ORIGINAL ARTICLE

Pattern and Severity of Adverse Drug Reactions Associated with Antitubercular Therapy

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Abstract

Background: Adverse drug reactions (ADRs) associated with antitubercular therapy (ATT) remain a major challenge in tuberculosis (TB) management, particularly in developing countries such as India, where the TB burden is high. ADRs may adversely affect treatment adherence, increase treatment interruption, and contribute to treatment failure and drug resistance. **Objective:** The objective of the study was to assess the pattern, severity, causality, and suspected drugs associated with ADRs among TB patients receiving ATT at a district hospital. **Materials and Methods:** A prospective observational study was conducted among 124 TB patients receiving ATT at a district hospital in Madanapalle, Andhra Pradesh. Patient demographic details, clinical characteristics, treatment regimens, and ADRs were recorded using a structured data collection form. Causality assessment was performed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale, while severity assessment was performed using the Hartwig and Siegel severity scale. Data were analyzed using descriptive statistics and expressed as frequencies and percentages. **Results:** Among the study participants, 52.4% were males, and pulmonary TB accounted for 69.35% of cases. The most frequently reported ADRs were nausea, vomiting, and gastritis (16.93%), peripheral neuropathy (15.32%), skin rashes (15.32%), and hepatotoxicity (14.51%). Neurological ADRs constituted the most commonly affected organ system (22.58%). Most ADRs were categorized as probable according to the WHO-UMC assessment (64.51%), while mild and moderate reactions each accounted for 38.7% of cases. Pyrazinamide and isoniazid were the most commonly implicated drugs. Inferential analysis demonstrated a significant association between second-line ATT and severe ADRs ($P = 0.001$), as well as neurological ADRs ($P = 0.024$). **Conclusion:** ADRs associated with ATT are common and frequently involve the neurological and gastrointestinal systems. Second-line ATT was significantly associated with severe and neurological ADRs, highlighting the need for intensive pharmacovigilance, early ADR detection, and close clinical monitoring during TB treatment.

Key words: Adverse drug reactions, antitubercular therapy, directly observed therapy, pharmacovigilance, tuberculosis, World Health Organization-Uppsala Monitoring Centre

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INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious diseases contributing to global morbidity and mortality, particularly in low- and middle-income countries. According to the World Health Organization (WHO), India continues to account for a substantial proportion of the global TB burden, with millions of new cases reported annually.[1] Despite major advances in TB control programs and the widespread implementation of directly observed treatment strategies, TB continues to pose a significant public health challenge in India. Antitubercular therapy (ATT) has considerably improved treatment outcomes and reduced TB-related mortality. First-line antitubercular drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol, form the cornerstone of TB management due to their potent activity against *Mycobacterium* TB. However, prolonged administration of these agents is frequently associated with adverse drug reactions (ADRs), which may involve multiple organ systems such as gastrointestinal, hepatic, dermatological, neurological, musculoskeletal, ophthalmic, and hematological systems.[2,3] The severity of these ADRs may vary from mild and self-limiting reactions to severe complications requiring treatment interruption, dose modification, hospitalization, or permanent discontinuation of therapy.

The occurrence of ADRs during ATT represents a major barrier to successful TB management. Drug-related toxicities may negatively affect patient adherence, resulting in poor treatment compliance, relapse, treatment failure, prolonged infectivity, and emergence of multidrug-resistant TB.[4] In addition, second-line antitubercular drugs used in resistant TB are often associated with increased toxicity and a higher risk of severe ADRs. Therefore, early identification, continuous monitoring, and appropriate management of ADRs are essential components of effective TB care and pharmacovigilance practice.[5]

Several pharmacovigilance studies conducted in India and other countries have reported varying frequencies and patterns of ADRs associated with ATT. Gastrointestinal disturbances, hepatotoxicity, peripheral neuropathy, skin reactions, and neuropsychiatric manifestations are among the most commonly reported ADRs.[6] The occurrence and severity of these reactions may be influenced by multiple factors, including age, gender, nutritional status, alcohol consumption, smoking habits, comorbidities, previous treatment exposure, and treatment regimen characteristics. However, ADR profiles may vary across different healthcare settings and patient populations.

Despite the high burden of TB in South India, limited prospective observational studies have comprehensively evaluated the pattern, severity, causality, and treatment-related factors associated with ADRs at district-level healthcare facilities. Furthermore, data regarding the relationship between treatment regimen type and severity of ADRs remains limited in routine clinical practice settings. Hence, the present study was undertaken to assess the pattern, severity, causality, and suspected drugs associated with ADRs among TB patients receiving ATT at a district hospital in Madanapalle, Andhra Pradesh.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted to evaluate ADRs associated with ATT at a district hospital in Madanapalle, Andhra Pradesh. A total of 124 patients diagnosed with pulmonary or extrapulmonary TB and receiving ATT were enrolled. Patients willing to provide informed participation were included, while those who declined participation, had incomplete clinical data, or were critically ill and unable to furnish relevant information were excluded from the study.

