

## Adverse Drug Reaction Profile of Drugs Used in Patients Suffering from Respiratory Disorders in a Tertiary Care Centre of Hyderabad India

Aleemuddin NM<sup>1</sup>, Farahbahmed<sup>2</sup>, Mohammed Shakeel Mohammed Bashir<sup>3</sup>, Aamir Ali<sup>2</sup>, Salma Khatoun<sup>5</sup>, Md Mohib Hussain<sup>6</sup>, Afshan Khatoun<sup>7</sup>

<sup>1</sup>Associate Professor of Pulmonology, Deccan college of Medical Sciences

<sup>2</sup>Assistant Professor of Physiology, Deccan college of Medical Sciences

<sup>3</sup>Associate Professor of Pharmacology, RIMS Adilabad

<sup>4</sup>Assistant Professor of Pharmacy, Deccan School of Pharmacy

<sup>5</sup>Tutor in Pulmonology, Deccan college of Medical Sciences

<sup>6</sup>Postgraduate in Anaesthesia, Deccan college of Medical Sciences

<sup>7</sup>Tutor in Pulmonology Deccan college of Medical Science

<http://dx.doi.org/10.18049/jcmad/216>

### Abstract

**Objectives:** Adverse drug reactions (ADRs) represent a sizeable part of overall medical expenses. Pattern of ADR can be different in various geographical areas. Hence the present study was conducted to know the pattern of ADRs due to various drugs used in the management of number respiratory disorders affecting the population of South India. **Material and Methods:** Adverse Drug Reactions (ADR) of a total of 152 patients of tuberculosis and chest department of Deccan College of Medical Sciences, Hyderabad, India who were suffering from various respiratory disorders recorded and treated by respective physician. Suspected drug for the ADR was identified. **Results:** Total number of drugs prescribed in all the 152 patients was 2246 and average number of drugs per patient was 14.78. 80 adverse drug events were observed in 49 patients. Commonest ADRs were constipation and restlessness (7 event) each followed by hyperglycemia, insomnia, nausea and vomiting (6, 7.5%) each were observed. Most of the adverse drug reactions were observed with Theophylline as it was responsible for 32 events when 133 times administered to patients. **Conclusion:** Theophylline has adverse drug reaction probability more in comparison to other drugs which are used in respiratory disorders. Hepatitis is serious ADR which can occur with the use of anti tubercular drugs. Number of drugs per prescription should be decreased but without compromising the disease management protocol.

**Key words:** ADR, Drug prescription, Respiratory disorders

**Address for correspondence:** Dr. Aleemuddin NM, Residential address, 20-6-530 Shahlibunda, Hyderabad 500065 Andhrapradesh India. Mobile Number: 09949671249, Email: [aleem95@yahoo.com](mailto:aleem95@yahoo.com)

### Introduction

Drug utilization studies are very important tool of evaluation of health care system. [1] The main aim of such studies is to work towards promotion of rational use of drugs in populations. Pattern of adverse drug reaction (ADR); ADR is defined by WHO as “A response to a drug which is noxious and unintended and which occurs at doses normally

used in man for the prophylaxis, diagnosis or therapy for a disease and for the modification of function excluding failure to accomplish the intended purpose” [2] can be evaluated by these studies. The science which deals with adverse drug reactions is called as Pharmacovigilance which is defined as “The science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or any other medicine related problem”. [2] In Pharmacovigilance program, the causality

assessment of ADRs can be recorded in the specify proforma designed by the National Pharmacovigilance Program. Causality assessment using the Naranjo's Scale evaluates the degree of association of an adverse effect with the suspected drug and involves a set of questionnaires, which are ascribed a certain score (ranging from -1 to +2). Total score for a particular drug ADR combination is calculated and the association is termed - highly probable, probable, possible or doubtful-depending on the score. <sup>[3,4]</sup> Such database provides a basis for the ongoing assessment of adverse drug reactions during hospital stay in order to:

1. To study drug exposure in medical inpatients,
2. To determine the frequency of medication-related events,
3. To estimate the contribution of ADRs to hospital admissions,
4. To characterize types of ADRs observed,
5. To determine predisposing risk factors and
6. To estimate the costs of ADRs in terms of ADR-related excess hospital stay. <sup>[5]</sup>

Adverse drug reactions (ADRs) represent a sizeable part of overall medical expenses. It has been estimated that 3 to 8% of hospital admissions in Internal Medicine are related to ADRs, and these occur in addition in up to 20% of all hospitalized patients and it is the fourth leading cause of death ahead of pulmonary disease, diabetes mellitus, AIDS, pneumonia and automobile deaths. As the number of ADRs usually increase with the number of medications prescribed/taken, ADRs monitoring is essential for drugs with narrow therapeutic index.

