INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

A PROSPECTIVE OBSERVATIONAL STUDY ON THE EVALUATION OF ANTI-TUBERCULAR THERAPY INDUCED ADVERSE DRUG REACTIONS IN PATIENTS WITH TUBERCULOSIS

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ARTICLE INFO

Article history
Received 29/05/2018
Available online
05/06/2018

Keywords
Adverse Drug Reactions,
Tuberculosis,
Category-I,
Category-II,
WHO-UMC SCALE.

ABSTRACT

BACKGROUND: Tuberculosis is a disease of great antiquity and ranks the second highest contagious disease globally which is caused by Mycobacterium Tuberculosis. According to WHO, an adverse drug reaction is defined as "a response to a drug which is noxious, unintended and which occurs at normal doses used for prophylaxis diagnosis or therapy of disease or for the modification of physiological functions". METHODOLOGY: This study was conducted with the objective to evaluate the anti- tubercular therapy induced adverse drug reactions in patients who were diagnosed with sputum positive tuberculosis in Govt. General and Chest Hospital, Erragadda, Hyderabad. This study is observational in nature and the subjects enrolled under this study were about 150. Informed consent was obtained from all the subjects. Subjects recruited in the study were admitted as in-patients in the hospital. The causality assessment of suspected ADR'S was done by using WHO-UMC SCALE and severity assessment by using modified Hartwig and Siegel scale. RESULTS: This study identifies the incidence and patterns of adverse drug reactions in patients who were prescribed with DOTS Therapy (category I and category II drug regimens). Out of 150 patients, 44 patients were suspected with 53 ADR'S, in which female patients(60.3%) were more prone to the occurrence of ADR'S when compared with male patients(39.7%).Based upon the categories of the drug regimens more number of ADR'S were associated with category II (63%) than ADR'S associated with category I (37%).More number of probable reactions (51%) and moderate reactions (55%) were identified by using WHO-UMC scale and Hartwig and Siegel scale respectively. CONCLUSION: Major adverse reactions in anti-tubercular drugs can cause significant morbidity and compromise treatment regimens for tuberculosis. These events may result in substantial additional costs because of added outpatient visits, investigations and in more serious instances hospitalization. As a result, the risk of treatment failure and relapse are higher.Regular ADR monitoring is required to reduce morbidity and to improve patient compliance after initiation of anti-tubercular therapy. Further study is required for preventing the occurrence of ADR'S.

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*Please cite this article in press as **Dr. Syeda Zaineb Humaira Hussaini** et al. A Prospective Observational Study on the Evaluation of Anti-Tubercular Therapy Induced Adverse Drug Reactions in Patients with Tuberculosis. Indo American Journal of Pharmaceutical Research.2018:8(05).*

INTRODUCTION

The World Health Organization declared tuberculosis (TB) a global health emergency. Tuberculosis is a potentially fatal contagious disease that can affect almost any part of the body but is mainly an infection of the lungs. TB ranks second to human immunodeficiency virus as the leading cause of death worldwide from an infectious disease. [1]

The understanding of the epidemiology of Mycobacterium tuberculosis is critical for effective control. According to the World Health Organization, nearly one third of the world has an asymptomatic or latent tuberculosis infection. In some cases this is harmless, but the ability of tuberculosis to survive treatment and spread makes diagnosing and understanding infections vital to combating its lethality and global prevalence. [2,3]

There are several TB tests available to diagnosis TB: Sputum smear test, TB Culture test, TB Skin test, TB Interferon gamma release assays (IGRAS). [4,5]

TREATMENT:

The recommendation from the World Health Organization (WHO) is that for smear positive TB patients treated with first line drugs, the patients should have smear microscopy performed at the end of the two month intensive phase of treatment. Sputum should be collected when the patient is given the last dose of the intensive phase of treatment.[6,7]

National TB treatment guidelines strongly recommend using a patient-centered case management approach - including directly observed therapy ("DOT") - when treating persons with active TB disease. [8] DOT is especially critical for patients with drug-resistant TB, HIV-infected patients, and those on intermittent treatment regimens (i.e., 2 or 3 times weekly). [9]Tuberculosis treatment is given according to the category i.e. CAT I and CAT II drugs. The CAT I and CAT II drug schedule is selected based on the guidelines of RNTCP (Revised National Tuberculosis Control Programme) [10,11] which is as follows:

