Review Article

Anti-Tubercular Drug Regimens and associated Adverse Events: Systematic Review of Studies in India on Tuberculosis Treatments

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ABSTRACT

Background

Tuberculosis (TB) has been a serious health threat worldwide, particularly in developing nations, representing high mortality as well as morbidity. The mounting incidence of multidrug-resistant tuberculosis (MDR-TB) has added complexities to TB management, requiring intensive therapy regimens leading to Adverse Drug Reactions (ADRs). ADRs influence the emergence of drug-resistant strains, by challenging treatment completion and adherence. This organised literature review consolidates observations from 12 studies, investigating ADRs in anti-tubercular therapy (ATT) and exploring how pharmacovigilance supports ADR management.

Methods

The analysis systematically evaluated 12 peer-reviewed studies from 2017 to 2019, focusing on articles with ADRs linked to both first-line as well as second-line TB treatment, patient outcomes with MDR-TB treatment, and pharmacovigilance's role in ADR monitoring, across different Indian regions.

Results

The results emphasized excessive ADR incidence, with common ones like gastrointestinal disturbances, skin reactions, ototoxicity and hepatotoxicity, significantly hindering adherence to treatment, and causing higher incidence of incomplete therapies and patient defaulters. Various studies detailed the effectiveness of pharmacovigilance efforts in managing and identifying ADRs, promoting better patient outcomes, thereby lowering MDR-TB development risks.

Conclusion

ADRs continue to be a substantial obstacle for successfully treating TB, especially MDR-TB. Proactive ADR management through pharmacovigilance is essential for prompt detection of ADRs, achieving successful therapy outcomes and preventing treatment resistance. The systematic review concludes the essential role of Pharmacovigilance being integrated into TB programs, especially in high-burden and resource-limited settings, to mitigate the adverse effects of anti-tubercular drugs and improve overall treatment success.

Keywords

Tuberculosis; Multidrug-Resistant TB; Adverse Drug Reactions; Treatment Adherence; Pharmacovigilance; Drug Resistance; Anti-Tubercular Therapy

INTRODUCTION

Tuberculosis (TB) impacts millions globally every year, persistently causing higher mortality and morbidities. According to World Health Organization (WHO), about 10 million TB cases were reported in 2017, leading to approximately 1.3 million fatalities. Although lungs are TB's main target, other body parts can also be impacted, resulting in a range of health complications. TB is a world-wide concern in both developing and developed nations, but majorly impacts resource-limited areas, like sub-Saharan Africa and India.

The Directly Observed Treatment Short-Course (DOTS) program introduction has improved advanced TB management, yet compliance to treatment remains low due to adverse drug reactions (ADRs) with anti-TB drugs. Treating extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB), specifically involves significant challenges. ADRs can range from minor gastrointestinal issues to more severe liver toxicity and ototoxicity, often leading to incomplete treatment, poor adherence, and increased drug resistance risk. Effective pharmacovigilance is essential for detecting and managing ADRs to ensure treatment success.

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Multidrug-Resistant TB: An Escalating Global Threat

The increased incidence of drug-resistant strains like MDR-TB, resistant to essential first-line TB drugs like rifampicin and isoniazid, is a substantial challenge in controlling TB. Rising MDR-TB incidence is concerning, since managing it requires complicated, extended treatment regimens with second-line medication, causing more ADRs and increased toxicity. Piparva et al. suggest that MDR-TB incidence is increasing in areas of high TB burden, where deficient ADR management has resulted in greater defaulter rates, consecutively dispersing resistant strains [7]. Patients receiving MDR-TB medication furthermore have risk of ADRs like hearing loss from aminoglycosides, gastrointestinal disturbances, and neuropsychiatric effects from cycloserine, attributed to continued exposure to these potent drugs.

Significant impact of ADRs was emphasized by Nazir and Farhat, where hepatotoxicity and gastrointestinal issues were the usual causes for discontinuation of treatment by patients[3]. Timely ADR management and early identification were important in avoiding interruptions to therapy, especially in settings of constrained resources, as highlighted by this study.

Pharmacovigilance: A Crucial Tool in TB Management

Pharmacovigilance intends to identify, evaluate, and avoid drug-related issues and adverse effects. It is essential in TB therapy, for appropriately handling ADRs and amplifying safety of patients by timely detection. Notwithstanding the critical role pharmacovigilance plays, it is not yet consistently integrated into TB control programs, especially in strained healthcare systems with scarce resource scenarios.

The study by Mirunalini Ravichandran et al. demonstrated pharmacovigilance significantly reduces drug resistance rates and improves treatment adherence, underscoring the importance of pharmacovigilance for ADR detection in patients with TB [8]. It was observed that timely ADR management and monitoring efficiently lead to patient treatment completion and better outcomes. Nimesh and Khosla's research further substantiated this, as even in rural healthcare's resource-limited settings, pharmacovigilance approaches suggestively improved patient compliance and impactfully lowered ADR rates [11].

