



## BURDEN OF ADVERSE DRUG REACTIONS ENCOUNTERED DURING MANAGEMENT OF CHRONIC RESPIRATORY DISEASES IN A NEWLY SET UP TERTIARY CARE HOSPITAL: A CROSS SECTIONAL STUDY.

### Pharmacology

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### ABSTRACT

Drugs used for various chronic pulmonary ailments contribute significantly to the global burden of Adverse Drug Reactions (ADRs). This cross-sectional study was conducted on patients visiting the pulmonary department for various non-oncological Lung conditions with an aim to determine the pattern, frequency, causality and preventability of ADRs. Relevant details about the drugs, ADRs, investigations, and drug history etc. were recorded on ADR reporting form. A total of 65 patients experienced 124 ADRs over 6 months duration. Vomiting & nausea (35%), anorexia (23%), headache (15%), and some serious adverse reaction like hepatitis (necessitating drug withdrawal) (17%), vision impairment (3%) were the commonest ADRs encountered. Causality analysis classified most of the ADRs (83.07%) as possible and 16.92% in probable category. Almost 67.69% reactions were definitely preventable, 32.30% reactions were probably preventable. Most of the ADRs recovered over time. Further extensive and long term studies are required to elicit more comprehensive and elaborate data.

### KEYWORDS:

Adverse Drug Reactions, Pulmonary department, Causality, Preventability.

### Introduction

Respiratory diseases are among the dominant causes of death worldwide. The Forum of International Respiratory Societies in its report entitled Respiratory Disease in the World: Realities of Today—Opportunities for Tomorrow, identifies five conditions that primarily contribute to the global burden of respiratory disease (asthma, chronic obstructive pulmonary disease, acute respiratory infections, tuberculosis, and lung cancer). Among the leading causes of death, lower respiratory infections were ranked 4th, whereas COPD was ranked 3rd in 2010. The Global burden of Disease (GBD) Study also presented rankings for years lived with disability, among which asthma ranked 13th, while COPD ranked 5th in 2010<sup>1,2</sup>. Even in India respiratory diseases create havoc with patients' well being. According to a report by the World Health Organisation (WHO), the deaths due to lung diseases in India were on the rise accounting for 11% of the total deaths. As many as 142.09 in every 1 lac, died of one form of lung disease or the other, giving India the dubious distinction of ranking first in lung disease deaths in the world<sup>3</sup>. Considering their potential morbidity and magnitude; targeting overall quality of life of the community, it is thus obvious that we cannot be oblivious to diseases of the respiratory system and all associated risk factors.

The quality of life of patients with lung diseases is not only adversely impacted by the disease itself and other environmental and genetic influences but unfortunately, also by the very drugs used to treat these conditions. Anti-tubercular therapy (ATT), antibiotics, steroids used in other Lung conditions and especially Theophylline used for asthma have the potential to cause several ADRs. Peripheral neuritis, seizures, jaundice and methemoglobinemia are quite common and troublesome for a patient taking Isoniazid, a drug in the 1st line ATT. Hepatic damage with Isoniazid and Pyrazinamide is directly related with increasing age and pre-existing hepatic dysfunction; necessitating discontinuation of therapy. Similarly, Optic neuritis with Ethambutol is closely associated with increasing age, prolonged duration of drug, a higher dose, hypertension, poor renal function, diabetes, and concurrent optic neuritis, related to tobacco and alcohol<sup>4</sup>. Ototoxicity and nephrotoxicity with Streptomycin debilitate a patient considerably; risk factors being renal and hepatic failure, pregnancy, noise in surroundings and concomitant administration of ototoxic drugs<sup>5</sup>. While there is a great deal of enthusiasm for inhaled glucocorticoids in asthma, local and systemic adverse effects remain a concern. Oropharyngeal candidiasis and, more frequently, dysphonia can be encountered. The incidence of candidiasis can be reduced substantially by rinsing the mouth and throat with water after each use and by employing spacer or reservoir devices attached to the dispenser to decrease drug deposition in the oral cavity. Theophylline levels may

reach toxic levels and produce severe CNS (confusion, delirium, coma) and CVS side effects (arrhythmia, tachycardia) if prescription errors and errors in dose calculation are done. Co morbid conditions that impair elimination (cirrhosis, hypothyroidism etc.), taking a drug that interferes with theophylline elimination (cimetidine, fluoroquinolone antibiotics, oral contraceptives etc.), stopping a drug that enhances theophylline elimination without adjusting the dose (Phenobarbital, Phenytoin, rifampin etc.), treating a comorbid condition with increased theophylline elimination without adjusting the dose (treated hyperthyroidism, stopped smoking cigarettes, stopped smoking marijuana) – may all cause potentially life threatening Theophylline toxicity<sup>6,7</sup>.

