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FREQUENCY AND CHARACTERISTICS OF ADVERSE EVENTS ASSOCIATED WITH ANTI-TUBERCULOSIS DRUGS DURING THE TREATMENT OF DRUG-RESISTANT PULMONARY TUBERCULOSIS

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Abstract

Background: Drug-resistant pulmonary tuberculosis (DR-TB) remains one of the most significant challenges in global tuberculosis control. Treatment regimens for multidrug-resistant and extensively drug-resistant tuberculosis involve prolonged use of multiple anti-tuberculosis drugs, often resulting in adverse drug reactions (ADRs) that may affect treatment adherence and outcomes.

Objective: To assess the frequency, spectrum, and clinical characteristics of adverse events associated with anti-tuberculosis medications in patients receiving treatment for drug-resistant pulmonary tuberculosis.

Methods: A retrospective observational study was conducted involving 200 patients diagnosed with drug-resistant pulmonary tuberculosis. Adverse events were analyzed according to severity, affected organ systems, and implicated anti-tuberculosis drugs.

Keywords: Tuberculosis, drug-resistant tuberculosis, adverse drug reactions, anti-tuberculosis drugs, MDR-TB, pharmacovigilance.

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Introduction

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide. According to the World Health Organization, millions of new tuberculosis cases are diagnosed annually, and drug-resistant forms continue to represent a major public health concern.

Drug-resistant pulmonary tuberculosis develops when Mycobacterium tuberculosis acquires resistance to one or more anti-tuberculosis drugs. Multidrug-resistant tuberculosis (MDR-TB) is characterized by resistance to at least isoniazid and rifampicin, while extensively drug-resistant tuberculosis (XDR-TB) includes additional resistance to fluoroquinolones and other second-line medications.

Treatment of drug-resistant tuberculosis requires prolonged administration of multiple medications, including bedaquiline, linezolid, levofloxacin, clofazimine, cycloserine, and delamanid. Although these regimens have improved treatment outcomes, they are frequently associated with adverse drug reactions that can compromise adherence, reduce treatment effectiveness, and increase healthcare costs.

The study of adverse events associated with anti-tuberculosis therapy is therefore essential for optimizing patient management and improving treatment success rates.

Materials and Methods

A retrospective observational study was conducted to evaluate the frequency and characteristics of adverse events associated with anti-tuberculosis drugs among patients receiving treatment for drug-resistant pulmonary tuberculosis. The study included 200 adult patients who underwent treatment at specialized tuberculosis treatment centers between January 2022 and December 2025.

Eligible participants were adults aged 18 years and older with bacteriologically confirmed drug-resistant pulmonary tuberculosis. Drug resistance was

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established through molecular diagnostic methods, including GeneXpert MTB/RIF and line probe assays, as well as conventional culture-based drug susceptibility testing. Patients diagnosed with multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant tuberculosis (pre-XDR-TB), and extensively drug-resistant tuberculosis (XDR-TB) were included in the analysis. Individuals with incomplete medical records, patients transferred to other treatment facilities, and those who discontinued treatment within the first month for non-medical reasons were excluded from the study.

Data were extracted from patient medical records, treatment monitoring forms, laboratory reports, and pharmacovigilance databases. The collected information included demographic characteristics, clinical presentation, bacteriological findings, drug-resistance patterns, treatment regimens, duration of therapy, laboratory parameters, and documented adverse drug reactions. Particular attention was paid to adverse events affecting the gastrointestinal, hepatic, neurological, psychiatric, cardiovascular, auditory, visual, and dermatological systems.

Treatment regimens were prescribed according to national tuberculosis treatment guidelines and recommendations of the World Health Organization. Most patients received all-oral regimens containing combinations of bedaquiline, linezolid, levofloxacin or moxifloxacin, clofazimine, cycloserine, delamanid, and other second-line anti-tuberculosis drugs. Patients were routinely monitored through clinical examinations, biochemical blood tests, complete blood counts, electrocardiography, audiometric testing, and neurological assessments throughout treatment.