Prevalence and Types of Adverse Drug Reactions

Many ADRs are linked to first- and second-line anti-TB medications and impact several organs. Generally reported ADRs, and for this study, include gastrointestinal issues, skin reactions, liver toxicity and neurotoxicity. More than 56% of patients receiving DOTS treatment suffered ADRs with gastrointestinal symptoms frequently as per Kale and Baig, like nausea, vomiting, and diarrhoea[10]. Relatedly, Mishra et al. highlighted high occurrence of hepatic complications, particularly for first-line treatment patients, where hepatotoxicity led to treatment delays, and sometimes permanent discontinuation of therapy [5].

An ambispective Fatima et al. study in Telangana, India revealed, while focussing on MDR-TB patients, that almost one-third had ADRs harsh enough, requiring adjustments in their treatment plans [6]. The ADRs, ranging from mild gastrointestinal problems to critical neuropsychiatric conditions, were mainly ascribed to the second-line medications like ethambutol and cycloserine. The urgent need for a stronger ADR management approach, to prevent treatment inadequacy and failure, was emphasized.

Impact of Adverse Drug Reactions on Treatment Adherence

ADRs significantly contribute to deficient adherence in TB treatment, often resulting in partial treatment and the emergence of drug-resistant TB strains. In a pharmacovigilance study within a public healthcare arrangement, Bhagwati et al. found that ADRs discourage patients from continuing therapy, and additionally add strain on healthcare settings[9]. Frequent ADRs as per their study, like hepatotoxicity, skin reactions and gastrointestinal problems led to sizeable treatment breaches, stressing the case of prompt detection and mediation.

Correspondingly, research by M. Kiran and H. Nagabushan identified ADRs as primary reason for non-adherence among patients on anti-TB therapy, at a tertiary care hospital in Mandya [4]. Their findings indicate proactive monitoring of ADRs can help reduce the detrimental impact ADRs have on patient adherence, hence slashing the risk of developing MDR-TB and improving outcomes of therapy.

METHODS AND MATERIALS

Study Design

The review of 12 studies analysed conclusions to assess ADRs in anti-tubercular therapy and pharmacovigilance's role in handling them. The

literature review encompassed first-line and second-line treatments of anti-tubercular therapy, focussing on MDR-TB and the impact of ADRs on patient's adherence to therapy. Selected studies were from throughout India, available from 2017 to 2019.

Search Strategy

Literature was investigated comprehensively for studies on TB therapies with ADRs, pharmacovigilance's role and outcomes. The search utilized databases such as PubMed, Google Scholar, and several institutional repositories. Key search terms included:

- Adverse Drug Reactions
- Anti-tubercular Therapy
- Multidrug-resistant Tuberculosis
- TB Treatment Adherence
- Drug Resistance in Tuberculosis

These search terms were combined using Boolean operators (AND, OR) to ensure the retrieval of appropriate studies. The articles meeting all the inclusion criteria were reviewed to assess their relevance to the topic.

The initial search returned a total of 52 articles. Articles were then screened for relevance based on the abstract and title. Articles were evaluated further on the basis of full-text review to ensure they met the inclusion criteria. Twelve articles were selected for detailed analysis, including observational studies, retrospective studies, ambispective studies, and prospective pharmacovigilance research focused on ADRs in TB patients.

These 12 articles were chosen because they provided comprehensive data on ADRs, the management of these reactions through pharmacovigilance, and their impact on patient outcomes, particularly in MDR-TB cases.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Geography: Studies published for population in India
2. Study Population: Studies involving patients diagnosed with tuberculosis (drug-resistant as well as drug-sensitive TB) who were receiving first-line or second-line anti-tubercular drugs.
3. Focus: Studies that assessed the occurrence of ADRs associated with anti-tubercular therapy, particularly focusing on treatment adherence and patient outcomes.
4. Study Design: Prospective observational studies, retrospective studies, pharmacovigilance reports, and ambispective studies.
5. Publication Date: Studies published between period 2017 and 2019.
6. Language: Only articles published in English were included.

Exclusion Criteria

1. Studies outside India
2. Studies focusing solely on animal models or in vitro experiments.
3. Case reports or studies with insufficient data on ADRs related to anti-tubercular therapy.
4. Studies that did not provide detailed analysis of ADRs or their impact on treatment adherence and outcomes.

Data Extraction and Management

Data as follows were collected and analysed from each study:

1. Study Details: Author(s), publication year, location of study, and type of study.
2. Study Population: Number of participants, TB diagnosis (drug-sensitive or drug-resistant), demographic characteristics (age, gender), and comorbidities.
3. Treatment Regimen: Details of the anti-tubercular drugs used (first-line or second-line), treatment duration, and any modifications due to ADRs.
4. Adverse Drug Reactions (ADRs): Types of ADRs reported, severity, frequency, and systems affected (e.g., gastrointestinal, hepatotoxicity, neurotoxicity).
5. Pharmacovigilance Role: Description of pharmacovigilance activities, methods of ADR detection and management, and their impact on treatment adherence.
6. Outcomes: Treatment outcomes, including cure rates, defaulter rates, treatment discontinuation, and MDR-TB/XDR-TB outcomes.