Category And Type Of Patient	Duration Of Treatment	Drug Regimen
CATEGORY I	For all such cases	INH + RMP + PZA + ETB
*Newly diagnosed sputum positive pulmonary tuberculosis	Intensive phase (2 months)	INH + RMP
*Sputum negative pulmonary tuberculosis with extensive parenchymal involvement.	Followed by : Continuation phase (4 months)	
*Severe form of extra pulmonary tuberculosis	Total 6 months	
CATEGORY II	For all such cases	2 months: INH + RMP + PZA + ETB + SM
*Treatment failure cases	Intensive phase (2+1= 3 months)	1 month: INH + RMP + PZA + ETB
* Relapse cases	Followed by:	INH + RMP + ETB
* Return after interruption	Continuation phase (5 months)	

*Key words: INH-Isoniazid; RMP-Rifampicin; PZA-Pyrazinamide; ETB-Ethambutol; SM-Streptomycin.

ADVERSE DRUG REACTIONS:

Adverse drug reactions can be simply classified into mild, moderate and severe depending upon their severity. For dose-related adverse drug reactions, modifying the dose or eliminating or reducing precipitating factors may suffice. Increasing the rate of drug elimination is rarely necessary. [12]

The causality and severity assessment of ADR'S is done by using WHO-UMC and Hartwig and Siegel scale respectively. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions.[13]

The term severity is often used to describe the intensity of a medical event, as in grading 'mild', 'moderate' and 'severe'. Severity assessment categorizes the ADRs as mild, moderate, or severe based on the steps taken for the management of the ADRs.[14,15] Hartwig et al categorized ADRs into seven levels as per their severity. Level 1 & 2 fall under mild category, level 3 & 4 under moderate and level 5, 6 & 7 fall under category severe.[16,17]

OBJECTIVES

- To collect the demographic details of the patients receiving anti tubercular therapy.
- To evaluate the anti-tubercular therapy induced adverse drug reactions.
- To identify the incidence and patterns of Adverse Reactions associated with the use of Drugs in Tuberculosis infection.
- To assess the causality and severity of ADRs by Hartwig and siegel severity assessment scale and WHO Uppsala monitoring centre (WHO-UMC) scale.

METHODS AND METHODOLOGY:

The study was performed in Govt. General and Chest Hospital, Telangana, India. It is a well-recognized hospital where patients with various pulmonological ailments visit to get their disease treated. Informed consent was obtained from all the subjects. Subjects recruited in the study were admitted inpatients ward the hospital. This study evaluates the adverse drug reactions induced by the anti-tubercular therapy and the reactions encountered were assessed using standard causality (WHO-UMC scale) and severity scales (Modified Hartwig and Siegel scale).

RESEARCH PARTICIPANTS

A total of 150 patients including 89 males and 61 females were taken and the disease condition was assessed after taking the informed consent from each of them. The patients were asked about their demographic details, past medical and medication history. After completing the history, clinical details has been collected from the case reports. The obtained clinical data and the test results were re-examined and entered in the data collection forms and further the results obtained were tabulated. The patients were also counseled which helped them improve and manage their disease condition, improve quality of life and to a certain extent helped in prevention of minor ADR'S.

RESULTS

PATIENT POPULATION DEMOGRAPHICS

Table 1: Distribution of patients based on Gender:

GENDER	NO. OF PATIENTS	PERCENTAGE
Males	89	59.33%
Females	61	40.67%
Total	150	100.00%

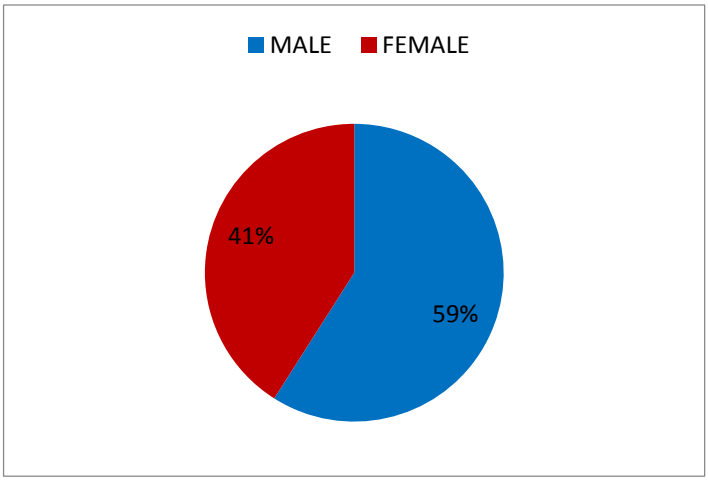

Figure 1: Distribution of patients based on Gender.