These and many other ADRs encountered in the pulmonary department can be prevented if appropriate ameliorative strategies are studied and then implemented properly. Only when databases pertaining to our Indian population (with its intrinsic cultural, ethnic, geographical diversity) are generated that effective strategies to alleviate ADRs can be implemented<sup>8</sup>. Moreover, ADR monitoring becomes very important for certain drugs with narrow therapeutic index used in pulmonary diseases e.g. Theophylline used for the treatment of asthma and COPD<sup>9</sup>.

ADRs, seemingly a common occurrence and regarded as such by patients and physicians are often the cause of major physical, emotional, socio economic trauma. With an incidence of about 7%, ADRs are the 4th to 6th leading cause of death in hospitalized patients<sup>10</sup>. Drug attributed deaths are estimated to be about 0.17% in all medical inpatients. About 0.40% of ADRs are directly linked to high costs. So, it is apparent that drug toxicity also impacts the economy of health care negatively<sup>11</sup>. These findings cannot be overlooked. In depth and exhaustive studies about magnitude, pattern, risk factors, contribution of ADRs towards hospital admissions and other aspects of ADRs will generate a database offering valuable pearls of wisdom for effective drug therapy. An important step in this context is to establish an exemplary ADR monitoring and reporting attitude.

The selection of the ideal medicine for a given individual, by the prescribing practitioner, requires continually amended and renewed knowledge about ADRs. Therefore, there should be consistent and aggressive attempts to categorise and supplement ADR databases. Only then will this unnecessary burden of reactions suffered by patients, be abrogated. Motivating Health Care Professionals (HCPs) and patients and educating them about the importance of ADR reporting will yield better results in the novel environment of a newly set up tertiary care hospital. Therefore, this study was planned to

analyse the ADR profiles of pulmonary drugs in patients attending the Chest and TB department of a tertiary care institution with the aim to device strategies to decrease and prevent the appearance of ADRs, ultimately leading to an improvement not only in overall health of the patients but also the costs associated with medical care.

**Subjects and Methods:**

This was a cross sectional study conducted over a period of 6 months after obtaining permission from Institutional Ethics Committee. Patients of either sex, above 18 years of age presenting to the OPD for non-oncological lung conditions and those admitted to the IPD for the same and suffering from any untoward event following drug therapy were included in the study, after obtaining informed consent . Before initiation of the study, an awareness program on the importance of ADR reporting by health care professionals (HCP) was conducted in pulmonary department. Patients’ demographic details, details of baseline investigations, treatment given, ADRs observed and interventions done to prevent and manage the ADRs were recorded. For each patient with suspected ADR, a detailed history including drug history, personal history, family history, present and past medical history, and history of previous drug allergy were documented. Any untoward event was labeled as ADR after discussion with the treating physician and Pharmacology department. A thorough clinical evaluation and scrutiny of data was done to assess pattern, extent, severity and duration of the ADRs, to detect any predisposing or Underlying disease/pathological factors, and to assess any other organ/ system involvement as a part of the drug reaction.

The drug groups/regimens and drug(s) prescribed most frequently and those causing ADRs most frequently were determined. Probability assessment was done according to WHO UMC guidelines that classify ADRs as certain, probable, possible, unlikely and unclassifiable<sup>12, 13</sup>. Preventability of the ADRs according to the modified Schumock Thornton Criteria was analyzed and categorized as definitely preventable, probably preventable or not preventable<sup>14</sup>. ADRs were classified into various levels of severity as mild, moderate and severe according to Modified Hartwig severity scale<sup>15</sup>. Outcome of the ADRs as per WHO criteria as fatal, continuing, recovering, recovered, unknown, or any other was observed. Reactions noticed for the first time in medical literature were also recorded.

Descriptive statistics were used to present the data. Interpretation & analysis of association of ADRs with various risk factors was carried out by application of Chi-square test to ascertain level of significance wherever possible. Regular awareness and motivational programme for the patients to report any suspected ADR to our Pharmacovigilance unit was conducted. They were Motivated to report the suspected ADRs verbally or through the ADR reporting form.

