Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230-8407 [LINKING]

SPECTRUM AND SEVERITY OF ADVERSE DRUG REACTIONS DURING TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS

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How to cite: Dr. Vinod Kumar[1], Dr. Vinod Kumar Chhipa[2], Dr. Prerna Sharma[3], Dr. Sodha[4], Dr. Vigneswaran[5]. **SPECTRUM AND SEVERITY OF ADVERSE DRUG REACTIONS DURING TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS**. International Research Journal of Pharmacy. 2026; 17:9:11-17

DOI: http://doi.org/10.56802/irjp.2026.v17.i9.pp11-17

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ABSTRACT

INTRODUCTION: Tuberculosis is a bacterial disease spread from one person to another principally by airborne transmission. The causal agent is Mycobacterium tuberculosis (the tubercle bacillus). Tuberculosis can affect any organ in the body.

AIM: To determine the spectrum and severity of adverse drug reaction during treatment of MDR-TB patients

METHODOLOGY: This is a Hospital based prospective study.Patients diagnosed with MDR-TB in Respiratory Medicine Department in P.B.M. and associated group of hospital, Bikaner, Rajasthan was form the material for our study. Inclusion and exclusion criteria were applied while registering the subjects for study.The duration of study was from 1 March 2025 to 28 Feb 2026.

RESULT: Adverse drug reactions (ADRs) were observed in 80% of patients receiving MDR-TB treatment, with gastrointestinal disturbances, arthralgia, and headache being the most common adverse effects. Most ADRs were managed with symptomatic treatment, counselling, and temporary drug interruption, while severe psychiatric reactions required permanent discontinuation of cycloserine in a few patients.

CONCLUSION: ADRs are highly prevalent during MDR-TB therapy and significantly influence treatment adherence and clinical outcomes. Early recognition, prompt management, and regular monitoring of ADRs are essential to ensure successful treatment completion and improve patient safety.
KEYWORDS: Multidrug-resistant tuberculosis (MDR-TB),Adverse drug reactions (ADRs),Treatment adherence

INTRODUCTION

Tuberculosis is a bacterial disease spread from one person to another principally by airborne transmission. The causal agent is Mycobacterium tuberculosis (the tubercle bacillus)[1]. Tuberculosis can affect any organ in the body. Pulmonary tuberculosis is the most frequent site of involvement; extrapulmonary tuberculosis is less frequent. Only pulmonary tuberculosis is infectious.India has been engaged in Tuberculosis (TB control activities for more than 50 years). Of the 24 lakh TB cases 90% (N=21.6 lakhs) were incident TB cases (New and Relapse/ Recurrent)[2].This translates to an incident notification rate of approximately 159 cases/lakh against the estimated incidence rate of 199 cases lakh population; thus,closing the gap between the estimated and notified incident cases to just 40 Cases per lakh population, or an approximate of 5.4 lakh missing cases across India. An estimated 354 million people are latently infected with tuberculosis in India and form the next generation of future.TB contact investigations are rarely and inconsistently carried out in resource-limited settings. In most low- and middle-income countries, it is included in the national policy to control and prevent TB; however, in the vast majority of countries,[3] it is either not undertaken or is implemented on the basis of no or poor standards, because of the absence of clear definitions of index cases, contacts and procedures[4]. Due to limited resource settings sputum culture is limited to only MDR-TB Patients and category 2 previously treated patients.TB bacteria resistant to fluoroquinolones, rifampin, and isoniazid are named as causing pre-extensively drug-resistant tuberculosis (pre-XDR TB).[5,6] Since isoniazid and rifampicin are the most effective first-line TB medications, missing doses of these medications can cause multi-drug resistance tuberculosis (MDR-TB) to arise. Since the beginning of anti-tubercular chemotherapy, there has been evidence of drug-resistant tuberculosis (DR-TB).[7-9] However, more recently, MDR-TB has become a source of increasing concern and is posing a danger to efforts being made worldwide to combat the disease. In NTEP, ADSm (Active Drug Safety monitoring) is part of pharmacovigilance. In this study we have studied ADRs to Anti TB drugs in DRTB.Since the introduction of newer anti TB drugs such as delamanid and bedaquiline, and newer regimens in India through the Programmatic Management of Drug Resistant Tuberculosis Guidelines in 2021, there has been a pressing need for more studies outlining their adverse effects and tolerability.[10,11] Timely detection and intervention for ADR is necessary to improve patient compliance and ensure the MDR TB is effectively treated. In our study we were documenting all the adverse effects encountered in patients on DOTS plus.