Data collection

Patient demographic details, including age, gender, type of TB, treatment category, history of comorbidities, smoking history, alcohol consumption, drug allergy history, treatment regimen, and details related to ADRs, were collected using a structured data collection form. All eligible TB patients receiving ATT during the study period were monitored regularly for the development of ADRs. Clinical symptoms, laboratory findings, and patient complaints suggestive of ADRs were carefully documented throughout the treatment period. The observed ADRs were subsequently categorized according to the affected organ system for further analysis.

Causality assessment of the reported ADRs was performed using the WHO–Uppsala Monitoring Centre (UMC) causality assessment scale. Based on the temporal relationship between drug administration and occurrence of the reaction, ADRs were categorized as certain, probable, possible, unlikely, conditional, or unassessable.

The severity of the reported ADRs was evaluated using the Hartwig and Siegel severity assessment scale. According to this scale, ADRs were classified into mild, moderate, and severe categories based on the extent of clinical impact, requirement for treatment modification, hospitalization, or additional therapeutic intervention.[7]

Statistical analysis

The collected data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences. Categorical variables were expressed as frequencies and percentages. Descriptive statistics were used to summarize

Table 1: Baseline characteristics of study participants (*n*=124)

Variable	Category	Frequency (n)	Percentage
Gender	Male	65	52.4
	Female	59	47.5
Age (Y)	18–28	11	8.87
	28–38	34	27.41
	38–48	41	33.06
	48–58	24	19.35
	58–68	13	10.48
	≥68	1	0.8
Type of TB	Pulmonary TB	86	69.35
	Extrapulmonary TB	38	30.64
Category of TB	New case	29	23.38
	Relapse	46	37.09
	Treatment after failure	32	25.8
	Treatment after loss to follow-up	17	13.7
Comorbidities	Diabetes mellitus	26	20.96
	Hypertension	28	22.58
	HIV	6	4.83
	Liver diseases	11	8.87
	Renal diseases	9	7.25
	HTN with DM	6	4.83
	HTN with liver diseases	2	1.61
	Others	36	29.03
Alcohol history	Alcoholic	63	50.8
	Non-alcoholic	61	49.19
Smoking history	Smoker	61	49.19
	Non-smoker	63	50.8
Drug allergy history	Drug allergy present	25	20.16
	No drug allergy	99	79.83
Treatment regimen	First-line ATT	95	76.61
	Second-line ATT	29	23.38

TB: Tuberculosis, ATT: Antitubercular therapy, HTN: Hypertension, DM: Diabetes mellitus, HIV: Human Immunodeficiency Virus, n: Number of cases

demographic and clinical characteristics of the study participants. The Pearson chi-square test was applied to evaluate the association between categorical variables, including treatment regimen type and severity of ADRs. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 124 TB patients receiving ATT were included in the present study. Among them, 65 patients (52.4%) were males and 59 patients (47.5%) were females. The majority of patients belonged to the age group of 38–48 years (33.06%), followed by 28–38 years (27.41%), while patients aged ≥68 years constituted the lowest proportion (0.80%). Pulmonary TB was more commonly observed in 86 patients (69.35%), whereas extrapulmonary TB was reported in 38 patients (30.64%). Among the treatment categories, relapse cases accounted for the highest proportion (37.09%), followed by treatment after failure (25.80%), new cases (23.38%), and treatment after loss to follow-up (13.70%). Hypertension (22.58%) and diabetes mellitus (20.96%) were the most common comorbidities observed among the study participants. Alcohol consumption and smoking history were reported in 50.80% and 49.19% of patients, respectively. A history of drug allergy was present in 20.16% of patients. Regarding treatment regimens, first-line ATT was prescribed in 95 patients (76.61%), while second-line therapy was administered in 29 patients (23.38%) [Table 1].