Adverse events were classified according to severity using internationally accepted pharmacovigilance criteria. Mild adverse events were defined as reactions causing minimal discomfort without requiring modification of treatment. Moderate adverse events required symptomatic treatment or closer monitoring but did not necessarily lead to interruption of anti-tuberculosis

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therapy. Severe adverse events were those resulting in hospitalization, permanent disability, life-threatening conditions, or significant modification of the treatment regimen.

Statistical analysis was performed using standard descriptive methods. Continuous variables were expressed as means and standard deviations, whereas categorical variables were presented as frequencies and percentages. The prevalence of adverse events was calculated for the entire study population and according to the specific medications administered. Statistical significance was considered at $p < 0.05$ where applicable.

Results

The study population consisted of 200 patients with drug-resistant pulmonary tuberculosis. Men represented the majority of participants, accounting for 62.0% of cases, while women accounted for 38.0%. The average age of patients was 41.6 years, with a range from 18 to 74 years. Multidrug-resistant tuberculosis was diagnosed in 81.0% of patients, whereas extensively drug-resistant tuberculosis was identified in 19.0%. HIV co-infection was documented in 14.0% of cases.

Analysis of treatment safety demonstrated that adverse drug reactions were extremely common during therapy. A total of 157 patients (78.5%) experienced at least one adverse event during the treatment period. Furthermore, many patients developed multiple adverse reactions affecting different organ systems simultaneously. The average number of documented adverse events per affected patient was 2.3.

Gastrointestinal complications were the most frequently observed adverse reactions, affecting 35.0% of patients. These manifestations included nausea, vomiting, abdominal pain, dyspepsia, diarrhea, decreased appetite, and weight loss. Although most gastrointestinal symptoms were mild to moderate in severity, they frequently contributed to reduced treatment adherence and required supportive therapy.

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Hepatotoxicity was identified in 22.5% of patients and was characterized by elevated liver enzymes, jaundice, and clinical signs of hepatic dysfunction. In several cases, temporary discontinuation of potentially hepatotoxic medications was necessary until liver function normalized. Patients with pre-existing liver disease and HIV co-infection appeared to have a higher risk of developing hepatotoxic reactions.

Peripheral neuropathy was reported in 18.0% of patients, primarily among those receiving linezolid-containing regimens. Symptoms included numbness, tingling sensations, burning pain, and reduced sensitivity in the extremities. Neurological complications often developed after several months of treatment and occasionally persisted even after drug discontinuation.

Psychiatric adverse reactions occurred in 15.0% of patients. These manifestations ranged from mild anxiety and insomnia to severe depression and psychotic symptoms. Most psychiatric complications were associated with cycloserine-containing regimens. Several patients required psychiatric consultation and adjunctive pharmacological treatment to continue tuberculosis therapy successfully.

Ototoxicity was observed in 12.5% of patients and included hearing impairment, tinnitus, and vestibular dysfunction. Although the introduction of all-oral regimens has reduced the use of injectable agents, hearing-related complications remain clinically important, particularly among patients previously exposed to aminoglycosides.

Electrocardiographic monitoring revealed QT interval prolongation in 9.0% of patients. The majority of these cases were associated with bedaquiline-containing regimens. While most episodes were asymptomatic, intensive cardiac monitoring was required to prevent potentially serious arrhythmias.

Severe adverse events requiring treatment modification were documented in 14.5% of patients. Among these individuals, anti-tuberculosis regimens were adjusted through dose reduction, temporary interruption, or replacement of the

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suspected medication. Despite these complications, the majority of patients successfully completed treatment after appropriate management of adverse reactions.