AIM

To determine the spectrum and severity of adverse drug reaction during treatment of MDR-TB patients

METHODOLOGY

This is a Hospital based prospective study.Patients diagnosed with MDR-TB in Respiratory Medicine Department in P.B.M. and associated group of hospital, Bikaner, Rajasthan was form the material for our study. Inclusion and exclusion criteria were applied while registering the subjects for study.The duration of study was from 1 March 2025 to 28 Feb 2026.Inclusion criteria included Patient diagnosed with MDR-TB in respiratory medicine department, Patients age between 18 to 65 years from both genders,Patients or caregivers agreed to participate in the study.Mentally retarded or unconscious patients. Patients already on other antipsychotic agents and drug abuse, Non cooperative patients,Patients with age < 18 year and > 65 year,Pregnant and lactating females,Drop outs will be excluded.

RESULT

Table 1. Frequency of ADR in study subjects

Total no. of patients	100
No of patients develop ADR	80
Frequency of ADR	80.00%

ADR was seen in 80 (80%) participants out of 100 in our study.

Table 2. Age wise distribution of study subjects

Age in years	**Patients (n=100)**	**Developed ADR (n=80)**	**p-value**
Mean	46.38	48.16	0.87
SD	9.56	8.97	

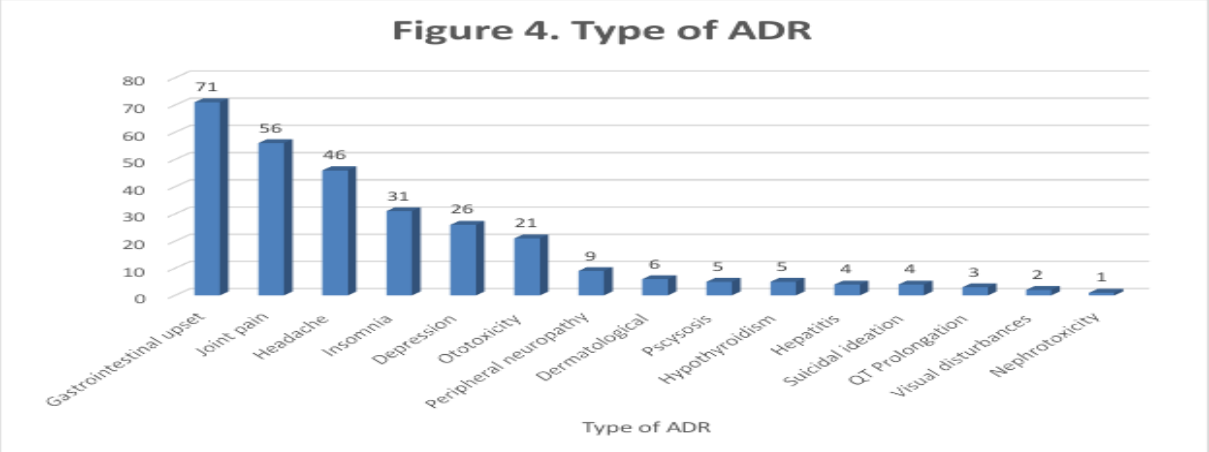
Age wise difference between patients and ADR developed patients was found statically Insignificant.