Respiratory problems are on rise, specifically in developing countries due to environmental pollutions and various other factors. Chronic obstructive pulmonary disease (COPD) is one of the major respiratory disorders. It is usually treated with inhaled steroids, oral theophylline, oral steroids, antibiotics, etc. Incidence of Tuberculosis is also rising. The frequency and nature of Anti-TB induced ADRs have been the matter of concern in many communities. One of the serious ADRs is hepatotoxicity with a mortality of 6% to 12%. There are differences in reported rate of hepatotoxicity induced by Anti-TB drugs in different studies. This reaction could be affected by the genotype of patients

receiving these drugs e.g. rapid-acetylator patients are more susceptible for isoniazid induced hepatotoxicity. Pattern of ADR can be different in various geographical areas. Hence the present study was conducted to know the pattern of ADRs due to various drugs used in the management of number respiratory disorders affecting the population of South India so that suitable precautions can be taken and adequate modification can be done in the drug protocols of respiratory disease managements.

## **Materials and Methods**

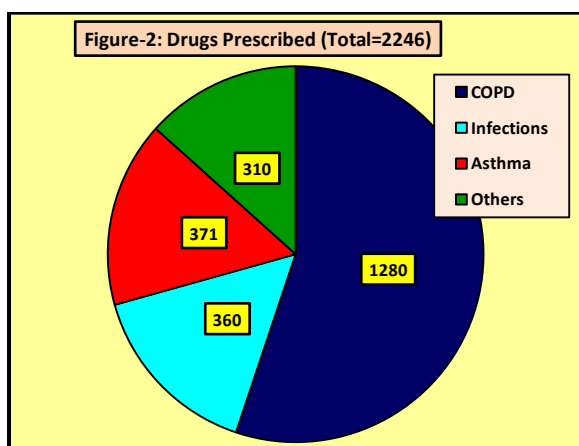
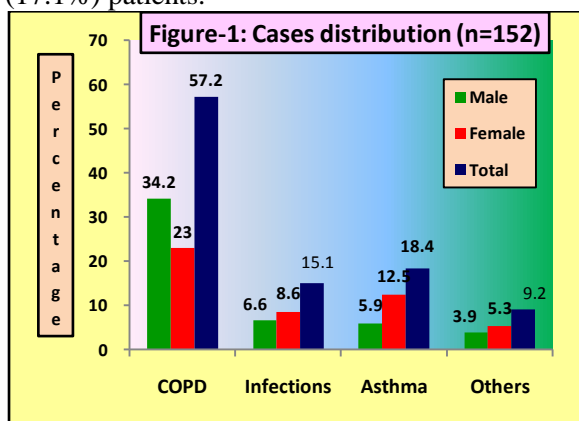
Present prospective study was conducted in the department of tuberculosis and chest department at Deccan College of Medical Sciences, Hyderabad, India during the period of January 2012 to June 2013. A total of 152 patients suffering from respiratory disorders including respiratory infections were included in the study in which 3 (2.00%) patients were died during the study period. In the study 77 (50.7%) patients were males and 75 (49.3%) were females with the age range of in between 19 years to 90 years. Mean age was 55.51 years while male/female ratio was 1.026. Patients' demographic details like age, sex, socioeconomic status also recorded and complete prescription from case report form was noted and analyzed. Adverse Drug Reactions (ADR) if any were observed noted and treated by respective physician. Suspected drug for the ADR was identified. Necessary permission from institutional authorities and ethical clearance was obtained before starting the study.

