Norfloracin	3
		Amoxicillin	5
		Others	3
Ayurvedic drugs			62
Homeopathic drugs			45

treatment of fever, body ache, head ache etc. Most preferred drugs under this category include Paracetamol, Ibuprofen and Diclofenac. About 73 % prefer to overcome nutritional loss by themselves by taking Becousules, Calcium and Multivitamin. 39% treats cold and cough by themselves and only 11% of the study population prefers antimicrobials. Regarding the ayurvedic system of medicine surprising results were obtained as 62% of the population tends to prefer kitchen medicines for the chronic illnesses like joint pain, asthma, obesity, baldness etc. and 45 % prefer homeopathic medication keeping in view that they are free from side effects.

The trend of self medication was high in adults as compared to children and old aged persons who mostly tend to prefer ayurvedic medication, if asked for the self medication. Table 2, shows that 50% of adults, 15% of child and only 10% of old

aged persons go for self medication. When asked about the source of information 75% agreed that they take medication in consultation with chemists rather than going for formal prescription from doctors, reason being lack of time and money. 30% take medicines on the advice of relatives and friends. The trend of self medication has been increased as result of the advertisement; about 16% agreed that they prefer medicines on the basis of advertisement. All the above data was found to be good enough to support the previous studies that the trend towards self medication is increasing day by day but coming to the part of knowledge regarding safety and efficacy results observed were disappointing as only 32% had the knowledge regarding the dose of the drug (Table 2) 23% knows the side effect of the drug taken by them as self medication and only few reported adverse drug reaction like sedation, rashes etc.

Parameters	Percent
<b>Life Cycle</b>	
Adults	50
Children	15
Old aged	10
<b>Source of information</b>	
Chemist	75
Friends	30
Advertisement	16
<b>General awareness</b>	
Dose	32
Side effects	23
<b>Reasons of self medication</b>	
Doctors advise not needed for common illness	58
Lack of time to visit doctor	26
Unaffordable doctors fee	35

On asking for the reasons of the self medication most of the population (58%) agreed that there is no need of doctors visits in case of minor illness like cold, cough, fever, itching etc. 26% respondents said that they prefer self medication because of lack of time to visit doctors and 35% said that they are not capable of paying fees to doctors.

## DISCUSSION

In the present study, trend of self medication was found high in educated compared to uneducated population. Similar results were obtained in the study carried by Deshpande and Tiwari. In their study 26% of graduates and 23.1 % of illiterate

people practiced self medication.<sup>13</sup> Other studies also have shown the prevalence of self medication as 37% in urban areas and 17% in rural areas in India,<sup>14</sup> where as 12.7% to 95% in other developing countries.<sup>3, 15, 16</sup> Antipyretics and analgesics were the most commonly used class of drugs for self medication. A study carried by Rajput et al also showed similar results. In their study about 85.38% preferred antipyretics and analgesics.<sup>17</sup> Other studies also support the results.<sup>18,19</sup> Followed by them are food supplements, drugs used for treatment of cold and cough and the antimicrobials. About 39 % of the population tends to prefer cough and cold remedies by themselves. Antimicrobials are also preferred class of self medication. The information regarding dose of the drug was quite rare. There was little or no information regarding the side effects and drug interactions which was in accordance with the previous studies.<sup>12, 20</sup> All the information was gathered using self administered questionnaires supported by interview in local language.

Trend was observed towards homeopathic and ayurvedic system of medicines for chronic illness likes joint pains, bronchial asthma, obesity, baldness. Moreover herbs and homeopathic drugs were considered safe and free from adverse effects, but the risk of possible drug interactions is always with their use. However no serious side effects were reported with drugs used as self medication. However few episodes of epigastric discomfort, sedation and rashes were observed with the use of NSAIDS, cough and cold remedies.

Previous studies<sup>21</sup> showed chemists as prime source of drug information, similar trend was observed in the current study also. Drug advertisement was also an important source of information. Although patients use of advertised medicines could have important health benefits if used appropriately in the early stages of disease.

There are various factors that play important role in influencing this type of self-medication pattern among the population. These factors include patient satisfaction with the health care providers, cost of the drugs, education level, socioeconomic factors, age and gender. Our study indicated the variation in pattern of self medication among educated and uneducated population and this variation could probably be because educated group has more ability to self medication. Education appeared to be more important variable as higher the consumer education, more the compiled with reading the patient's information sheet, following the label instructions and reading the expiry date, but socioeconomic variation was difficult to assess because of

knowledge of true income of the family for multiple source of income. Moreover, failure on part of gender and age was due to non-availability of all the members at the time of interview, which could be considered as lacuna of our study. However respondents were very cooperative and answered all in questions properly.

Although, self medication, using non-prescription drugs, could be beneficial to patients, healthcare professionals, the pharmaceutical industry and government, provided these drugs are used rationally. This asks for the quite important role to be played by the pharmacists regarding education of the persons for rational use of the drug as the practice of self medication often has many severe adverse effects and can lead to many problems.

Hence, provisions should be made for proper education regarding rational use of the drug by the consumers. Apart from community education, safety and efficacy of OTC drugs must be assured, so that these products could be safe even in the event of improper use. For registration as an OTC drug, specific efficacy trials may be conducted in real self-medication situation. Due to the difficulty in accessing health care services, self medication is often the simplest option for the patients. Since traditional practitioners are easily accessible, people also turn to them for their health care needs. However, traditional practitioners need to be educated about when to refer a patient for more specialized care.

## CONCLUSION

The prevalence of self medication practices is alarming in the state. Fever, cough and cold were the most common reasons for non doctor prescription. NSAIDs were the drugs most commonly used for self medication and tonics and food supplements were frequently taken without prescription. We recommend that holistic approach should be taken to prevent this problem, which include proper awareness and education regarding the self medication and strictness regarding pharmaceutical advertising. More-over especially in case of Punjab state ban should be applied in free sale of medicines in buses and other traveling modes. Dispensing modes in the state needs to be improved through proper education, regulatory and managerial strategies.

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# Assessment of college students awareness about tuberculosis in Moradabad

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## ABSTRACT

Submitted: 14/1/2011

Accepted: 19/4/2011

Lack of knowledge and awareness about Tuberculosis (TB) as well as Direct observed therapy short course (DOTS) are a persistent and major community problem due to which suffering and mortality rate increases tremendously. So it is responsibility of pharmacists to develop a common awareness for prevention, care and treatment of TB in the community. This survey is strictly based on assessing the awareness about TB among undergraduate (UG) and postgraduate (PG) students of nonmedical stream in Institute of Foreign Trade & Management, Moradabad (U.P.) India. In the present study, 59.41% were male and 52.78% were female. 60.81% P.G. students and 54.31% UG students were answered among them. It represents that male student's awareness were higher than the female students. The survey results also revealed that both UG & PG students of I.F.T.M. possessed very poor knowledge about type of TB, multi drug resistance (MDR) & Mantoux test, and the knowledge of UG students was very poor as compared to PG students. Pharmacists should realise their role in health education programs in the community to improve the public awareness about health burden diseases like tuberculosis.

**Keywords:** Directly observed therapy short course, multi drug resistance, mass miniature radiography, National Tuberculosis Control Programme,

## INTRODUCTION

Tuberculosis (TB) remains a major public health problem in India. World Tuberculosis Day is observed on 24 March of every year and is designed to build the public awareness about TB as an epidemic. In India two TB patients are losing their life in every three minutes; nearly 3 lakh School children give up study because of TB per year. Tuberculosis is a barrier to socio economic development. The greatest burden of tuberculosis incidence and mortality in India is in adults aged 15-16 years & higher prevalence seen in persons aged 60 years and above while lowest in childhood. While may be due to decrease immunity in old age people.<sup>1</sup> Despite the failure to reach many of the goals of the first and second national health policies, several health indicators have shown consistent improvement since the 1980s. Between 1980 and 2006, infant mortality fell from 113 to 59 deaths per thousand live births, total fertility from five to three births per adult female and maternal mortality from seven to three deaths per 1000 live

births<sup>2</sup> This system is coordinated by a specialized human resources development (HRD) unit within the Central TB Division. However, a programme review noted that the concept of HRD was not well understood at the state and district level, and there were insufficient staff dedicated to manage the development process at the central and state level<sup>3</sup>. The 2009 budget allocates US\$ 34 million for human resources to ensure adequate numbers of TB dedicated staff and to fill gaps in essential general health services posts, e.g. medical officers, laboratory technicians, etc. The health care, as in today's Indian society is centralized in the hands of physician but in a sense of pharmacy practice, pharmacist serve the role of community care taker, diagnosing disease and then managing them by compounding individual remedies<sup>4</sup> and DOTS implementation is responsible for rapid reduction of tuberculosis prevalence.<sup>5</sup>

A pharmacist can play a vital role in development of action plans to increase adherence on medication. They have the ability to gather information, review of data, patient counseling and involve in the disease management.

## MATERIAL AND METHODS

The study was conducted during January to April 2009 in

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IIFTM Campus, Moradabad (U.P.) India. Three hundred sixty students (both male and female) in the age group of 16-24 years responded to the questionnaire. A well design fifteen item questionnaire was developed (Annexure 1). For each question two choices were given (Yes or No). The respondents were advised to give answers on the basis of their previous awareness and knowledge about TB. The survey was performed on B. Tech, MBA and BBA students.

**RESULTS**

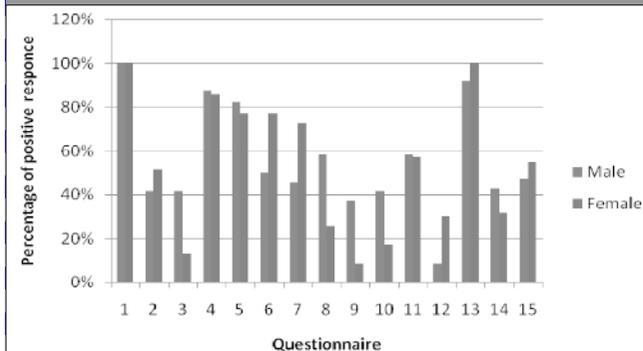
From the Survey of 360 students of under graduate & Post graduate in which number of PG students were 142 (both male and female) and the number of under graduate students were 218 (both male & female). From the result of survey on the basis of education level (both UG & PG), (54.31 %) U.G students & (60.81%) P.G. students were responded correctly. Students without having awareness of TB were (59.41%) male & female (52.78) (Table I).