**Results:**

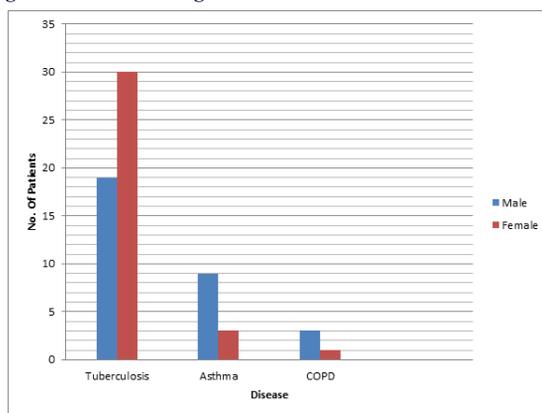
During the study period a total of 210 patients were monitored. Out of which 124 ADRs were observed in 65 patients (accounting for a31% incidence), over the 6 months’ case study. Among the 110 female and 100 male patients monitored ADRs appeared in 34 females (31%) and 31males (31%) respectively.

**Table 1: Demographic characteristics**

Sex	No. of patients	Age (years) (Mean ±SD)	No. of smokers n= 20	No. of Alcoholics n=7	No. of patients with H/O Allergies n=7
M	31(47.7%)	37.03±8.53	12(60%)	7(100%)	4(57.14%)
F	34(52.3%)	34.9±8.22	8(40%)	0(0%)	3(42.86%)
Total M+F	65(100%)	35.92±5.91	20 (30.76%)	7(10.76%)	7(10.76%)

Mean age of the 65 patients was 35.92±5.91; with the mean age of males being 37.03±8.53 and of females 34.9±8.22 (Table 1). Baseline characteristics were comparable as all patients were middle age, below average weight. Strong association between pulmonary diseases and smoking was seen. Out of 65 patients, reporting ADRs the most common diagnosis (Figure 1) was TB (49) followed by Asthma (12) and COPD (4).Most of the reactions appeared in the patients with TB (55%) followed by asthma (25%) and COPD (20%).

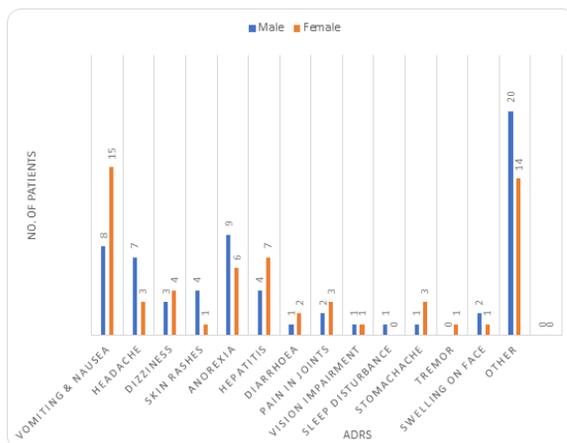
**Figure 1: Common Diagnosis**



**Tuberculosis followed by Asthma and COPD was the most common diagnosis**

Majority of the patients suffered with atleast one ADR. Two patients had 6 ADRs and fifteen patients had 3 ADRs. Every patient on an average had 1.90 ADRs. Of the many reactions observed vomiting & nausea (35%), anorexia (23%), headache (15%), dizziness (11%) rash (8%), pain in joints (8%), stomach ache (6%) etc. and and some serious adverse reaction like hepatitis (17%) and vision impairment (3%) were the commonest (Figure 2).

**Figure2: ADRs commonly observed (n=124)**



Nausea and vomiting was the most common ADR in females and Anorexia was the most common ADR in males

Nausea and vomiting was commonly associated with Ethambutol and other anti tubercular drugs as well as Azithromycin, anorexia with Pyrazinamide and other Anti tubercular agents as well as Formoterol, Hepatitis with Isoniazid (Table 2). The incidence of ADRs increased with increase in the number of drugs in the prescription. The greatest numbers of ADRs were seen with the use of Isoniazid and Ethambutol.

