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ADVERSE DRUG REACTIONS IN LONG-DURATION ANTI-TUBERCULAR THERAPY: RISK FACTORS, CLINICAL MANIFESTATIONS, AND MANAGEMENT

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ABSTRACT

Tuberculosis continues to pose a significant global health burden, often requiring prolonged anti- tubercular therapy (ATT) in conditions such as extrapulmonary, central nervous system, skeletal, and multidrug-resistant tuberculosis. While standard short-course regimens are generally well tolerated, extended treatment durations lead to increased cumulative drug exposure and a higher likelihood of adverse drug reactions (ADRs). These reactions can range from relatively mild effects, such as gastrointestinal discomfort, to serious complications including hepatotoxicity, optic neuritis, ototoxicity, and neuropsychiatric disturbances. Importantly, ADRs are a major contributor to treatment interruption, poor adherence, and ultimately therapeutic failure, which may facilitate the development of drug resistance. This review aims to provide a comprehensive overview of the epidemiology, underlying mechanisms, risk factors, and clinical manifestations of ADRs associated with long-duration ATT. It also emphasizes the importance of early detection, regular monitoring, and preventive strategies to improve patient safety and treatment outcomes.

1. INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. According to the World Health Organization, millions of new cases are reported annually, underscoring its persistent global burden. Although drug-susceptible pulmonary TB is typically managed with a standard 6- month regimen, several clinical forms require prolonged anti-tubercular therapy (ATT). These include tuberculous meningitis, spinal tuberculosis, disseminated tuberculosis, and multidrug-resistant tuberculosis (MDR-TB), where treatment duration may extend from 9 to 24 months or longer.[1]

Prolonged ATT is associated with increased cumulative exposure to multiple pharmacological agents, many of which possess well-documented toxicity profiles. Consequently, adverse drug reactions (ADRs) are more frequently encountered in extended regimens and represent a significant challenge in clinical practice. These reactions may necessitate dose adjustment, treatment interruption, or permanent discontinuation, thereby adversely affecting treatment adherence and therapeutic outcomes.

This review aims to systematically evaluate ADRs associated with long-duration ATT, with particular emphasis on their epidemiology, risk factors, underlying mechanisms, clinical manifestations, and current management approaches.

2. METHODS

A structured literature review was conducted using electronic databases, including PubMed, Scopus, Embase, and Google Scholar. The search strategy incorporated combinations of keywords and Medical Subject Headings (MeSH) terms such as “long-duration anti-tubercular therapy,” “adverse drug reactions AND tuberculosis,” “hepatotoxicity AND anti-tubercular therapy,” “ethambutol optic neuritis,” “isoniazid-induced neuropathy,” and “second-line anti-tuberculosis drug toxicity.”

Studies were selected based on their relevance to adverse drug reactions associated with prolonged anti-tubercular therapy. Priority was given to studies involving treatment

durations exceeding six months, as well as those focusing on extrapulmonary tuberculosis and drug-resistant tuberculosis. Eligible study designs included observational studies, cohort studies, randomized controlled trials, systematic reviews, and relevant guideline documents, including those from the World Health Organization.

Publications exclusively addressing short-course therapy for drug-susceptible pulmonary tuberculosis without extended treatment duration were excluded. Articles not available in English or lacking sufficient clinical or safety data were also excluded.

3. Anti-Tubercular Drugs in Long-Duration Therapy

Long-duration anti-tubercular therapy (ATT), particularly in extrapulmonary and drug-resistant tuberculosis, involves the use of both first-line and second-line agents. While first-line drugs form the backbone of standard therapy, second-line agents are commonly employed in multidrug- resistant tuberculosis (MDR-TB) and are often associated with higher toxicity profiles.[3] Prolonged administration of these agents increases cumulative drug exposure, thereby elevating the risk of adverse drug reactions and clinically significant drug–drug interactions.

Table 1: Anti-tubercular drugs used in long-duration therapy and their clinical relevance.

Drug Class	Drug	Role in Therapy	Key Concern in Long-Term Use
First- line	Isoniazid	Core bactericidal agent	Hepatotoxicity, Peripheral Neuropathy
	Rifampicin	Sterilizing activity	Hepatotoxicity, drug interactions (CYP induction)
	Pyrazinamide	Intensive phase drug	Hepatotoxicity, hyperuricemia
	Ethambutol	Prevents resistance	Optic neuritis
Second- line	Fluoroquinolones (e.g., levofloxacin, moxifloxacin)	MDR-TB backbone	QT prolongation, tendinopathy
	Aminoglycosides (e.g., amikacin, kanamycin)	Injectable agents	Ototoxicity, nephrotoxicity
	Linezolid	Oral MDR-TB option	Myelosuppression, neuropathy
	Ethionamide	Oral second- line	GI intolerance, hypothyroidism
	Cycloserine	CNS-penetrating drug	Neuropsychiatric effects
	Bedaquiline	Novel MDR-TB agent	QT prolongation, hepatotoxicity

