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INCIDENCE AND PATTERN OF ADVERSE DRUG REACTIONS (ADRs) IN PATIENTS TREATED FOR TUBERCULOSIS UNDER DOTS AT A TERTIARY CARE HOSPITAL OF NORTHERN INDIA

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Tuberculosis, Adverse drug reactions, Directly observed treatment short course, Incidence, Northern India

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ABSTRACT: Background: WHO statistics for 2015 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9 million thus making India accountable for almost one-third of the global TB burden. The first-line antitubercular drugs include H (Isoniazid), R (Rifampicin), Z (Pyrazinamide), E (Ethambutol) and S (Streptomycin). The treatment of tuberculosis being of longer duration being a multidrug regime and of longer duration gets associated with various adverse effects. **Objective:** The study aimed to determine the incidence and pattern of adverse drug reactions (ADRs) of anti-tubercular drugs in tuberculosis patients treated under DOTS at tertiary care hospital of Northern India. **Material and Method:** A total of 115 patients were monitored for the period of 12 months. The diagnosis of tuberculosis was confirmed by sputum smear prior to enrolment. Before the patients were started on DOTS regimen, they were submitted to some pretreatment investigation and then they have been followed up to look for any adverse effects which have been recorded onto the CDSCO suspected adverse drug reaction reporting form. **Results:** Out of 115 patients, 58.26% *i.e.* 67 patients developed ADR. If we compare what percentage each age group contributed to total pool of ADR, we observe that age group 41-50 constituted (29.85%), 31-40 (22.39%); 18-30(17.91%) of the population (n=67) who developed ADR. Incidence of ADRs in category I was 57.6% while 60% in category II. Incidence of ADR in pulmonary cases came out as 57.69% while it was 56.75% in extrapulmonary cases.

INTRODUCTION: Undoubtedly modern drugs have increased life expectancy and improved quality of life for millions of people. However, despite all these benefits, evidence continues to suggest that adverse reactions to medicines are common, though often preventable, cause illness, disability and even death.

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As per WHO pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicines-related problems". During the last few decades health professionals and the public have started to recognize morbidity and mortality due to medicine as one of the major health hazards [1].

Tuberculosis (TB) is caused by bacteria of the *Mycobacterium tuberculosis* complex. It is one of the oldest diseases known to mankind and was as well as still been responsible for huge death toll worldwide. India is the country with the highest burden of TB.

The World Health Organization (WHO) statistics for 2015 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9 million thus making India accountable for almost one-third of the global TB burden [2]. Anti-tubercular drugs are mainly classified as first- and second-line drugs. Conventionally, there are five first-line drugs: H (Isoniazid), R (Rifampicin), Z (Pyrazinamide), E (Ethambutol), and S (Streptomycin). Second-line drugs include the aminoglycosides kanamycin and amikacin, the polypeptide capreomycin, PAS, cycloserine, terizidone, the thioamides ethionamide and prothionamide and several fluoroquinolones such as moxifloxacin, levofloxacin and gatifloxacin. All these first line drugs have been associated with various side effects. Some of the frequently encountered side effects of these first line drugs are:

Isoniazid: Hepatitis, peripheral neuropathy, rashes.

Rifampicin: Orange urine/body fluids (sweat), flu-like syndrome, hepatitis.

Pyrazinamide: Hepatitis, hyperuricemia, arthralgia, rashes.

Ethambutol: Optic neuritis (red-green color blindness), hyperuricemia.

Streptomycin: Ototoxic effects, generally manifesting as dizziness, vertigo.

These are just few side effects been mentioned here and they just represent a sector of the vast canopy of side effects produced by anti-tubercular drugs. The monitoring of adverse drug reactions will also help in spreading awareness in the patients to be vigilant by themselves for some adverse signs which can help the physicians to address them in time [3]. Citing some previous studies like Gurprit Singh Nanda *et al*., [4] conducted in Jalandhar, has showed an incidence of ADR due to first line anti-tubercular drugs to be 20.4%.

