**ISSN: 0975-5160**

**Available online on www.ijtpr.com**

**International Journal of Toxicological and Pharmacological Research 2021; 11(3); 30-36**

**Original Research Article**

# Adverse Drug Reaction Monitoring in OPD of Chronic Obstructive Pulmonary Disease and their Assessment of Causality and Severity

**Dr. Narendra Kumar Tripathi**

**Tutor, Department of Pharmacology, Santosh Medical College and Hospital, Ghaziabad, UP, India.**

**Received: 10-03-2021 / Revised: 28-04-2021 / Accepted: 10-06-2021**
**Corresponding author: Dr. Narendra Kumar Tripathi**
**Conflict of interest: Nil**

**Abstract**

**Aim**: the aim of the present study to evaluate the adverse drug reaction monitoring in out patients of chronic obstructive pulmonary disease and their assessment of causality and severity.

**Methods:** A prospective, observational study was conducted in the Department of Pharmacology, Santosh Medical College and Hospital, Ghaziabad, UP, India for 1 year. All the patient selection was random and the patient population was divided into four broad categories based on diagnosis as: • Chronic obstructive pulmonary disease • Infections (pneumonia, tuberculosis (TB), lower respiratory track infection) • Asthma • Others (pleural effusion, anti-tubercular drug induced hepatitis, obstructive sleep apnea, interstitial lung disease, pleurisy, obesity hypoventilation syndrome, corpulmonale).

**Results:** During the study period, a total of 304 patients were monitored, of which 160 ADRs were observed in 98 patients accounting 32.23% of the incidence). Majority of the patients (n = 60) experienced one ADR, followed by 24 patients who suffered from two ADRs, eight patient experienced three ADRs, four patients experienced four ADRs, while two patient have experienced six ADRs. During the study, it was observed that each patient on an average experienced at least 1.63 ADRs. Based on sex, distribution of ADRs .

Among 154 male patients monitored, the incidence of ADRs was 32.5% (n = 50) in males, which were almost similar to 32% (n = 48) observed in females). 32.09% of adults experienced ADRs, which was slightly higher in geriatric patients (32.39%). Drugs contributing majorly to ADRs were theophylline (19.39%), paracetamol (6.66%), salbutamol (5.45%) and levocetirizine (5.45%), respectively. Gastrointestinal system (38.75%) was the most common organ system affected due to ADR's followed by a neurological system (22.5%), cardiovascular system (12.5%).

**Conclusion:** A relatively high incidence of adverse drug events (32.2%) have been recorded which shows that not only geriatric patients but also adults are more susceptible to adverse drug effects.

**Keywords:** ADR, COPD, Asthma

## Introduction

The World Health Organization (WHO) defines the adverse drug reactions (ADRs) as noxious and unintended responses to a medicinal product[1]. ADRs are also related to increased mortality and changes in morbidity patterns. Many studies point out that ADRs are underreported and therefore their importance is under-evaluated[2]. That is why ADRs should be more thoroughly evaluated for seriousness, causality, expectedness and severity[3]. Seriousness of an ADR is related to its life threatening nature and is defined as any untoward reaction to the medicinal product that may result in death, requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event or reaction[4]. The causality of ADRs describes the connection between the ADRs appearance and medicinal product utilization. It requires solid medical judgment based on observations of its onset and patient's status[5]. There are different algorithms for evaluation of causality of ADRs. Among them are the Jones' algorithm, the Naranjo algorithm, the Yale algorithm, the Adverse drug reaction advisory committee (ADRAC), the WHO Uppsala Monitoring Center (WHO-UMC), and a newer quantitative approach Algorithm[6]. One of the most commonly used algorithms is that of Naranjo et al[7]. It is designed as a questionnaire for determining the likelihood of whether an ADR is actually due to the drug rather than a result of other factors. Probability is assigned via score termed as definite, probable, possible or doubtful. Expectedness of the ADRs depends on their connection with the main pharmacological action of the drug[8]. There are two classes according to this criteria as Type A ADRs which are pharmacologically predictable and Type B ADRs which are idiosyncratic. Type A ADRs are most common, usually are dose related and are due to the primary or secondary pharmacological characteristics of the drug. Factors that predispose to these ADRs include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug–drug interactions. Pharmacological ADRs occur when drug concentration in plasma or tissue exceeds the "therapeutic window" or when there is increased sensitivity to the drug. Type B ADRs are hazardous and are not related to the main pharmacological action. Type B ADRs could also appear after a long-term exposure to drug or in combination with other factors such as lifestyle or food factors[8].

