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Original Research Article

Retrospective assessment of adverse drug reactions linked to first-line antituberculosis drugs at a tertiary healthcare facility in Northern India

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ABSTRACT

Background: Tuberculosis (TB) continues to pose a major health challenge in India, where the burden remains among the highest globally. First-line anti-tubercular therapy (ATT), though effective, often leads to adverse drug reactions (ADRs) that may interfere with patient adherence and overall treatment success. This study aimed to assess the pattern and severity of ADRs associated with ATT in a real-world clinical setting.
Methods: This retrospective review analyzed 102 reports of adverse drug reactions (ADRs) submitted to the Pharmacovigilance Programme of India (PvPI). Data were obtained from the ADR Monitoring Centre at Motilal Nehru Medical College, Prayagraj. Although the data were collected between 2015 and 2018, the analysis was performed in 2025 to derive retrospective insights into ADR trends. Given the consistency of the standard ATT regimen over the years, the findings remain clinically relevant. The study evaluated types of ADRs, severity using the modified Hartwig and Siegel scale, and causality using WHO-UMC criteria. Statistical analysis was performed using SPSS version 25.
Results: Drug-induced hepatitis was the most frequently observed ADR (58.8%), followed by gastrointestinal symptoms (22.5%) and skin-related reactions (8.8%). Most ADRs occurred in male patients (63.7%) and during the intensive phase of ATT (73.5%). A significant correlation was noted between the type of ADR and the treatment phase (chi-square =56.29; $p<0.001$).
Conclusions: ADRs with first-line ATT are not uncommon, with liver toxicity being especially prevalent during the initial months of treatment. Strengthening ADR monitoring and early intervention can help improve treatment adherence and patient safety.

Keywords: Adverse drug reactions, Anti-tubercular therapy, Hepatotoxicity, India, Pharmacovigilance, Tuberculosis

INTRODUCTION

Despite advances in public health, TB, caused by *Mycobacterium TB*, continues to be a significant danger to world health. It remains one of the ten leading causes of death and is the most lethal infection attributed to a single pathogen.[1] The Global Tuberculosis Report 2023 estimates that in 2022, TB affected around 10.6 million people worldwide, of whom 167,000 people died from co-infection with HIV, while 1.3 million people died from HIV-negative causes.[2]

India continues to carry the highest tuberculosis burden worldwide, with approximately 21.4 lakh new TB cases reported in 2022- a 13% increase compared to the previous year, as outlined in the India TB Report 2023.[3] By 2025, The National Tuberculosis Elimination Programme (NTEP) of the Ministry of Health and Family Welfare aims to eradicate TB across the country. through strategies such as early case detection, comprehensive drug-resistance testing, and patient-focused, individualized care.[4]

First-line anti-tubercular medications, like ethambutol, pyrazinamide, rifampicin, or isoniazid have played a

crucial role in enhancing treatment outcomes for tuberculosis patients.[5] Nevertheless, their use can be associated with adverse drug reactions (ADRs), ranging from mild gastrointestinal discomfort to more severe complications such as liver toxicity, allergic responses, and visual disturbances.[6-8]

Adverse medication reactions can prolong the course of treatment and impair patient adherence. elevate the likelihood of developing drug resistance, and, in severe cases, pose life-threatening risks.[9] As such, ongoing monitoring and prompt recognition of ADRs are critical to enhancing treatment compliance and minimizing TB-related health complications.[10]

The Indian Pharmacopoeia Commission established the PvPI to facilitate structured monitoring and evaluation of drug safety, including ADRs associated with anti-tubercular therapy.[11] The foundation of post-marketing pharmacovigilance is the spontaneous reporting of ADRs by medical practitioners to approved AMCs, essential for reducing clinical hazards.[12]

In a Northern Indian tertiary healthcare facility, this study sought to determine the prevalence, kinds, seriousness, and causation of adverse drug reactions linked to first-line anti-tubercular medications. Insights drawn from real-world pharmacovigilance data can assist healthcare professionals in making better-informed decisions, ultimately enhancing patient safety and reducing the incidence of drug-related adverse outcomes.

METHODS

Study framework

This research was designed as a retrospective observational study at the AMC, housed within the department of pharmacology at Motilal Nehru Medical College, Prayagraj. We reviewed ADR reporting forms submitted over four years, covering the period from January 2015 to December 2018.[13]

Justification of study period

Although the data used in this study were collected from 2015 to 2018, the analysis was conducted recently in 2025 to gain retrospective insights into the pattern and severity of ADRs associated with first-line ATT. The typical first-line ATT regimen, which consists of ethambutol, pyrazinamide, rifampicin, and isoniazid, has remained largely consistent over the years, so the findings retain significant clinical relevance.