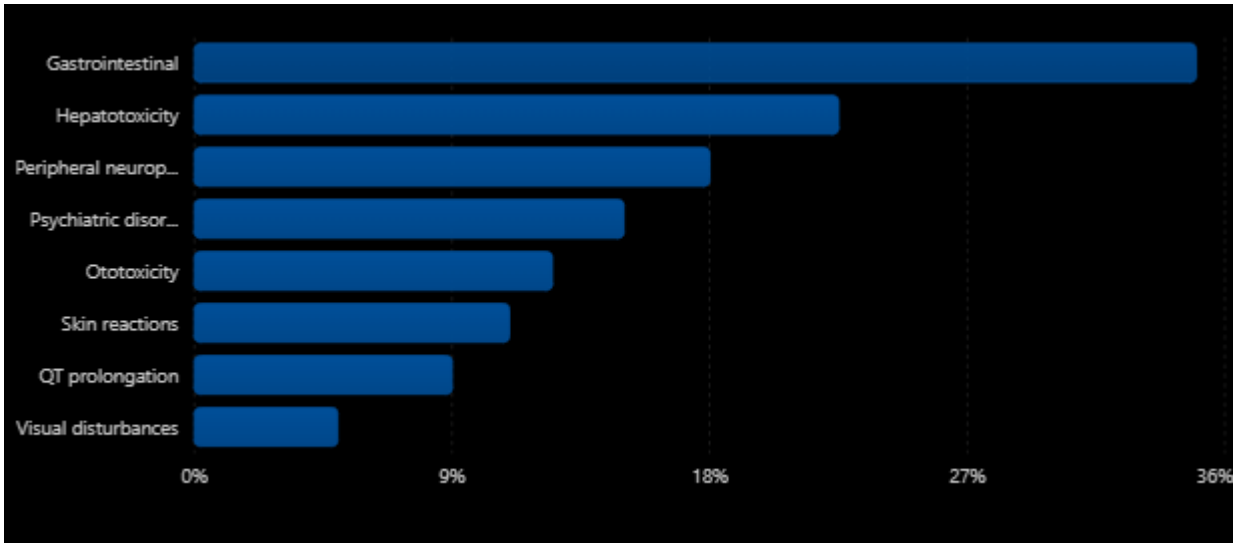

Diagram 1. Distribution of Major Adverse Events

Major adverse events during DR-TB treatment

Frequency of adverse reactions among patients receiving anti-tuberculosis therapy.

Adverse Event	Number of Cases	Percentage (%)
Gastrointestinal disorders	70	35.0
Hepatotoxicity	45	22.5
Peripheral neuropathy	36	18.0
Psychiatric disturbances	30	15.0
Ototoxicity	25	12.5
Skin reactions	22	11.0
QT interval prolongation	18	9.0
Visual disturbances	10	5.0

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The analysis of drug-specific adverse reactions revealed a clear association between linezolid and peripheral neuropathy, bedaquiline and QT prolongation, clofazimine and skin pigmentation changes, cycloserine and psychiatric disturbances, and ethionamide and hepatotoxicity. These findings emphasize the importance of individualized monitoring strategies tailored to the adverse-effect profile of each medication.

Diagram 2. Severity Distribution

Severity of adverse drug reactions. Distribution of adverse event severity among patients.

Severity	Number of Patients	Percentage (%)
Mild	85	42.5
Moderate	43	21.5
Severe	29	14.5
No adverse events	43	21.5