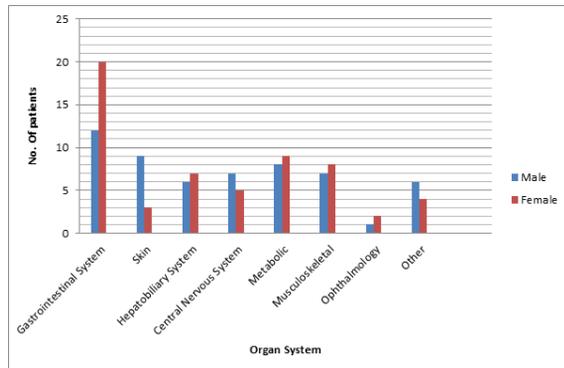
**Table 2: ADRs associated with the various drugs used (in descending order)**

ADRs	Causative Agents
Vomiting, Nausea	Ethambutol, Rifampicin, Isoniazid, Pyrazinamide, Streptomycin, Azithromycin
Anorexia	Pyrazinamide, Isoniazid, Rifampicin, Ethambutol, Streptomycin, Formoterol, Diethylcarbamazine
Hepatitis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
Skin rashes and itching	Ethambutol, Rifampicin, Streptomycin, Isoniazid, Pyrazinamide, Methylprednisolone, Formoterol, Ranitidine, Azithromycin
Diarrhoea	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin, Clarithromycin
Dryness of mouth	Fluticasone, Salmeterol, Tiotropium Bromide

Tremors	Formoterol, Budesonide
Optic Neuritis	Ethambutol
Swelling on face	Budesonide, Formoterol
Dizziness	Salbutamol, Streptomycin, Azithromycin Isoniazid, Rifampicin, Ethambutol, Ipratropium bromide
Sleep disturbance	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
Headache	Clarithromycin, Pyrazinamide, Isoniazid
Thigh pain	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
Throat irritation	Formoterol, Budesonide

GIT was the most commonly involved system (49%) (Figure 3).

**Figure 3: Organ system effected**



**GIT was the most common system involved**

Drugs were withdrawn (de challenge) in 5 patients (hepatitis) and treatment for the management of ADRs was administered to 18 patients (skin rash, anorexia, diarrhoea, insomnia, and headache). Full recovery from their side effects was obtained in 45 patients. 25 patients were re-challenged with the drug which resulted in the reappearance of the ADRs

Most of the ADRs (83.07%) fell in possible and 16.92% in probable category. According to modified Hartwig severity scale 35 % reactions were moderate, 56% mild and 9 % severe in intensity. Preventability scale classified 67.69% reactions as definitely preventable, 32.30% reaction as probably preventable and none as not preventable.

**Discussion:**

Although there has been a dramatic improvement in the way diseases are currently managed, drug therapy today is still hampered by the many adverse effects that patients must bear. India as of now, holds the top-ranking position among Lung diseases<sup>3</sup>. Most of the morbidity suffered by patients with Lung diseases is due to the ADRs, so prevalent with drug therapy.

There was no statistical difference between the number of males and females with ADRs (34 females and 31 males). It is well known that the risk in female patients is 1.5- to 1.7-times greater as compared to males. Some of the most established risk factors for ADRs are age, polypharmacy, and female sex. Females suffer more ADRs possibly due to gender-related differences in pharmacokinetic, immunological and hormonal factors, metabolizing capacity, liver and renal function etc. Drug usage and awareness to reporting ADRs is also more common in females<sup>16</sup>. The low sample size of the study was possibly why the number of females and males with ADRs were almost the same.

Mean age of the 65 patients was 35.92±5.91. According to a report, the incidence and severity of lung diseases were similar for men and women, but prevalence increased with age. For example, 17 % of people between 60 to 79 years of age had COPD or asthma compared with about 14 %of those 40 to 59 years of age<sup>17</sup>. Changing pharmacokinetics and pharmacodynamics, presence of co morbidities, polypharmacy and other age related changes increase the incidence of ADRs in the elderly. Geriatric prescriptions thus need greater dose

modification and individualisation. The reason for lower age group of people in the present study could be the low sample size and because young people are less tolerant towards their ailments and hence report more!

Strong association between pulmonary diseases and smoking was seen. 12 out of 31 males in the study were smokers. Smoking has adverse health effects on the entire lung—affecting every aspect of lung structure and function—including impairing lung defenses against infection and causing the sustained lung injury. Smokers increase their risk of lung disease, including lung cancer. But they also increase their risk of other illnesses such as heart disease, stroke, and oral cancer<sup>18</sup>. Surprisingly 8 out of the 34 females in the study also smoked. Women smokers have double the risk of lung cancer compared with their male counterparts, and often suffer more aggressive forms of the disease due to smaller bodyweight, smaller blood vessels , capacity to extract more toxins from the same number of cigarettes smoked etc. Women smokers in certain age groups are up to 38 times more likely to develop COPD than women who have never smoked<sup>19</sup>.