## Materials and Methods

A prospective, observational study was conducted in the Department of Pharmacology, Santosh Medical College and Hospital, Ghaziabad, UP, India, for 1 year. after taking the approval of the protocol review committee and institutional ethics committee.

## Methodology

After taking informed consent detailed history was taken from the patient or the relatives. The technique, risks, benefits, results and associated complications of the procedure were discussed with all patients. all the patient selection was random and the patient population was divided into four broad categories based on diagnosis as: • Chronic obstructive pulmonary disease • Infections (pneumonia, tuberculosis (TB), lower respiratory track infection) • Asthma • Others (pleural effusion, anti-tubercular drug induced

hepatitis, obstructive sleep apnea, interstitial lung disease, pleurisy, obesity hypoventilation syndrome, corpulmonale). Verbal Informed consent (in the vernacular language) was sought from the patients before their enrollment, on the basis of inclusion and exclusion criteria. Patients of either gender above 18 years admitted into (Pulmonology Department) were included in the study. Pediatrics and pregnant patients were excluded from the study. During the study, patients were monitored from the day of admission till the day of discharge. Sources of data were case sheets and verbal information while counseling the patients. The details were collected in patient profile form designed for the study purpose. The details included: Demographics, medical history, medication history, laboratory data, history of drug allergy along with causative drug, current therapy, suspected ADR, description of ADR, date of onset, management and outcome aspects. Suspected ADRs were reported, analyzed and a causality assessment was carried out using Naranjo's algorithm scale.

## Results

During the study period, a total of 304 patients were monitored, of which 160 ADRs were observed in 98 patients accounting 32.23% of the incidence). Majority of the patients (n = 60) experienced one ADR, followed by 24 patients who suffered from two ADRs, eight patient experienced three ADRs, four patients experienced four ADRs, while two patient have experienced six ADRs. During the study, it was observed that each patient on an average experienced at least 1.63 ADRs. Based on sex, distribution of ADRs is shown in Table 1.

Among 154 male patients monitored, the incidence of ADRs was 32.5% (n = 50) in males, which were almost similar to 32% (n = 48) observed in females). 32.09% of adults experienced ADRs, which was slightly higher in geriatric patients (32.39%). The patients categorized in other group had the highest incidence of ADRs (78.57%) in contrast to 56.52% in infection group, 50% in asthmatic patients and 48.72% in COPD patients). Female adults' experienced highest (72 out of 160 events i.e. 45%) while least in male adults (18 out of 160 events, i.e. 11.25%). This high prevalence of ADRs could be attributed to multiple drug intakes, which was evident in our study as 14.78 drugs prescribed to patients irrespective of the age, gender and diagnosis).

Drugs contributing majorly to ADRs were theophylline (19.39%), paracetamol (6.66%), salbutamol (5.45%) and levocetirizine (5.45%), respectively. Gastrointestinal system (38.75%) was the most common organ system affected due to ADR's followed by a neurological system (22.5%), cardiovascular system (12.5%) as shown in the Table 2. Where as Ceftazidine and Ranitidine showed highest prevalence rate of ADR. The detailed drug vs prevalence rate of ADR is shown in Table 3. Whereas Ceftazidine and Ranitidine showed highest prevalence rate of ADR. The detailed drug vs prevalence rate of ADR is shown in Table 3.

Out of 98patients with ADRs, drug was withdrawn (de-challenged) in 12 patient (hypotension, tachycardia, palpitation, hepatitis, pruritis, hyperkalemia) and specific treatment was administered to 32 (abdominal pain-4, constipation-6, diarrhoea-6, anemia-4, insomnia-4, hypotension-2, Pruritis-6) patients in view of clinical status. Full recovery was observed in 68 patients and rest of the patients had partial recovery. More over the causative drug for 12.24% of ADRs were withdrawn owing the risk involved, which resulted in the recovery of 69 Specific treatment for the management of suspected reaction.38% patients. Four patients were re-challenged with the drug, which resulted in the reappearance of ADRs.

Specific treatment for the management of suspected reaction was administered in 32.65% of ADR reports.