Additionally, analyzing this data contributes valuable information to long-term pharmacovigilance trends. It helps understand the historical burden of ADRs, thereby assisting in refining current monitoring strategies under the NTEP.

Study population

The study included patients who were administered first-line anti-tubercular medications and were suspected to have encountered ADRs throughout the designated study period. A total of 102 adverse medication reaction cases were evaluated, all of which were spontaneously reported to the AMC functioning under the Pharmacovigilance Programme of India (PvPI).[14]

Inclusion criteria

Only those ADR reports associated with ethambutol, pyrazinamide, rifampicin, and isoniazid are the first-line anti-tubercular drugs- were considered for inclusion in the study.[15] Reports submitted between January 2015 to December 2018. Adequate information about patient demographics, treatment details, and nature of ADR.

Exclusion criteria

Reports related to second-line or newer anti-TB agents (e.g., bedaquiline, delamanid). Incomplete or illegible ADR forms. Duplicate or follow-up entries.

Data source and collection

In this retrospective observational study on ADRs linked to anti-tubercular therapy, we used as part of the PvPI, IPC, which is housed within the Ministry of Health and Family Welfare, produced the ‘suspected adverse drug reaction reporting form’ (version 1.3).[16] This form is intended to let healthcare professionals- such as physicians, pharmacists, dentists, or nurses- voluntarily report ADR. It collects essential clinical and pharmacological information required for effective pharmacovigilance assessments and early detection of safety signals.[17]

The reporting form starts by capturing key patient demographics- such as initials, age, gender, and weight- while maintaining confidentiality. It then focuses on the specifics of the adverse event, including its onset, duration, and clinical presentation, encouraging healthcare professionals to describe the reaction in clear, straightforward language, along with any treatment provided. The form also collects relevant medical history, such as alcohol use, allergies, or comorbidities, which may influence drug response. A critical component involves documenting the suspected drug, including its name, dosage, route, and duration of administration. This section also notes whether the medication was discontinued or continued and if a similar reaction occurred upon re-administration. Space is provided for listing other concurrent medications, including over-the-counter or herbal products. Lastly, the form includes the reporter’s contact information, allowing PvPI to follow up if needed. Rather than being a simple checklist, the form serves as a comprehensive tool for capturing the clinical context of ADRs, thereby promoting safer medication practices nationwide.

All collected data were anonymized and entered into a predesigned Microsoft Excel database for analysis.

Assessment of ADRs

We have assessed the ADRs by following mentioned scales-

Each reported ADR was evaluated evaluating the possibility that the medicine and the reaction are causally related using the WHO-Uppsala Monitoring Centre (UMC) standards. According to these criteria, the occurrences were categorized as plausible, possible, unlikely, or certain.[18]

Using a modified Hartwig and Siegel scale, the severity of adverse medication reactions was assessed. a validated tool that classifies reactions as mild, moderate, or severe.[19]

Statistical methods

SPSS version 25.0 was used to analyze the data (IBM, Armonk, NY). The categorical variables were summarized using descriptive statistics and presented as frequencies along with their respective percentages. To determine potential correlations, Chi-square (χ^2) tests were applied to assess relationships between adverse drug reaction type, patient gender, phase of treatment, severity grading, and causality classification. A p value of less than 0.05 indicated statistical significance.[20]

Ethical considerations

This study's analysis was based on anonymized data reported through the national pharmacovigilance system. As no direct patient identifiers were used and no intervention was involved, formal ethical approval was not required.[21]

RESULTS

In total, 102 adverse drug reaction reports were examined in individuals receiving first-line anti-tubercular drugs.

Name of adverse drug reactions

The most frequently reported ADR was drug-induced hepatitis, observed in 60 cases (58.8%) Figure 1. This was followed by gastrointestinal (GI) disturbances: 23 cases (22.5%), cutaneous adverse drug reactions (CADRs): 9 cases (8.8%), other ADRs (e.g., arthralgia, visual disturbances): 10 cases (9.8%).

A significant statistical relationship was observed between the type of ADR and the phase of treatment (χ^2=56.29, p<0.001), indicating ADRs like hepatitis were more likely to occur during the intensive phase of therapy which is consistent with previous studies.[22]

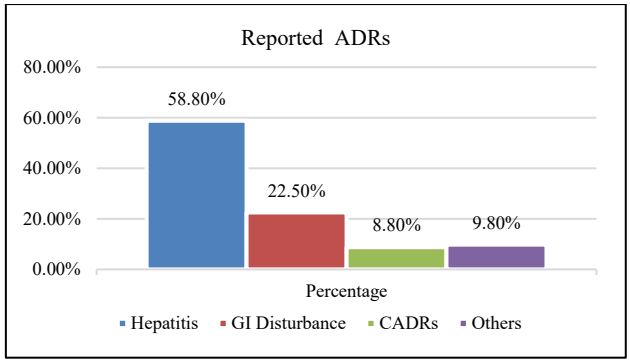

Figure 1: Name of the ADRs reported.