While in the study conducted by Kumarjit Sinha *et al*., [5] which included 102 patients showed the incidence rate of ADR as 69.01%. Arindam Chakraborty *et al*., [6] included 196 patients in his study and found 42% incidence rate of ADRs due to first line anti-tubercular drugs. Similarly studies on first line anti-tubercular drugs by Chhetri *et al*., [7] in Nepal among 137 patients, Jeong *et al*., [8] in Korea among 105 patients and Qureshi *et al*., [9] in India among 50 patients showed an incidence rate of adverse drug reactions to DOTS therapy as 54.74%, 57% and as 60% respectively. Thus working on the path showed by these studies a similar study was conducted with the objective of determining the incidence and pattern of adverse drug reactions (ADRs) of anti-tubercular drugs in tuberculosis patients treated under DOTS.

MATERIALS AND METHODS: The study was conducted at the Department of Respiratory Medicine, King George's Medical University, Lucknow. The study was started after ethical clearance from the Institutional Ethics Committee of King George's Medical University, Lucknow. All patients with proven tuberculosis and put on DOTS regimen under RNTCP and meeting our inclusion criteria were recruited from the Department of Respiratory Medicine of King George's Medical University. The total duration of study was 12 months *i.e*. May 2016 to April 2017

Subject Selection: All patients with proven tuberculosis and put on DOTS regimen under RNTCP were screened for the study. Those who satisfied our inclusion / exclusion criteria were included in the study after taking written informed consent.

Inclusion Criteria:

- Newly diagnosed patients of tuberculosis.
- Patients of either sex with age more than 18 years.
- Patients having normal base line (pretreatment) parameters like liver function tests, kidney function tests, thyroid function tests, psychiatric screening, and chest X-ray other than blood sugar (fasting and post-prandial) and HIV seropositivity.
- Patients having no associated comorbidities except HIV and diabetes mellitus.

Exclusion Criteria:

- Patients who were unwilling to participate and did not give consent in the study.
- Patients who were unable to give interview.
- Patients with incomplete medical record.

- Patients with chronic liver disease such as cirrhosis, chronic hepatitis and acute viral hepatitis.
- Patients with concurrent major psychiatric illness and/or concurrent major medical illnesses.
- Patients with abnormal laboratory value at baseline evaluation while analysing for that particular adverse effect.
- Terminally ill patients.

Study Design: The patients were monitored for the period of 12 months from the day of commencement of treatment. The diagnosis of tuberculosis was confirmed by sputum smear prior to enrolment. Before the patients were started on DOTS regimen, they were submitted to some pre-treatment investigation such as, liver function tests, kidney function tests (blood urea, serum creatinine), thyroid function tests, blood sugar levels (fasting and post-prandial), psychiatric screening, HIV seropositivity test and chest X-ray.

The treatment had been initiated as per their categorization into category I or II. The intensive phase generally consists of five drugs like Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin while that of continuation phase consists of Isoniazid and Rifampicin. Patients were allotted a unique patient identification number for ease of follow up. If admitted then initially, they were monitored daily for any adverse drug reactions after starting regimen and after getting discharged they were monitored and followed up on a monthly basis. The patients who used to visit the drug distribution centre were followed up weekly Patients were monitored for any of their complaints. During subsequent visits biochemical investigations were repeated. Chest X-ray was done when required. Patients with severe adverse drug reactions were referred to concerned clinical departments and followed up regularly. The patients were interviewed and data was captured onto the CDSCO suspected adverse drug reaction reporting form. Information regarding demographic details, current medication, health status, previous history and adverse events experienced were recorded.