4. Epidemiology of Adverse Drug Reactions in Long-Duration ATT

The incidence of adverse drug reactions (ADRs) during standard 6-month anti-tubercular therapy (ATT) has been reported to range between 5% and 30%, depending on the study population, pharmacovigilance practices, and monitoring intensity. In contrast, prolonged treatment regimens are associated with a substantially higher burden of ADRs, with reported incidence rates exceeding 40%, particularly among patients receiving therapy for multidrug-resistant tuberculosis (MDR-TB). Hepatotoxicity remains the most frequently reported serious ADR associated with ATT, especially with first-line agents such as Isoniazid, Rifampicin, and Pyrazinamide. Other commonly observed adverse effects include peripheral neuropathy, dermatological reactions, and visual disturbances, the latter being primarily associated with Ethambutol.[4–9]

Notably, second-line anti-tubercular regimens, which are frequently used in MDR-TB, demonstrate significantly higher toxicity profiles. These regimens are associated with a broader spectrum of adverse effects, including ototoxicity, neuropsychiatric disturbances, and cardiotoxicity, thereby necessitating close clinical and laboratory monitoring throughout the treatment duration.

5. Major Adverse Drug Reactions

5.1 Hepatotoxicity

Hepatotoxicity represents the most clinically significant adverse drug reaction associated with anti- tubercular therapy (ATT). It is primarily linked to first-line agents such as Isoniazid, Rifampicin, and Pyrazinamide. The underlying mechanisms include toxic metabolite formation, immune- mediated liver injury, and oxidative stress.

Clinically, hepatotoxicity may present with asymptomatic elevation of transaminases, jaundice, or features of acute hepatitis, and in rare cases may progress to fulminant hepatic failure. The risk is further amplified with prolonged drug exposure and in patients with pre-existing liver disease, chronic alcohol use, malnutrition, or co-infection with HIV.

5.2 Peripheral Neuropathy

Peripheral neuropathy is most commonly associated with Isoniazid, which interferes with pyridoxine metabolism, leading to neuronal dysfunction. Patients typically present with paresthesia, burning sensations, and distal numbness, predominantly affecting the lower limbs.[10,11]

The risk is higher in vulnerable populations, including individuals with diabetes mellitus, HIV infection,

pregnancy, malnutrition, and chronic renal disease. Prolonged therapy increases cumulative risk; however, pyridoxine supplementation has a well-established protective role.

5.3 Optic Neuritis

Optic neuritis is a well-recognized adverse effect of Ethambutol and is closely related to both dose and duration of therapy. Clinical manifestations include reduced visual acuity, impairment of red– green color discrimination, and visual field defects.[10]

Early detection is essential, as delayed recognition may result in irreversible visual impairment. Regular ophthalmological monitoring is therefore recommended in patients receiving prolonged ethambutol therapy.

5.4 Gastrointestinal Intolerance

Gastrointestinal adverse effects, including nausea, vomiting, anorexia, and gastritis, are commonly reported during ATT. Although these symptoms are generally mild and self-limiting, persistent intolerance can significantly impact patient adherence, particularly in long-duration regimens.

5.5 Dermatologic Reactions

Cutaneous adverse reactions range from mild maculopapular eruptions to severe hypersensitivity reactions, including Stevens–Johnson syndrome. While mild reactions may be managed symptomatically, severe presentations necessitate immediate discontinuation of the offending agent and appropriate supportive care.

5.6 Neuropsychiatric Toxicity

Neuropsychiatric adverse effects are more frequently associated with second-line anti-tubercular drugs. Agents such as cycloserine are linked to depression and psychosis, while fluoroquinolones may cause agitation and insomnia. Rarely, Isoniazid has been associated with seizure activity.

The risk of these effects increases with prolonged therapy and cumulative exposure, highlighting the importance of early recognition and appropriate dose modification or drug substitution.[10]

5.7 Ototoxicity and Nephrotoxicity

Injectable aminoglycosides, commonly used in multidrug-resistant tuberculosis (MDR-TB), are associated with significant ototoxic and nephrotoxic effects. These include sensorineural hearing loss, vestibular dysfunction, and renal impairment.[10]
Such toxicities are often dose- and duration-dependent and may be irreversible, particularly with prolonged use. Regular auditory and renal function monitoring is therefore essential during therapy.

6. Risk Factors for ADRs in Long-Duration Therapy

The risk of adverse drug reactions (ADRs) during long-duration anti-tubercular therapy (ATT) is influenced by a combination of patient-related and treatment-related factors. These determinants often act synergistically, increasing both the frequency and severity of drug-induced toxicity.