**Table 1: Distribution of ADRs based on sex**

| Gender | Number | Percentage |
|---|---|---|
| Male | 66 | 50 |
| Female | 94 | 48 |
| Total | 160 | 98 |

**Table 2: Distribution of ADRs in different systems of the body**

| Organ system | Frequency |
|---|---|
| Gastrointestinal | 62 |
| Hematological | 6 |
| Respiratory | 2 |
| Neurological | 36 |
| Cardiovascular | 20 |
| Endocrinological | 14 |
| Dermatological | 8 |
| Others | 12 |

**Table 3: Prevalence of ADRs in the study**

| | | | |
|---|---|---|---|
| Pantoprazole | 282 | 12 | 0.04 |
| Clarithromycin | 14 | 4 | 0.29 |
| Cefoperazone+sulbactam | 98 | 4 | 0.04 |
| Levofloxacin | 6 | 4 | 0.67 |
| Isoniazid | 30 | 2 | 0.07 |
| Pyrazinamide | 30 | 4 | 0.13 |
| Furosemide | 74 | 14 | 0.19 |
| Levocetirizine | 202 | 18 | 0.09 |
| Ondansetron | 76 | 10 | 0.13 |
| Ursodiol | 6 | 2 | 0.33 |
| Chlorphinaramine maleate | 4 | 2 | 0.5 |
| Chlordiazepoxide | 4 | 2 | 0.5 |
| Piperacillin+tazobactam | 36 | 14 | 0.39 |
| Iron | 36 | 8 | 0.22 |
| Sucralfate | 56 | 4 | 0.07 |
| Paracetamol | 144 | 22 | 0.15 |
| ORS | 44 | 2 | 0.04 |
| Ceftazidine | 2 | 2 | 1 |
| Budesonide | 288 | 16 | 0.06 |
| Metronidazole | 22 | 8 | 0.36 |
| Linezolid | 4 | 2 | 0.5 |
| Zolpidem | 8 | 2 | 0.25 |
| Losartan | 8 | 2 | 0.25 |

| | | | |
|---|---|---|---|
| Prazosin | 6 | 2 | 0.33 |
| Amiodarone | 6 | 2 | 0.33 |
| Levothyroxine | 12 | 2 | 0.17 |
| Amlodipine | 44 | 8 | 0.18 |
| Atenolol | 14 | 2 | 0.14 |
| Salbutamol | 288 | 18 | 0.06 |
| Montelukast | 194 | 4 | 0.02 |
| Theophylline | 266 | 64 | 0.24 |
| Rabeprazole | 6 | 4 | 0.67 |
| Amoxicillin+clavulanate | 158 | 6 | 0.04 |
| Methyl prednisolone | 112 | 14 | 0.12 |
| Hydrocortisone | 110 | 8 | 0.07 |
| Moxifloxacin | 44 | 6 | 0.14 |
| Rosuvastatin | 8 | 2 | 0.25 |
| Terbutaline | 10 | 2 | 0.20 |
| Ethambutol | 30 | 2 | 0.07 |
| Torsemide | 16 | 2 | 0.12 |
| Butyl scopolamine | 18 | 2 | 0.11 |
| Diclofenac | 16 | 2 | 0.12 |
| HRZE | 30 | 4 | 0.13 |
| Metoprolol | 16 | 2 | 0.12 |
| Insulin | 90 | 2 | 0.02 |
| Rifampicin | 30 | 2 | 0.07 |
| Ranitidine | 2 | 2 | 1 |
| Furosemide spironolactone | 8 | 2 | 0.25 |
| Tramadol | 44 | 4 | 0.09 |

**Table 4: Severity-Assessment of ADRs**

| Severity | Number of ADRs | Percentage of ADRs |
|---|---|---|
| Definite (>9) | 4 | 2.5 |
| Probable (5-8) | 88 | 55 |
| Possible (1-4) | 68 | 42.5 |

Naranjo algorithm was used to assess the causality which revealed that ADRs can be categorized into 55% probable, 42.5% as possible and 2.5% of ADRs as definite which is shown in Table 4.

Severity assessment indicated that 51.25% ($n$ = 82) of the suspected reactions were mild while 27.5% ($n$ = 44) were moderate and 21.25% ($n$ = 34) of them were severe in nature as shown in Table 4.

**Discussion**

Our study determines the incidence of ADR s in Pulmonology department and establishes the strategies to reduce and prevent the occurrence of ADRs. Such approaches will not only improve the quality of life of patients,' but also minimize the cost associated with ADRs' contingency.