A student based survey about the TB revealed that the PG students exhibited more knowledge about TB than UG students. The most striking features that emerges from this survey was the extent of awareness about TB among the post graduate on the basic issues like transmission, treatment & drug therapy was found to be 59.15% where as in UG students it was found to be 56%. Therefore, we can assume that PG students awareness was significantly higher than the UG

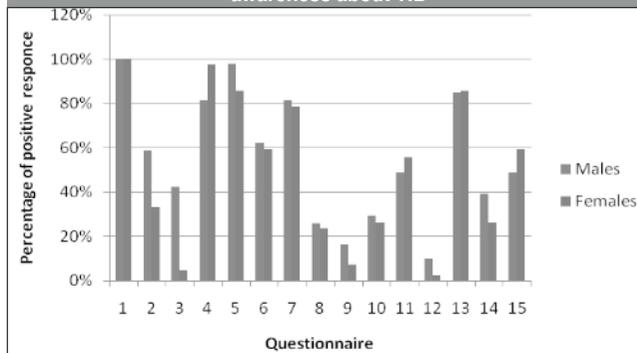
**Table 1: Distribution of students on based of sex and education level.**

Sl. No.	Sex/ Education level	No of students	Correct response (%)	Incorrect response (%)
1	Male	162	59.41	40.59
2	Female	198	52.78	47.22
3	P.G.	142	60.81	39.29
4	U.G.	218	54.31	45.69

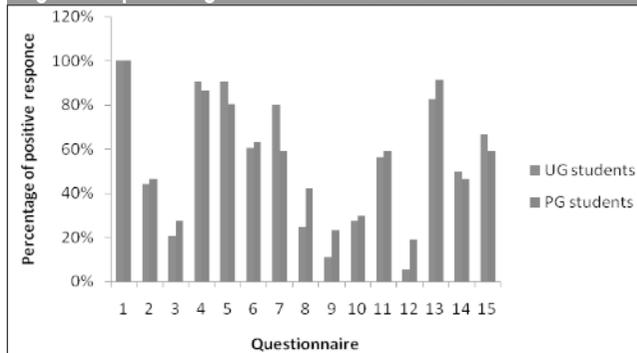
**Fig. 1: The percentage of P.G students (Male & Female) awareness about T.B**



**Fig. 2: The percentage of U.G students (Male & Female) awareness about T.B**



**Fig. 3: The percentage of U.G & P.G students awareness about T.B**



students. Percentage result from the survey about symptoms of T.B. methods for detection of TB showed that knowledge of UG students were 31.65% & 46.47% in PG students. This reveals that UG students were not having sufficient information about the symptoms & diagnosis. In over all study we found that the knowledge regarding TB is higher in male than female. The survey results also reveal that both PG & UG students of I.F.T.M possessed very poor knowledge about Type of T.B, multi drug resistance (MDR) & Mantoux test. From the survey results the percentage of correct response of UG students about detection method like X-ray, which was found to be 27.50% while knowledge about MDR was found to be 11%, knowledge about change in urine colour was found to be 24.77% which reveal that knowledge of the UG students were significantly poor as compared to PG students (Fig 1, 2 and 3).

**DISCUSSION**

In the present study, assessment of student's awareness about TB in I.F.T.M, Moradabad (U.P.) India showed that the knowledge of students is not satisfactory. The goal of national health policy 2002 was to increase the awareness of TB in both educated & uneducated people. In 1959 the Government of India, with the help of WHO, established the National TB Institute (NTI) in Bangalore to develop a national TB control

programme (NTP), with the aim of establishing prompt awareness, diagnosis and ambulatory treatment which were integrated into general health services.<sup>6</sup> In contrast in a study among tribes of Andhra Pradesh, only 44% had heard of tuberculosis.<sup>7</sup> Over half of total students knew about BCG vaccination as a preventive tool against tuberculosis, only about forty percent cases knew that tuberculosis is now a fully curable disease knowledge about BCG vaccination was present in only 14% rural population in a study from Tamilnadu.<sup>8</sup>

In the present study, the level of awareness among the students was very poor. Therefore, pharmacy students can contribute to achieve satisfactory response and prevention in the following aspects: Mobilise students for BCG vaccination & increase the awareness about BCG revaccination; create awareness among the students for the knowledge of treatment and prevention; effectively communicate & give knowledge about colour change in urine due to use of TB drugs (Isoniazid, Rifampicin) during treatment; TB affected women can breast feed her baby; sanitation procedure to be followed during infection; disinfection procedure to be followed for disinfecting house & articles; advising the students & to provide sufficient information at college level about free medical treatment, detection test, DOTS centers and mode of transmission. Our study showed that the PG students exhibited more aware about TB when compared with the UG students. A high level of ignorance, wrong knowledge, wrong attitudes and wrong practices was demonstrated among senior secondary students in a study by Tanimowa from Zambia<sup>9</sup>

Many studies have revealed that a lot of awareness and knowledge is still required among the students of schools and colleges. In spite of the advertisement of DOTS centers through media pamphlet, banners on public places, the awareness of students were not satisfactory. Therefore, the central and state Government and principals of school & colleges must uplift some new steps in increasing the awareness of DOTS, methods of treatment, transmission and detection of TB. Pharmacist are often considered as first point of contact in Health Care System and also a UG and PG students of pharmacy can contribute to enhance the awareness in other department of students.

## CONCLUSION

In conclusion, our study findings indicate that post graduate (P.G) student's awareness was significantly higher than under graduate (U.G) students. PG students

awareness regarding cause, symptom, transmission, treatment of TB was higher compared to the UG students. Thus for the upliftment of student's knowledge about TB pharmacy students should join hands with the other students of college to uproot the cause of lack of awareness about TB by organizing various programmes, debates and seminar in collaboration with hospitals and primary health centers which ultimately will increase the awareness of TB among all students of professional colleges. If these measures are implemented firmly, it can increase the awareness of tuberculosis and ultimately TB free community can be created in India.

## ACKNOWLEDGEMENT

The authors are grateful to Dr. R.M. Dubey, Managing Director, IFTM for his constant encouragement, valuable insight and facilities at all stages of this work.

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#### ANNEXURE 1 (QUESTIONNAIRE)

1. Have you heard about TB?
2. What is the cause of TB?
3. Do you know different types of TB?
4. Is TB curable or not?
5. Whether TB can be transmitted to other family members from a person having TB?
6. Do you know about DOTS?

7. Do you know about MDR?

8. Do you know free treatment is being provided by Govt. in case of TB?

9. Can a lady with TB breast feed her baby?

10. Do you know about the mode of transmission of TB?

11. Do you know the symptoms of TB?

12. What is the effect of TB on body weight?

13. Is there any change in urine colour occurs during the treatment of TB?

14. Do you know about Mantoux test?

15. Have you ever heard or seen an X-ray of a TB patient?

# Evaluation of drug information services in a tertiary care hospital in kanchipuram district and community pharmacies in neighbouring areas

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## ABSTRACT

Submitted: 14/1/2011

Accepted: 19/4/2011

Drug information service refers to activities carried out by pharmacists in providing any drug related information to healthcare professionals to provide better patient care. The study was aimed to evaluate the drug information services provided by a drug information centre in a teaching hospital in Kanchipuram district and community pharmacies in neighbouring areas. A total of 158 queries were received which were retrospectively evaluated for a period of six months, from August 2010 to January 2011. Majority of the enquirers were the interns (44.3%) and physicians (25.9%), from the general medicine department (56.3%). Most of the questions were asked by direct access (86.7%). Answers to queries were most often needed immediately (48.1%) and in most cases was answered verbally (56.3%). Most frequently asked questions were about adverse drug reactions (30.3%) followed by dosage and indication (27.8%) and the purpose of the queries were for better patient care (44.9%) and to update knowledge (40.03%). The quality of drug information services provided was assessed both from the receivers' as well as from the providers' perspective using feedback questionnaires and guidelines from the DSE/WHO seminar respectively. Assessment of the feedback questionnaire indicated that majority of the enquirers (98.2%) found the quality of the service provided by the centre to be satisfactory. Evaluation of queries answered by the centre from the providers' perspective revealed that they were within the acceptable limits of quality. In conclusion, the services provided by the centre cater to the need of healthcare professionals towards better patient care.

**Keywords:** Drug information service, Drug information Centre, Pharmacist, Healthcare professionals.

## INTRODUCTION

Drug information service is the service rendered by pharmacists to provide accurate, unbiased, factual information on any aspect of drug use received from healthcare professionals.<sup>1</sup> The provision of drug information is one of the professional responsibilities of clinical pharmacists in healthcare system. As per the definition of Society of Hospital Pharmacists of Australia (SHPA), drug information is the provision of written and/or verbal information or advice about drugs and drug therapy in response to a request from other healthcare providers, organisations, committees, patients or members of the public. This may relate to specific patient or consist of general information promoting the safe and effective use of medications.<sup>2</sup>

In 1962, at the University of Kentucky Medical Centre, the first drug information centre was started which was intended to be utilized as a source of accurate, unbiased, selected,

comprehensive drug information to cater to the needs of the healthcare team.<sup>3</sup> In India, Rosemary Sharp, a missionary from UK, started the first drug information centre at Christian Medical College, Vellore in the early 1970s. This centre provides information on drugs to doctors, pharmacists, nurses and other personnel of various departments.<sup>4</sup>

Till the recent past, the drugs available were few in number and hence, the need for drug information was minimal. But now, the present situation has changed with new modes of treatment, tremendous information explosion and great number of drug products being available each year. Therefore, it is very important to procure accurate unbiased information. In India, irrational use of drugs is common and this has led to antibiotic resistance, adverse drug reactions, drug interactions and other drug related problems. Among the many factors that make clinicians unable to update their knowledge about drugs, lack of unbiased drug information, availability of more than 60,000 formulations and lack of time are few notable reasons which ultimately lead to an increasing demand for independent, specific and unbiased drug information for better patient care.<sup>5</sup> To maintain consistency in the service provided and for better functioning of the centre, it is important to evaluate the functioning and

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quality of the services provided by the centre at constant intervals<sup>6</sup>. Improper functioning of the drug information centre may contribute to poor patient outcomes in terms of health and economics due to provision of biased and limited drug information<sup>7</sup>. The present study was aimed at evaluating drug information services in a tertiary care hospital in Kanchipuram district and community pharmacies in neighbouring areas for a period of six months.

## MATERIALS AND METHOD

The study was conducted in SRM Medical College Hospital and Research Centre, which is a 750 bedded tertiary care hospital in Kanchipuram district, Tamil Nadu and community pharmacies in neighbouring areas. The study was approved by institutional ethical committee. The drug information centre is a part of the department of pharmacy practice in SRM College of Pharmacy, which was established in 2009 in the hospital. The centre is efficiently equipped with trained pharmacists and a library stocked with textbooks, national and international journals and other resources. It is also facilitated with computer and internet access along with electronic databases. The centre is managed by the faculty members and postgraduate students of the pharmacy practice department. A query box is placed outside the centre and other speciality departments of the hospital which can be availed at all times.

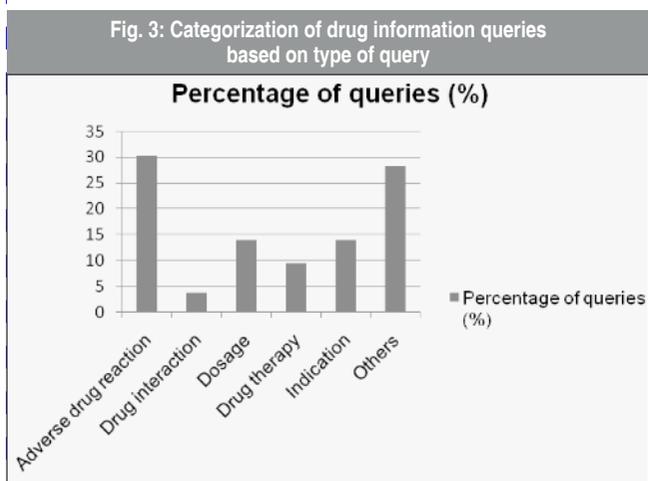
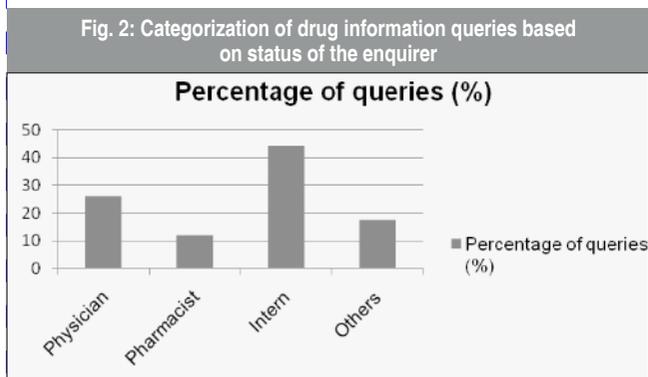
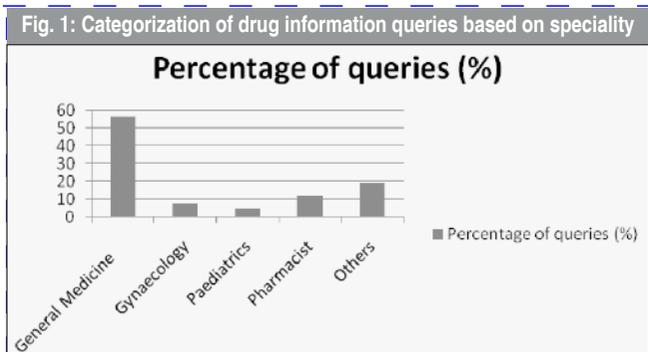
The drug information centre caters to the need of doctors, pharmacists, nurses and other healthcare professionals working in various departments of the hospital. The study also takes up voluntary requests from sources other than the hospital and community pharmacies. The services of the drug information centre can be accessed by direct access, telephone, email and during ward rounds. Evaluation of drug information queries received is undertaken and answers are formulated and provided according to the modified systematic approach. The drug information request and documentation forms prepared by the department are utilized to document the drug information requests and answers, which are then filed and maintained by the department. The first step in the evaluation of drug information services involved assessment of drug information request and documentation forms retrospectively for a period of six months, from August 2010 to January 2011, for various parameters such as status of the enquirer, speciality of practice, mode of receipt of query, category of question, purpose of enquiry, timeframe to reply and references used.