Table 2: Distribution of patients based on Age groups.

AGE (IN YRS)	MALE	% (MALES)	FEMALES	% (FEMALES)
16 - 25	8	8.99%	32	52.46%
26 - 35	18	20.22%	16	26.23%
36 - 45	28	31.46%	8	13.11%
46 - 55	19	21.35%	2	3.28%
56 - 65	10	11.24%	2	3.28%
>65	6	6.74%	1	1.64%
TOTAL	89	100.00%	61	100.00%

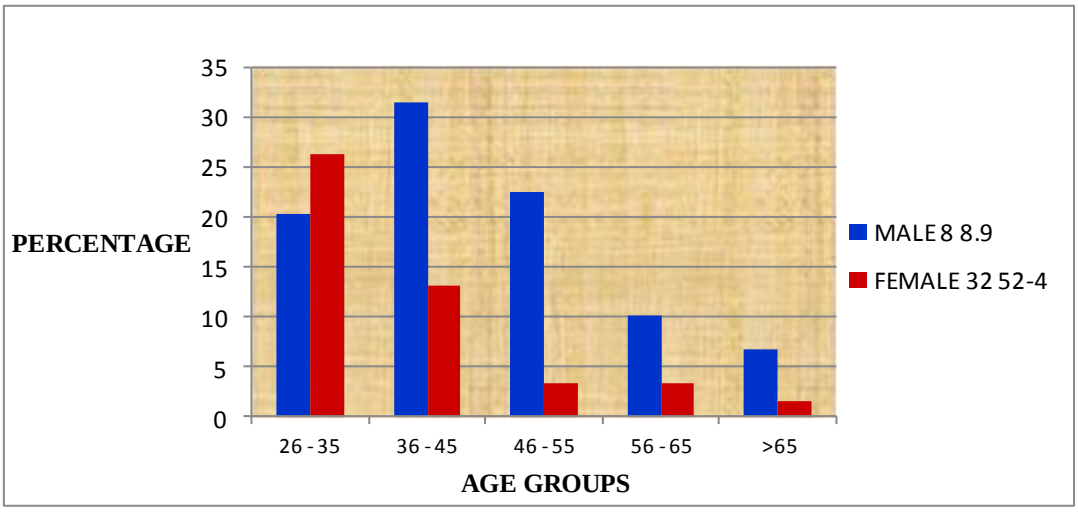

Figure 2: Distribution of patients based on Age groups.

Table 3: Distribution of patients based on the Present Complaints.

S.NO	SYMPTOMS	SEX	NO. OF PATIENTS
1.	COUGH WITH EXPECTORATION	M	85
		F	54
2.	SHORTNESS OF BREATH	M	80
		F	52
3.	CHEST PAIN	M	35
		F	28
4.	FEVER ASSOCIATED WITH CHILLS	M	70
		F	48
5.	GENERALISED WEAKNESS	M	68
		F	55
6.	LOSS OF APPETITE	M	82
		F	65
7.	WEIGHT LOSS	M	80
		F	64