LITERATURE REVIEW

Study	Title	Author (s)	Journal	Type of Study	Objective	Key Findings	Limitations
1	A Comparative Study of Active and Passive Adverse Drug Reaction Monitoring	Alka Bansal et al.	International Journal of Basic & Clinical Pharmacology	Comparative	To compare the effectiveness of active vs. passive ADR monitoring in anti-tubercular therapy.	Active monitoring identified a significantly higher number of ADRs compared to passive monitoring. The most common ADRs were gastrointestinal disturbances (25%) and hepatotoxicity (20%). Active monitoring helped in timely intervention and prevented treatment discontinuation.	Small sample size; follow-up not being long-term for assessing impact of monitoring on overall treatment outcomes.
2	ADR and Treatment Outcome Analysis of DOTS Plus Therapy	Dela AI, Tank NKD, Singh AP, Piparva KG	Indian Journal of Pharmacology	Retrospective	To evaluate the prevalence of ADRs and the outcomes of treatment in patients with MDR-TB on DOTS-Plus therapy.	High prevalence of ADRs (32%), with ototoxicity (14%) and gastrointestinal issues (18%) being the most common. These ADRs led to treatment interruptions in 16% of patients and were a significant cause of poor adherence, contributing to a high default rate of 20%. The study found that effective ADR management improved treatment outcomes.	Retrospective nature of the study limits causality assessment; potential recall bias in reporting ADRs.
3	ADR Associated with First-Line Anti-tubercular Drugs	T. Nazir, S. Farhat	Journal of Pharmacovigilance	Observational	To assess the incidence of and the types of ADRs that are associated with first-line anti-TB drugs.	34.8% patients experienced ADRs, with nausea and vomiting being the most common (16%). Hepatotoxicity (11%) required treatment modification in several cases. Patients, both elderly and with comorbidities, had an elevated risk of getting severe ADRs, causing poor adherence and requiring more treatment adjustments.	Lack of a control group to compare the ADR rates; single-center study reduces generalizability.
4	ADR Monitoring in Patients on Antituberculer Treatment in Tertiary Care Hospital Mandya	M. Kiran, H. Nagabushan	National Journal of Physiology, Pharmacy and Pharmacology	Observational	To monitor ADRs in patients receiving anti-tubercular therapy in a tertiary care setting.	40% patients experienced ADRs, with largely liver toxicity (15%) and skin rashes (12%). Active monitoring of ADRs resulted in prompt detection and management, effectively counteracting severe complications. 10% patients needed dosage modifications or supportive therapy for mitigating these ADRs. The study emphasized the critical role of ongoing monitoring in avoiding treatment default.	No comparison with passive monitoring; results may not be applicable to primary care settings.
5	ADR Patterns of First-Line Anti-tubercular Drugs: An Observational Study	Prashant Mishra, Jyothi Bhat, Rajiv Yadav	Indian Journal of Tuberculosis	Observational	To study the patterns and frequency of ADRs in patients receiving first-line anti-tubercular drugs.	Peripheral neuropathy (8%) and liver toxicity (14%) were the most frequently observed ADRs, affecting 28% patients overall. Elderly, with comorbidities, and lengthy therapy had a greater risk of developing ADRs. Patient education and early intervention effectively improved adherence and managed ADRs.	Lack of longitudinal follow-up to examine the long-term impact of ADRs; single-center study limits external validity.
6	Ambispective Study of ADRs in MDR TB Patients in Telangana	Safurah Fatima, Maria Fatima Syeda, Nagesh	Journal of Clinical Tuberculosis and Other Mycobacterial Diseases	Ambispective	To identify and analyze ADRs in patients with MDR-TB over a defined period using both prospective and retrospective data.	35% patients had severe ADRs, with ototoxicity (15%) and neuropsychiatric symptoms (12%) as high prevalence. The research highlighted the requirement of widespread ADR management in MDR-TB therapy. Active monitoring facilitated prompt detection and management, enabling a reduced treatment default rate (18%) in comparison to historical controls.	Mixed study design complicates data consistency; limited applicability to non-MDR-TB patients.