The second step involved assessment of the quality of services provided from the receivers' perspective on the basis of the feedback questionnaire circulated, which comprised of questions pertaining to awareness, utilization, ease of contact and quality of service provided by the centre. Suggestions from the requestors on the drug information centre were also solicited. The filled questionnaires were collected on the same day from individual respondents.

The third step involved assessment of quality and effectiveness of drug information services from the providers' perspective using guidelines developed in the DSE/WHO seminar.<sup>8</sup> According to these guidelines, the queries were categorised into judgemental and nonjudgemental types. The former type of queries require judgement, integration of new data with pre-existing knowledge and experience and extensive searching of secondary and tertiary references and a primary literature review. These types of queries are often patient specific. Nonjudgemental responses characterize a lower degree of complexity and do not require judgement. The aspects which were considered for evaluation included effectiveness in obtaining the demographic data of the enquirer and collecting background information, level of understanding of the question, using search strategy, evaluation of literature and the response given by the provider. From the total queries handled during the study period, a total of 30 queries of 15 each of the judgemental and nonjudgemental type were selected. Queries after evaluation were scored from 1-5, 5 indicating that the information given was excellent, 4 as very good, 3 as good, 2 as adequate and 1 indicating that the consultation was unacceptable for use. The minimum acceptable level of rating was considered to be 3.

## RESULTS

The drug information centre received a total of 158 drug information queries during the study period. More number of queries was from the general medicine department (56.3%). Queries were also obtained from various other departments such as gynaecology (7.5%), paediatrics (5.06%), ophthalmology (0.6%), nephrology (1.2%), dermatology (2.5%), cardiology (1.8%), respiratory medicine (5.06%), pharmacists (12.02%) and others (7.5%) as shown in Figure 1. Majority of the questions were asked by the interns (44.3%) and physicians (25.9%). Pharmacists (12.02%), postgraduate students (8.2%), nurses (5.6%), residents (0.6%) and others (3%) also availed this service as indicated in Figure 2. Most of the queries were received by direct access (86.7%). Queries were also received through telephone (10.7%) and during



ward rounds (2.5%). Answers to the queries were most often needed immediately (48.1%) and in most cases was answered verbally (56.3%). In other cases, answers were required either on the same day (8.8%), next day (27.8%) or within the week (15.2%). In such cases, the answers were provided in a printed format (43.6%). Reply was also provided via email on the request of the enquirer. Categories of questions most frequently asked were about adverse drug reactions (30.3%) and dosage and indication (27.8%). Queries were also asked about drug therapy, interactions, generic name, administration, availability, pharmacodynamics, pharmacokinetics, drug profile and others as shown in Figure 3.

**Table 1: Categorization of the drug information queries**

Categorization of Queries	Number of Queries	Percentage of Queries (%)
<b>Speciality</b>		
General Medicine	89	56.3
Gynaecology	12	7.5
Paediatrics	08	5.06
Pharmacist	19	12.02
Others	30	18.9
<b>Status of the enquirer</b>		
Physician	41	25.9
Pharmacist	19	12.02
Intern	70	44.3
Others	28	17.7
<b>Mode of request</b>		
Direct access	13	86.7
During ward rounds	04	2.5
Telephone	17	10.7
<b>Purpose of query</b>		
Better patient care	71	44.9
To update knowledge	68	43.03
Educational purpose	19	12.02
<b>Time frame to reply</b>		
Immediately	76	48.1
Same day	14	8.8
Next day	44	27.8
When time permits	24	15.1
<b>Mode of reply</b>		
Verbal	89	56.3
Printed	69	43.6
<b>Type of query</b>		
Adverse drug reaction	48	30.3
Drug interaction	06	3.7
Dosage	22	13.9
Drug therapy	15	9.4
Indication	22	13.9
Others	45	28.4
<b>References</b>		
Textbooks	60	37.9
Websites	58	36.7
Electronic database	25	15.8
Medline	10	6.3
Others	05	3.2

Questions were mostly asked for the purpose of providing better patient care (44.9%) and to update knowledge (43.03%). Questions for educational purpose (12.02%) were asked to a lesser extent. Textbooks (37.9%), websites (36.7%)

and electronic databases (15.8%) were the most commonly used resources for answering queries. Medline (6.3%) and other resources (3.2%) were used to answer queries to a lesser extent as shown in Table 1. A total of 141 questionnaires (Annexure1) were distributed to the enquirers of various departments of the hospital for their feedback, out of which, all 141 (100%) responded. For a question on the awareness about the drug information centre, 78% of them responded positively and 70% utilized the services of the centre at least few times. Among the respondents who utilized the services 98.2% received the appropriate answer within the stipulated time. Some of the suggestions put forward by the enquirers to improve the performance of the drug information centre were 24 hour drug information service and need for awareness program in hospital. Out of the total number of queries, 15 judgemental and 15 nonjudgemental queries were randomly selected for evaluation using quality assurance form. Evaluation of nonjudgemental queries revealed that 9 (60%) of the queries were rated as 5 which was the highest rating, 5 (33%) of the queries were rated as 4 and 1 (6%) query was rated as 3. Rating of judgemental queries showed that 8 (53%) queries were rated as 5, 5 (33%) queries were rated as 4 and 2 (13%) queries were rated as 3. The results showed better rating for nonjudgemental than judgemental queries. All the responses were rated above 3, thereby satisfying the minimum acceptable level of quality (Table 2).

## DISCUSSION

Among the 158 queries received by the drug information centre during the study period, a great percentage of the queries were from the general medicine department. This could be due to the utilization of vast number of drugs in the department that necessitates the need for specific unbiased and timely information. The service was utilised by interns and physicians to a greater extent compared to pharmacists, postgraduates, nurses and other healthcare professionals. Majority of the queries were asked for better patient care and hence required an immediate answer, leading to a great

number of queries being answered verbally, which was similar to the results of a study reported by Beena G *et al*<sup>9</sup>. Most of the queries were received by direct access, which could be accounted by the easy accessibility of the centre and its service. Results of a study by Venkatraghavan S *et al* showed that the drug information queries most commonly asked were related to adverse drug reactions and dosage/administration and drug therapy<sup>10</sup>. The present study also indicated similar results. For providing answers to the queries received, most commonly used resources were tertiary resources such as textbooks and websites followed by electronic databases. This might be because of ease of retrieval of information from textbooks and ease of use of computers and internet and availability of recent and relevant information from them. In the survey conducted among the healthcare professionals, a great percent of the respondents were aware of the drug information service and about seventy percent of them used it several times. Almost all of the enquirers received the appropriate answer within an acceptable time. A few suggestions put forward to improve the performance of the centre were provision of a 24 hour service and increasing the interaction of clinical pharmacists and other healthcare professions. Among the 15 nonjudgemental queries randomly selected, nine of them received a rating of 5, five of them a rating of 4 and 1 was rated 3. These types of queries required the highest level of sophistication and clinical judgement. Queries which were rated 4 and above indicated that the consultation was very good and trivial problems with documentation, comprehensiveness, timeliness or other essential problems existed. Responses rated less than 3 represented significant deficiencies with regard to documentation, comprehensiveness, timeliness or other important aspects. Among the 15 judgemental queries randomly selected, eight were rated 5, five rated as 4 and two were rated as 3. All the responses were rated above 3, thereby satisfying the minimum acceptable level of quality. Judgemental responses

Table 2: Qualitative assessment and evaluation of randomly selected drug information queries from the providers perspective

Rating	Judgemental (n=15)		Nonjudgemental (n=15)	
	Number	Percentage	Number	Percentage
Excellent (5)	8	53%	9	60%
Very good (4)	5	33%	5	33%
Good (3)	2	13%	2	6%
Adequate (2)	0	0	0	0
Unacceptable (1)	0	0	0	0



require extensive searching and clinical judgement compared to nonjudgemental queries, thus making the latter type of queries easier to answer effectively. The overall performance of the drug information centre was found to be good and this shows that the centre is maintaining the quality of service.

## CONCLUSION

Upon evaluation of the feedback questionnaires, it was found that the quality of the services provided by the centre was appreciated by majority of its users. However there is a need for greater awareness about the service in the hospital and encouragement to healthcare professionals to utilise the services for better patient care. On the whole, the study showed that drug information services provided by the department of pharmacy practice caters to the need of health care professionals towards rendering better patient care and in future more studies should be conducted to assess the improvement in the performance.

## ACKNOWLEDGEMENT

We thank Dr. K. S. Lakshmi, Dean, SRM College of Pharmacy and Dr. James Pandian, Dean, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, for providing necessary facilities to carry out this work.

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# Prescription pattern of antibiotic usage for urinary tract infection treated in a rural tertiary care hospital.

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## ABSTRACT

Submitted: 13/3/2011

Accepted: 19/4/2011

Urinary tract infections are the second most common infectious disease in the community medical practice. The objective was to study the prescription pattern of antibiotics used in the treatment of UTI. A prospective cross sectional study was conducted on patients diagnosed with UTI. The study was carried out in the General medicine, OBG, Surgery and Urology departments of both in-patients and out-patients, for a period of 9 months (June 2010 to Feb 2011). Urinary Tract Infection patients who were in the age group of 18-80 years were included after obtaining their informed consent. A suitable data collection form was prepared and used to collect the required data. Among 136 patients, 41 were in-patients and 95 were out-patients. Most of the in-patients were prescribed with Ceftriaxone 28(68.3%), Cefotaxim 5(12.2%), and Ciprofloxacin 3 (7.3%) respectively. In out-patients, Ciprofloxacin 27(28.4%), Norfloxacin 21(22.1%) and Nitrofurantoin 18(18.9%) were prescribed respectively. The study found that gram negative organisms like E. coli was the most predominant organism. It was also found that Cephalosporins were most commonly used and Quinolones were the second most commonly used drugs for the treatment of UTI. The third category drug used in UTI female patients was nitrofurantoin which is relatively inexpensive and safe for both pregnant and non-pregnant women.

