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Review Article

Adverse Drug Reactions in the Treatment of Drug-Resistant Tuberculosis: A Narrative Review

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Abstract

Drug-resistant tuberculosis (DR TB), which includes 'multidrug-resistant TB' (MDR TB) and 'extensively drug-resistant TB' (XDR TB), is a significant global health challenge. The treatment response and outcomes are even more challenging in regions with high poverty, malnutrition, and high rates of HIV co-infection. Despite advancements in treatment regimens, 'adverse drug reactions' (ADRs) are still a critical barrier to treatment success, contributing to non-compliance, regimen modifications, and treatment failure. This review investigates the occurrence, severity, and types of ADRs related to DR-TB treatment, highlighting their impact on patient outcomes. Specific ADRs linked to commonly used second-line anti-TB drugs include peripheral neuropathy, anaemia, and optic neuritis with linezolid; tendinitis with fluoroquinolones; QT prolongation and hepatotoxicity with bedaquiline; skin discoloration with clofazimine; psychiatric disorders and seizures with cycloserine; hypothyroidism, gynecomastia, and gastrointestinal side effects with ethionamide; nephrotoxicity and vestibular toxicity with amikacin/kanamycin; and hypothyroidism and hepatitis with para-amino salicylic acid (PAS).

The complexity, cost, and duration of current treatment regimens exacerbate these challenges, undermining the WHO's target of an 80% treatment success rate. Enhanced pharmacovigilance, patient-centered care, and tailored regimens are crucial to managing ADRs and ensuring adherence to therapy. Developing safer therapies and effective mitigation strategies is crucial for enhancing treatment outcomes for DR-TB and advancing global initiatives to control and eradicate tuberculosis.

Keywords: Adverse drug reactions, Drug resistance, Tuberculosis.

Introduction

Tuberculosis (TB) is a transmissible infectious disease that significantly impacts global health, causing substantial illness and death. According to the World Health Organization (WHO), TB is among the top 10 leading causes of death and is second to COVID-19 as the leading infectious killer, surpassing HIV/AIDS. In 2022, TB developed in approximately 10.6 million people, and about 1.6 million succumbed due to the disease[1]. TB is most prevalent in regions affected by poverty, malnutrition, overcrowding, and HIV co-infection, with 86% of new cases reported from the regions of Southeast Asia, Africa, and the Western Pacific.

Certain strains of *Mycobacterium tuberculosis* exhibit resistance to anti-tuberculosis drugs, necessitating the use of 'second-line treatment' options. Drug resistance is categorized based on the extent and type of resistance. Multidrug-resistant TB (MDR-TB) is defined as resistance to both rifampicin and isoniazid. When MDR-TB strains also resist fluoroquinolones and one additional Group A drug (bedaquiline or linezolid (or both), the condition is classified as 'extensively drug-resistant TB' (XDR-TB).[2,3]

As per WHO data from 2021, the number of TB cases increased to 10.6 million worldwide, of which 6.4 million (60.3%) were recorded and treated, while 4.2 million (39.7%) were unreported or undiagnosed.[4] Among TB patients in 2021, 161,746 were enrolled in treatment for multidrug-resistant TB

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or rifampicin-resistant TB (MDR/RR-TB), reflecting a modest 7.5% rise from 150,469 in 2020, though still below the 181,533 cases treated in 2019. worldwide, 78% of rifampicin-resistant TB (RR-TB) cases were classified as multidrug-resistant.[1] Approximated incidence of MDR-TB was 2.84% in new cases and 11.6% in previously treated patients according to survey done by Government of India (2014–2016), highlighting the urgent need for effective intervention strategies.[5]The distribution of multidrug-resistant tuberculosis (MDR-TB) cases in developing nations have crucial challenges for effective TB control and eradication. Despite overall efforts by the World Health Organization (WHO) and other national initiatives, the treatment success rate for MDR-TB remains low. While the WHO aims for a treatment success rate up to 80%, recent data indicate that the current success rate is around 59%.[6,7] Low socioeconomic position, HIV infection, poverty, alcoholism, overcrowded living conditions, homelessness and immune-compromising illnesses are the major risk factors for MDR-TB. Ineffective anti-TB medication use can exacerbate the illness, raise mortality, and cause more drug resistance, all of which increase the financial strain on patients and healthcare systems.[8]

Currently, there are several WHO-recommended treatment regimens for MDR-TB: the BpaL-M and BpaL regimens (of 6 months duration), shorter regimens of 9 to 11 months, and all oral longer regimens of 18 to 24 months. These regimens, however, are costly, lengthy, and complex, often leading to adverse drug reactions (ADRs) that result in treatment interruption, non-adherence, and failure, potentially increasing MDR-TB transmission in communities.[9,10]

A few basic concepts regarding drug-related adverse reactions are recapitulated in Table 1

ADRs associated with MDR-TB treatment compromise nausea, vomiting, hyperuricemia, allergies, fever, and more. While many ADRs are mild or moderate and may resolve over time, others can be severe and necessitate drug discontinuation, dose modification, or alternative treatments.[10,11]

Table 1: Concepts promoting drug-related adverse reactions

1	Incorrect diagnosis
2	Prescription of inappropriate drugs.
3	Incorrect dosage of drugs.
4	An unknown medical/genetic/allergic condition that may cause a drug reaction.
5	Self-medication
6	Drug-to-drug interactions
7	Drug-to-food interactions
8	Use of poor-quality drugs/composition
9	Use of counterfeit drugs
10	Patient-related factors - pharmacokinetics, pharmacodynamics and metabolism.