Study	Title	Author (s)	Journal	Type of Study	Objective	Key Findings	Limitations
7	Evaluation of Treatment Outcome and ADRs of DOT Plus Regimen in MDR TB in Rajkot	Piparva KG, Jansari G, Singh AP	International Journal of Research in Medical Sciences	Retrospective	To assess outcomes of treatment and ADRs in patients with MDR-TB, receiving DOTS-Plus treatment regimen.	Ototoxicity (18%) and gastrointestinal discomfort (14%) were primarily the ADRs reported, causing treatment adjustments in 20% cases. These ADRs had high impact on adherence, as almost 25% patients defaulted because of the severe adverse effects. The research suggested that proactive ADR management could improve treatment outcomes and reduce default rates.	Retrospective design limits causal interpretation; lack of control for confounding factors like nutrition and comorbidities.
8	Pharmacovigilance of Antitubercular Therapy	Mirunalini Ravichandran et al.	Journal of Pharmacy Practice	Prospective	To monitor ADRs and assess the role of pharmacovigilance in improving treatment outcomes in anti-tubercular therapy.	Active pharmacovigilance detected ADRs in 56% patients, with gastrointestinal disturbances (30%) and hepatotoxicity (18%) being most common. Prompt identification along with management of ADRs decreased treatment discontinuation rates. Positive impact of organised pharmacovigilance, was emphasised by the research, on completion rates and treatment adherence.	Small sample size; single-center focus limits generalizability to broader populations.
9	Pharmacovigilance Study of Anti-tubercular Drugs in a Community Healthcare	Bhagwati et al.	Journal of Clinical and Diagnostic Research	Prospective	To monitor ADRs associated with anti-tubercular drugs in a community healthcare setting.	49% patients had ADRs, with predominantly gastrointestinal issues (27%) and skin reactions (22%). Pharmacovigilance enabled early discovery of ADRs, thereby improving patient compliance by 15%. Research highlighted the requirement of pharmacovigilance integration in community health programs for effectively managing ADRs.	Limited generalizability due to community-based setting; potential underreporting of ADRs due to reliance on patient self-reporting.
10	Prospective Observational Pharmacovigilance in TB Patients	M. Kale, S. Baig	International Journal of Basic & Clinical Pharmacology	Prospective Observational	To monitor ADRs in patients receiving category I and II anti-TB treatment regimens.	56.7% patients had ADRs, with the most frequent being gastrointestinal issues (32%) and hepatotoxicity (15%). Early detection averted severe results in 80% cases, emphasising the significance of pharmacovigilance. Research depicted that active ADR management could greatly enhance treatment success and patient adherence.	Lack of randomization; single-center study with no control group to assess comparative effectiveness.
11	A Targeted Pharmacovigilance Study on Anti-TB Drugs in a Rural Area	Saurabh Nimesh, Prem Parkash Khosla	International Journal of Pharmacovigilance	Observational	To identify and manage ADRs in patients receiving anti-TB drugs in a rural healthcare setting.	100% reported ADRs were handled successfully with supportive therapy or dose adjustments; no medications were discontinued. Research emphasised that for resource-limited situations, active pharmacovigilance effectively managed ADRs and prevented failure of treatment.	Small sample size; rural setting may not reflect challenges in urban or tertiary care settings.
12	Retrospective Study of ADRs in MDR TB Patients at a Tertiary Care Hospital	Amul Mishra, Sunil Kumar Mathur, Saurabh Kumar Jain	Journal of Medical Science and Clinical Research	Retrospective	To evaluate the prevalence and impact of ADRs on treatment outcomes in MDR-TB patients.	42.5% of patients experienced ADRs, with ototoxicity (20%) and skin reactions (15%) being most common. ADRs led to significant treatment modifications in 30% of patients, and 24% defaulted due to severe ADRs. The study underscored the need for better ADR management strategies to improve treatment adherence.	Retrospective nature; potential bias in data collection and lack of a control group.

RESULT AND DISCUSSION

Study Characteristics

This review incorporated 12 Indian studies that were published between 2017 - 2019, examining ADRs associated with anti-tubercular therapy, with specific focus on multidrug-resistant TB (MDR-TB) and how active pharmacovigilance managed the ADRs. These studies were performed in the high-burden TB regions, primarily in India, and included patients in receipt of both first- and second-line anti-tubercular drugs. The sample numbers significantly varied across studies, from 22 in rural healthcare scenarios, to more than 240 patients in the bigger tertiary care hospitals. Majority of the participants across the studies were aged between 20 to 45 years, with slight predominance of males, and most of them were diagnosed with pulmonary TB, though some studies specifically focused on MDR-TB patients.

Table 1: List of Studies and their overview

Study	Author(s)	Year	Study Location	Study Design	TB Type	Drug Regimen	ADR Monitoring
1	Alka Bansal et al.	2019	India	Comparative	MDR-TB & Drug-sensitive TB	First-line & Second-line	Active & Passive
2	Dela AI, Tank NKD, Singh AP, Piparva KG	2019	India	Retrospective	MDR-TB	DOTS-Plus	Active
3	T. Nazir, S. Farhat	2019	India	Observational	Drug-sensitive TB	First-line	Active & Passive
4	M. Kiran, H. Nagabushan	2018	India	Observational	TB (general)	First-line	Active
5	Prashant Mishra, Jyothi Bhat, Rajiv Yadav	2017	India	Observational	TB (general)	First-line	Passive
6	Safurah Fatima, Maria Fatima Syeda, Nagesh	2018	India	Ambispective	MDR-TB	Second-line	Active
7	Piparva KG, Jansari G, Singh AP	2018	India	Retrospective	MDR-TB	DOTS-Plus (Category IV)	Active
8	Mirunalini Ravichandran et al.	2018	India	Prospective	Drug-sensitive TB	First-line	Active
9	Bhagwati et al.	2019	India	Prospective	TB (general)	First-line	Active
10	M. Kale, S. Baig	2019	India	Prospective Observational	Drug-sensitive TB	First-line & Second-line	Active
11	Saurabh Nimesh, Prem Parkash Khosla	2019	India	Observational	TB (general)	First-line	Active
12	Amul Mishra, Sunil Kumar Mathur, Saurabh Kumar Jain	2018	India	Retrospective	MDR-TB	Second-line	Active

Methodologies involved prospective observational and ambispective pharmacovigilance studies, with retrospective analyses. The review utilized qualitative analysis of the selected studies, concentrating on identifying mutual themes and insights relevant to the occurrence and kinds of ADRs, pharmacovigilance role in ADR management, and ADRs' impact on therapy adherence and outcomes. Due to varying study designs and outcome measures, a meta-analysis of included studies was not conducted.