**Keywords:** Urinary tract infection, Antibiotics, Prescription.

## INTRODUCTION

Urinary tract infection (UTI) is also defined as the presence of micro-organisms in the urine that cannot be accounted by contamination. The organisms have the potential to invade the tissues of the urinary tract and adjacent structures.<sup>1</sup>

Urinary tract infection is an extremely common condition that occurs in both male and female of all the ages. The prevalence and incidence of UTI is higher in women than in men, due to several clinical factors including anatomic differences, hormonal effects and behavioral patterns.<sup>2</sup> A foreign body in the urinary system may act as a nidus for infection and may be associated with recurrent infections which may be due to calculi and indwelling catheters. Post – menopausal women are at higher risk for UTI than younger women, because they lack estrogen, which is essential to maintain the normal acidity of vaginal fluid. E-coli accounts for approx 85% of community acquired urinary tract infections and 50% of hospital acquired UTIs. Non-bacterial infections are less

common and tend to occur more often in immunosuppressed individuals or those with Diabetes Mellitus.<sup>2</sup>

Urinary tract infection in pregnancy may result in low birth weight infants, premature delivery and occasionally stillbirth. It is well documented that effective treatment of UTI's significantly reduces the incidence of pyelonephritis, premature deliveries and low birth weight infants.

The practice of prescribing antibacterial drugs for pregnant Urinary Tract Infection patients varies in different countries. Apart from economic factors, the problem of selecting an antibacterial agent for treatment of UTI in pregnancy is the possible confusion between a well established and well tolerated drug and empirically known to be harmless to the fetus, and also a drug to which there is a low level of bacterial resistance.

The general drugs prescribed for uncomplicated urinary tract infections are trimethoprim, nitrofurantoin and norfloxacin, ciprofloxacin and cotrimoxazole for Nitrofurantoin is the commonly used drug to treat UTIs in pregnancy.<sup>3</sup>

Prescribing drugs is an important skill which needs to be continuously assessed and refined accordingly. Commonly, the prescription behavior is influenced by many factors like

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unethical drug promotion, lack of knowledge, direct consumer advertising and non-availability of drugs. So there is a chance of prescribing irrational drugs.

The assessment of the prescription will help to know the attitude of the physicians towards their prescribing, their therapeutic knowledge upgrading need/requirement and to ensure rationality in the prescription. The rationality of the prescriptions will help the physician in selecting the most appropriate cost effective treatment.<sup>4</sup>

No similar study has been conducted in this set-up previously. The antibiotic usage study in UTI, data will help in establishing a proper antibiotic utilisation guideline and promotes the rational prescribing of medicines. Hence, the present study was taken up to study the prescription pattern of antibiotics usage for urinary tract infection patients at rural tertiary care hospital.

## MATERIAL AND METHOD

This was a prospective cross sectional study conducted in the General medicine, OBG, Surgery and Urology departments of Adichunchanagiri Hospital and Research Centre; B.G. Nagara, for a period of 9 months (June 2010-Feb 2011).

Ethical committee clearance was obtained on 22/6/2010 (Ref: AIMS/EC/601/2010-11) from Adichunchanagiri Hospital and Research Centre.

### Study criteria:

#### 1. Inclusion Criteria

Urinary tract infection patients (i.e. both recently diagnosed and recurrent UTI patients) treated with antibiotics in the age group of 18 to 80 years.

#### 2. Exclusion Criteria:

Patients visiting departments other than OBG, General Medicine, Surgery and Urology and below 18 years of age. Because most of the UTI cases were observed only in the said departments and there is a good cooperation/encouragement of health care professionals. Very few/rarely, the UTI cases were observed in the pediatric population.

### Sources of data:

- Patient case sheet, medication chart and lab reports.
- Patient interview.

### Study procedure:

Prescriptions of out-patients and the treatment charts of in-patients were reviewed for the treatment of the UTI in

different departments. Patient consent was obtained before collecting the required data.

### Determination of Prescription Pattern:

Patients diagnosed with UTI were interviewed to collect the socio-demographics and therapeutic data such as drugs prescribed, doses, route of administration, duration and other laboratory data were obtained by reviewing treatment charts and prescriptions. The follow-up of the patients was done everyday for in-patients and weekly once for out-patients. The changes in the prescribing drugs or their doses or duration were also documented. The drug-drug interactions were identified by using the MICROMEDEX software and also using the tertiary sources available in the library. Drug interactions were classified based on the severity and onset. Safety of antibiotics in pregnancy was assessed by using the tertiary sources such as Drugs in Pregnancy and Lactation and Lexi Company's Drug Information Hand Book. The category of the antibiotic and possible side effects due to the drug to both mother and the fetus were checked from the available sources.

**Statistical methods:** Descriptive statistical analysis has been carried out in the present study.

## RESULTS

A total of 600 prescriptions were screened for UTI patients, in the outpatient department of OBG, General Medicine, Surgery and Urology departments, in which 95 UTI prescriptions were found and showed an antibiotic for its treatment. For in-patients nearly 226 case records have been reviewed, out of which 41 UTI case records have been identified and which was prescribed with antibiotics for treatment. Among in-patients, male were 25 and female were 16. In out-patients, male were 14 and female were 81.

Out of 136 patients, female patients were 97(71.3%) and male were 39(28.7%) respectively. Table.1 shows the incidence of UTI in male was more in patients with age group of 61-70 years 12 (30.8%) and least in age group of 51-60 (10.3%) & 71-80 (10.3%). There was no incidence of UTI in the age group of 18- 20 year in male patients. Out of 97 female patients, majority of the patients 31(31.9%) belongs to the age group of 21-30 years and least observed in the age group of 71-80 years i.e. 1(1.0%). The mean age distribution of the study population is  $41.65 \pm 16.87$ .

The incidence of UTI cases admitted/referred to the OBG department were about 54.4% and 4.4% of cases to surgery department as shown in Table 2.

In our study, most of the in-patients were prescribed with empirical therapy with Ceftriaxone 28(68.3%) and drugs like Norfloxacin, Amikacin and Cefixime were prescribed to one patient each respectively. Drugs like Nitrofurantoin and Cephalexin were not prescribed to the in-patients, Ciprofloxacin is the most common drug prescribed among out-patients 27(28.4%). Female patients were more symptomatic (63.9%) compared to male(46.2%) with a P value =0.057+ . This was observed due to their hormonal changes and also due to their structural and anatomical difference. Culture sensitivity positive report was statistically similar in male 3(2.2%) and in female i.e. 9(9.3%) (P value=0.768).

Positive culture sensitivity reports of female UTI patients 6(6.2%) showed E.coli as a highest incidence of occurrence, where as other organisms like Citrobacter, Streptococcus and Proteus were found in 3 female patients respectively. Among 2 male positive culture sensitivity reports one presented with Citrobacter and the other with E.coli. In the remaining 124(91.2%) patients, culture sensitivity test was not performed, which shows that treatment was given empirically. Incidence of UTI recurrence was significantly more associated with male patients 33.3% compared to female 14.4% (P Value=0.012\*). Incidence of recurrence is strongly significant in in-patients (p=0.007\*\*) as shown in the Table 3. One of the physical parameter observance/incidence like, urine appearance showed more turbidity in male 20(51.3%) than female 26(26.8%).

From among the study population of 136 patients, 5 drug-drug interactions were found, out of which 3 were moderately severe and the onset was rapid. Two interactions were found with major severity but the onset was unspecified, which is shown in Table 4 and 5. The overall rate of incidence of drug interaction was found to be 3.674%.

In pregnancy, the most commonly prescribed drug in first trimester was Nitrofurantoin (7) and the least was Trimethoprim(1). During the second trimester, Nitrofurantoin was prescribed in 3 patients and Ampicillin in 1 patient. During the third trimester, Cefixime and Cephalexin were prescribed in 4 patients respectively as represented in Table 6.

Ceftriaxone was most widely preferred drug to treat 28(68.3%) in-patients. Only 1(2.4%) patient was administered with Amikacin through IV route. Drugs such as Cefixime (1), Cefotaxime (2) and Amoxicillin (2) were also given to in-patients. The mean duration of treatment for in-patients was 6.32 days. Maximum number out-patients 26

were prescribed with Ciprofloxacin, followed by Norfloxacin in 21 patients, Nitrofurantoin to 18 patients. Mean duration of treatment for out-patients was 6.80 days as shown in Table 7.

## DISCUSSION

The study of prescribing pattern is a component of medical audit, which seeks monitoring, evaluation in the prescribing practices of prescribers to achieve rational and cost effective medical care. It is necessary to define prescribing pattern and to identify irrational prescribing habits to drive a remedial message to the prescribers.

Our study showed that, majority of UTI patients were female mainly due to the structural and anatomical differences like shorter urethra. The same observations were made by several resources like Tomas.L, Greibling studies, and text books of pharmacotherapeutics by Herfindal and Roger walker.<sup>2, 5, 6</sup> The present study was conducted in the age group of 18 – 80 years. The mean age of male was found to be  $52.10 \pm 17.41$  and in female was  $37.44 \pm 14.77$ . The mean age of the total study population was  $41.65 \pm 16.87$ . Majority of female patients 31(31.9%) showed the incidence of UTI at the age group of 21-30 years, which is the child bearing age as well as sexually active period. During the post-menopausal period, most of the women shows the chances of UTI and its symptoms, this is also observed in our study. Twenty five (25.8%) female patients in the age group of 41-50 years were presented with UTI, similar results were observed and reported by William Bakey.<sup>7</sup>

The present study included 136 as the total number of patients, out of which 41 were inpatients and 95 were outpatients. Maximum of the females visited OBG department 74(76.2%) and minimum to surgery department 1(1.0%). Males 24(61.5%) mostly visited to the department of general medicine and least number of males 5(12.8%) visited to the department of surgery. Ten males (25.6%) visited urology department whereas females were only 5 (5.1%). Female UTI patients who visited the OBG department were more because of female patients generally prefer to check/diagnose with the same gender, for exchange of information freely and more availability of female doctors. Some female patients who visited this department for UTI complications, their final diagnosis report confirmed that either they were pregnant or diabetic along with UTI.

Among 39 male patients 21 (53.8%) were asymptomatic and 18(46.2%) were symptomatic. Among 97 female patients, 62(63.9%) were symptomatic and the remaining 35(36.1%) were asymptomatic with a suggestive significant value.

Table 1: Age wise distribution of the patients

Age in years	Male		Female		Total	
	N	%	N	%	N	%
18-20	0	0.0	10	10.3	10	7.4
21-30	6	15.4	31	31.9	37	27.2
31-40	5	12.8	13	13.4	18	13.2
41-50	8	20.5	25	25.8	33	24.3
51-60	4	10.3	9	9.3	13	9.5
61-70	12	30.8	8	8.2	20	14.7
71-80	4	10.3	1	1.0	5	3.7
Total	39	100.0	97	100.0	136	100.0
Mean $\pm$ SD	52.10 $\pm$ 17.41		37.44 $\pm$ 14.77		41.65 $\pm$ 16.87	

Table 2: Distribution of patients based on the department wise

Department	Male		Female		Total	
	N	%	N	%	N	%
Medicine	24	61.5	17	17.5	41	30.1
OBG	0	0.0	74	76.2	74	54.4
Surgery	5	12.8	1	1.0	6	4.4
Urology	10	25.6	5	5.1	15	11.0
Total	39	100.0	97	100.0	136	100.0

OBG: Obstetrics and Gynecology, N: Total number of patients.

Table 3: Incidence of Recurrence

Incidence of recurrence	IP		OP		Total	
	N	%	N	%	N	%
Observed	15	36.6	15	15.8	30	22.1
Not Observed	26	63.4	80	84.2	106	77.9
Total	41	100.0	95	100.0	136	100.0
Inference	Incidence of recurrence is significantly associated with Inpatients with a P Value=0.007**					

IP-Inpatients; OP- Outpatients; N- Total number of Patients.