Table 3. Gender wise distribution of study subjects

Gender	**Patients (n=100)**	**Developed ADR (n=80)**	**P value**
Male	68	56	0.241
Female	32	24	

In the present study, out of 100 patients 68 patients were male and 32 patients were female. Out of 80 patients who developed ADR, 56 patients were male and 24 patients were female.

Figure 1: Type of ADR



A total of 15 kinds of ADRs were recorded. The prevalence of gastrointestinal upset was reported in 71 cases (87.50%), making it the most prevalent symptom. This was followed by joint pain in 56 cases (70.00%) and headache in 46 cases (57.50%). Other symptoms included insomnia in 31 cases (38.75%), depression in 26 cases (32.50%), ototoxicity in 21 cases

Table 4.Modified Hartwig and Siegel scale for severity assessment of ADRs

Level		No of Patients	Percentage
Mild	Level 1	6	7.50
	Level 2	0	0.00
Moderate	Level 3	52	65.00
	Level 4	13	16.25
Severe	Level 5	0	0.00
	Level 6	9	11.25
	Level 7	0	0

The ADR Hartwig's scale was used for the assessment, and a majority of the patients (65.00%) had level three responses.

Table 5. Number of ADRs among patients

Number of ADRs	No of Patients	Percentage
1	9	11.25
2	13	16.25
3	31	38.75
≥4	27	33.75

In the present study, 27 (33.75%) of the patients had four or more kinds of responses.

Table 7. ADR management

ADR management	No of Patients	Percentage
Symptomatic	48	60.00
Discontinued drug	26	32.50
Treatment not required	6	7.50

Among the 80 patients afflicted by ADR, 48 individuals (60%) had relief in symptoms by symptomatic therapy, eliminating the requirement for medication withdrawal. 26 individuals, accounting for 32.50% of the total, necessitated discontinuation of the problematic medication and substitution with an alternative. 6 patients, accounting for 7.50% of the total, were only treated with counselling and assurance.

DISCUSSION

India has been classified as a nation with a significant prevalence of pulmonary tuberculosis, multidrug-resistant tuberculosis, and tuberculosis co-infected with HIV. Drug resistant TB provide significant challenges in terms of therapy, since they need extended administration of less effective and more toxic medications. ADRs linked to these medications add complexity to the situation, leading to patients

discontinuing treatment, inadequate therapy, and thereby impacting the success rate. Effectively managing ADRs and addressing the associated treatment costs are crucial aspects that need attention. ADR was seen in 80 (80%) participants out of 100 in our research. A total of15 kinds of ADRs were recorded. The prevalent adverse effects were gastrointestinal disturbance, arthralgia, and cephalalgia. Gastrointestinal distress and arthralgia were the prevailing symptoms in prior investigations as well. In a study conducted by Patel et al,[12] at Smt. N.H.L. Municipal Medical College in Ahmedabad, India, it was found that out of 142 patients, 78 experienced ADRs. The most frequently reported side effects after 6 months and 24 months of therapy were gastrointestinal disturbances, headaches, and arthralgias. A modification of the medication regimen was necessary in 9.84% of patients at the first follow-up, 5.97% during the second follow-up, and in 4.47% of patients at the 24th month of therapy, resulting in a reduction in drug dosage. In a separate investigation conducted by Pawar et al,[13] it was shown that out of the 120 patients observed, a total of 117 (97.5%) individuals encountered one or more ADRs during the intensive phase. The predominant adverse response seen was gastrointestinal side effects, reported by 85 individuals (72.6%), followed by joint discomfort, reported by 66 individuals (56.4%). 11 (9.1%) individuals had their treatment regimen adjusted during the intense phase owing to medication toxicity. In a separate trial carried out by Yang etal,[14] in South Korea, 37.1% of the 256 patients had one or more adverse symptoms. The research found that the most prevalent adverse effects were gastrointestinal disturbance (18.4%), mental problem (5.5%), and arthralgia (4.7%). A total of 54 individuals necessitated discontinuation of medication therapy, mostly owing to adverse effects of PAS, followed by cycloserine and kanamycin.