Gender distribution

Among the affected patients, 65 (63.7%) were male and 37 (36.3%) were female (Figure 2). Although ADRs were more commonly reported in males, no statistically significant association was found between ADR type and gender (χ^2=3.84, p=0.2794).

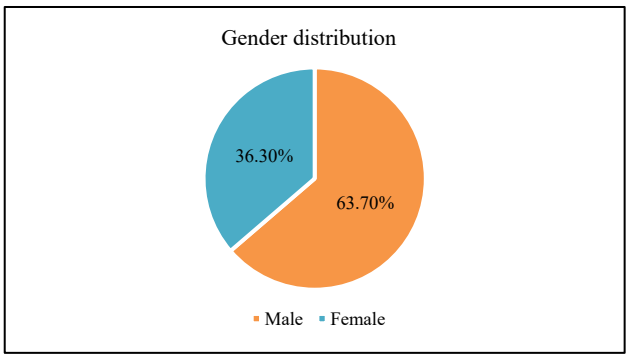

Figure 2: Gender distribution of ADRs reported.

Treatment phase distribution

The intensive phase accounted for 75 cases (73.5%) of ADRs, while the continuation phase was associated with 27 cases (26.5%) (Figure 3). This aligns with the significant correlation found between ADR type and treatment phase.

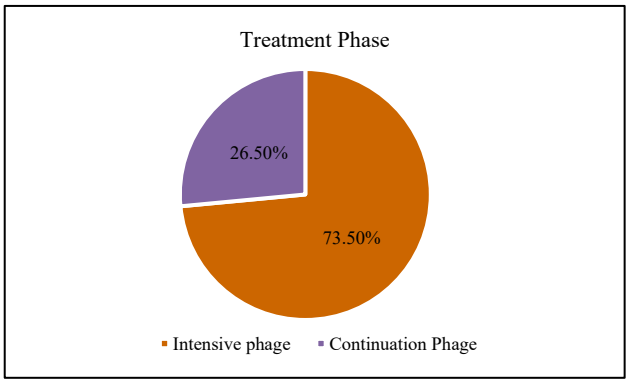

Figure 3: Treatment phase distribution.

Grading the severity of adverse drug reactions

To classify the severity of adverse medication responses, the modified Hartwig and Siegel classification system as details shown in Figure 4. We observed moderate cases 52 in number (51.0%), mild were 30 cases (29.4%) and severe cases observed were 20 (19.6%).

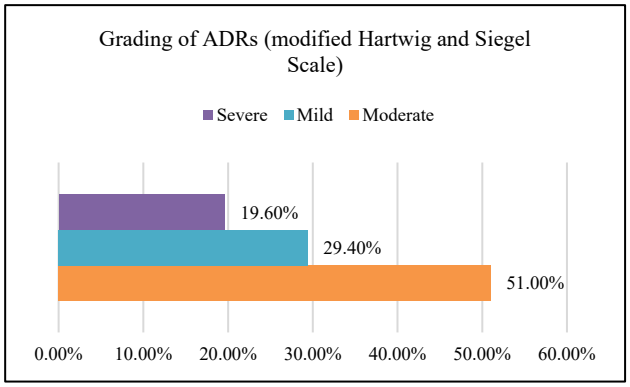

Figure 4: Severity of ADRs reported.

Causality assessment (WHO-UMC criteria)

Causality assessments showed following results as shown in Figure 5. The reported ADR' causation analysis showed that 48 cases (47.1%) were deemed 'probable', 44 cases (43.1%) were assessed as 'possible', and 5 cases each (4.9%) were identified as 'certain' and 'unlikely'.

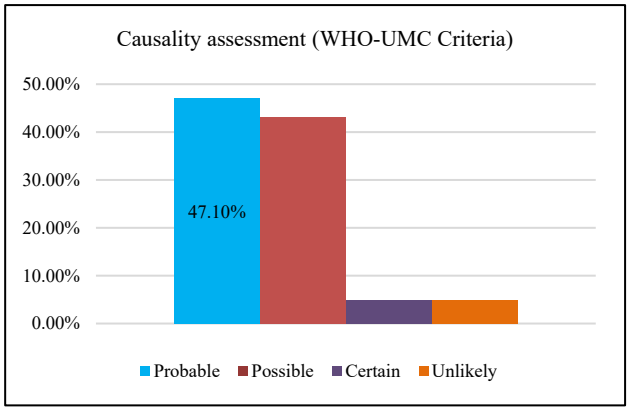

Figure 5: Causality assessment according to WHO-UMC criteria.