Table 4: Evaluation of Drug - Drug interactions based on severity

Index drug	Interacting Drug	Interacting effect	Severity		
			Major	Moderate	Minor
Ciprofloxacin	Diclofenac	Increased ciprofloxacin plasma concentrations	-	Yes	-
Ciprofloxacin	Diclofenac	Increased ciprofloxacin plasma concentrations	-	Yes	-
Ciprofloxacin	Glimipride	Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia	Yes	-	-
Norfloxacin	Iron	Decreased norfloxacin effectiveness	-	Yes	-
Levofloxacin	Insulin	Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia	Yes	-	-

Table 5: Evaluation of Drug - Drug interactions based on onset

Index drug	Interacting drug	Onset		
		Rapid	Delayed	Unspecified
Ciprofloxacin	Diclofenac	-	-	Yes
Ciprofloxacin	Diclofenac	-	-	Yes
Ciprofloxacin	Glimipride	Yes	-	-
Norfloxacin	Iron	Yes	-	-
Levofloxacin	Insulin	Yes	-	-

Table 6: Assessment of antibiotic safety in pregnancy

Drugs	Pregnant			Category
	1 <sup>st</sup> trimester N	2 <sup>nd</sup> trimester N	3 <sup>rd</sup> trimester N	
Nitrofurantoin	7	3	0	B
Cefixime	0	2	4	B
Cephalexin	1	0	4	B
Ampicillin	0	1	0	B
Trimethoprim	1	0	0	B
Total	9	6	8	

N – Number of patients

Table 7: Comparison of antibiotic use between inpatients and outpatients

Prescribing pattern of antibiotics	IP					OP				
	N	%	Duration	Oral	IV	N	%	Duration	Oral	IV
Ceftriaxone	28	68.3	5.39	0	28	2	2.1	7.00	2	0
Ciprofloxacin	3	7.3	6.50	0	3	27	28.4	6.35	26	0
Norfloxacin	1	2.4	8.00	0	1	21	22.1	7.29	21	0
Nitrofurantoin	0	0.0	-	0	0	18	18.9	6.44	18	0
Cefixime	1	2.4	3.00	1	0	9	9.5	4.56	9	0
Cefotaxim	5	12.2	10.40	2	3	2	2.1	18.50	2	0
Cephalexin	0	0.0	-	0	0	7	7.4	5.29	7	0
Amoxicillin	2	4.8	7.00	2	0	5	5.3	7.17	6	0
Amikacin	1	2.4	12.00	0	1	3	3.2	11.67	3	0
Others	0	0.0	-	0	0	1	1.1	5.00	1	0
Total	41	100.0	6.32	5	36	95	100.0	6.80	95	0

IP: Inpatient, OP: Outpatient, N: Total number of patients, IV: Intravenous.

Symptomatic UTIs can occur essentially in all age groups of the population but are most prevalent in females. The same observations were identified in the epidemiology of urinary tract infection.<sup>5</sup>

Among 136 patients, culture sensitivity test was performed only for 12(8.8%) out of which 3(2.2%) were male and 9(9.3%) were female. Culture sensitivity tests were not performed in 124(91.2%) patients because of non-affordability or financial/socio-economic issues of the rural patients. The results of culture sensitivity in 12 patients showed presence of Citrobacter species 2(1.5%) of male and

1(1.0%) in female. The highest incidence of micro organism was E.Coli found in 6(6.2) females and 1(0.7%) male. In our study we found that 2 elderly Benign prostrate hyperplasia male's urine sample culture sensitivity tests showed Citrobacter species for symptoms of UTI. Similar observations were found in other case reports.<sup>11</sup> Proteus and Streptococcus organisms were found in 1(1.0%) female patient each. The study also found that E. coli was the most predominant organism. This finding is in concordance with the other study<sup>9,12,13</sup> The incidence of recurrence is associated more in male 13(33.3%) than female 14(14.4%) because of

their associated disease conditions like Hypertension, Chronic Kidney disease and Diabetes.

The prescribing pattern of antibiotics usage study in in-patients and out-patients showed 10 types of antibiotics prescribed. Ceftriaxone was prescribed to in-patients 28(68.3%), whereas it was prescribed for 2(2.1%) out-patients. Ciprofloxacin prescribed in in-patients was 3(7.3%) and out-patients was 27 (28.4%). Norfloxacin was prescribed to 1(2.4%) in in-patients and 21(22.1%) out-patients. Nitrofurantoin was prescribed to 18(18.9%) out-patients. Cefixime was prescribed in 1 in-patient (2.4%) and 9(9.5%) out-patients. Cefotaxim was prescribed to 5(12.2%) of in-patients and 2(2.1%) of out-patients. Seven out-patients were prescribed with Cephalexin at the rate of 7.4%. Among the total of seven Amoxicillin prescriptions 2(4.8%) belongs to in-patients and the rest of 5(5.3%) were given to out-patients. Four Amikacin prescriptions were present, 1(2.4%) for in-patients and 3(3.2%) for out-patients. Only one out-patient was prescribed with drug of other category at the rate of 1.1%.

Cephalosporin's and Fluoroquinolones was the most commonly used antibiotics in the hospital practice for the treatment of UTI.<sup>8,9</sup> Fluoroquinolones remains the choice among the orally administered antibiotics, followed by second and third generation Cephalosporin's. The prescribing pattern of antibiotics for the treatment of UTI in our hospital, showed that Cephalosporin's 54 (55.6%) and Quinolones 52(47.1%) was most commonly prescribed antibiotics. Similar findings were observed in the studies conducted by Mathi E etal and Joe etal and Kallen etal.<sup>8,9,10</sup>

The commonly occurring drug interactions were found with fluoroquinolone antibiotics so monitoring of such prescription by the pharmacist will helped in avoiding of further problems by using suitable strategies.

Our study also found the antibiotics safety in pregnancy UTI. This showed that nitrofurantoin is safe and efficacious in I and II trimester. This drug is not recommended in the third trimester due to haemolytic effects. The safe use of antibiotics was observed with cephalosporins like cefixime and cephelexine in the third trimester. Similar study supported by Cimoli and Kay sam.<sup>14,15</sup>

The inappropriate selection and use of antibiotic not only causes resistance but also causes more harm thus leading to recurrence of the UTI. Concerns about increased resistance have contributed to greater use of fluoroquinolones, but widespread empiric use of this class of medications might promote resistance to fluoroquinolones. Hence,

fluoroquinolones should not be considered as first-line therapy. While guidelines for treatment of UTIs have been developed, their usefulness is compromised by their conflicting recommendations.<sup>16</sup> This is also seen in 4 year descriptive study by Laura G Aurelio S.<sup>16,17</sup>

The main limitation of this study was, short duration and less number of pregnant UTI patients enrolment.

Our study showed a few potential directions for future research are establishing of antibiotic guidelines for UTI, prescribing pattern study in Pregnant UTI in large samples and antibiotic resistance studies.

## CONCLUSION

Complications from inadequately treated UTIs contribute to increased patient morbidity, increased health care costs, and increased drug resistance. The study found that E. coli was the most predominant organism. It was also found that Cephalosporin's were most commonly used and Quinolones were the second most commonly used drugs, for the treatment of UTI. Nitrofurantoin, a relatively inexpensive and safe drug for the treatment of UTI was used in both pregnant and non pregnant patients. Widespread empirical use of Fluoroquinolones also might promote microbial resistance to Fluoroquinolone group of drugs. Hence, Fluoroquinolones should not be considered as first-line therapy. Our findings indicate an urgent need for the establishment of proper guidelines, dissemination of information to practitioners and supervision of antibiotic usage in low income countries like India.

## ACKNOWLEDGEMENT

My sincere pranas to Sri Sri Sri Dr.Balagangadharanatha Swamiji and SAC Shikshana trust. I would like to thank Dr.B.Ramesh, Principal, SACCPC, Dr. Mohan, Ex Principal, AIMS, Dr.Sriram Principal, AIMS and staffs of clinical pharmacy department for their timely support and suggestions at all stages of this work.

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# Drug prescribing pattern among paediatricians in an out-patient department of tertiary care teaching hospital

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## ABSTRACT

Submitted: 17/1/2011

Accepted: 16/5/2011

Children are more vulnerable to various adverse events related to drugs and the poor understanding of instructions on prescription by the patient or caretakers were likely to cause medication error and less effective treatment. To compare the drug prescribing patterns of pediatricians in an outpatient department and to assess the understanding of instructions on prescription by the patients or caretakers after consultation with physicians. A prospective cross-sectional study was conducted for a period of six months. 863 prescriptions written by the consultants (Professor/Asst. Professor/Post Graduate trainee) were collected and analyzed for the patterns and the patients were subjected to analysis for their understanding of instructions on prescription provided by the consultants by using a semi-scientific scale. Out of 863 prescriptions 76 were written by Professors, 229 by Asst. professors, 558 by Postgraduate trainees. On an average each consultant (professor/Asst.professor/post graduate trainee) prescribed 2.07 (Mean±SD 2.07±0.9) drugs per prescription suggesting there were no discernible difference between the prescribing behaviors of physicians in the pediatric unit. Patients or caretakers understanding of instructions on prescription provided by the consultants were ranged from 23.9% for the well understood, 58% for the moderately understood, 18.1% for the poorly understood. The study provides important insights in to the drug use patterns of pediatricians and helped to identify significant problem involved in knowledge gap of patients or caretakers understanding of instructions on prescription provided by the consultants.

**Keywords:** Prescribing pattern, pediatricians, Prescription instruction, Drug utilization.

## INTRODUCTION

Prescribing practices are a reflection of health professional's abilities to discriminate among the various choices of drugs and determine the ones that will most benefit their patients.<sup>1</sup> The study of prescribing patterns is a part of the medical audit and seeks to monitor, evaluate and if necessary, suggest modifications in prescribing practices to make medical care rational and cost effective.<sup>2</sup> Appropriate drug utilization studies are important tools to evaluate whether drugs are properly utilized in terms of efficacy, safety, convenience and economic aspects at all levels in the chain of drug use.<sup>3</sup> Regardless of considerable improvements in the availability and control of drugs in the hospitals, rational drug use is still a worldwide concern.<sup>4</sup> The measurement of these interventions is an integral part of the program such as drug utilization review studies and drug utilization review programs. Drug utilization review studies are usually one time project, not

routinely conducted. They provide for only minimal feedback to the involved prescriber and, most importantly, do not include any follow up measures to ascertain whether any changes in drug therapy have occurred whereas drug utilization review program is an intervention in the form of an authorized, structured and ongoing system for improving the quality of drug use within a given health care institution.

Children constitute about 40% of India's population. Infants and children suffer from frequent but usually non-serious illness. Most of these are self-limiting<sup>5</sup>, and are treated not only inappropriately, but also reporting to polypharmacy.<sup>6</sup> Compared to adult medicines, drug use in pediatrics is not extensively researched and the range of licensed drug in appropriate dosage form is limited.<sup>7</sup> Prescribers and consumers are flooded with a vast array of pharmaceutical preparations with innumerable trade names, available often at an unaffordable price.

Physicians may assume that prescription instructions are well understood by the patients. Davis et al (2008) says that, four out of five patients (79%) in his study misinterpreted one or more of the ten common prescription label instructions they

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encountered.<sup>8</sup> Although the instructions were brief and of minimal reading difficulty, Rate of patient or caretakers understanding varied widely particularly in case of pediatric population.

Epidemiological evaluation of medicine use in the elderly is now a highly visible topic, but drug utilization studies in pediatric population have been limited. The assessment of medicine utilization is important for clinical, educational, and economic purpose<sup>9</sup>, so the ultimate goal is to achieve rational and cost effective medical care, particularly in the economically developing countries.

**METHODOLOGY**

**Place of study:** The study was conducted in the outpatient department of pediatrics of Sri Ramachandra medical centre, a tertiary care teaching hospital, Chennai,

**Period of study:** six months.

**Type of study:** Prospective cross-sectional study.

**Study population:**

863 prescriptions written by the consultants (Professor/Asst.professor/Post graduate trainee/) of outpatient department of Pediatrics.