## **Results**

Out of 152 cases most of the patients (87, 57.2%) were diagnosed as Chronic Obstructive Pulmonary Diseases (COPD) while 23 (15.1%) as infectious, 28 (18.4%) as asthma and 14 (9.2%) as other respiratory disorder cases (Figure- 1). 71 (46.&%) patients had respiratory disorder associated co-morbid conditions in which most common (33 cases, 21.7%) was cardiovascular disorders along with endocrine diseases (Diabetes) followed by cardiovascular diseases alone (26 cases, 17.1%) and endocrine

diseases (9 cases, 5.9%). Schizophrenia, psoriasis and haemorrhoids was also diagnosed along with respiratory disorders in one (0.7%) each cases.

Total number of drugs prescribed in all the 152 patients was 2246 and average number of drugs per patient was 14.78. Most of the drugs were prescribed to COPD patients (1280, 57%) while least number of drugs were given in other disorder cases (310, 13.80%) figure- 2. In 66 (43.4%) patients 11-15 drugs were used for disease management while in 60 (39.5%) patients 16 or more drugs were used. 10 or less number of drugs was also prescribed to 26 (17.1%) patients.



Total number of 80 adverse drug events was observed in 49 patients in which 25 patients were male and 24 were females. Almost equal numbers of cases were from geriatric (23) and adult (26) population. Commonest adverse effects observed were constipation (7 event, 8.75%) and restlessness (7 event, 8.75%) followed by hyperglycemia, insomnia, nausea and vomiting (6, 7.5%) each. 5(6.3%) events of

and 3(3.8%) each event of anemia, anorexia, fatigue, headache & pruritus were observed.

**Table- 2: Frequency of ADR**

Drug	No. of times drug given	Frequency of ADR
Pantoprazole	141	6
Clarithromycin	7	2
Cefoperazone+Sulbac	49	2
Levofloxacin	3	2
Isoniazid	15	1
Pyrazinamide	15	2
Furosemide	37	7
Ondansetron	38	5
Ursodiol	3	1
Chlorphinaramine	2	1
Chlordiazepoxide	2	1
Piperacillin+Tazobact	18	7
Iron	18	4
Sucralfate	28	2
Ceftazidine	1	1
Metronidazole	11	4
Linezolid	2	1
Zolpidem	4	1
Losartan	4	1
Prazosin	3	1
Amiodarone	3	1
Levothyroxine	6	1
Amlodipine	22	4
Atenolol	7	1
Salbutamol	144	14
Montelukast	97	2
Theophylline	133	32
Rabeprazole	3	2
Amox + clavulanate	79	3
Methyl prednisolone	56	7
Hydrocortisone	55	4
Moxifloxacin	22	3
Rosuvastatin	4	1
Terbutaline	5	1
Ethambutol	15	1
Torseamide	8	1
Butyl scopolamine	9	1
Diclofenac	8	1
HRZE	15	2
Metoprolol	8	1
Insulin	45	1
Rifampacin	15	1
Ranitidine	1	1
Furosemide	4	1
Spironolactone	4	1
Tramadol	22	2

2(2.5%) each events of palpitation, abdominal pain, dizziness, hepatitis, hypotension, hypertension and tachycardia were recorded while one (1.3%) of each event of hyperkalemia, oliguria, orthostatic hypotension, red color urine and sweating was also recorded. Suspected drugs responsible for adverse drug reaction are given in table -1. Unusual adverse drug reactions were not observed. The adverse drug

reaction which can occur due to suspected drugs were in between highly probable to possible category on Naranjo adverse drug reaction probability scale like constipation with Iron, diarrhea with amoxicillin/ metronidazole and hepatitis with HRZE (Table-1). Most of the adverse drug reactions were with Theophylline as it was responsible for 32 events when 133 times administered to patients (Table-2).