Strong and heavy alcohol intake predisposes to several lung disease through multiple mechanisms. It impairs mucociliary clearance, and act as trigger for airway disease exacerbations especially in atopic asthmatics and in Asian populations who have a reduced capacity to metabolize alcohol. Although we tried to ascertain the relation between alcohol intake and lung disease, we could not discover much. Only 7/65 patients took alcohol and that too apparently occasionally. Research has highlighted the role of alcohol mediated damage to airways, which should be further established by several studies<sup>20</sup>.

The incidence of ADRs increased exponentially with polypharmacy as has been seen in several earlier studies<sup>21</sup>. Patients suffering from lung disease (acute or chronic) by default must practice polypharmacy which increases their exposure and subsequent susceptibility to ADRs, necessitating vigorous monitoring and reporting measures.

The contribution of ATT in the burden of ADRs was slightly more in our study in contrast to antibiotics and other drugs used in the pulmonary department. The most plausible explanation for this being more number of TB patients. This could also be due to lesser awareness and focus being given to reporting of the ADRs of anti infectives, bronchodilators etc in contrast to those from anti tubercular drugs. Good dose modification in this study guaranteed the decrease in the toxicity with Theophylline and other drugs with narrow therapeutic index. A study by Khan et al. reports a similar incidence of ADRs with ATT<sup>22</sup>. Focussing on ADRs of extensively used drugs helps in formulating hospital drug usage policies.

Of the many reactions observed vomiting & nausea, rash, headache, fever etc. were quite common in accordance with previous studies. Possibly the most serious ADRs were hepatitis (11 out of 65 patients) and optic neuritis (2 out of 65 patients). A number of risk factors have been associated with hepatitis which was commonly seen with ATT in this study. There was a rise in SGOT, SGPT and bilirubin at 45 days which subsided in about 3 months. A number of studies by Agarwal et al. and Athira et al. have reported similar findings<sup>23,24</sup>.

Most of the ADRs involved the GIT. This is consistent with other similar studies. It also points towards a slowly increasing awareness among the medical fraternity that it is not just the reactions involving skin and its appendages that need to be reported<sup>25,26</sup>.

In this study 67.69% reactions were definitely preventable and 32.30% reactions probably preventable. A higher rate of preventable reactions has been reported in a variety of studies (a range of 30-70%)<sup>26,27</sup>. This suggests that educational strategies and preventive measures are effective very well placed in our setting.

It is obvious that differences exist in the rate of reported ADRs and other related parameters in various geographical and ethnic areas due to variability in patients' demographics, number of OPD attendance and beds available, medications used and also the ADR definition and methods followed and also the disoriented and chaotic environment of a new organisation<sup>28</sup>.

**Limitations:** The small sample size as this is a newly set up tertiary care center with limited OPD attendance is possibly the biggest limitation of the study. A number of risk factors thus could not be

evaluated. Lesser involvement of pediatric and geriatric population also hampered accurate readings. Pathological and other laboratory markers which give a more objective basis to results, could not be monitored.

**Conclusions:** The importance of this study was in garnering results from a specialised unit. A number of ADRs were seen even in such a limited sample, underscoring the need for measures to decrease their burden. Figures generated were indicative of a low grade reporting culture. ADR monitoring activities in high risk populations such as those found in hospitals may help in formulating mechanisms to educate HCPs to participate aggressively in ADR reporting. Specialized clinics associated with Pulmonary and other departments may yield focussed results.