Table 2: Pattern of adverse drug reactions observed among study participants

Adverse drug reaction	Frequency (n)	Percentage
Nausea, vomiting, and gastritis	21	16.93
Skin rashes	19	15.32
Peripheral neuropathy	19	15.32
Hepatotoxicity	18	14.51
Blurred vision	12	9.67
Joint pains	12	9.67
Ototoxicity	5	4.03
Thrombocytopenia	3	2.41
Palpitations	2	1.61
Insomnia	2	1.61
Hypothyroidism	2	1.61
Fever and headache	2	1.61
Jaundice	2	1.61
Renal toxicity	2	1.61
Convulsions	1	0.8
Hallucinations	1	0.8
Depression with suicidal thoughts	1	0.8

Table 3: Organ system involvement, causality, and severity assessment of ADRs

Parameter	Category	Frequency (n)	Percentage
Organ system affected	Neurological	28	22.58
	Gastrointestinal	20	16.12
	Hepatic	20	16.12
	Dermatological	19	15.32
	Ophthalmic	14	11.29
	Others	12	9.67
	Musculoskeletal	11	8.87
WHO-UMC causality assessment	Probable	80	64.51
	Possible	29	23.38
	Certain	10	8.06
	Unlikely	2	1.61
	Conditional	2	1.61
	Unassessable	1	0.8
Hartwig and Siegel severity assessment	Mild	48	38.7
	Moderate	48	38.7
	Severe	28	22.5

WHO-UMC: World Health Organization-Uppsala Monitoring Centre, ADRs: Adverse drug reactions

Analysis of ADRs revealed that nausea, vomiting, and gastritis were the most commonly reported ADRs, accounting for 21 cases (16.93%). Skin rashes and peripheral neuropathy were each reported in 19 patients (15.32%), followed by hepatotoxicity in 18 patients (14.51%). Blurred vision and joint pains were each observed in 12 cases (9.67%), while ototoxicity was reported in 5 patients (4.03%). Less frequently observed ADRs included thrombocytopenia, hypothyroidism, insomnia, palpitations, and fever with headache, jaundice, renal toxicity, hallucinations, convulsions, and depression with suicidal thoughts [Table 2].

Table 4: Suspected antitubercular drugs associated with adverse drug reactions

Suspected drug	Frequency (n)	Percentage
Pyrazinamide	23	18.5
Isoniazid	22	17.7
Rifampicin	18	14.5
Ethambutol	14	11.2
Isoniazid+Rifampicin	15	12
Cycloserine	6	4.8
Isoniazid+Pyrazinamide	6	4.8
Streptomycin	4	3.2
Linezolid	3	2.4
Ethionamide	3	2.4
Amikacin	2	1.6
Kanamycin	2	1.6
Para-aminosalicylic acid	2	1.6
Levofloxacin	2	1.6
Clofazimine	1	0.8
Bedaquiline	1	0.8

Table 5: Association of treatment regimen with severity and neurological ADRs

Parameter	First-line ATT n (%)	Second-line ATT n (%)	*P*-value
Severity of ADRs			
Mild	43 (44.8)	6 (21.4)	0.001
Moderate	39 (40.6)	9 (32.1)	
Severe	14 (14.6)	13 (46.4)	
Type of ADRs			
Neurological ADRs	18 (18.8)	11 (39.3)	0.024
Non-neurological ADRs	78 (81.2)	17 (60.7)	

ADRs: Adverse drug reactions, ATT: Antitubercular therapy

Organ system-wise analysis demonstrated that neurological manifestations were the most commonly affected system, accounting for 28 cases (22.58%). Gastrointestinal and hepatic systems were each affected in 20 patients (16.12%). Dermatological ADRs were observed in 19 cases (15.32%), while ophthalmic manifestations accounted for 14 cases (11.29%). Musculoskeletal involvement was reported in

11 patients (8.87%), whereas other organ systems collectively contributed to 12 cases (9.67%) [Table 3].

Causality assessment using the WHO-UMC scale revealed that the majority of ADRs were categorized as probable, accounting for 80 cases (64.51%). Possible ADRs were observed in 29 cases (23.38%), while certain ADRs constituted 10 cases (8.06%). Unlikely and conditional ADRs each accounted for 2 cases (1.61%), whereas one ADR (0.80%) was classified as unassessable.

Severity assessment performed using the Hartwig and Siegel severity scale demonstrated that mild and moderate ADRs were equally distributed, with 48 cases (38.7%) each. Severe ADRs accounted for 28 cases (22.5%), indicating that a clinically significant proportion of patients experienced severe reactions requiring careful monitoring and management.

Drug-wise analysis showed that pyrazinamide was the most commonly suspected drug associated with ADRs, accounting for 23 cases (18.5%), followed by isoniazid in 22 cases (17.7%) and rifampicin in 18 cases (14.5%). Ethambutol was implicated in 14 cases (11.2%), while cycloserine accounted for 6 cases (4.8%). Other suspected drugs included streptomycin, linezolid, ethionamide, amikacin, kanamycin, para-aminosalicylic acid, levofloxacin, clofazimine, and bedaquiline. Combination regimens such as isoniazid plus rifampicin and isoniazid plus pyrazinamide were also associated with ADR occurrence [Table 4].

