IJPSR (2025), Volume 16, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 April 2025; received in revised form, 25 April 2025; accepted, 02 May 2025; published 01 September 2025

ADVERSE DRUG REACTION MONITORING IN DRUG SENSITIVE TUBERCULOSIS PATIENTS: A CROSS-SECTIONAL STUDY IN A TERTIARY CARE HOSPITAL

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Keywords:

Adverse drug monitoring, Drug sensitive Tuberculosis, ATT, Causality assessment, Severity assessment

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ABSTRACT: Tuberculosis (TB) continues to rank among the world's most serious health problems despite the remarkable biomedical achievements. The objective of the study is to describe and characterize the adverse drug reactions associated with Anti Tubercular Therapy (ATT) in a tertiary care hospital. This was a cross sectional study done in the Department of Thoracic medicine, Government Medical College Krishnagiri between May 2023 and July 2023(3 months). Around 240 patients taking anti-tubercular drugs were screened and 98 patients (40.8%) among them were found to have adverse reactions to the therapy. Incidence of ADR was highest (8.3%) among (21-30) and (51-60) age groups. Among the type of detected adverse drug reactions induced by anti-TB drugs, gastritis (8.3%) was the most common, followed by rash (5%), hepatitis (4.2%) with hard of hearing (0.8%) and vision abnormality (0.8%) being the least common. Causality assessment revealed around 64 ADRs (26.7%) had possible relation to the drug usage. severity assessment of ADRs induced by ATT revealed mild in 52 patients (21.7%), moderate in 44 patients (18.3%) and severe in 2 patients (0.8%). Regarding the various modes of management in patients with ADR induced by ATT, around 42 patients (17.5%) with ADR continued the same medication with reassurance alone and only in 10 patients (4.2%), the current regimen was discontinued and was substituted with an another drug.

INTRODUCTION: Tuberculosis (TB) continues to rank among the world's most serious health problems despite the remarkable biomedical achievements of discovering effective diagnostic and treatment measures. According to a recent World Health Organization (WHO) report, 10.6 million people fell ill with TB in 2022 equivalent to 133 incident cases per 1,00,000 population [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(9).2608-12

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(9).2608-12

Around eight countries accounted for more than two thirds of global TB cases in 2022, and India has stood among them contributing 27% of cases. Directly Observed Treatment Short Course (DOTS) was introduced in India as a part of Revised National Tuberculosis Control Programme in 1993.

The objective of RNTCP is to achieve a cure rate of 85% through this regimen. India accounted for an estimated 24.2 lakh notified cases in 2022 after a drop-in notification rate during covid [2]. Despite the availability of effective chemotherapy, TB is still a major health problem is most countries. This can be attributed to primary multidrug resistance, to poor patient compliance, and noncompliance, partly due to adverse drug reactions [3].

WHO's definition of adverse drug reaction (ADR) is "Any noxious or unintended response to a drug which occurs at doses normally used in human for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function". ADRs can lead to treatment interruption before completion, and can contribute to drug-resistance, avoidable morbidity, reduced quality of life, treatment failure, or death [4]. Hence, proper identification, reporting and management of ADRs should be prioritized [5]. To our knowledge, there is no report regarding adverse drug reaction due to anti-tubercular therapy in our hospital, hence aimed to get an overview of ADRs due to anti-tubercular therapy.

Objective: To describe and characterize the adverse drug reactions associated with anti tubercular therapy (ATT) in a tertiary care hospital.

Methodology:
Type of Study: Cross sectional study.

Study Centre: Department of Thoracic medicine, Government Medical College Krishnagiri.

Study Population: 240 patients.

Study Period: May 2023 - July 2023 (3months).

Inclusion Criteria:

- ✓ Patients of all age groups diagnosed with drug sensitive Tuberculosis who have been started with the combination of anti-tubercular drugs (ATT) consisting of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide & Streptomycin.

Exclusion Criteria:

- ✓ Patients with chronic hepatic illness, renal failure.
- ✓ Patients with H/O Hypertension and Diabetes.
- ✓ Patients with H/O Hypersensitive reactions prior to ATT.
- ✓ Psychiatric patients are unable to give adequate. details about his signs and symptoms of adverse drug reactions.
- ✓ Patients with serious disease with a prognosis shorter than 6 months.
- ✓ Patients on other treatment regimens such as Antiretroviral therapy.
- ✓ Patients who abandoned treatment.
- ✓ Alcohol or illicit drug use.
- ✓ H/O Seizure disorder.

Study Procedure: Study protocol was approved by the Institutional Ethics Committee, Government Medical College krishnagiri (IEC Approval no: 02062023 dated 23/4/23). Patients satisfying the inclusion criteria and exclusion criteria were enrolled in the study and written informed consent was obtained from them prior to the study. The various study tools used were the patient profile form which recorded all the information, such as name, age, sex, socioeconomic status, lifestyle factors, dietary factors, pregnancy status (for female patients) and outcomes of delivery and birth in case of pregnant patients, any concurrent diseases and medications other than anti tubercular agents that the patients might be taking.