DISCUSSION

This retrospective analysis, based on real-world data from a tertiary care center, brings attention to significant trends in the incidence, clinical manifestations, and therapeutic relevance of ADR associated with first-line ATT.

The most often seen ADR in this study was drug-induced hepatitis (58.8%), a finding consistent with multiple Indian and international studies reporting hepatotoxicity as the primary complication of isoniazid, rifampicin, and pyrazinamide combination therapy.[23,24] Hepatotoxicity often needs treatment interruption, thus posing a risk for poor adherence and drug resistance.[25]

Gastrointestinal disturbances (22.5%) and cutaneous adverse drug reactions (CADRs) (8.8%) were the next most common. These findings align with the findings published by Kaur et al and Adhikari et al, who also reported nausea, vomiting, and skin rashes as common non-hepatic adverse reactions during the intensive phase of ATT. [26,27]

Phase-wise analysis of treatment revealed that most adverse drug reactions occurred during the intensive phase, showing a statistically significant correlation ($p<0.001$). This is plausible as hepatotoxic drugs like pyrazinamide are given during the intensive phase, increasing the cumulative hepatic burden.[28] On the other hand, the gender-based distribution showed no statistically significant difference, although ADRs were more frequent among male patients- a trend observed in previous Indian studies.[29]

Severity assessment showed that moderate reactions (51%) were most common, followed by mild (29.4%) and severe ADRs (19.6%), suggesting a substantial proportion required clinical intervention.[30] Most ADRs were assessed as probable (47.1%) or possible (43.1%) per WHO-UMC causality criteria, which aligns with the observational nature of pharmacovigilance data.[31] As summarized in (Table 1), various anti-tubercular medications have been linked to distinct adverse drug reactions, as supported by existing literature.

Table 1: Suspected anti-tubercular drugs and associated ADRs based on literature.

Adverse drug reaction	Commonly suspected drug(s)	Supporting references
Hepatotoxicity	Isoniazid, Rifampicin, Pyrazinamide	23-25
Gastrointestinal disturbances	Pyrazinamide, Rifampicin	26
Cutaneous reactions (CADRs)	Isoniazid, Rifampicin, Ethambutol	27
Arthralgia	Pyrazinamide	28
Visual disturbances	Ethambutol	29

These results highlight the necessity of evaluating liver function at baseline. effective patient education, and consistent monitoring- especially throughout the intensive phase of treatment.[30] Incorporating pharmacovigilance insights into standard TB care practices can strengthen the safety profile of anti-tubercular treatment regimens and contribute to better long-term patient outcomes.

This study has a few important limitations that must be acknowledged. A constraint of the research is the utilization of retrospective data collected between 2015 and 2018. However, their clinical relevance remains high due to the continued use of the same first-line ATT regimen. The study's retrospective design also makes it possible to assess long-term ADR trends and strengthens pharmacovigilance practices under the current TB control framework. Because it is based on retrospective data, it relied heavily on the quality and completeness of ADR forms that had already been submitted, some of which lacked key clinical details. The voluntary nature of reporting may have led to selective documentation, where severe or unusual cases were more likely to be reported than mild or routine ones.[31]

Another concern was the absence of follow-up data, which limited our ability to comment on the long-term consequences of the reported reactions. In addition, most patients received multiple drugs simultaneously, making it difficult to assign causality to a single agent confidently. Lastly, as the data originated from a single institutional context, the results may not be entirely generalizable to patient populations in different regions or healthcare settings.[32]

CONCLUSION

Although the study is retrospective, the findings remain clinically meaningful because the standard ATT regimens have not significantly changed over the years. This study clearly demonstrates the significant burden of ADR connected to first-line anti-tubercular drugs, especially when treatment is at its most intensive. Among the reported adverse drug reactions, drug-induced hepatitis was the most common, followed by gastrointestinal issues and skin-related manifestations. The results emphasize the importance of early identification, risk stratification, and close monitoring of patients, especially during the initial months of ATT when the hepatic load is highest. The predominance of moderate and probable ADRs suggests that many cases may be managed with supportive care or minor regimen adjustments if identified promptly. This study reinforces the value of active pharmacovigilance systems like the PvPI in capturing real-world drug safety data. Integrating such systems into routine TB management can improve patient safety, reduce non-adherence, and contribute to national TB elimination goals.

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