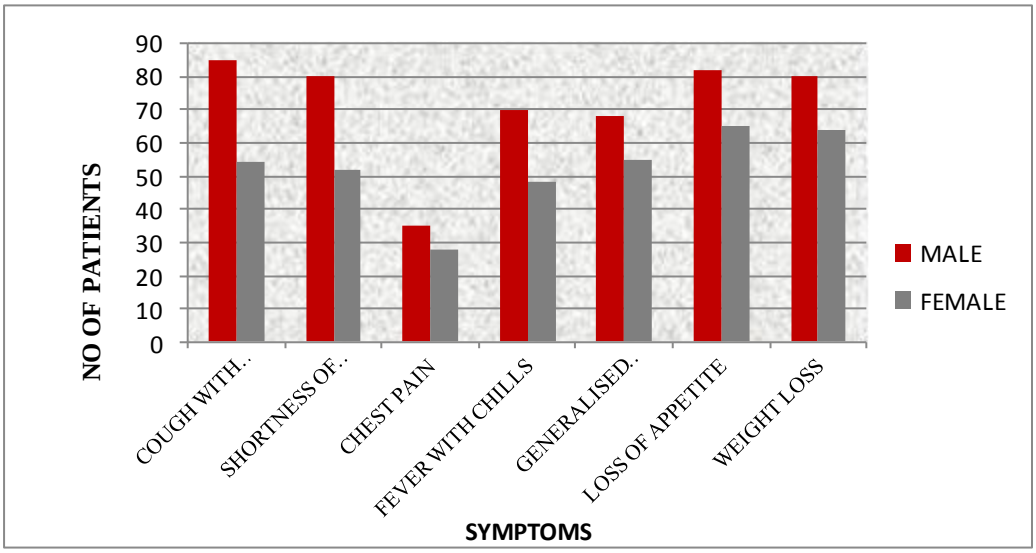

Figure 3: Distribution of patients based on the present complaints.

Table 4: Distribution of patients based on Personal History.

S. NO	PERSONAL HISTORY	SEX	NO. OF PATIENTS
1.	TOBACCO CHEWER	M	5
		F	3
2.	SMOKERS	M	6
		F	0
3.	ALCOHOLICS	M	11
		F	0
4.	SMOKERS + ALCOHOLICS	M	47
		F	0
		M	36
5.	NO ADDICTIONS	F	42

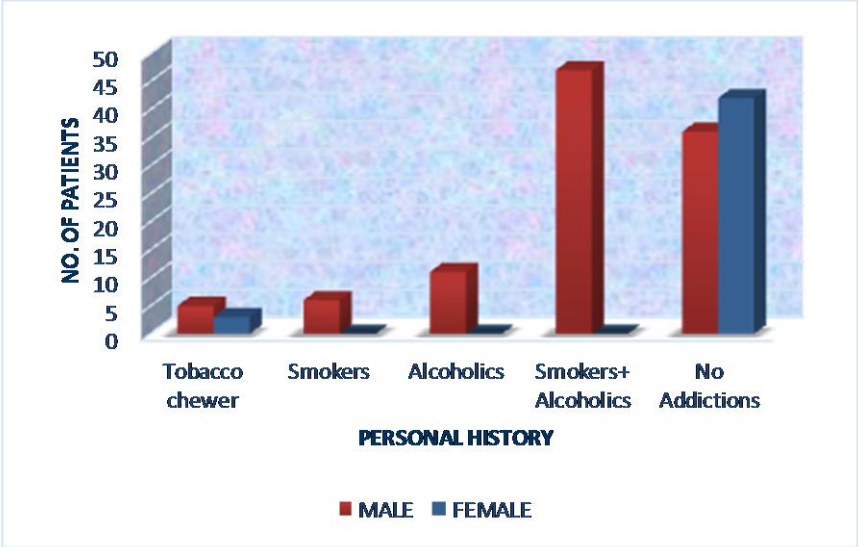

Figure 4: Distribution of patients based on the personal History.

The occurrence of ADR"S in patients who were given anti-tubercular therapy included ,8 (37%) males and 12 (44%) females with CAT I drugs and 13 (63%) males and 15 (56%) with CAT II drugs.

Table5:Distribution of patients based on Occurrence of ADR'S in CAT-I AND CAT-II.

S NO.	CATEGORY	MALE	FEMALE
1	CAT I	10(18.8%)	13 (24.5%)
2	CAT II	14 (27%)	16 (30%)

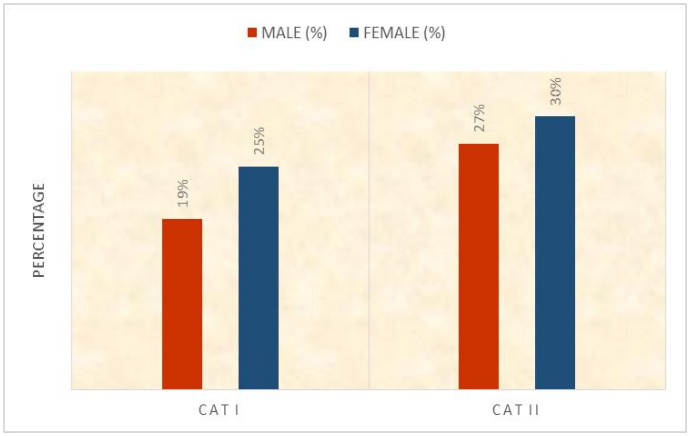

Figure 5: **Distribution of patients based on Occurrence of ADR'S in CAT-I AND CAT-II.**

The patients were divided based upon the occurrence of ADR'S, whether the patient had single ADR or multiple ADR'S. 86.36% of patients had single ADR and 13.6% of patients had reported of multiple ADR'S.