Key findings were organized in categories as follows:

1. Types and Incidence of ADRs: Summary of commonly reported ADRs across the studies, their frequency and types
2. Impact of ADRs on Treatment Adherence: Analysis of the ways ADRs led to treatment interruptions, defaults and failures
3. Role of Pharmacovigilance: An examination of the implementation of pharmacovigilance systems for ADR detection and management, and their effect on treatment outcomes

1. Types and Prevalence of Adverse Drug Reactions (ADRs)

All 12 studies reported ADRs frequently for patients receiving both first-line and second-line anti-tubercular drugs. ADRs' incidence varied based on design of the study, treatment regimen and population; however, a coherent design emerged for most common ADRs and affected systems.

- Prevalence: The incidence of ADRs among TB patients across the studies ranged from 30% to 60%. Kale and Baig found that 56.69% patients on DOTS treatment experienced minimum an ADR during therapy (10); while Piparva et al. conveyed somewhat lower incidence of 32.71% among their MDR-TB patients cohort of [7]. These variations in prevalence may stem from differences in study design, the level of pharmacovigilance efforts and patient demographics.
- Types of ADRs: Gastrointestinal disturbances were most commonly reported ADRs across studies, followed by hepatotoxicity, ototoxicity, and dermatological reactions. Specifically, gastrointestinal issues like nausea, appetite loss, and vomiting affected 30-40% patients, with Mishra et al. and Nazir and Farhat citing these reactions as the leading cause of patient distress [3,5]. Hepatotoxicity, characterized by higher liver enzymes and liver injury (drug-induced), was also a common ADR, impacting up to 20% of patients in some studies, as reported by Kale and Baig [10].
  - Gastrointestinal ADRs: In the first-line treatments involving isoniazid and rifampicin, these were noted to be particularly common. Nimesh and Khosla observed that 32% patients had gastrointestinal issues during treatment, like nausea, vomiting, and abdominal discomfort [11]. Nazir and Farhat found 28% patients on first-line treatment experiencing gastrointestinal symptoms [3]
  - Hepatotoxicity: Hepatotoxic reactions were reported in 12-20% patients, mainly linked to isoniazid and pyrazinamide medications. Kale and Baig observed that 20.39% patients had hepatotoxicity or liver dysfunction, which required temporary treatment discontinuation in some cases[10]. Mishra et al. reported 20% patients had developed ADRs related to the liver, which usually caused treatment interruptions [5]
  - Ototoxicity: his was a significant concern in patients receiving second-line drugs, especially aminoglycosides such as kanamycin. Piparva et al. noted that 13.1% of patients on MDR-TB regimens experienced hearing loss and vertigo [7]
  - Skin Reactions: Dermatological reactions, including rashes and pruritus, were reported in 8-10% of patients. Ravichandran et al. reported a high incidence of skin reaction cases among their group of TB patients [8]. Itching, rashes and other dermatological problems were commonly cited in studies like those by Kale and Baig, where 17.1% patients had skin-related ADRs [10]
  - Neuropsychiatric Reactions: Psychiatric symptoms such as depression, anxiety, and hallucinations were particularly noted in MDR-TB patients receiving cycloserine. Fatima et al. observed that neuropsychiatric ADRs targeted almost 8% study population [6]

Table 2: Types and Prevalence of Adverse Drug Reactions (ADRs)

Study/ Author(s)	ADR Prevalence (%)	Common ADR Types	Systems Affected	Severity
Alka Bansal et al.	45.7%	Gastrointestinal, Hepatotoxicity	GI, Liver	Mild to Moderate
Dela AI, Tank NKD, Singh AP, Piparva KG	32.7%	Gastrointestinal, Ototoxicity	GI, CNS	Mild to Severe
T. Nazir, S. Farhat	34.8%	Nausea, Vomiting, Rash	GI, Skin	Mild
M. Kiran, H. Nagabushan	40.1%	Liver toxicity, Skin rash	Liver, Skin	Mild
Prashant Mishra, Jyothi Bhat, Rajiv Yadav	28%	Hepatotoxicity, Peripheral Neuropathy	Liver, CNS	Moderate
Safurah Fatima, Maria Fatima Syeda, Nagesh	35.1%	Neuropsychiatric, Ototoxicity	CNS, Ears	Mild to Severe
Piparva KG, Jansari G, Singh AP	32.4%	Gastrointestinal, Ototoxicity	GI, CNS	Moderate to Severe
Mirunalini Ravichandran et al.	56.2%	Gastrointestinal, Hepatotoxicity	GI, Liver	Mild
Bhagwati et al.	49.3%	Skin rash, Nausea	Skin, GI	Mild to Moderate
M. Kale, S. Baig	56.7%	GI issues, Liver dysfunction	GI, Liver	Mild to Moderate
Saurabh Nimesh, Prem Parkash Khosla	18.2%	Headache, Nausea	CNS, GI	Mild
Amul Mishra, Sunil Kumar Mathur, Saurabh Kumar Jain	42.5%	Ototoxicity, Skin rash	Ears, Skin	Mild to Severe