#### References:

1. The burden of Lung Disease. Retrieved from <http://www.erswhitebook.org/chapters/the-burden-of-lung-disease/>.
2. Ferkol, T., Schraufnagel, D. (2014). The Global burden of Respiratory Disease. *Annals of the American Thoracic Society*, 11(3), 404-6.
3. India tops world in lung disease deaths. Retrieved from <http://www.thehindu.com/news/national/andhra-pradesh/india-tops-world-in-lung-disease-deaths/article7372468.ece>.
4. Koul, P.A. (2015). Ocular Toxicity with Ethambutol therapy : Timely precaution. *Lung India*, 32(1), 1-3.
5. World Health Organisation. Report of an Informal Consultation on strategies for prevention of hearing impairment from ototoxic drugs. Geneva, (1994). Retrieved from [http://www.who.int/pbd/deafness/ototoxic\\_drugs.pdf?ua=1](http://www.who.int/pbd/deafness/ototoxic_drugs.pdf?ua=1)
6. Edwards, D.J., Zarowitz, B.J., Slaughter, R.L. (1986). Chapter 13: Theophylline. pages 13-1 to 13-38. IN: Evans WE, Schentag JJ, et al (editors). *Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring*. Applied Therapeutics, Inc..
7. Shannon, M. (1999). Life-threatening events after theophylline overdose. A 10-year prospective analysis. *Archives of Internal Medicine*, 159, 989-994.
8. Chabner BA. (2011). General Principles of Cancer Chemotherapy. In: Brunton LL, Chabner BA, Knollman BC, editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: Mc Graw Hill
9. Newnham, D.M. (2001). Asthma medications and their potential adverse effects in the elderly: recommendations for prescribing. *Drug safety*, 24, 1065-80.
10. Routledge, P.A., O'Mahony, M.S., Woodhouse, K.W. (2004). Adverse drug reactions in elderly patients. *British Journal of Clinical Pharmacology*, 57(2), 121-6.
11. Surendiran, A., Balamurugan, N., Gunaseelan, K., Shahid, A., Reddy, K., Adithan, C. (2010). Adverse drug reaction profile of cisplatin-based chemotherapy regimen in a tertiary care hospital in India: An evaluative study. *Indian Journal of Pharmacology*, 42(1), 40-3.
12. The use of WHO- UMC system for standardised case causality assessment. Retrieved from <http://www.who-umc.org/graphics/24734.pdf>.
13. Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics*, 30, 239-45.
14. Lau, P.M., Stewart, K., Dooley, M. (2004). The ten most common adverse drug reactions in oncology (ADRs) in oncology patients : Do they matter to you? *Support Care Cancer*, 12, 626-33.
15. Hartwig, S.C., Siegel, J., Schneider, P.J. (1992). Preventability and severity assessment in reporting adverse drug reactions. *American Journal of Hospital Pharmacy*, 49, 2229-32.
16. Rademaker, M. (2001). Do women have more Adverse Drug Reactions? *American Journal of Clinical dermatology*, 2(6), 349-51.
17. About 1 in 7 older Adults has lung Disease: CDC. Retrieved from <http://www.webmd.com/lung/copd/news/20150106/about-1-in-7-older-adults-has-some-form-of-lung-disease-cdc#1>
18. The health consequences of smoking: report of the surgeon general. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK44694/>
19. Women and Smoking. Retrieved from [https://www.cdc.gov/tobacco/data\\_statistics/sgr/50th-anniversary/pdfs/fs\\_women\\_smoking\\_508.pdf](https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/pdfs/fs_women_smoking_508.pdf)
20. Sisson, J.H. (2007). Alcohol and Airways function in Health and Disease. *Alcohol*, 41(5), 293-307.
21. Ahmed, B., Nanji K., Mujeeb, R., Patel, M.J. (2014). Effect of Polypharmacy on Adverse Drug Reactions among geriatric Outpatients at a Tertiary care hospital in Karachi: A prospective Cohort study. *PLOS One*, 9(11), e112133
22. Khan, A., Adil, M.S., Nematullah, K., Ihtisham, S., Aamer, K., Aamir, S. (2015). Causality Assessment of adverse drug reaction in pulmonology department of a tertiary care teaching hospital. *Journal of Basic and Clinical Pharmacy*, 6(3), 84-88.
23. Athira, B., Manju, C.S., Jyothi, E. (2015). A study on adverse drug reactions to first line antitubercular drugs in DOTS therapy. *International Journal of Pharmacology and Clinical Sciences*, 4(1), 7-11.
24. Agarwal, R., Goel, A., Rai, J., Kajal, N.C. (2017). Pharmacovigilance of first line anti-tubercular therapy in category I patients of pulmonary tuberculosis. *International Journal of Basic & Clinical Pharmacology*, 6(3), 643-647.
25. Baniasadi, S., Fahmi, F. (2011). Adverse Drug Reactions in a pulmonary Teaching Hospital: Incidence, Seriousness and Preventability. *Current Drug Safety*, 6(4), 1-7.
26. Bates, D.W., Cullen, D.J., Laird, N., Peterson, L.A., Small, S. D., Servi, D., . . . Leape, L.L. (1995). Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *The Journal of The American Medical Association*, 274(1), 29-34.
27. Ducharme, M.M., Boothby, L.A. (2007). Analysis of adverse drug reactions for preventability. *International Journal of Clinical Practice*, 61(1), 157-61.
28. Sullivan, K.M., Spoons, L.M. (2008). Adverse Drug Reaction reporting by pharmacy students in a teaching hospital. *American journal of health System pharmacy*, 65(12), 1177-9.