Table6: Distribution of patients based on Occurrence of Single ADR and Multiple ADR'S.

S.NO	ADVERSE DRUG REACTIONS	NO. OF PATIENTS	PERCENTAGE
1	SINGLE ADR	38	86.36%
2	MULTIPLE ADR'S	6	13.64%
	TOTAL	44	100.00%

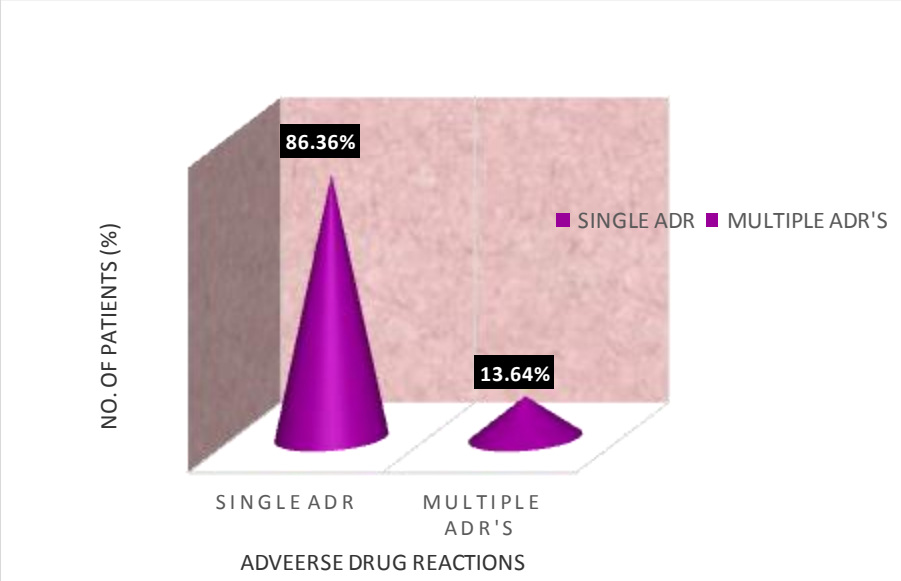

Figure 6: **Distribution of patients based on Occurrence of Single ADR and Multiple ADR'S.**

The anti-tubercular therapy induced adverse drug reactions occurred mostly due to combination drug regimen of DOTS (47.1%) and rarely due to specified drug.

Table7: Distribution of patients based on Occurrence of ADR By COMBINATION of DRUGS or with SPECIFIC DRUG.

S.NO	DRUGS	NO. OF PATIENTS	PERCENTAGE
1	COMBINATION OF DRUG	25	47.17%
2	ISONIAZID	6	11.32%
3	RIFAMPCIN	8	15.09%
4	PYRAZINAMIDE	10	18.87%
5	ETHAMBUTOL	0	0.00%
6	STREPTOMYCIN	4	7.55%
	TOTAL	53	100.00%

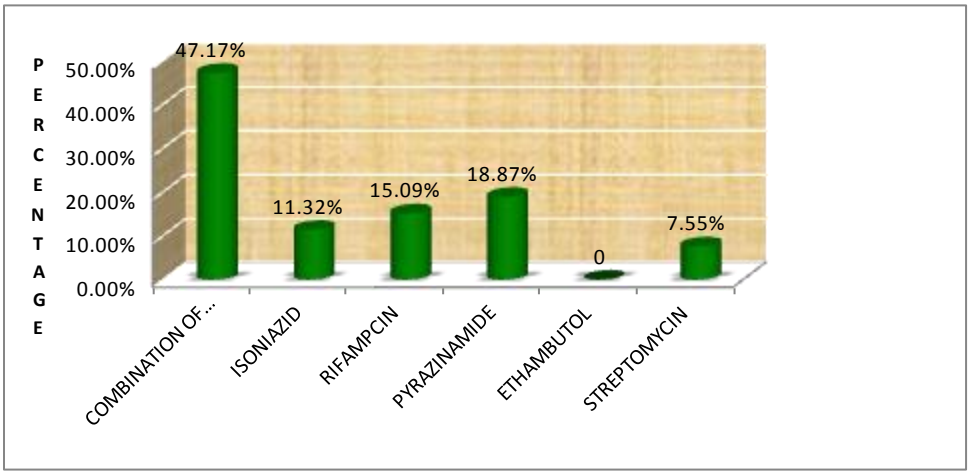

Figure 7: **Distribution of patients based on Occurrence of ADR By Combination of DRUGS or with Specific drug.**

Frequencies of various ADR'S are given in the table below. In which gastritis (35.85%) was the most frequently occurred ADR and the less frequently occurred ADR'S include renal failure, arthralgia and thrombocytopenia.