Statistical Analysis: Categorical variables were presented in number and percentage (%). Qualitative variables were compared using Chi-Square test / Fisher's exact test as appropriate. A p value of <0.05 were considered statistically significant. Statistical analysis was performed using GraphPadQuickCalcs software available online at http://graphpad.com/quickcalcs/. The data were entered in MS EXCEL spreadsheet and analysis will be done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS:

Incidence and Pattern of Adverse Drug Reactions: Out of 115 patients, 58.26% *i.e.* 67 patients developed ADR

TABLE 1: AGE WISE DISTRIBUTION OF PATIENTS DEVELOPING ADRS

Age	18-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-70 n (%)	71-80 n (%)	81 and above n (%)	Total
Male	7 (58.33)	9(60)	12(60)	4(44.44)	3(60)	2(50)	1(50)	38
Female	5 (41.67)	6(40)	8(40)	5(55.56)	2(40)	2(50)	1(50)	29
Total	12	15	20	9	5	4	2	67

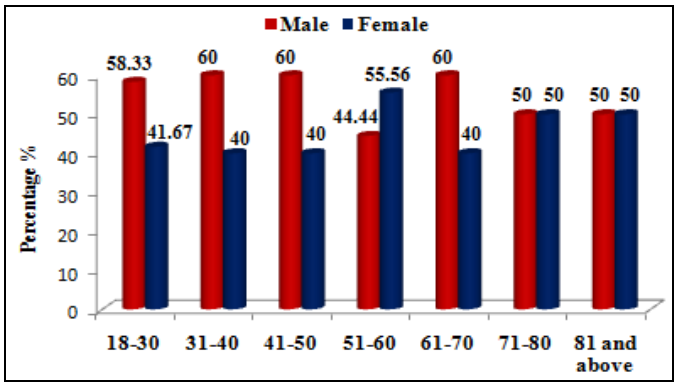

FIG. 1: AGE WISE DISTRIBUTION OF PATIENTS DEVELOPING ADRs

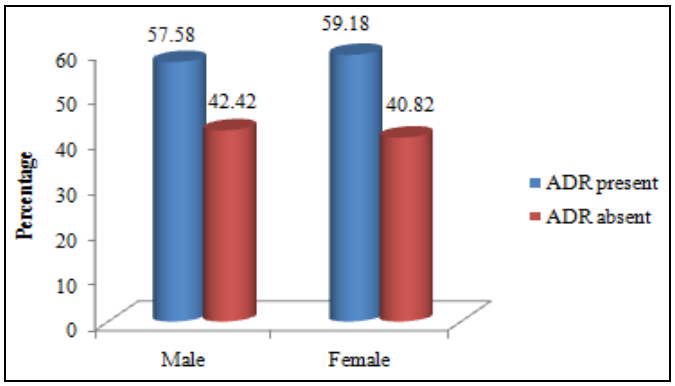

FIG. 2: INCIDENCE PATTERN OF ADRs (GENDER-WISE)

TABLE 2: INCIDENCE PATTERN DISTRIBUTION BASED ON GENDER OF PATIENTS

ADR	Male	Female
ADR present	38(57.58%)	29(59.18%)
ADR absent	28(42.42%)	20(40.82%)
Total	66	49

If we compare what percentage each age group contributed to total pool of ADR, we observe that age group 41-50 constituted (29.85%), 31-40 (22.39%) ; 18-30(17.91%) of the population (n=67) who developed ADR. Thus it has been observed that 47(63.51%) out of total 74 patients of age group 18-50 years developed ADR. **Table 1**, **Fig. 1**. The incidence pattern of ADRs in male population was 38/66 (57.57%) and in females was 29/49 (59.18%) **Table 2**, **Fig. 2**. Incidence of ADRs in category I was 57.6 % while 60 % in category II **Table 3**, **Fig. 3**.