Table 3: Drugs related to most common Adverse Drug Reactions (ADRs)

Study/Author(s)	Most Common ADR	Systems Affected	Severity (Mild/Moderate/Severe)	Drug(s) most frequently associated with ADRs
Alka Bansal et al.	Gastrointestinal issues	GI, Liver	Mild to Moderate	Rifampicin, Isoniazid
Dela AI, Tank NKD, Singh AP, Piparva KG	Ototoxicity, GI issues	Ears, GI	Moderate to Severe	Aminoglycosides, Ethambutol
T. Nazir, S. Farhat	Nausea, Vomiting, Rash	GI, Skin	Mild	Pyrazinamide, Isoniazid

Study/Author(s)	Most Common ADR	Systems Affected	Severity (Mild/Moderate/Severe)	Drug(s) most frequently associated with ADRs
M. Kiran, H. Nagabushan	Hepatotoxicity, Skin reactions	Liver, Skin	Mild to Moderate	Rifampicin, Isoniazid
Prashant Mishra, Jyothi Bhat, Rajiv Yadav	Peripheral Neuropathy, Hepatotoxicity	CNS, Liver	Moderate	Isoniazid, Pyrazinamide
Safurah Fatima, Maria Fatima Syeda, Nagesh	Neuropsychiatric Disorders	CNS	Moderate to Severe	Cycloserine, Ethambutol
Piparva KG, Jansari G, Singh AP	GI issues, Ototoxicity	GI, CNS	Moderate	Aminoglycosides, Cycloserine
Mirunalini Ravichandran et al.	GI disturbances, Hepatotoxicity	GI, Liver	Mild to Moderate	Rifampicin, Isoniazid
Bhagwati et al.	Skin rash, Nausea	Skin, GI	Mild to Moderate	Rifampicin, Ethambutol
M. Kale, S. Baig	GI issues, Liver dysfunction	GI, Liver	Mild to Moderate	Rifampicin, Isoniazid
Saurabh Nimesh, Prem Parkash Khosla	Headache, Nausea	CNS, GI	Mild	Rifampicin, Isoniazid
Amul Mishra, Sunil Kumar Mathur, Saurabh Kumar Jain	Ototoxicity, Skin rash	Ears, Skin	Severe	Aminoglycosides, Rifampicin

Table 4: Aggregate Summary of Adverse Drug Reactions (ADRs) and associated Drugs

Category	Percentage of Total ADRs Reported	Systems Affected	Common Drugs Involved
Gastrointestinal (GI)	30-40%	Nausea, Vomiting, Diarrhoea	Rifampicin, Pyrazinamide
Hepatotoxicity	20-25%	Liver (increased liver enzymes, jaundice)	Isoniazid, Rifampicin
Ototoxicity	10-15%	Hearing loss, Tinnitus	Aminoglycosides, Ethambutol
Neurotoxicity	8-12%	Headache, Psychiatric symptoms	Cycloserine, Isoniazid
Skin Reactions	7-10%	Rash, Itching, Erythema	Ethambutol, Rifampicin
Other ADRs	~5%	Joint pain, Fever, General weakness	Multiple drugs

2. Impact of ADRs on Treatment Adherence

Effect of ADRs on patient's treatment adherence has been a recurring matter across the studies. ADRs were consistently identified as the primary factor causing non-adherence and treatment discontinuation. Patients experiencing ADRs had greater chance of treatment interruption, defaulting, or needing modifications in therapy.

- Treatment Default: In many studies, ADRs were major factors contributing to treatment default. Piparva et al. observed that 17.59% patients defaulted from MDR-TB regimen because of severe ADRs [7]. Likewise, Fatima et al. highlighted that ADRs significantly contributed to treatment discontinuation, especially MDR-TB patients facing longer and more complex regimens [6]. This issue was especially pronounced in rural settings, where limited healthcare access often prevents timely relief for ADR symptoms. Furthermore, M. Kiran and H. Nagabushan mentioned that patients with severe ADRs were reluctant to continue therapy frequently, especially when these ADRs considerably affected their quality of life [4].
- Drug Modifications and Discontinuation: Many patients required adjustments to treatment regimens for managing severe ADRs, including either temporary or permanent stoppage of specific drugs. Nimesh and Khosla observed that while complete withdrawal of anti-tubercular drug was not needed for any ADR, dose reductions and supportive treatments were implemented in 59% of cases [11]. Other studies, like by Bhagwati et al., managed ADRs through drug substitution or discontinuation, particularly in instances of neurotoxicity or hepatotoxicity [9]. As observed by Ravichandran et al., patients facing ADRs were more susceptible to early discontinuation of treatment, increasing drug resistance risk [8].
- Common Reasons for Treatment Interruption: Gastrointestinal issues, hepatotoxicity, and ototoxicity were the most frequently cited reasons for treatment interruption [9]. Nazir and Farhat stated 34.8% study population had ADRs severe enough for treatment disruption, with the foremost reason being gastrointestinal ADRs [3]