Table 8: Frequencies of different Adverse Drug Reactions Observed in the study.

S NO.	ADVERSE DRUG REACTIONS	FREQUENCY	PERCENTAGE
1	GASTRITIS	19	35.85%
2	HEPATITIS	2	3.77%
3	JAUNDICE	2	3.77%%
4	HEPATOTOXICITY	5	9.43%
5	PSYCHOSIS	4	7.55%
6	SEIZURES	2	3.77%
7	RASHES AND PRURITIS	7	13.21%
8	PAIN AT INJECTION SITE	1	1.89%
9	ANAEMIA	2	3.77%
10	THROMBOCYTOPENIA	2	3.77%
11	RENAL FAILURE	2	3.77%
12	ARTHRALGIA	2	3.77%
13	HEARING LOSS	3	5.66%
	TOTAL	53	100.00%

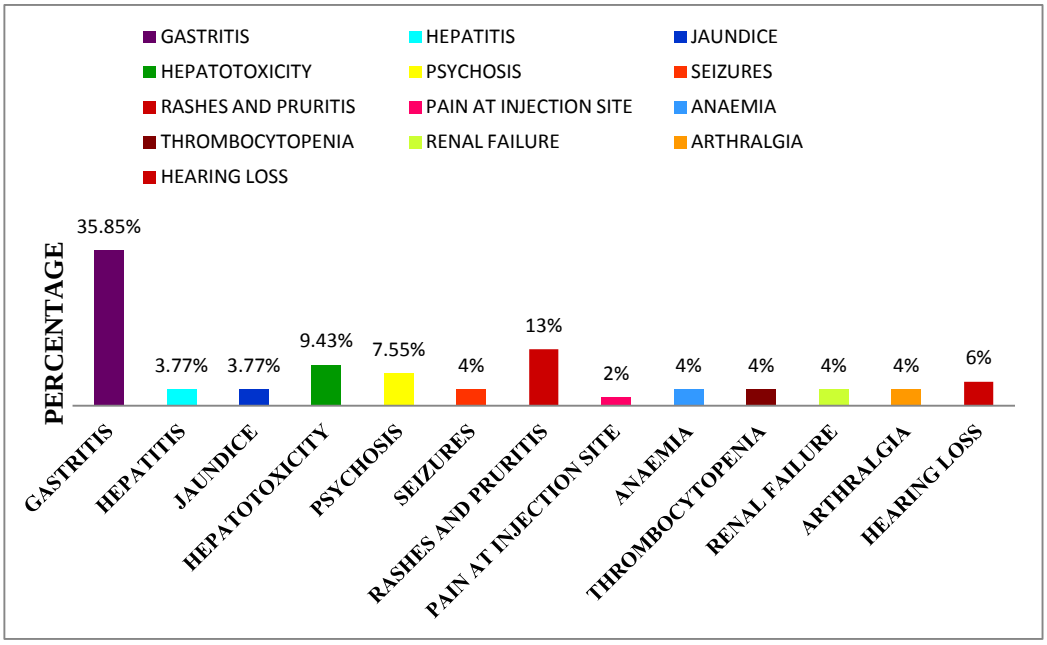

Figure 8: **Frequencies of different Adverse Drug Reactions Observed in the study.**

The adverse drug reactions were distributed based on organ system of the body. The GI system accounted for the most number of ADR'S and renal system accounted for least number of ADR'S and cardiovascular system with no ADR'S.

Table9: Distribution of ADR'S based on Organ systems of the body.