**Study procedure:**

A patient data collection form was specially designed for the study which includes patients demographic details, physician details (Professor/Asst.professor/Postgraduate trainee), drug details and Patients/Caretakers understanding of their Drug use parameters: Indication, Dose, Frequency, to be taken Before/After food, Duration, Awareness of side effects after consultation with physician was recorded. In a Pediatric OPD there were 4 units, each unit contains 6 physicians which include (Professor/Asst.professor/Postgraduate trainee). The prescriptions written by them were collected and a copy of the original prescription was used for data collection.

As the study was conducted in a tertiary care teaching hospital, all the patients who attended the Pediatric OPD were first reviewed by post graduate trainees and if required they sent the patient to the Assistant Professor and Professor Level.

The patients who were not willing to participate in the study were excluded and the data collected from 863 prescriptions were analyzed for the following indicators:

- Common Pediatric problems.
- Prescribing pattern among physicians.

(Professor/Asst.Professor/Post Graduate Trainee).

- Average number of Drugs per prescription.
- Medicines prescribed by Brand/Generic names.
- Antibiotic usage.
- Dose appropriateness based on body weight.
- Patients/Caretakers understanding of their Drug use (Indication, Dose, Frequency, Duration, to be taken Before/After Food, and Awareness of side effects).
- Average cost per prescription.
- Interactions (D-D, D-F, D-Disease).

The prescriptions were subjected to analysis by measuring the indicators mentioned above. The Patients/Caretakers understanding of their drug use were measured by using grading scale.<sup>10</sup> It is a semi scientific scale, evolved by us to asses whether patients/caretakers understood the instructions given by the physician at the end of the consultation. For measuring the scale, the following parameters were used to asses their adequacy and inadequacy. (Indication of the drug (for what), Dose, Frequency, to be taken Before/After food, Duration and Awareness of side effects). Patients/caretakers adequacy of each parameter was given a score of 1 and score of 0 for inadequacy. Based on these six parameters and criteria, each patient could have a score of minimum “0” to a maximum of “6”. After assigning a score to each parameter, the sum of scores obtained by the patient was considered as a grade for their adequacy in understanding the instructions given by the physician. The scores obtained by the patients/Caretakers were rated as follows.

**RESULTS**

Out of 863 patients 54.9% were Males and 45.1% were Females with age ranging from 1 month to 16 years. In the study, the 76 prescriptions issued by professors of pediatrics had a mean of 2.1 (9.2%) drugs per prescription, whereas the 229 prescriptions issued by the Asst.professor had 2.1 (27.9%) drugs per prescription and for PG's 2.0 (62.9%) drugs per prescriptions out of 558 prescriptions (p=0.075) (Table 1).

SCORE	RATING
>3	well understood
3	Moderately understood
<3	Poorly understood

The results were analyzed and tabulated statistically.

On an average 2.07 (Mean±SD of 2.07±0.9) drugs were prescribed per prescription. Only 377 (21.1%) out of 1788 drugs were found to be prescribed in generic names. Paracetamol, Albendazole, Amoxicillin were the most common drugs prescribed by their generic name (Table 2). Of 1788 drugs prescribed 226 (12.6%) drugs were found to be Antibiotics (Table 3). Among the Antibiotics, the Penicillin group (39%) was most commonly prescribed followed by Macrolide (30.1%) and Cephalosporin (11%). 60.4% of Medicines were prescribed as syrup/suspension/oral drops/liquids/nasal drops and 32% was prescribed as Tablets/capsules. All other dosage forms comprised about 7.6% (Table 4). The traditional cough suppressants and medicines against the common cold are the drugs most commonly given as syrups. Only 6 patients received benzathine penicillin injection for treating rheumatic fever. No other patients received any injections. The diagnostic patterns of outpatients enrolled in the study shows that upper respiratory tract illness was the most common problem affecting 364 patients (42.2%) in this study which was followed by others. In dose appropriate status 94.8% of prescriptions were found to have appropriate dose whereas, only 5.2% of prescriptions were found with in-appropriate doses. The average cost per prescription was found to be Rs.66.84. As the average number of drugs in each prescription

was only 2.07 and no major interactions were found.

Although the instructions were brief, Rate of patient understanding varied widely. In this study 58% of patients/caretakers were found to have moderately understood, whereas, 23.9% were found to have well understood and 18.1% were found to have poorly understood (Table 5).

## DISCUSSION

The type and volume of drugs prescribed and the prescribing pattern of the individual physician have provided useful information for effective therapy. The focus of this study was to review Prescription orders for drug use evaluation by a clinical pharmacist. As this study was conducted in a tertiary care teaching hospital, the majority of prescriptions were written by postgraduate students who are in a formative period of training. However this increases the responsibility of senior physicians/professors in providing the right kind of training inputs that make way for rational prescribing. The result of this study (2.07 drugs per prescription) conformed to WHO prescribing standards recommending a limit of 2.0<sup>(11)</sup> drugs per prescription. Prescribing by generic names is known to reduce the cost of drug treatment, rationalize drug therapy, avoids confusion. Despite this clinicians often prefer to prescribe by brand name, with which they are confident,

Table: 1 Number of Drugs/Prescription by Physicians (Professor/Asst.Professor/Postgraduate Trainee)

No. Of Drugs	Professor (n=76)	Asst.Prof (n=229)	PG (n=558)	Total (n=863)
1 Drug	16 (21.1%)	44 (19.2%)	164 (29.4%)	224 (25.9%)
2 Drugs	39 (51.3%)	114 (49.8%)	260 (46.4%)	413 (47.9%)
3 Drugs	17 (22.4%)	58 (25.3%)	97 (17.4%)	172 (19.9%)
4 Drugs	3 (3.9%)	11 (4.8%)	35 (6.3%)	49 (5.7%)
5 Drugs	1 (1.3%)	2 (0.9%)	2 (0.3%)	5 (0.6%)
Total (n)	76	229	558	863
P value	0.075 Not Significant (chi-square test)			

Table: 1 Number of Drugs/Prescription by Physicians (Professor/Asst.Professor/Postgraduate Trainee)

Physician	Total No. of Drugs (n=1788)	No. of Drugs by Generic Names	No. of Drugs by Brand Names
PROFESSOR	162(9.2%)	37(22.8%)	125(77.2%)
ASST.PROF	500(27.9%)	103(20.6%)	397(79.4%)
PG	1126(62.9%)	237(21.1%)	889(78.9%)
TOTAL	1788	377(21.1%)	1411(78.9%)
P value	0.077		0.324
Not Significant (chi-square test)			

Table 3: Antibiotics Used

Class of Antibiotic	No. of Drugs (n=226)	P Value
Penicillin Group	88 (39%)	0.000 Significant (chi-square Test)
Cephalosporin Group	24 (11%)	
Fluroquinolone	23 (10.2%)	
Macrolide	69 (30.1%)	
Others	22 (9.7%)	
Total	226 (12.6%)	

OTHERS: Sulphonamides, urinary antiseptic, amino glycosides, Oxzolidinediones.

Table 4: Various Dosage Forms Used in Each age Group

Formulations	Age (yrs)					Total (n=1778)
	≤ 1	> 1 - ≤ 4	>4 - ≤ 8	>8 - ≤ 12	>12 - ≤ 16	
Oral Drop	93	21	0	0	0	114(6.4%)
Suspension	25	104	46	2	1	178(9.9%)
Syrup	79	262	135	67	21	564(31.6%)
Nasal Drop	72	47	12	6	3	140(7.8%)
Liquid	11	19	26	16	11	83(4.7%)
Tablet	2	41	122	200	165	530(29.7%)
Capsule	0	1	10	13	18	42(2.3%)
Others	43	49	13	19	13	137(7.6%)

OTHERS: Ointments, Suppositories, Cream, Lotion, Respiratory solution for nebulisation.

Table 5: Patients/caretakers Understanding of Instructions on Prescription Provided by the Consultants

Physician	No. of Prescriptions (n=863)	Well Understood	Moderately Understood	Poorly Understood
Professor	76	13 (17.1%)	50 (65.8%)	13(17.1%)
Asst. Prof	229	60 (26.2%)	134 (58.5%)	35(15.3%)
PG	558	133 (23.8%)	317(56.8%)	108(19.4%)
Total	863	206 (23.9%)	501(58.0%)	156(18.1%)
P value	0.348 Not Significant (chi-square test)			

familiar and the patients find them easier to procure. Children, differ from adults in their response to drugs. So, special care is needed in children and doses should always be calculated with care. Hence, it is important to monitor the appropriateness of doses in children. Considering the fact that the study was conducted in a tertiary care teaching institution, a high proportion of appropriateness is only to be expected.

The interactions are generally more in patients who received more number of medications.<sup>12</sup> As the study contains the average number of drugs in each prescription with 2.07 and reduces the possibilities for major interactions. Physicians may assume that prescription instructions are well understood by the patients. Davis et al (2008) says that, four out of five patients (79%) in his study misinterpreted one or more of the

ten common prescription label instructions they encountered.<sup>8</sup> Although the instructions were brief, Rate of patient understanding varied widely. There was a significant knowledge gap in patient understanding of drug use. Therefore explicit instructions to patients on “when to take” the medicines using time periods (e.g. 8 am, 5 pm) may be better understood compared to instructions that more vaguely state the number of times per day or hourly intervals. All attempts to enhance quality of prescribing by a clinical pharmacist should be encouraged and also education of patients / caretakers remains crucial.

## CONCLUSION

This study provides important insights in to the Drug use patterns in the pediatric out Patient department of a Tertiary

care Teaching Hospital. It has helped to identify significant problems involved in knowledge gap of patients or caretakers understanding of instructions on prescription provided by the consultants. Hence the clinical pharmacist must be considered to be an integral part of the multidisciplinary healthcare team. They should be involved in collection and presentation of prescribing data as part of clinical audit and also education of patients / caretakers.

#### ACKNOWLEDGEMENTS

The authors duly acknowledge the contribution and help of patients and physicians of pediatric department without whom the study would not be possible.

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# Antimicrobial resistance pattern of cephalosporins in treatment of diabetic foot infection

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## ABSTRACT

Submitted: 17/1/2011

Accepted: 16/5/2011

Diabetes mellitus is a chronic disorder and affects large segment of population and is a major public health problem. Diabetic foot problems, such as ulcerations, infections and gangrene are the most common cause of hospitalization among diabetic patients. Although widely accepted as broad-spectrum antibiotics, cephalosporins are not active against all the bacteria commonly isolated in a hospital microbiological laboratory. Increasing prevalence of anti-microbial resistance is a major factor determining morbidity and mortality. The objective of the study is to study prescribing practice of cephalosporins, evaluate the sensitivity pattern of different generations of cephalosporins and to assess the treatment failure of cephalosporins in diabetic foot infections. A prospective study was done on 77 patients who fulfilled the inclusion criteria and had diabetic foot were included; prescribing pattern of cephalosporins and culture and sensitivity testing was studied for a period of 9 months. Retrospectively culture and sensitivity reports of 230 patients from last one year were screened. Cefotaxime was the most commonly prescribed antibiotic. Sensitivity pattern showed that 41.5% of gram-positive cocci were sensitive to cefotaxime, whereas 25% of gram-negative bacilli were sensitive. Gram-positive cocci were 29.3% resistant to Cefotaxime, whereas 57.1% of gram-negative bacilli were also resistant. Finally, organisms which were originally sensitive developed resistance approximately in a span of two weeks, probably due to antibiotic pressure. Treatment for longer duration may result in drug resistance. Finally, cefotaxime remains an active player in the treatment of diabetic foot infections, only when cautiously used resistance can be contained.