- ➢ **ADR reporting form** was used to record all the essential information regarding the adverse effects: the onset and severity of the ADRs experienced, the drug(s) involved, the date of starting the suspected drugs and the date of reporting of the ADRs.
- ➢ **Age group wise and system wise distribution of ADRs** was tabulated and analyzed.
- ➢ **WHO-UMC causality assessment system** was used to categorize ADRs as certainly, probably or possibly due to a certain drug. It is based on the event or laboratory test abnormality, with reasonable time relationship to drug intake, dechallenge and rechallenge to the suspected drug [6].
- ➢ **Modified Hartwig and Siegel severity scale** was used to categorize the reported adverse drug reactions as mild, moderate or severe based on the treatment and requirement of hospitalization for the management of the ADRs. Both these scales were employed to categorize the type of ADRs [7].
- ➢ **Modes of Management in Patients with ADR** such as discontinuation, continuation, addition of other drug, reduction in dose or substitution of other drug to the current regimen was tabulated. Data obtained were statistically

analyzed using descriptive statistics and expressed in percentage.

RESULTS: In thoracic medicine OPD, around 240 patients taking anti-tubercular drugs were screened and 98 patients (40.8%) among them were found to have adverse reactions to the therapy **Table 1.**

Table 1 shows the age group wise distribution of ADRs in patients taking anti-TB drugs. Incidence of ADR was highest (8.3%) among (21-30) and (51-60) groups.

TABLE 1: ATT INDUCED ADVERSE REACTIONS IN DIFFERENT AGE GROUPS

Age group	Total number of patients	Patients with ADR n (%)
0-10	8	Nil
11-20	10	6 (2.5%)
21-30	58	20 (8.3%)
31-40	46	18 (7.5%)
41-50	42	18 (7.5%)
51-60	54	20 (8.3%)
>60	22	16 (6.7%)
Total	240	98(40.8%)

TABLE 2: TYPES OF DETECTED ADVERSE DRUG REACTIONS INDUCED BY ATT

Reactions	Frequency (n)	Percentage (%)
Gastritis	20	8.3
Rash	12	5
Hepatitis	10	4.2
Peripheral neuropathy	8	3.3
Diarrhoea	8	3.3
Headache	6	2.5
Dysuria	6	2.5
Arthralgia	6	2.5
Hyperglycemia	6	2.5
Constipation	4	1.7
Renal failure	4	1.7
Psychiatric reaction	4	1.7
Hard of hearing	2	0.8
Vision abnormality	2	0.8

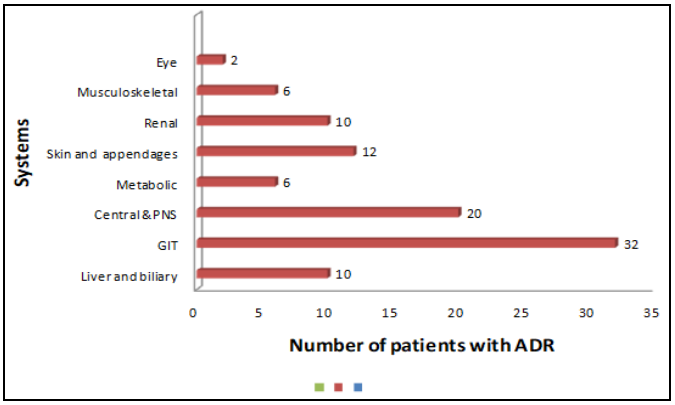

FIG. 1: SYSTEM WISE DISTRIBUTION OF ADR

Table 2 shows the type of detected adverse drug reactions induced by anti-TB drugs and gastritis (8.3%) was the most common among them, followed by rash (5%), hepatitis (4.2%) with hard of hearing (0.8%) and vision abnormality (0.8%) being the least common.

Fig. 1 gives the interpretation of the system wise distribution of ADRs among patients taking anti-tubercular drugs with gastrointestinal system (13.3%) showing highest number of adverse drug reactions.

TABLE 3: CAUSALITY ASSESSMENT OF ADR'S INDUCED BY ANTI-TB DRUGS

Causality	Frequency (n)	Percentage (%)
Possible	64	26.7
Probable	12	5
Certain	22	9.2

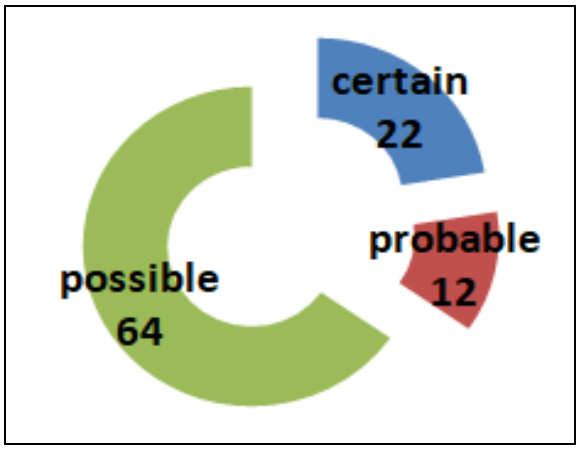

FIG. 2: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS INDUCED BY ATT

Table 3 and **Fig. 2** gives an idea about the causality of adverse drug reactions induced by ATT. Around 64 ADRs (26.7%) had possible relation to the drug, 12 ADRs (5%) had probable relation to the drug and 22 ADRs (9.2%) had certain relation to the drug.