S NO.	ORGAN SYSTEEM	NO. OF ADVERSE DRUG REACTIONS	PERCENTAGE
1	GI SYSTEM	19	36%
2	HEPATOBILIARY	9	17%
3	NEUROLOGICAL	6	11%
4	CARDIOVASCULAR	0	0%
5	DERMATOLOGICAL	8	15%
6	MUSCULOSKELETAL	2	4%
7	HAEMATOLOGICAL	4	8%
8	RENAL SYSTEM	2	4%
9	OTHERS	3	6%
	TOTAL	53	100%

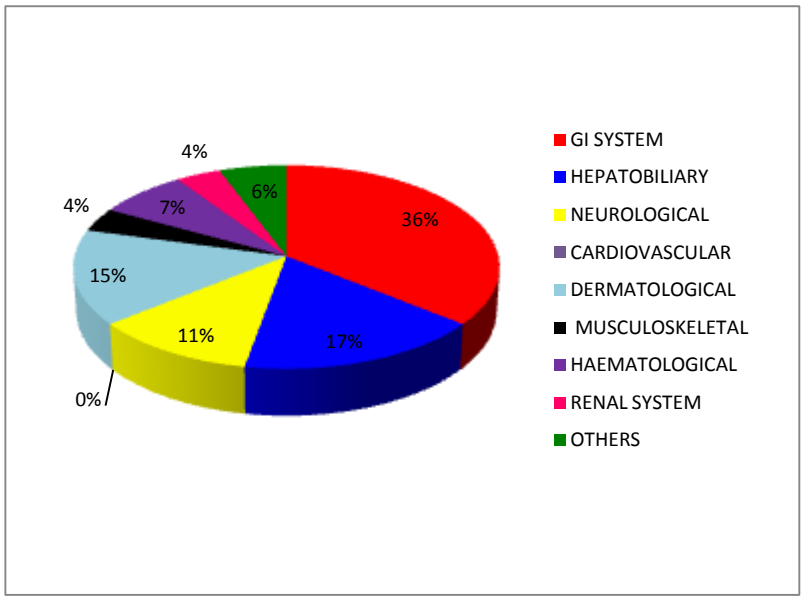

Figure 9: **Distribution of ADR'S based on Organ systems of the body.**

The causality assessment of ADR'S was done using WHO-UMC scale. The most common reaction was probable reaction (51%), followed by possible reactions (21%) and certain reactions (9%).

Table 10: CAUSALITY ASSESSMENT OF ADR'S BY USING WHO-UMC SCALE.

CAUSALITY	NO. OF ADVERSE DRUG REACTIIONS	PERCENTAGE
CERTAIN	5	9%
PROBABLE	27	50.9%
POSSIBLE	21	40%
UNLIKELY	0	0%
UNCLASSIFIABLE	0	0%
UNASSESSABLE	0	0%
TOTAL	53	100%

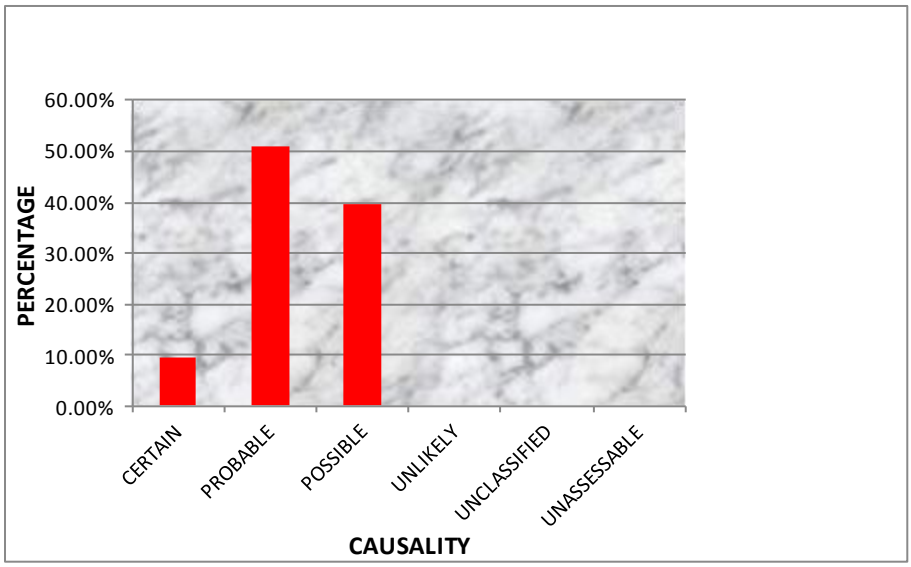

Figure 10: **CAUSALITY ASSESSMENT OF ADR'S BY USING WHO-UMC SCALE.**

The severity assessment of ADR'S was done using Hartwig and Siegel scale .moderate adverse drug reactions accounted for 55% and mild adverse drug reactions accounted for 45%.