According to a research done by Bhardwaj et al, [15] 83.33% of all patients had at least one sort of adverse response. The most prevalent adverse effects of this medication were gastrointestinal issues (76% of patients had them), mental symptoms (44.7%), arthralgia and hyperuricemia (31.3%), central nervous system problems (22.7%), and ototoxicity (22%). Eleven individuals need a modification in their treatment plan, while five patients discontinued therapy during the continuation phase due to the adverse effects of cycloserine.Shinde et al.[16] shown that among 468 individuals, 60 (12.82%) had at least one side event and required hospitalisation as a result. Out of the 109 documented ADRs, the most frequently reported ADR was gastrointestinal discomfort, accounting for 5.98% of the cases. Other commonly reported ADRs were psychosis (4.91%) and ototoxicity (2.99%).

A research done by Bhatt and Kc.[17] in Nepal examined MDR patients and identified unfavourable effects in 101 individuals. The predominant side effects seen were arthralgia (21.2%), nausea (20.3%), otological impairments (11%), gastrointestinal disturbances (9.9%), and a subset of 22 patients (18%) had severe adverse reactions necessitating discontinuation of the implicated medication(s). Cycloserine induced significant psychotic adverse events in 15 patients, leading to its discontinuation in these individuals. Hearing loss led to the discontinuation of Kanamycin in five individuals due to severe adverse effects. Consistent with the aforementioned research, the present investigation likewise identified gastrointestinal symptoms as the most prevalent. The symptoms were successfully alleviated with counselling and the use of a proton pump inhibitor. Drug administration was halted for a duration of 1-2 weeks in some individuals due to suspected drug use. In a research performed by Shinde et al,[16] and Pawar et al,[13] it was found that the most often implicated medicines were ethionamide and pyrazinamide. 68 individuals, accounting for 56.67% of the total, had joint discomfort. Pyrazinamide was halted for a duration of 2 weeks in a group of 20 patients. Pyrazinamide and levofloxacin were the medications responsible for the adverse effects. The symptoms of Hyperuricemia were managed with a dosage of 40 mg of Febuxostat administered twice daily. Nonsteroidal anti-inflammatory medicines were used to alleviate the symptoms. Nevertheless, pyrazinamide was discontinued in 3 individuals. The medications cycloserine, fluoroquinolones, and ethionamide are responsible for ADRs affecting the central nervous system (CNS), such as psychosis, seizures, headache, sleeplessness, and suicidal thoughts. Cycloserine was identified as the primary causative agent for psychosis and depression. Prior

research has shown increased prevalence of psychosis and depression. The variation may be attributed to the administration of a consistent and elevated dosage of cycloserine (1000 mg) in the subjects included inthese investigations. The majority of patients had positive responses to counselling, whereas a portion of the cases were managed with antidepressant medications such as clonazepam and escitalopram. Cycloserine was typically discontinued for a brief duration of time, ranging from 1 to 4 weeks. Six individuals have had permanent discontinuation of Cycloserine. Out of the total number of patients, 9 had severe psychosis, while 5 acquired suicidal thoughts. These conditions were addressed by prescribing antipsychotic drugs recommended by a psychiatrist.

CONCLUSION

Over 50% of the individuals in this trial had ADRs. The majority of ADRs may be managed by symptomatic treatment. The prevailing symptoms were gastrointestinal discomfort, followed by joint pain and headache. The occurrence of significant side effects such as damage to the ears and neurological signs may result in the discontinuation of essential medications from the treatment plan. Therefore, it is important to provide counselling on these crucial signs and to thoroughly explain the treatment strategies in a proactive manner. By continuously monitoring patients in the intense phase of therapy and promptly identifying ADRs, we may effectively reduce morbidity.

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