TABLE 4: SEVERITY OF ADVERSE DRUG REACTIONS INDUCED BY ANTI-TB DRUGS

Severity	Frequency (n)	Percentage (%)
Mild	52	21.7
Moderate	44	18.3
Severe	2	0.8

Table 4 shows the severity of ADRs induced by anti-TB drugs. ADRs has been classified into mild in 52 patients (21.7%), moderate in 44 patients (18.3%) and severe in 2 patients (0.8%).

TABLE 5: MODES OF MANAGEMENT IN PATIENTS WITH ADR

Treatment	Number of ADRs (n)	Percentage (%)
Continued the same medication	42	17.5
Dechallenge and rechallenge	22	9.2
Added another drug to treat ADR	16	6.7
Substituted another drug	10	4.2
Decrease in dosage	6	2.5

Table 5 represents the various modes of management in patients with ADR induced by ATT. Around 42 patients (17.5%) with ADR continued the same medication with reassurance alone. Only in 10 patients (4.2%), the current regimen was discontinued and was substituted with another drug.

DISCUSSION: Tuberculosis continues to be the serious public health problem in India. The emergence of MDR-TB and the spread of HIV/AIDS are contributing to the worsening impact of the disease. Major adverse reactions to anti-TB drugs can cause high morbidity and compromise treatment regimens for TB [8].

In our study, the incidence of ADR was highest among 21-30 and 51-60 age groups (8.3%). In 21-30 group, it was because of the involvement of this age group in activities like smoking and large alcohol intake which resulted in weakening of immunity. In 51-60 group, the higher numbers may be due to the co existing disease and drug interactions [9].

The most common ADR in our study was gastritis (8.3%) followed by rash (5%) and hepatitis (4.2%) which is comparable to the study by Araujo-Pereira M *et al* where the most prevalent system affected was the digestive system followed by skin. Rifampicin serum peak is associated with gastrointestinal reactions. Symptoms disappear once the Rifampicin blood concentration decreases due to its auto metabolism. Also, gastrointestinal effects are attributable to the intake of multiple drugs through oral route [10]. Gastrointestinal disturbances have occasionally required discontinuation of the drug [11].

Rash is frequently noted with Rifampicin, Ethambutol and Capreomycin [12] and these drugs are usually dechallenged in severe cases and rechallenged after 2 weeks. Hepatitis which is the third common ADR in our study may be due to Pyrazinamide, Isoniazid, Rifampicin, Ehionamide and Clarithromycin which too requires dechallenging and rechallenging. Although, 60-70% of Indians are slow acetylators having greater risk of peripheral neuropathy and a variety of neurological manifestations, the incidence of peripheral neuropathy is less in our patients. This may be due to the prophylactic use of Pyridoxine (10 mg/day).

The permanent disabilities reported in our study were mainly hard of hearing (0.8%) and visual toxicity (0.8%) mostly accounted to the use of Kanamycin and Ethambutol respectively which stresses regular monitoring and early detection of the problem.

The result of our study gives the interpretation that the majority of the ADRs were possibly related (26.7%) to the drug and the severity assessment of the reported ADRs revealed that most of the ADRs were mild (21.7%), which did not need modification of treatment or administration of specific antidotes in 17.5% of patients. This is similar to the study by Anusha *et al* where the severity of ADRs were mild [13]. This alleviates the wrong belief in patients regarding the anti-tubercular therapy thereby improving the patient compliance.

Thus, it is well understood that ADRs due to anti-TB drugs are not rare, but they should be followed up by close monitoring after initiation of the therapy which is possible only with patient counseling to report ADRs so that detection, timely prevention and management is possible at the earliest [14]

Limitations:

- Firstly, there is a difficulty in identification of a particular drug that causes ADR due to the use of multiple drugs with overlapping toxicities.
- Second, the sample size seems to be too small and the duration of the study is too short. Hence

further studies involving larger subset of patients for a longer duration of time will provide more appealing results.

CONCLUSION: To conclude, by proper monitoring of ADRs we can prevent serious complications, promote continuity of care, improve patient-health care provider relationship, encourage adherence and thereby ensure successful completion of the treatment.

ACNOWLEDGEMENTS: Authors thank the Department of Thoracic medicine, Government Medical College Krishnagiri for their support

Financial Support and Sponsorship: Nil.

CONFLICTS OF INTEREST: There are no conflicts of interest.

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How to cite this article:
Vishnupriya R, Meeradevi A and Jayakumar N: Adverse drug reaction monitoring in drug sensitive tuberculosis patients: a cross sectional study in a Tertiary Care Hospital. Int J Pharm Sci & Res 2025; 16(9): 2608-12. doi: 10.13040/IJPSR.0975-8232.16(9).2608-12.