Table 11: SEVERITY ASSESSMENT OF ADVERSE DRUG REACTIONS USING HARTWIG AND SIEGEL SCALE.

SEVERITY	NO. OF ADVERSE DRUG REACTIONS	PERCENTAGE
MILD	24	45%
MODERATE	29	55%
SEVERE	0	0%
TOTAL	53	100%

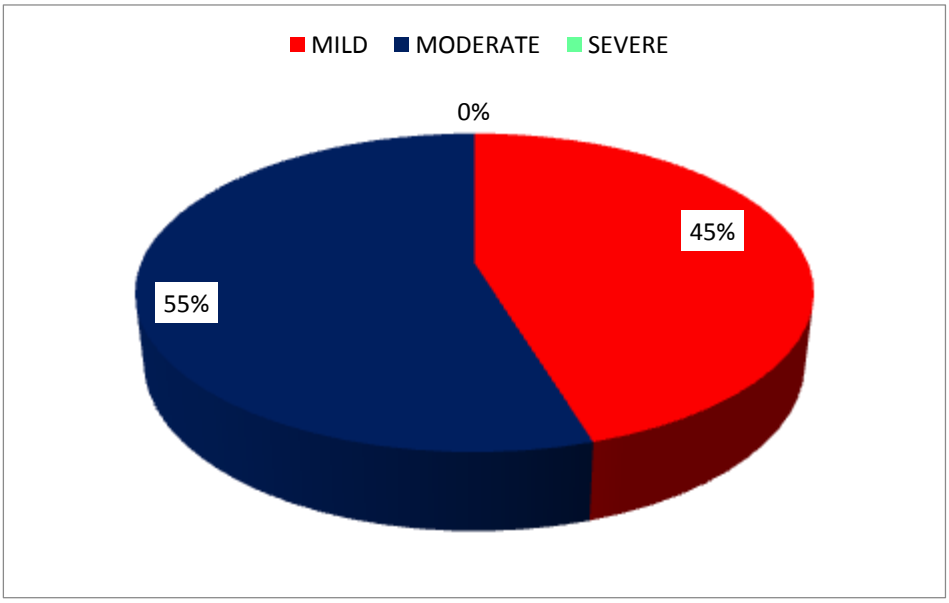

Figure 11: **SEVERITY ASSESSMENT OF ADVERSE DRUG REACTIONS USING HARTWIG AND SIEGEL SCALE.**

CONCLUSION

The occurrence of ADR's induced by anti-tubercular therapy was assessed in tertiary care hospital, by using WHO-UMC scale for causality and Hartwig and Siegel's scale for the assessment of severity.

From this study, it was concluded that females were more prone to occurrence of ADR'S when compared with males. 53 ADR'S were found to be suspected in 44 patients. Among CAT I and CAT II drug regimens, patients receiving CAT II drug regimen had more ADR'S. The patients were further evaluated by assessing the occurrence of ADR'S in initial and continuous phase. Patients in initial phase were reported to have more number of ADR'S.

The patients with single ADR'S were found to be more than patients with multiple ADR'S. Mostly the ADR'S occurred due to combination of drugs and rarely due to a specific drug. Assessing the frequencies of various ADR'S showed gastritis as the most commonly occurring ADR.

The causality assessment was done using WHO-UMC SCALE which showed higher number of probable reactions and modified Hartwig and Siegel scale showed higher number of moderate reactions. The outcomes of the treatment were also evaluated in this study. Major adverse reactions in anti-tubercular drugs can cause significant morbidity and compromise treatment regimens for tuberculosis. These events may result in substantial additional costs because of added outpatient visits, investigations and in more serious instances hospitalization. As a result, the risk of treatment failure and relapse are higher. Regular ADR monitoring is required to reduce morbidity and to improve patient compliance after initiation of anti-tubercular therapy.

The patients should be counselled about the occurrence of ADR'S and preventions for occurrence of ADR'S such as proper intake of balanced diet, timely medication, cessation of personal habits such as smoking, chewing tobacco and consumption of alcohol for better treatment outcomes. In addition, a proper educational counselling may promote more ADR reporting by patients. These strategies may improve the patient adherence to treatment and therapeutic outcome. This study needs further research to prevent the occurrence of the disease.

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