**Table- 1: Adverse drug reactions and suspected drugs**

<b>Adverse Reaction</b>	<b>Drug</b>	<b>Number of Events</b>	<b>Suspected Drugs</b>
Abdominal Pain		2	Pantaprazole, Clarithromycin
Anemia		3	Cefoperazone, Isoniazid, Pyrazinamide
Anorexia		3	Furosemide
Constipation		7	Iron, Ondansetron, Chlordiazepoxide, Sucralfate, Chlorpheniramine, Piperacillin
Diarrhea		5	Amoxicillin, Cefoperazone, Ceftazidime, Piperacillin, Linezolid, Pantoprazole, Metronidazole, Ondansetron
Dizziness		2	Prazosin, Zolpidem, Losartan
Fatigue		3	Cetirizine, Amiodarone, Levothyroxin, Amlodipine, Cetirizine, Atenolol
Headache		3	Salbutamol, Montelukast, Piperacillin/Tazobactam, Theophylline, Tramadol, Cetirizine, Pantoprazole, Rabeprazole
Heartburn		2	Amoxicillin
Hyperglycemia		6	Furosemide, Methhyl Prednisolone, Hydrocortisone, Prednisolone
Hepatitis		2	Isoniazide, Rifampicin, Pyrizinamide, Ethambutol (HRZE)
Hyperkalemia		1	Metoprolol
Hypertension		2	Methylprednisolone, Hydrocortisone, Prednisolone
Hypotension		2	Theophylline, Furosemide
Insomnia		6	Theophylline, Piperacillin/Tazobactam, Prednisolone
Nausea		6	Iron, Moxifloxacin, Piperacillin, Salbutamol, Theophylline, Metronidazole, Tramadol, Amlodipine, Rosuvastatin, Levofloxacin, Piperacillin
Oliguria		1	Methyl Prednisolone
Orthostatic Hypotension		1	Furosemide+Spironolactone
Injection site pain		1	Insulin
Palpitation		2	Salbutamol, Terbutaline, Theophylline
Pruritus		3	Ethambutol, Ondonsetron, Salbutamol, Torsemide, Pyrizinamide
Red color urine		1	Rifampicin
Restlessness		7	Theophylline
Sweating		1	Amlodipine
Tachycardia		2	Scopolamine, Amlodipine
Vomiting		6	Theophylline, Clarithromycin

## Discussion

In the present study commonest respiratory disorder was COPD (57.2%) among all the cases in both the genders and both the age groups; adult and geriatric. We found an average prescription of 14.78 drugs per patients. Awinash Pandey found use of multiple drug therapy (81%) in significant number of patients as compared to single drug therapy (19%) in patients suffering from asthma at Gorakhpur hospitals in Uttar Pradesh India. [6] Patel Pindal et al also revealed that multiple drug therapy was opted for a significant number of patients as compared to single drug therapy in asthma cases. [7] Common practice of multiple drug utilization is might be because of complicated conditions as well as association of chronic conditions like diabetes and or chronic cardiovascular diseases which need multiple drugs hence number of drugs prescribed more.

In the present study commonest adverse effects observed were constipation (7 event, 8.75%) and restlessness (7 event, 8.75%) followed by hyperglycemia, insomnia, nausea and vomiting (6, 7.5%) each. Theophylline was the only drug responsible for restlessness while constipation was due to number of drugs like Iron, Sucralfate etc. Nausea, vomiting and insomnia were also observed with Theophylline although other drugs also produced these adverse drug reactions (Table- 1). We found close association of drugs with adverse reactions as these were in between highly probable to possible category on Naranjo adverse drug reaction probability scale. But we cannot say that a particular drug caused definitely the particular type of adverse drug reaction as per the criteria of Naranjo ADR probability scale as few questions of the scale were not answered like, we have not done the re-challenging task for identification of ADR. But these ADRs are typical documented ADRs of drugs, for examples constipation with Iron, diarrhea with amoxicillin/ metronidazole, hepatitis with HRZE and red color urine with Rifampicin.

N Tyagi et al conducted a study about adverse drug reactions in patients of chronic obstructive pulmonary disease with specific focus on theophylline. Common adverse drug reactions