6.1 Patient-Related Factors

Several host-related characteristics predispose individuals to an increased risk of ADRs. Advanced age is associated with reduced hepatic and renal functional reserve, thereby impairing drug metabolism and clearance. Female sex has been identified as a potential risk factor in some studies, possibly due to differences in pharmacokinetics and hormonal influences.

Malnutrition remains a critical contributor, particularly in tuberculosis-endemic settings, as it affects drug metabolism and increases susceptibility to toxicity. Chronic alcohol consumption and underlying liver disease significantly elevate the risk of hepatotoxicity, especially with drugs such as Isoniazid and Rifampicin.[11]

Comorbid conditions, including renal impairment, HIV infection, and diabetes mellitus, further increase vulnerability to ADRs by altering drug handling, immune response, and tissue sensitivity to toxic effects.

6.2 Treatment-Related Factors

Treatment-related variables also play a central role in the development of ADRs. Prolonged duration of therapy leads to cumulative drug exposure, which is a key driver of toxicity in long-term regimens. Higher cumulative doses further amplify this risk.

Polypharmacy, particularly in multidrug-resistant tuberculosis (MDR-TB), increases the likelihood of drug–drug interactions and overlapping toxicities. The use of second-line agents, which generally have less favorable safety profiles compared to first-line drugs, is strongly associated with increased incidence and severity of ADRs.[12]

Table 2: Risk factors associated with ADRs in long-duration ATT.

Category	Risk Factor	Clinical Implication
Patient-related	Advanced age	Reduced drug clearance, increased toxicity
	Female sex	Possible pharmacokinetic variability
	Malnutrition	Increased susceptibility to toxicity
	Alcohol use	Higher risk of hepatotoxicity
	Chronic liver disease	Impaired metabolism of hepatotoxic drugs
	Renal impairment	Drug accumulation, especially with second-line agents

	HIV infection	Increased ADR susceptibility, drug interactions
	Diabetes mellitus	Higher risk of neuropathy and delayed recovery
Treatment- related	Prolonged therapy duration	Cumulative toxicity
	High cumulative dose	Dose-dependent adverse effects
	Polypharmacy	Increased drug–drug interactions
	Second-line agents	Higher toxicity burden
	Drug–drug interactions	Altered drug levels and adverse effects

7. Impact of ADRs on Treatment Outcomes

Adverse drug reactions (ADRs) have a substantial impact on the effectiveness of anti-tubercular therapy (ATT), particularly in long-duration regimens. The occurrence of ADRs often necessitates treatment interruption, dose reduction, or modification of the therapeutic regimen, all of which can compromise the bactericidal efficacy of therapy.[13,14]

Treatment interruptions and poor tolerability frequently lead to reduced patient adherence, which is a critical determinant of treatment success. Suboptimal adherence not only increases the risk of disease relapse but also contributes to the emergence of drug resistance, especially in the context of multidrug-resistant tuberculosis (MDR-TB). In such cases, the limited availability of effective alternative agents further complicates management.

In severe forms of tuberculosis, including central nervous system and spinal involvement, uninterrupted therapy is essential to prevent disease progression. Any delay or discontinuation due to ADRs may result in irreversible complications, including permanent neurological deficits and functional impairment.[15,17]

Overall, ADRs represent a major barrier to successful treatment outcomes, underscoring the importance of early identification, proactive management, and patient-centered approaches to ensure treatment continuity.

8. MONITORING AND PREVENTION STRATEGIES

Early identification and proactive monitoring are essential to minimize the incidence and severity of adverse drug reactions (ADRs) during long-duration anti-tubercular therapy (ATT). A structured approach that includes baseline assessment, ongoing surveillance, and patient education is critical for ensuring treatment safety and continuity.[18]

8.1 Baseline Evaluation

A comprehensive baseline evaluation should be performed prior to initiation of therapy to identify pre-existing risk factors and establish reference values for monitoring. This includes assessment of liver function, renal function, and visual acuity. In patients receiving second-line agents, particularly in multidrug-resistant tuberculosis (MDR-TB), baseline audiometric evaluation is recommended due to the risk of ototoxicity associated with aminoglycosides.[19,20]

8.2 Monitoring During Treatment

Regular clinical and laboratory monitoring is essential throughout the treatment course, especially in prolonged regimens. Periodic liver function testing is recommended to detect early hepatotoxicity, particularly in patients receiving Isoniazid, Rifampicin, and Pyrazinamide.

Monthly clinical evaluations should be conducted to assess adherence, emerging symptoms, and overall tolerability. Visual function monitoring is necessary for patients on Ethambutol to detect early signs of optic neuropathy. Similarly, periodic audiometric assessment is required in patients receiving aminoglycosides to identify early ototoxicity.[21]

Routine pyridoxine supplementation is recommended, particularly in patients receiving isoniazid, to prevent peripheral neuropathy.