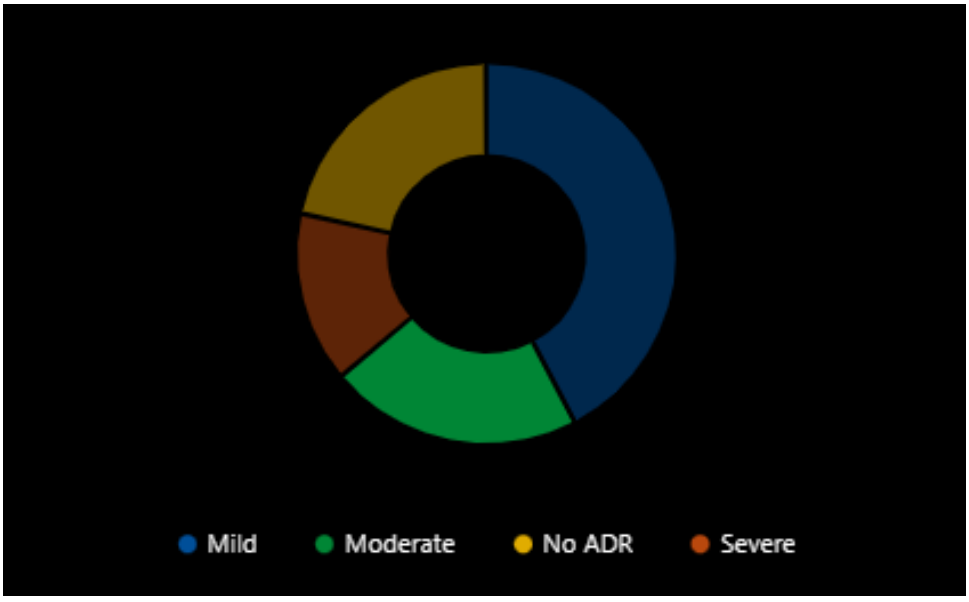

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Table 1. Most Common Drug-Associated Adverse Events

Drug	Most Frequent Adverse Event
Linezolid	Peripheral neuropathy
Bedaquiline	QT prolongation
Clofazimine	Skin pigmentation
Cycloserine	Psychiatric disorders
Levofloxacin	Gastrointestinal symptoms
Ethionamide	Hepatotoxicity

Discussion

The findings of this study demonstrate a high prevalence of adverse drug reactions among patients receiving treatment for drug-resistant pulmonary tuberculosis. Nearly four out of five patients experienced at least one adverse event during therapy.

The predominance of gastrointestinal symptoms is consistent with previous studies evaluating second-line anti-tuberculosis treatment. Gastrointestinal intolerance frequently affects adherence and may necessitate supportive therapy.

Hepatotoxicity remains a significant concern because several anti-tuberculosis drugs are metabolized by the liver. Regular monitoring of liver function tests is therefore recommended throughout treatment.

Peripheral neuropathy, particularly associated with linezolid, represents an increasingly recognized complication of modern MDR-TB treatment regimens. Long-term exposure may result in persistent neurological deficits and reduced quality of life.

Psychiatric adverse events were primarily associated with cycloserine-containing regimens. These reactions highlight the importance of integrating psychological assessment and mental health support into tuberculosis care programs.

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QT interval prolongation was observed in patients receiving bedaquiline-containing regimens. Although relatively uncommon, this complication may predispose susceptible individuals to potentially life-threatening cardiac arrhythmias.

The occurrence of severe adverse reactions in approximately 15% of patients emphasizes the necessity of individualized treatment approaches, active pharmacovigilance, and multidisciplinary patient management.

Conclusion

The present study demonstrates that adverse drug reactions remain a major challenge in the treatment of drug-resistant pulmonary tuberculosis. Nearly four out of five patients experienced at least one adverse event during therapy, highlighting the substantial burden of treatment-related complications in this population.

The most frequently observed adverse reactions included gastrointestinal disorders, hepatotoxicity, peripheral neuropathy, psychiatric disturbances, ototoxicity, dermatological manifestations, and QT interval prolongation. Although the majority of adverse events were mild or moderate in severity, approximately one in seven patients developed severe complications requiring modification of the treatment regimen.

The findings confirm that modern anti-tuberculosis medications, while highly effective against drug-resistant Mycobacterium tuberculosis, are associated with significant toxicity that may compromise treatment adherence and clinical outcomes. Early recognition and prompt management of adverse events are therefore essential components of comprehensive tuberculosis care. Routine clinical assessment, laboratory monitoring, electrocardiographic surveillance, neurological evaluation, and psychological support should be integrated into all treatment programs for drug-resistant tuberculosis.

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Special attention should be given to high-risk groups, including elderly patients, individuals with HIV co-infection, patients with chronic liver disease, and those receiving prolonged linezolid-containing regimens. Individualized treatment approaches and active pharmacovigilance systems may reduce the incidence of severe adverse reactions and improve patient safety.

Overall, the study highlights the critical importance of comprehensive adverse-event monitoring during anti-tuberculosis treatment and supports the implementation of multidisciplinary approaches aimed at maximizing both treatment efficacy and patient safety.

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