**Keywords:** Diabetic foot infections, Prescribing practices, Cephalosporins, Cefotaxime, Culture/sensitivity testing.

## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by high Blood sugar levels that result from defects in Insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycaemia) lead to spillage of glucose into the urine, hence the term sweet urine. Diabetes mellitus is a chronic disorder and affects large segment of population and is a major public health problem. In general 252 million people are diabetics worldwide. India alone currently counts over 40 million people with Diabetes, which is estimated to touch 73.5 million by 2025 as a consequence of longer life expectancy, sedentary lifestyle and changing dietary patterns. The population of India is more than 1 billion, and with a

prevalence of type 2 diabetes of between 2.4% and 6.5%, it is estimated that there are 35 million Indians with type 2 diabetes.

Foot infections are the most common problems in people with diabetes. Diabetic foot infections are infections that can develop in the skin, muscles, or bones of the foot as a result of the nerve damage and poor circulation that is associated with diabetes. People who have diabetes have a greater than average chance of developing foot infections because a person who has diabetes may not feel foot pain or discomfort, problems can remain undetected until fever, weakness, or other signs of systemic infection appear. As a result, even minor irritations occur more often, heal more slowly and / or more likely to result in serious health problems.<sup>1</sup>

Foot infections increases drastically in hospital stays. In this 4% of diabetics develop foot ulcer annually, 25% in lifetime, 45-75% of all lower extremity amputations are in diabetics, 85% of these preceded by foot ulcer, two-thirds of elderly patients undergoing amputation do not return to independent life, studies have shown less cost for saving a limb than amputation.

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Diabetic foot infections result from the simultaneous action of multiple contributing causes. The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease. More than 60% of diabetic foot ulcers are the result of underlying neuropathy. The development of neuropathy in affected patients has been shown in animal and in vitro models to be a result of hyperglycemia-induced metabolic abnormalities. Peripheral arterial disease (PAD) is a contributing factor to the development of foot ulcers in up to 50% of cases. It commonly affects the tibial and peroneal arteries of the calf. Endothelial cell dysfunction and smooth cell abnormalities develop in peripheral arteries as a consequence of the persistent hyperglycemic state. There is a resultant decrease in endothelium-derived vasodilators leading to constriction.<sup>2</sup>

Antibiotics are chemotherapeutic agents that inhibit or abolish the growth of microorganisms, such as bacteria, fungi or protozoans, and are developed to kill microorganisms. Microorganisms develop and disseminate resistance as a reaction to antimicrobials in accordance with the rules of physics, evolution and natural selection. In spite of considerable developments in antibiotics, antibiotherapy, science, medicine and medical care, infectious diseases and infectious complications related to resistant bacteria, such as staphylococci, respiratory pathogens (e.g., *Streptococcus pneumoniae*), Gram-negative bacilli, as well as fungi and viruses, remain important causes of human morbidity and mortality.<sup>3</sup>

Antibiotics fight bacteria through a variety of mechanisms. Penicillins, cephalosporins, carbapenems, and vancomycin kill bacteria by damaging or inhibiting the synthesis of bacterial cell walls. Other antibiotics act through effects on bacterial DNA or RNA (quinolones and rifampin), proteins (aminoglycosides, chloramphenicol, tetracyclines, and macrolide antibiotics), or metabolism (trimethoprim and sulfonamides).

Bacteria are said to have “intrinsic resistance” to an antibiotic when their normal characteristics render them immune to the antibiotic's mechanism of effect. Intrinsic resistance is not affected by misuse of antibiotics. In fact, it is valuable in determining which antibiotic will be most effective against a certain microbe. For example, the outer membrane of gram-negative bacteria makes them relatively impermeable to hydrophobic compounds such as macrolide antibiotics, thus conferring intrinsic resistance to these drugs. Some bacteria can also use temporary strategies in which different genes are expressed or suppressed in order to enable survival in the presence of antibiotics, with expression patterns returning to normal once the threat posed by those particular drugs has passed.<sup>4</sup>

In 1945, after penicillin had been introduced into medicine, an antibiotic-producing species of *Cephalosporium* was isolated from a sewage outfall in Sardinia. Four years later in Oxford, this organism was found to produce several antibiotics, one of which was a penicillin with a new side-chain, penicillin N. During a chemical study in 1953, this penicillin was shown to be contaminated with a second substance, cephalosporin C, which contained a beta-lactam ring but was resistant to hydrolysis by a penicillinase (beta-lactamase). At that time, penicillinase-producing *Staphylococci* were causing a serious problem in hospitals. The isolation of the nucleus of cephalosporin C (7-ACA) enabled pharmaceutical manufacturers to produce many thousands of cephalosporins, some of which have been effective in the treatment of serious infections by a number of Gram-positive and Gram-negative bacteria. The cephalosporins, like the newer penicillins, have a very low toxicity and have greatly extended the range of chemotherapy. New, sensitive screening methods have revealed further families of clinically useful substances that contain a reactive beta-lactam ring.<sup>5</sup>

#### *Antimicrobial Resistance:*

Drug resistance is a global problem affecting both developed and undeveloped countries. Antimicrobial resistance is a natural consequence of antimicrobial use, which kills the sensitive organisms leaving the resistant ones to survive and multiply (selection of resistance). Overuse and misuse of antimicrobials do not help patients, they merely add to the problem of resistance and waste resources.

Antimicrobial resistance is on increase – threatening our ability to treat some of the infectious disease that causes most deaths. Infectious diseases still account for 45% of deaths in low income countries and for almost one in two premature deaths worldwide.

Today antibiotics remain the first line therapy for conquering bacterial infections. However, their indiscriminate use is no longer viewed as benign. Treatment with these drugs is acknowledged to be a two-edged sword. As antimicrobial agents have been misused or overused, bacteria have fought back with a selection process by which certain strains are no longer susceptible to one or more agents. Each new use of these drugs, in fact, contributes to the evolution of resistant microorganisms.<sup>6</sup> As a result bacteria that once seemed to be losing the battle for survival have re-emerged to create therapeutic dilemmas with resulting increased risk of treatment failure and disease complications.

Patients want antibiotics, and physicians continue to prescribe them in situations where antibiotics may be withheld for many reasons. From the patient's point of view, the prescribing of an antibiotic validates that the patient does

have an illness that a diagnosis has been made and the illness is amenable to treatment. The fact that there is a cure for their problem reassures them that the illness is not serious.<sup>7</sup>

The cephalosporin antibiotics have become a major part of the antibiotic formulary for hospitals in affluent countries. They are prescribed for a wide variety of infections every day. Their undoubted popularity relies upon lesser allergenic and toxicity risks as well as broad spectrum of activity. It is the latter feature; however, that encourages the selection of microorganisms that are resistant to these agents. There are long-term implications for the treatment and control of this heterogeneous group of super infections. When clinicians evaluate a septic patient, it is understandable that they choose empirical therapy with a cephalosporin whilst awaiting microbiological and other tests, since bacterial identification and antimicrobial testing usually require 24-48 h. The broad-spectrum capability of these drugs, however, encourages rapid overgrowth of some microorganisms that are neither eliminated nor inhibited by therapy. These organisms not only have pathogenic potential, they may also be multiply resistant to antibiotics. This review discusses the evidence that cephalosporin usage is the most important factor in the selection and propagation of microorganisms such as *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, Penicillin-resistant Pneumococci, multiply resistant coliforms and vancomycin-resistant Enterococci, the continuing increase of which threatens the future of antimicrobial therapy.

Although widely accepted as broad-spectrum antibiotics, cephalosporins are not active against all the bacteria commonly isolated in a hospital microbiology laboratory. Organisms that are not inhibited by cephalosporin therapy consequently overgrow, with varying potential to cause infection. Some of these are instantly recognizable as pathogens; others, although originally regarded as commensal or of low risk status, have subsequently been shown to cause disease.<sup>8</sup> Furthermore, there is an association between cephalosporin usage and the emergence of multiply resistant organisms.

Prescribing practices of physicians has become a major factor in today's scenario for treating foot infections. Inappropriate use of cephalosporins has become a major problem in the treatment, as there has been a marked increase in resistivity seen among bacterial pathogens due to over prescribing or under prescribing of antibiotics. The Objective of the study is to evaluate the prescribing pattern of different generations of cephalosporins, evaluate the sensitivity pattern and assess the treatment failure of cephalosporins in diabetic foot infections.

## METHODOLOGY

The study was carried out and patients were selected from surgery ward after obtaining clearance from Ethical Committee.

### Inclusion criteria:

- All male and female patients aged between 40-80 years, who were admitted to the surgical inpatient department with diabetic foot infections.
- Patients with type 1 diabetes, and above 40 years of age.
- Patients with type 2 diabetes.
- Patients prescribed with empirical treatment of cephalosporins.

### Exclusion criteria:

- Patients who were admitted to the surgical inpatients units, both male and female below the age of 40 years who had foot infections but were not diabetic.
- Patients with type 1 diabetes, who were below the age group of 40 years.
- Diabetic foot infected patients prescribed with empirical treatment of cephalosporins, but who were not referred for anti-microbial sensitivity testing.
- Diabetic foot infected patients prescribed with treatment other than cephalosporins.

Prospectively 77 patients who met the initial inclusion criteria were selected for the study during the study period of 9 months from August 2009 to April 2010. Prescription data was collected from the medical records that contain all the prescriptions for each patient, providing information about the demographic details, drugs prescribed empirically, culture and sensitivity reports of the patients were collected for analysis.

The data of the first culture (to determine the effect of empirical treatment) and sensitivity reports of 77 patients, repeat one culture one sensitivity and repeat two culture two sensitivity were collected (to determine the effect of cephalosporins).

Similarly, retrospectively culture and sensitivity reports of 230 patients were screened to determine the prevalence of sensitivity and resistance pattern of particular organism to different cephalosporins were determined. The data obtained was tabulated and results are interpreted using cross tabulation for SPSS software has been used. Significance was reported by 95% Confidence Interval which was calculated by binomial probability method.

**RESULTS AND DISCUSSION**

A total of 77 patients who fulfilled the inclusion criteria and who were admitted to any one of 6 surgical units of Rajah Muthiah Medical College and Hospital were included in this study, which was carried out for 9 months between August 2009 to April 2010.

Among the 77 patients with diabetic foot infections from surgical units, 70% were male and 30% were female. According to Llanes, male population accounts for more hospital admission than females in diabetic foot infections. In our study 90.4% patients had type 2 diabetes and only 9.6% had type 1 diabetes (table-1). We observed that 48.2% patients had ulcer followed by 27.27% with cellulitis and 20.78% with gangrene. According to a study by Anandi C, out of 107 patients with diabetic foot lesion, 56% had ulcer followed by 26.1% cellulitis and 15.9% gangrene.<sup>9</sup>

The present study illustrates the infection is due to gram-positive cocci, gram-negative bacilli and polymicrobials. Among these 65.6% were gram-negative bacilli followed by 20.02% gram-positive cocci and 14.92% polymicrobials were isolated. Out of which four types of gram-positive cocci and seven types of gram-negative bacilli were recorded. Our study revealed that *E. coli*(19.5%), *Klebsiella* (14.35%), *Pseudomonas* (10.8%) and *Citrobacter* (10.3%) were the most common gram-negative organisms isolated. *Staphylococcus aureus* (14.4%) and *Enterococcus* (11.8%) were the most common gram-positive pathogen isolated in our study.

These results were comparable with a similar study which was conducted in Bangalore by Vidya D et al, in diabetic foot infections where the most commonly isolated organisms were *Staphylococcus aureus*, *Citrobacter* species, *Pseudomonas* species, *Enterococcus* and *Pneumococci*.<sup>10</sup>

According to Motta RN et al, enterobacteriaceae group (97.8%) were the most frequently isolated bacteria.

<sup>11</sup>According to David BS, extended-spectrum  $\beta$ -lactamase (ESBL)-producing organisms are an increasing problem for practitioners dealing with infectious disease. *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* are the most common ESBL-producing pathogens.<sup>12</sup>

Sensitivity testing was done for patients with gram-negative bacilli in diabetic foot infection and it was found that organisms showed increased resistance patterns to cephalosporins, while in case of infections due to gram-positive cocci, cephalosporins were effective. Prevalence of polymicrobials and efficacy of cephalosporins on them was not studied separately.