8.3 Patient Education and Pharmacovigilance

Patient education plays a pivotal role in early detection and prevention of ADR-related complications. Patients should be counseled regarding the importance of adherence and trained to recognize early warning signs, including visual disturbances, jaundice, and neurological symptoms, and to report them promptly.

In addition, strengthening pharmacovigilance systems is essential for the systematic detection, reporting, and analysis of ADRs. Integration of clinical monitoring with national and global reporting frameworks, such as those supported by the World Health Organization, can further enhance drug safety surveillance and inform evidence-based practice.[22]

Table 3: Monitoring strategies during long-duration ATT.

Parameter	Baseline	During Treatment	Clinical Rationale
Liver function tests	✓	Periodic	Early detection of hepatotoxicity
Renal function tests	✓	Periodic (if risk)	Prevent drug accumulation
Visual acuity	✓	Regular (Ethambutol)	Detect optic neuritis early
Audiometry	✓ (MDR- TB)	Periodic	Monitor aminoglycoside toxicity
Clinical evaluation	✓	Monthly	Assess ADRs and adherence

Pyridoxine supplementation	—	Routine (if on isoniazid)	Prevent neuropathy

9. DISCUSSION

Long-duration anti-tubercular therapy (ATT) is consistently associated with a higher burden of adverse drug reactions (ADRs) compared with standard short-course regimens. This increased risk is largely driven by cumulative drug exposure, the use of second-line agents with less favorable safety profiles, and the presence of comorbid conditions that alter drug metabolism and tolerance. While first-line agents such as Isoniazid, Rifampicin, and Pyrazinamide are generally well tolerated under routine monitoring, prolonged administration increases the likelihood of clinically significant toxicities, including hepatotoxicity, peripheral neuropathy, optic neuritis, and neuropsychiatric complications.[23]

The findings synthesized in this review highlight that ADRs are not only frequent but also clinically consequential, often necessitating treatment modification or interruption. This has direct implications for treatment adherence, therapeutic success, and the potential development of drug resistance, particularly in multidrug-resistant tuberculosis (MDR-TB). The challenge is further compounded by overlapping toxicity profiles and drug–drug interactions in complex regimens.[24,25]

Despite the clinical importance of this issue, existing literature remains disproportionately focused on drug-susceptible pulmonary tuberculosis. There is a relative paucity of data specifically addressing ADR patterns in prolonged treatment settings, including extrapulmonary tuberculosis and drug-resistant TB populations. These groups often require individualized and extended regimens, yet evidence guiding optimal monitoring and management strategies remains limited.

Future research should prioritize prospective studies evaluating ADR incidence, risk stratification, and outcomes in long-duration ATT. In addition, the integration of pharmacovigilance data particularly through frameworks supported by the World Health Organization may provide valuable insights into real world safety profiles and inform more tailored, patient-centered treatment approaches.

10. CONCLUSION

Adverse drug reactions (ADRs) are frequently encountered during long-duration anti-tubercular therapy (ATT) and remain a major barrier to successful treatment completion. Clinically significant complications including hepatotoxicity, peripheral neuropathy, optic neuritis, neuropsychiatric disturbances, and ototoxicity are largely driven by cumulative drug exposure and the use of second- line agents.

Effective management of these risks requires a structured approach encompassing careful patient selection, baseline risk stratification, regular clinical and laboratory monitoring, and timely intervention. In particular, early recognition and prompt management of ADRs are essential to prevent treatment interruption, improve adherence, and optimize therapeutic outcomes.

Future research should focus on prospective pharmacovigilance studies, improved risk prediction models, and the development of safer and more tolerable therapeutic strategies for patients requiring prolonged tuberculosis treatment. Strengthening surveillance systems in alignment with global frameworks such as those supported by the World Health Organization will be critical in advancing patient safety.

Table 4: Major adverse drug reactions in long-duration anti-tubercular therapy.

Drug	Major ADRs	Mechanism	Key Risk Factors	Monitoring Strategy
Isoniazid	Hepatitis, peripheral neuropathy	Toxic metabolite formation; pyridoxine depletion	Alcohol use, diabetes, HIV infection	Liver function tests (LFTs); pyridoxine supplementation
Rifampicin	Hepatitis, drug–drug interactions	Hepatic enzyme induction	Polypharmacy	LFTs; medication review
Pyrazinamide	Hepatotoxicity	Dose-dependent liver injury	Pre-existing liver disease	LFTs
Ethambutol	Optic neuritis	Dose- and duration-related optic toxicity	Renal impairment	Visual acuity and color vision testing
Aminoglycosides (e.g., amikacin)	Ototoxicity, nephrotoxicity	Cochlear hair cell damage	Prolonged use, renal dysfunction	Audiometry; renal function tests
Cycloserine	Neuropsychiatric effects	Central nervous system toxicity	Pre-existing psychiatric illness	Mental status monitoring

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