Our finding discloses fact that the incidence of ADRs multiples with increase in number of drugs per prescription, which also has been highlighted by other previously published

studies[9]. The prevalence of adverse drug events, in our study, was nearly 1.5 times higher than a similar study conducted byTyagi *et al*[10,11].

Of all the drugs used in Pulmonology Department, the highest incidence of ADRs was seen with the use of theophylline, which replicates the findings of study conducted by Ohta *et al*.[12] The gastrointestinal effects of theophylline can be minimized by consuming it with food. As theophylline has a narrow therapeutic index, it serum levels should be monitored to prevent theophylline associated cardio-toxicity.

Number of ADEs caused by anti-TB drugs in our study was similar to a previous study carried out by Yee *et al*. However, the figure was four times higher in a study by Gholami *et al*[13,14]. The contribution of antibiotics to ADRs was slightly less when compared to a study conducted by Gallelli *et al*[12]. Recovery after drug withdrawal in Gallelli *et al*. study was higher than our study. This may be due to a high certainity of drug ADR relationship in their study[11].

The study re-establishes that patients suffering from severe or acute respiratory disorders generally use multiple drugs and have increased susceptibility to ADRs and such patients should be carefully monitored to reduce ADRs associated morbidity. In most of the clinical settings, there is no proper reporting and monitoring of ADRs. Lack of formal pharmacovigilance centers is a major issue in developing countries responsible for under-reporting of ADRs. Establishment of pharmacovigilance centers with effective monitoring and reporting will play a significant role in preventing and managing the ADRs.

## Conclusion

A relatively high incidence of adverse drug events (32.2%) have been recorded which shows that not only geriatric patients but also adults are more susceptible to adverse drug effects. A number of drugs in combination were used, and ADEs often get multiplied. Careful therapeutic monitoring and dose individualization is necessary. The incidence of ADRs was highest in geriatric patients. Nonetheless, adult patients also showed higher incidence, which could attribute to the use of multiple drugs administered, to minimize this high incidence of ADRs dose individualization and therapeutic monitoring of drugs is essential. Clinical studies to elicit the toxicodynamics of these ADEs and *safety versus risk* issues could be beneficial in devising strategies for its rational use in respiratory diseases.

## Reference

1. World Health Organization (WHO). International drug monitoring: the role of national centers. Technical report no. 498, 1972, http://www.who-umc.org/graphics/24756.pdf
2. Edwards IR and Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255- 1259.
3. Australian Government, Department of health and Ageing. Australian guideline for pharmacovigilance responsibilities of sponsors of registered medicines regulated by drug safety and evaluation branch (Amended 31 May 2005), 2003, http://apps. who.int/medicinedocs/documents/s17999en/s17999en.pdf
4. Nebeker JR, Barach P and Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004; 140: 795-801.
5. Khan FA, Nizamuddin S, Huda N, et al. A prospective study on prevalence of adverse drug reactions due to antibiotics usage in otolaryngology department of a tertiary care hospital in North India. Int

J Basic Clin Pharmacol 2013; 2: 548-553.
6. Kramer MS and Hutchinson TA. The Yale algorithm. Special workshop: clinical. Drug Inf J 1984; 18: 283–291.
7. Karch FE and Lasagna L. Towards the operational identification of adverse drug reaction. Clin Pharmacol Ther 1977; 21: 247–254.
8. Hubes ML, Whittlesea CM, Lusconbe DK, et al. An investigation into how symptoms are recognized as side effects of medication. Pharm J 2002; 269: 719–722
9. Khan FA, Nizamuddin S, Huda N, Mishra H. A prospective study on prevalence of adverse drug reactions due to antibiotics usage in otolaryngology department of a tertiary care hospital in North India. Int J Basic Clin Pharmacol 2013;2:548-53.
10. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998;45:301-8.
11. 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. Indian J Chest Dis Allied Sci 2008;50:199-202.
12. Gallelli L, Ferreri G, Colosimo M, Pirritano D, Guadagnino L, Pelaia G, *et al.* Adverse drug reactions to antibiotics observed in two pulmonology divisions of catanzaro, Italy: A six-year retrospective study. Pharmacol Res 2002;46:395-400.
13. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003;167:1472-7.
14. Gholami K, Kamali E, Hajiabdolbaghi M, Shalviri G. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. Pharm Pract (Granada) 2006;4:134-8.