According to the reporting at ICAAC conference, ESBLs are beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These cephalosporins include cefotaxime, ceftriaxone, and ceftazidime, as well as the oxyimino-monobactam aztreonam. The clinical relevance of ESBLs has been well documented by numerous published case reports describing clinical failures with the use of third generation cephalosporins such as these oxyimino-cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) as well as with the use of cefoxetin and the fourth generation cephalosporin, cefepime. Thus, the problem of ESBLs is clinically important, yet remains relatively unappreciated by most clinicians. This is because many clinical microbiology laboratories continue to mistakenly report these gram-negative bacillary isolates as

**Table No.1 Age Distribution with Sex**

Age in years	Male (%)	Female (%)	Overall (%)
41-50	14(25.92)	7(30.43)	21(27.27)
51-60	15(27.77)	9(39.13)	24(31.16)
61-70	17(31.48)	4(17.39)	21(27.27)
71-80	8(14.81)	3(13.04)	11(14.28)
Total	54(100.0)	23(100.0)	77(100.0)

**Table 2: Prescribing Pattern of Drugs**

Drug combination of Drug	Dosage	Empirical N=77(%)	After first culture N=77(%)	After repeat culture one N=48(%)	After repeat Culture two N=9(%)
Cefotaxime	1gm IV BD	41(53.24)	26(33.76)	5(10.41)	1(11.1)
Ceftriaxone	1gm IV BD	4(5.19)	13(16.38)	6(12.50)	1(11.11)
Cefoperazone +Sulbactam	1.5gm IV BD	28(36.36)	19(24.67)	10(20.83)	4(44.44)
Cefepime(Cpm)	1gm IV BD	3(3.89)	3(3.89)	1(2.08)	-
Cefexime(Cfx)	1gm IV BD	1(1.29)	2(2.59)	1(2.08)	-
Drugs other than cephalosporins	-	-	14(18.18)	25(52.08)	3(33.33)

susceptible due to difficulties in identifying which isolates possess this important beta-lactamases.<sup>13</sup>

In the present study, injection cefotaxime (53.24%) was the most commonly prescribed drug followed by injection cefoperazone + salbactam (36.36%) and injection ceftriaxone (5.19%). (Table-2).

Out of the 77 patients in first culture, 47 patients yielded growth, 17 had no growth and 13 had normal skin flora (Table-3). So the sample for repeat one culture is 47 (n=47) and similarly repeat two culture is 8 (n=8). (Table-3)

Out of 77 patients, 41 (53.24%) patients prescribed with cefotaxime as empirical treatment and pus sample were sent for culture and sensitivity test. In 19 (46.3%) patients, there was either no growth or normal flora and 22 (53.7%) patients

yielded growth. Antibigrams were available only for 17 isolates. Out of these 17, 8 gram-negative bacilli (47.1%) and 1 polymicrobial (5.9%) were resistant to empirical drug after first culture [With 95% CI of 26.17-69.04 and 95% CI of 1.05-26.98 respectively].

Without following the antibiograms, cefotaxime was discontinued in 2 (11.8%) (95% CI: 3.29-34.34) patients of the 17 isolates, even though it was sensitive and in 5 (29.4%) (95% CI: 13.28-53.13) patients where antibiograms were not available. It is prudent to inform the microbiologist to include the empirical drug for testing sensitivity pattern of organism in antibiogram, before continuing or discontinuing the drug.

In 4 (23.5%) (95% CI: 9.56-47.26) patients (3 gram-negative and 1 gram-positive organisms isolated), the patients were sensitive to organisms after first culture and developed

**Table 3: Growth of Organisms at different points of culture**

Contents	First Culture (N=77)	Repeat Culture (N=47)	Repeat Two (N=8)
Normal flora skin	13(16.88%)	4(10.41%)	-
Growth	47(61.03%)	39(81.25%)	8(100.0%)
No Growth	17(22.07%)	4(8.33%)	-
Total	77(100.0%)	47(100.0%)	8(100.0%)

**Table 4: Frequency distribution of organisms isolated**

Sl.No	Gram-positive cocci	First culture (n=47)	Repeat one (n=39)	Repeat two (n=8)
1	Enterococcus (E.f)	3(6.38%)	2(5.12%)	-
2	Coagulase positive Staphylococcus aureus (Cps)	4(8.51%)	2(5.12%)	-
3	Coagulase negative Staphylococcus aureus (Cns)	-	-	1(12.5%)
4	Streptococcus (St)	2(4.25%)	2(5.12%)	-
	Total Gram- positive Cocci	9(11.68%)	6(15.38%)	1(12.5%)
	<b>Gram-negative bacilli</b>	<b>First culture (N=47)</b>	<b>Repeat one (N=39)</b>	<b>Repeat two (N=8)</b>
	<b>Enterobacteriaceae group</b>			
1	Citrobacter (S)	7 (14.89%)	9 (23.07%)	1 (12.5%)
2	Klebsiella (K)	3 (6.38%)	4 (10.25%)	-
3	E. coli (E.c)	8 (16%)	5 (12.82%)	1 (12.5%)
4	Proteus spp (Pr)	5 (10.63%)	2 (5.12%)	2 (25%)
5	Enterobacter (E)	-	-	-
	<b>Other than gram-negative bacilli</b>			
6	Pseudomonas (P)	8 (17.02%)	3 (7.69%)	-
7	Nlfgnb	3 (6.38%)	5 (12.82%)	1 (12.5%)
	Total Gram-negative bacilli	34 (72.34%)	28 (71.79%)	5 (62.5%)
		<b>First culture (n=47)</b>	<b>Repeat one (n=39)</b>	<b>Repeat two (n=8)</b>
1	Polymicrobials	4 (8.51%)	5 (12.82%)	2 (25%)

Nlfgnb = Non-lactose fermentative gram-negative bacilli other than pseudomonas

Table 5: the percentage sensitivity pattern of organisms in relation to cephalosporins

Organism	Cefotaxime		Cefoperazone		Ceftriaxone		Cefepime		Cefdinir		Ceftazidime		Cefuroxime	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R
C	54.5	36.4	54.5	36.4	45.5	36.4	-	18.2	-	18.2	9.1	18.2	-	18.2
P	14.3	80.9	28.6	57.1	28.6	66.7	4.8	42.9	4.8	38.1	-	38.1	-	23.8
K	16.7	66.7	20.8	17.8	16.7	66.7	-	29.2	-	25.0	4.2	33.3	0	29.2
E.c	31.6	47.4	28.9	60.5	26.3	60.5	2.6	28.9	-	28.9	5.3	36.8	-	26.3
E.f	43.5	26.1	-	26.1	21.7	30.4	-	13.0	-	13.0	-	30.4	-	13.0
Cps	41.7	41.7	-	50.0	-	25.0	-	8.3	-	8.3	-	8.3	16.7	8.3
C	22.2	33.3	44.4	44.4	44.4	55.5	-	11.1	-	-	-	22.2	11.1	-
Pr	50.0	16.7	50.0	33.3	66.7	33.3	-	16.7	-	16.7	16.7	33.3	-	16.7
Nfgnb	-	75.0	8.3	91.7	8.3	75.0	8.3	33.3	-	50.0	-	41.7	-	33.3
St	66.7	-	-	-	33.3	-	-	-	-	-	-	-	-	33.3
K	25.0	75.0	75.0	50.0	25.0	50.0	-	25.0	-	50.0	-	75.0	-	50.0
E	50.0	-	-	50.0	-	-	-	-	-	-	-	-	-	-
Pr	-	100.0	-	-	-	-	-	100.0	-	-	-	-	-	-
Cns	-	33.3	33.3	33.3	-	-	-	-	-	33.3	-	33.3	-	33.3

S- Sensitive, R- Resistance.

Table 6: Frequency distribution of sensitivity pattern of gram-positive cocci and gram negative bacilli

Cephalosporins	Gram positive cocci		Gram negative bacilli	
	Sensitive	Resistant	Sensitive	Resistant
Cefotaxime	41.5%	29.3%	25.0%	57.1%
Cefoperazone	24.4%	31.7%	28.9%	59.4%
Ceftriaxone	14.6%	24.4%	27.3%	58.6%
Cefepime	-	9.8%	2.3%	28.9%
Cefdinir	-	12.2%	0.8%	26.6%
Ceftazidime	-	21.9%	3.9%	34.4%
Cefuroxime	4.9%	14.6%	0.8%	24.2%

resistance after repeat one culture. The CI value was significant at negative side. Irrational withdrawing or long-term prescription of cephalosporins can lead to such resistance.

In 22 patients, repeat culture one was done. Of which 18.2% yielded either commensals or remained sterile. Of the remaining where there was growth 13 (59.1%) (95% CI: 49.13-87.50) patients showed different organisms. Predominant organisms isolated in repeat one culture were: Pseudomonas, Klebsiella, Citrobacter, E. coli, Streptococcus and Enterococcus. The patients could have acquired these organisms as nosocomial spread. Out of 13 different organisms isolated in repeat one culture, 10 (76.92%), 95% CI (49.7%-91.8%) organisms were resistant to the drug. Resistance of nosocomial organisms to drug was biostatistically near to significant value.

Cefotaxime is an effective drug, provided appropriate barrier techniques are required in preventing nosocomial spread.

Organisms' originally sensitive developed resistance approximately in span of two weeks, which may probably be due to antibiotic pressure.

Out of 77 patients, 28 (36.36%) patients were prescribed with cefoperazone + salbactam empirically. After treatment, pus samples were sent for culture and sensitivity. In 6 (21.4%) patients there was no growth or normal flora. Out of the remaining, 22 (78.6%) patients yielded growth, antibiograms were available for 20 (71.4%) patients.

Out of 20 patients, 8 (40%) (95% CI: 21.88-61.34) gram-negative isolates, 3 (15%) gram-positive and 1 (5%) polymicrobial were resistant to first culture [12 (60%), 95% CI: 38.06-78.12].

In 5 (25%) (95% CI: 11.19-46.87) patients, gram-negative organisms isolated were sensitive after first culture and developed resistance after repeat one culture. Resistance of gram-negative organisms to cefoperazone+salbactam was bio statistically significant at negative side. This shows that

cefoperazone+salbactam may not be an ideal alternative for cefotaxime; however confidence interval (CI value) is significant on the negative side.

In 22 (78.6%) patients, repeat one culture was done, out of which 4 (18.1%) yielded either commensals or remained sterile. Of the remaining 18 where there was growth, in 11 (61.11%) (95% CI: 38.62-79.69) patients different organisms were isolated. Out of 11 different organisms isolated, 5 (45.45%) (95% CI: 21.3-71.9) were resistant to empirical drug.

### CONCLUSION

Although, Cefotaxime is still an active candidate in the treatment of Diabetic foot, the lengthening shadow of resistance implies that it may not be for long. Gram-negative bacilli dominated the resistant pattern compared to the gram positive cocci for Cephalosporin sensitivity.

Organisms which were originally sensitive, developed resistance approximately in a span of two weeks, which can probably be due to antibiotic pressure.

The control and containment of resistance towards antimicrobials by microbes represents universal challenge requiring national and international efforts, as ease of long distance to travel no longer limits spread.

### ACKNOWLEDGEMENT

We would like to thank Medical Superintendent and Dean of R. M. M. C and Hospital, Annamalai University, Annamalai Nagar for their relentless support during the study. We also thank Head of the department, Department of Pharmacy, Annamalai University for his treasured assistance to complete the work. The acknowledgement would be incomplete if we don't thank our professor P. K. Manna for his endless backing during the study.

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