Inferential analysis demonstrated a statistically significant association between second-line ATT and severe ADRs ($P = 0.001$). Additionally, neurological ADRs were significantly more frequent among patients receiving second-line ATT compared to first-line therapy ($P = 0.024$) [Table 5].

DISCUSSION

The present prospective observational study evaluated the pattern, severity, and causality of ADRs associated with ATT among TB patients receiving treatment at a district hospital in South India. Male patients slightly predominated over females, which is consistent with observations reported in previous Indian pharmacovigilance studies conducted by Kale *et al*. and Kuriachan *et al*., where TB and ADR occurrence were more common among males.[9,10] The majority of patients belonged to the economically productive age group of 28–48 years, reflecting the significant burden of TB among working-age adults.

Pulmonary TB was more common than extrapulmonary TB, which is comparable with previous epidemiological and pharmacovigilance studies.[8] A considerable proportion of patients in the present study were previously treated cases, indicating the ongoing challenge of treatment non-adherence, relapse, and possible drug resistance in TB management.

Gastrointestinal ADRs, particularly nausea, vomiting, and gastritis, were the most commonly reported reactions in the present study. Similar findings were reported by Kale *et al*., Mogali *et al*. who identified gastrointestinal disturbances as the predominant ADRs associated with first-line ATT.[9,11]

An important finding of the present study was the high frequency of neurological ADRs, which constituted the most commonly affected organ system. Peripheral neuropathy was frequently observed and may primarily be related to isoniazid-induced pyridoxine deficiency. Similar neurological manifestations have been reported by Joshi *et al*., Mafukidze *et al*., Shin *et al*. during prolonged ATT. Ototoxicity and neuropsychiatric manifestations observed in the present study may be associated with second-line drugs used in resistant TB management.[12-14]

Hepatotoxicity was also observed in a substantial proportion of patients. Previous studies by Tostmann *et al*., Gholami *et al*., and Oh *et al*. similarly identified hepatotoxicity as one of the most clinically significant ADRs associated with isoniazid, rifampicin, and pyrazinamide. Alcohol consumption and pre-existing liver disease were observed among several patients to hepatic toxicity.[6,15,16]

WHO-UMC in the present study, may have contributed causality assessment revealed that most ADRs were categorized as probable, indicating a reasonable temporal association between ATT and the observed reactions. Similar causality patterns have been reported by Kale *et al*., and Kuriachan *et al*., where the majority of ADRs were classified as probable or possible. Severity assessment using the Hartwig and Siegel scale demonstrated that most ADRs were mild to moderate in severity, although severe ADRs were also observed in a clinically important proportion of patients.[9,17]

Pyrazinamide and isoniazid were the most commonly suspected drugs associated with ADRs in the present study. Previous pharmacovigilance studies have similarly reported these drugs as major contributors to gastrointestinal disturbances, hepatotoxicity, and neurological ADRs.[6,9]

A statistically significant association was observed between second-line ATT and severe ADRs. Nearly half of the patients receiving second-line ATT experienced severe ADRs compared to those receiving first-line therapy. Similar findings have been reported in studies evaluating ADRs among patients receiving treatment for drug-resistant TB, where second-line antitubercular drugs were associated with a substantially higher burden of severe and serious ADRs. The increased toxicity associated with second-line drugs such as aminoglycosides, cycloserine, and linezolid highlights the importance of intensive pharmacovigilance and close clinical monitoring in resistant TB management.[14]

The present study also demonstrated a significant association between second-line ATT and neurological ADRs. Patients

receiving second-line ATT experienced a higher frequency of neurological manifestations compared to those receiving first-line therapy. This finding may be attributed to the neurotoxic potential of second-line drugs such as cycloserine, linezolid, and aminoglycosides, which are commonly associated with peripheral neuropathy, ototoxicity, and neuropsychiatric complications. Similar findings have been reported in studies evaluating ADRs among patients receiving treatment for drug-resistant TB.

Limitations

1. The study was conducted at a single center with a relatively limited sample size
2. Long-term follow-up of patients was not performed
3. Advanced analytical assessment of risk factors associated with ADRs was not carried out
4. Some ADRs may have been underreported due to reliance on patient self-reporting.

CONCLUSION

The present study demonstrated that ADRs associated with ATT are common among TB patients. Neurological and gastrointestinal systems were predominantly affected. Most ADRs were categorized as probable and moderate in severity according to WHO-UMC and Hartwig and Siegel assessments, respectively. Pyrazinamide and isoniazid were the most commonly suspected drugs associated with ADRs. Continuous monitoring, patient counseling, and strengthening pharmacovigilance practices are essential to improve adherence and minimize treatment-related complications during ATT.

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