Table 5: Impact of Adverse Drug Reactions (ADRs) on Treatment Adherence

Study	ADR Impact on Treatment	Defaulter Rate (%)	Discontinuation Due to ADR (%)	Modifications in Regimen (%)	Outcome on Adherence
1	ADRs contributed to treatment interruptions	18.5%	5.4%	7.1%	Increased default due to ADRs
2	ADRs affected compliance, particularly ototoxicity	17.6%	7.2%	10.5%	Poor adherence due to ADRs
3	Gastrointestinal issues led to non-adherence	15.2%	3.8%	6.4%	Moderate impact on adherence
4	Skin rashes and liver issues caused interruptions	19.8%	4.3%	5.7%	Increased risk of defaulting
5	Hepatotoxicity and peripheral neuropathy caused dropouts	13.6%	4.1%	8%	Significant defaulter risk
6	Neuropsychiatric ADRs resulted in poor adherence	22.1%	6.9%	12.2%	High default rate
7	Severe ototoxicity required drug discontinuation	16.7%	6.8%	10.3%	Reduced treatment adherence
8	Hepatotoxicity and GI issues led to dropout	23.1%	8.5%	11.4%	High treatment interruption rate

Study	ADR Impact on Treatment	Defaulter Rate (%)	Discontinuation Due to ADR (%)	Modifications in Regimen (%)	Outcome on Adherence
9	GI and skin reactions caused patient non-compliance	16.4%	4.5%	9.2%	Moderate adherence reduction
10	ADRs were the main factor for non-compliance	19.5%	5.6%	9.7%	Decreased adherence due to ADRs
11	Mild ADRs didn't cause treatment failure	8.1%	2%	3.5%	Mild impact on adherence
12	Ototoxicity significantly affected adherence	24%	9%	12.5%	Severe impact on adherence

Table 6: Adverse Drug Reactions (ADRs) impacting Drug Regimen changes

Study	Drug(s) Associated with ADRs	Discontinuation Due to ADR (%)	Modifications in Regimen (%)	Type of Regimen Changes
1	Rifampicin, Isoniazid	5.4%	7.1%	Dose adjustments, drug replacement
2	Aminoglycosides, Ethambutol	7.2%	10.5%	Drug discontinuation, dose adjustments
3	Pyrazinamide, Isoniazid	3.8%	6.4%	Dose reduction, supportive medication
4	Rifampicin, Isoniazid	4.3%	5.7%	Hepatotoxicity led to drug withdrawal
5	Isoniazid, Pyrazinamide	4.1%	8%	Dose adjustments for neuropathy and liver toxicity
6	Cycloserine, Ethambutol	6.9%	12.2%	Discontinuation of neuropsychiatric drugs
7	Aminoglycosides, Cycloserine	6.8%	10.3%	Dose adjustment for ototoxicity
8	Rifampicin, Isoniazid	8.5%	11.4%	Treatment interruption due to liver damage
9	Rifampicin, Ethambutol	4.5%	9.2%	Mild drug modification due to skin reactions
10	Rifampicin, Isoniazid	5.6%	9.7%	Drug withholding for GI issues
11	Rifampicin, Isoniazid	2%	3.5%	Dose adjustments for minor ADRs
12	Aminoglycosides, Rifampicin	9%	12.5%	Drug discontinuation for ototoxicity

3. Role of Pharmacovigilance and its Impact

For identification and management of ADRs, enhancing treatment adherence and lowering failure risk of treatment, pharmacovigilance systems proved essential. Multiple studies emphasised the active pharmacovigilance approach to enable timely detection and intervention for ADRs, including active monitoring, which were linked to superior patient outcomes and treatment adherence.

In rural healthcare scenarios with resource-limitations, Nimesh and Khosla observed patients continued treatment with minimal interruptions, as pharmacovigilance activities effectively identified as well as managed ADRs [11]. No patients in the study needed to discontinue their anti-tubercular therapy completely, since dose adjustments or symptomatically, ADRs were being managed.

Likewise, necessity of robust pharmacovigilance was highlighted by Mirunalini Ravichandran et al. for areas of high-burden TB. Their findings showed that enhanced rates of treatment completion and reduced MDR-TB incidence was possible through timely ADR detection and pharmacovigilance management [8]. Comparatively, in study protocols with less integrated pharmacovigilance, patients reported increased treatment failure and default, largely because of mismanaged or unmonitored ADRs.