TABLE 3: INCIDENCE PATTERN OF ADRs IN DIFFERENT CATEGORIES OF TREATMENT

ADR	Category I	Category II	Total
ADR +(present)	49 (57.6%)	18 (60%)	67 (58.3%)
ADR-(absent)	36 (42.4%)	12 (40%)	48 (41.7%)
Total	85	30	115

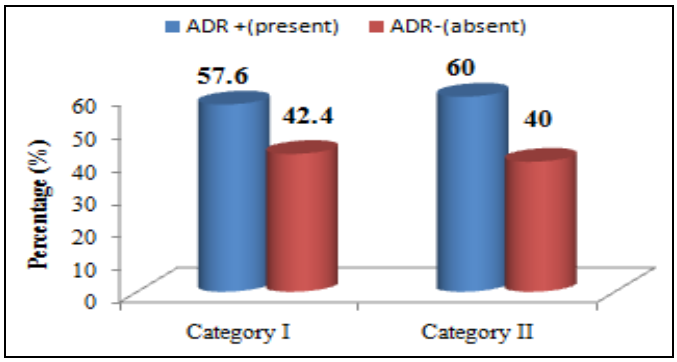

FIG. 3: INCIDENCE PATTERN OF ADRs IN DIFFERENT CATEGORIES OF TREATMENT

Incidence of ADR in pulmonary cases came out as 57.69% while it was 56.75% in extrapulmonary cases **Table 4**, **Fig. 4**.

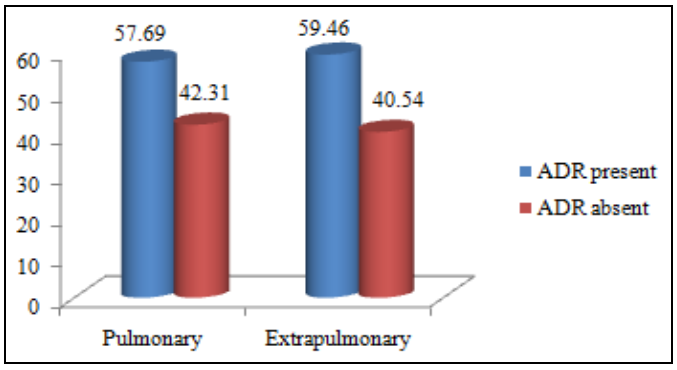

FIG. 4: INCIDENCE PATTERN OF ADRs IN DIFFERENT SITES OF THE DISEASE

TABLE 4: INCIDENCE PATTERN OF ADRS IN DIFFERENT SITES OF THE DISEASE

ADR	Pulmonary	Extrapulmonary	Total
ADR present	45(57.69%)	22(59.46%)	67(58.3%)
ADR absent	33(42.31%)	15(40.54%)	48(41.7%)
Total	78(100)	37(100)	115(100)

DISCUSSION: Here in our study the incidence of adverse drug reactions (ADR) came out to be 58.26%. On the similar lines study from Nepal conducted by Chhetri *et al.*, [7] found the incidence of ADR to be 54.74% while Kishore *et al.*, [10] found the incidence to be 12.27%. Qureshi *et al.*, [9] and Sinha *et al.*, [5] reported ADR to occur in frequency of 60% and 69.1% respectively, both conducted their study in India.

While Lv *et al.*, [11] in China reported ADR frequency as 17.33%. Jeong *et al.*, [8] in Korea reported the incidence of ADR as 57%. This difference observed that in the results from the previous studies and the present study can be attributed to the difference in the genetic, demographic, ethnicity, nutritional status in the different population groups.

In the present study majority of the ADRs were reported by the age group 41-50 years (29.85%). The mean age of the patients who developed ADRs was 45.63. On the similar lines a study conducted by Athira B *et al.*, [12] found out the maximum burden of ADRs has been carried by age group of 50-70 years with the mean age of 44.92 ± 17.22 years. Similarly the study conducted by S. Nemagouda *et al.*, [13] found that the maximum incidence of ADRs occurred in the age group of 41-60 years with the mean age of patients developing ADR to be 45.26 ± 13.45 years.

Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to males [10]. A study by Yee *et al.*, [14] and Shakya *et al.*, [15] have tried to consolidate this fact that female gender is a risk factor for the occurrence of ADRs due to anti-TB drugs. Similarly in this present study the incidence of ADR has been a notch higher in female 29 out of 49 (59.18%) as compared to male population 38 out of 66 (57.58 %). But as the male (n= 66) constitutes more than the female subjects (n=49), thus naturally male (38 out of 67, 56.7%) contributed more than female (29 out of 67, 43.3%) to the total patients who developed ADR (n=67).

The incidence of ADR in category I was 57.6% (49 out of 85 patients) while this incidence of ADR in category II was 60.00% (18 out of 30). Here thus among 67 patients who developed ADR, 49 patients (73.13%) were from category I and 18 patients (26.87%) belonged to category II. This was similar to the study done by Athira *et al*., [12], where among 93 patients with ADRs, 70 patients (75.26%) were from category I and 23 patients (24.73%) were from category II. In the study they also found out that among pulmonary tuberculosis patients, those with sputum positive (54%) developed more number of adverse drug reactions as compared to those who are sputum negative. Similarly in the study conducted by Anusha N *et al*., [16] it came that Cat I patients constituted 83.33% while Cat II patients 17.67% of the total patients who developed ADRs.

In our study that pulmonary cases constituted 67.83% (78 out of 115) while extrapulmonary cases formed 32.17% (37 out of 115). Here in our study the incidence of adverse drug reaction in pulmonary cases came out to be 57.69% (45 out of 78 pulmonary TB patients) while this incidence in extra-pulmonary cases came out to be 56.75% (21 out of 37 patients with extrapulmoary TB). Thus out of the total patients who developed ADR (N= 67) 67.16% (*i.e.* 45 out of 67) were pulmonary cases while 32.84% (21 out of 67) were extrapulmonary cases. Similarly in the study conducted by Athira *et al*., [12] it came out that incidence of ADR in pulmonary cases was 20.56% while that in extrapulmonary cases it was 15.28% which implies that in pulmonary case the incidence of ADR ranks a little higher that of extrapulmonary cases which goes in sync with our finding.

CONCLUSION: Out of 115 patients, 67 patients developed ADRs. The age group of 41-50 being more vulnerable showed higher incidence and outnumbered the patients in other group who developed ADRs. As compared to females, there were more males with ADRs because male constituted more of our sample population. Female with small body size and weight with alterations in their metabolism in different periods reported higher incidence of ADRs than in males. The incidence of ADRs was higher in category II patients as compared to category I, implying that category II patients due to a history of previous treatment gets more vulnerable to develop ADRs. The incidence of ADR was higher in patients with extra-pulmonary tuberculosis as compared to pulmonary type implying that due to dissemination of the disease in extrapulmonary tuberculosis in, the propensity to develop ADRs gets higher.

Clinical Outcome: Out of the total 115 patients followed up for these 12 months we landed up at these conclusions and clinical outcomes. Out of the 115 subjects we began our study with 99 (86.09%) of them got cured of this disease. 2 out of 115 (1.74%) were declared as “failure” as they failed to get their sputum smear converted negative. 7 out of 115 (6.09%) came out as “defaulters”. While 1 out of 115(0.87%) died during the course of the treatment. 6 out of 115 (5.22%) were transferred out of the centre.

Limitations: One of the major limitations of the study was that the study was of one-year duration with small sample size though the value of its result cannot be ignored. However, a large scale observational study with larger sample size along with longer follow-up period could have provided with better rate of incidence database for TB drug regimen associated ADRs. The patients who stay in far villages often do not report to us for minor side effects. Though we tried to contact them regularly telephonically they may not have reported minor side effects. However patients with significant ADRs visited our TB-DOTS centre and the ADRs have been recorded.

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CONFLICT OF INTEREST: Nil

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