with inhaled steroids were sore throat, dysgeusia, hoarseness of voice, hyper pigmentation of face glossitis, etc. The adverse drug reaction profile of oral theophylline included: spasm of muscles, dyspepsia, anxiety etc. All the adverse drug reactions recorded were of non-serious nature except those in two patient on N-acetyl cysteine requiring immediate stoppage of the drug.<sup>[3]</sup> Ken Ohta et al studied theophylline safety in 3810 elderly with asthma or COPD patients. They observed 261 theophylline related adverse events in 179 (4.71%) patients. The 5 most frequently observed adverse events were nausea (40 episodes, 1.05%), loss of appetite (22 episodes, 0.56%), hyperuricemia (16 episodes, 0.42%), palpitation (15 episodes, 0.39%) and increased alkaline phosphatase (11 episodes, 0.28%).<sup>[8]</sup> Pelletier et al in their study about 1<sup>st</sup> line anti tubercular drugs found that the serious adverse reactions to antitubercular drugs were common and pyrazinamide induced hepatotoxicity and rash was significantly higher than for the other first-line anti-TB drugs.<sup>[9]</sup> Kheiroollah Gholami et al found adverse drug reactions in 44 (53%) patients out of 83 patients receiving antitubercular drugs. ADRs were recognized as the major cause of hospital admission in 11 (13.3%) patients. The most frequent system-organ class affected by ADRs was liver and biliary system (37%). The most serious adverse reaction was hepatitis (25.9%), leading to death in two patients.<sup>[10]</sup>

## Conclusion

Theophylline has adverse drug reaction probability more in comparison to other drugs which are used in respiratory disorders although non-fatal in nature. Hepatitis is serious ADR which can occur with the use of anti tubercular drugs; hence we should be cautious while treating tuberculosis. Most of the ADRs with the drugs used in present study are non serious in nature and can be easily managed but still we should be careful while using these drugs. Furthermore, if we increase number of drugs per prescription, there are more chances of increase incidences of adverse drug reactions which ultimately increases overall disease management

cost. Hence as much as possible we should try to decrease number of drugs per prescription but without compromising the disease management protocol.

---

*Source(s) of support: Nil*

*Conflict of Interest: None declared*

---

## **Acknowledgement**

Amer Khan, Ihtisham Sultan, Nematullah Khan, Shoebullah Adil, Interns in Deccan School of Pharmacy, Darussalam, Hyderabad, helped us during data collection process. We appreciate their invaluable help and are greatly thankful to them.

## **References**

1. Laporte JR, Porta M, Capella D. Drug utilization studies: A tool for determining the effectiveness of drug use. *Br J Clin Pharmacol* 1983;16:301-4.
2. Tripathi KD. Aspects of pharmacotherapy; clinical pharmacology and drug development. In: *Essentials of medical pharmacology*. 6<sup>th</sup> edition. New Delhi: Jaypee Brothers; 2008. P. 68- 71.
3. Tyagi N, Gulati K, Vijayan VK, Ray A. A study to monitor Adverse Drug Reactions in patients of Chronic Obstructive Pulmonary Disease: Focus on Theophylline. *The Indian Journal of Chest Diseases & Allied Sciences* 2008;50: 199-202.
4. Moore N, Lecointre D, Noblet C, Mabile M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 1998;45(3): 301-308.
5. Fattinger K, Roos M, Vergères P, Hostenstein C, Kind B, Masche U, Stocker ND, Braunschweig S, Kullak-Ublick AG, Galeazzi LR, Follath F, Gasser T, Meier JP. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol* 2000;49:158-167.
6. Awinash Pandey, Poonam Tripathi, Rishab Dev Pandey. Prescription Pattern in Asthma therapy at Gorakhpur hospitals. *Lung India* 2012;27(1):8-10.
7. Patel Pindal D, Patel RK, Patel NJ. Analysis of Prescription Pattern and drug utilization in asthma therapy. *International Research Journal of Pharmacy* 2012;3 (7):257-260.
8. Ken Ohta, Yoshinosuke Fukuchi, Lawrence Grouse, Ryuji Mizutani, Klaus F Rabee, Stephen Rennard, Nan-Shan Zhong. A prospective clinical study of theophylline safety in 3810 elderly with asthma or COPD. *Respiratory Medicine* 2004;98:1016-1024.
9. Daphne Yee, Chantal Valiquette, Marthe Pelletier, Isabelle Parisien, Isabelle Rocher, Dick Menzies. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory & Critical care Medicine* 2003;167:1472-77.
10. Kheirollah Gholami, Elahe Kamali, Mahboubeh Hajiabdolbaghi, Shalviri G. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. *Pharmacy Practice* 2006;4(3):134-138.