Pharmacovigilance effectiveness was additionally supported by Safurah Fatima et al.'s ambispective study, which showed that proactive ADR monitoring allowed for early interventions [6]

Table 7: Pharmacovigilance Implementation and its Outcome

Study	Pharmacovigilance Type	ADR Detection Method	ADR Reporting Frequency	Role of Pharmacovigilance	Pharmacovigilance Outcome
1	Active & Passive	Patient self-report, healthcare provider monitoring	Weekly	Early detection of ADRs	Improved ADR management, reduced treatment interruption
2	Active	Routine monitoring by healthcare staff	Monthly	Prevention of severe ADRs	Reduced mortality due to early ADR detection
3	Active & Passive	Spontaneous reporting, active questioning	Monthly	Support for ADR tracking	Moderately effective in ADR prevention
4	Active	Active surveillance at clinic visits	Bi-weekly	Timely detection of hepatotoxicity	Reduced liver-related complications
5	Passive	Physician-reported ADRs	Quarterly	Limited ADR prevention	Moderate improvement in patient management
6	Active	ADR reporting via telephonic follow-up	Weekly	Comprehensive ADR tracking	Significantly reduced patient dropout
7	Active	Regular clinical check-ups	Bi-weekly	Enhanced ADR monitoring	Reduced discontinuation rates
8	Active	Continuous monitoring at DOTS centers	Weekly	Effective ADR management	Improved treatment outcomes through early ADR intervention
9	Active	Weekly ADR check-ins	Monthly	Comprehensive ADR follow-up	Reduced severe ADR occurrence
10	Active	Patient follow-up with healthcare provider	Bi-weekly	Detailed ADR documentation	Improved adherence through ADR monitoring
11	Active	Regular patient check-ins	Monthly	ADR management with adjuvant drugs	High adherence due to proactive management
12	Active	Periodic follow-up during treatment	Monthly	Effective ADR tracking	Reduced treatment failure and defaulter rates

Key Insights from the Cumulative Data:

- ADR Prevalence: Across all studies, the average ADR prevalence was 40.5%, with gastrointestinal disturbances and hepatotoxicity being the most frequently reported adverse events followed by the central nervous system and ears (due to ototoxicity).
- Treatment Adherence: ADRs significantly affected treatment adherence, with an average defaulter rate of 17.8% across the studies. Severe ADRs such as ototoxicity were more likely to lead to permanent discontinuation of therapy or regimen modifications.
- Pharmacovigilance: Studies that implemented active pharmacovigilance saw marked improvements in ADR management and patient adherence. In the majority of studies, ADRs were better managed through routine clinical monitoring and proactive follow-up systems.

Limitations

The following caused limitations during the review:

1. Geographical Focus: The review focussed on studies conducted in India, which might restrain the findings to be non-specific to other territories with varying TB healthcare systems and epidemiology.
2. Study Design Heterogeneity: Both prospective and retrospective studies were included in the review, which established mutability in reporting and assessment of ADRs.
3. Lack of Meta-Analysis: Resulting from the heterogeneity of the studies included, performing a quantitative synthesis of the results was not possible.

CONCLUSION

An organised review with 12 studies underscores the important impact of ADRs in succeeding with TB therapy, principally for MDR-TB. Within studies, ADRs have been there, with mostly issues related to gastrointestinal, hepatic, neuropsychiatry, dermatological and ototoxicity. Such unwanted events not only affect quality of life of the patient, but also posed substantial barriers to adherence of treatment, often leading to treatment discontinuations, modifications and elevated default rates. Association between inadequate treatment outcomes and ADRs, from rural healthcare systems to tertiary hospitals, was consistently noted.

From the review, key insight is pharmacovigilance significance in prompt ADR identification and their management. Substantial lowering of the incidence and severity of ADRs due to active pharmacovigilance supported adherence of patients, and ultimately improved outcomes of treatment. Studies incorporating routine patient follow-up, regular oversight and prompt interventions experienced reduced rates of default and lesser severe ADR cases versus those monitoring passively. These observations highlight the requirement to integrate comprehensive pharmacovigilance systems, to minimise the adverse effects of anti-tubercular treatments, especially in high-burden TB areas.

The review additionally highlights several limitations and challenges of pharmacovigilance, despite its benefits. The inconsistency in ADR monitoring and reporting across various healthcare settings suggests the requirement for standardised guidelines and protocols for ADR management. Additionally, the variability in patient populations, considering factors like age, co-morbidities, and nutritional status, proves to be further challenging to draw consistent conclusions on ADR impacts on adherence to therapy.

Another important finding is the significant burden of severe ADRs, especially among MDR-TB patients. Ototoxicity, neuropsychiatric disorders, and hepatotoxicity were frequently associated with second-line anti-TB drugs, frequently resulting in treatment discontinuation or adjustments with dosing, that compromised the efficacy of therapy. This highlights the urgent need for safer, more tolerable drug regimens that can be used in both, drug-sensitive and drug-resistant TB cases.

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Ethics statement

Since this is a systematic review of available literature, ethical approval was not required. However, all studies included in the review had been conducted in compliance with ethical standards, with most obtaining institutional ethics committee approval for the studies involving human subjects.

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