Table 2: Tools used for ADR severity evaluation

- Research Studies – Hartwig scale
- W.H.O – Uppsala monitoring centre (WHO-UMC)
- India – Modified Hartwig, WHO-UMC.
- ICD-10 – Edward and Aronson classification system.

To improve treatment outcomes, the National Tuberculosis Elimination Programme (NTEP) focuses on addressing the challenges of ADRs and non-compliance. Extended transmission, recurrence, treatment resistance, and elevated morbidity and death are all consequences of non-compliance. Understanding challenges in tuberculosis treatment and associated ADRs is crucial for enhancing treatment success. This review aims to understand:

- The adverse drug reactions (ADRs), including types and severity (Table 2), were observed in patients receiving treatment for drug-resistant tuberculosis (DR-TB).
- To identify the specific drugs responsible for these adverse events and assess the underlying risk factors that predispose patients to their development.
- To explore the impact of ADRs on treatment compliance, modifications to treatment regimens, and overall treatment outcomes.

Adverse Drug Reactions (ADRs)

Adverse Drug Reactions are defined as harmful, unwanted reactions to medicine that occur even at normal doses used for treatment. Severe adverse reaction is an adverse event leading to a life-threatening experience, or hospitalisation or prolonged hospital stay, to persistent or significant disability, or a congenital anomaly, or even death. Whenever a patient experiences any of such serious adverse events due to any of the second-line anti-TB drugs, ideally, he/she should be admitted to the DR-TB centre, and the committee should decide further management of the patient.[12,13]

Specific 'Adverse Drug Reactions' Associated with Anti-TB Drugs

Linezolid

Linezolid, an antibiotic from the oxazolidinone class, has shown significant efficacy against drug-resistant *Mycobacterium tuberculosis* in various clinical studies. The World Health Organization (WHO) has recommended its use in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. However, various serious adverse effects, including peripheral neuropathy, haematological toxicity, and optic neuropathy, have been associated with its use.[14,15]

Peripheral neuropathy caused by linezolid is linked to mitochondrial dysfunction due to the inhibition of protein synthesis and downregulation of LC3B protein expression, leading to neuronal and myelin sheath damage. Symptoms range from tingling, numbness, and burning sensations in the feet to difficulties in sensing footwear and loss of coordination. The reported incidence varies widely, from 13 to 93.3%.

Studies have documented a 31% incidence in a meta-analysis by Zhang *et al.*[16] while Agyeman *et al.*[17] reported a pooled incidence of 29.92% in a systematic review of 507 patients across 14 countries. Additional studies found rates of 28.5% (Huerga *et al.*[18]), 28% (Khanam M *et al.*[19]), and 26% (Lifan *et al.*[20]). Lower incidences were noted by Madhav *et al.*[21] (25%), Tiwari *et al.*[22] (18.75%), and Shin *et al.*[23] (13%), with Mishra *et al.*[24] reporting the highest at 93.33%.

Anaemia caused by linezolid is primarily due to bone marrow suppression stemming from mitochondrial toxicity. Linezolid binds to 50S subunit of RNA and inhibits protein synthesis in bacteria, but it also affects human mitochondrial ribosomes, impairing energy production and reducing red blood cell (RBC) production. Prolonged use can lead to pancytopenia or drug-induced aplastic anaemia, with the risk significantly increasing after two weeks of therapy due to cumulative mitochondrial damage[25]. Incidences of myelosuppression vary, with Huerga *et al.*[18] reporting 5.1%, Mishra *et al.*[24] noting anaemia in 4.44% of patients, and Lifan *et al.*[26] observing a 42% incidence. A meta-analysis by Agyeman *et al.*[17] divulges a pooled myelosuppression rate of 32.93%, and Lee *et al.*[27] identified anaemia as a frequent adverse effect of extended therapy.

Another significant complication of linezolid therapy is optic neuropathy, particularly in patients treated for tuberculosis. Symptoms include blurred vision, eye pain, and tingling sensations. The mitochondrial toxicity of linezolid, which inhibits mitochondrial protein synthesis and impairs energy production, is considered the primary mechanism of optic nerve damage. A meta-analysis reported an incidence of 13.2%, with Karuppannasamy *et al.*[28] and Javaheri *et al.*[29] supporting the role of mitochondrial dysfunction. Schecter *et al.*[30] found reduced activity of respiratory-chain complexes, especially complex IV (cytochrome c oxidase), in affected patients, providing further evidence of mitochondrial involvement. Smaller studies and cohorts reported lower prevalence rates, including 3.3% in a North American cohort, 1.3% in a Mumbai cohort[31] and 2.9% in a combined Mumbai[32] and South African MSF cohort.[33]

These findings underscore the importance of monitoring for adverse effects in patients receiving linezolid, especially during prolonged treatment. Anaemia typically develops in the first 2 to 4 weeks of the beginning of the therapy, with the risk increasing with both dose and duration of treatment. Studies have shown that cumulative doses and prolonged use (beyond 2 months) elevate the likelihood of hematologic toxicities, leading to a potential need for dose reduction or temporary discontinuation. In some cases, decreasing the dose to 300 mg daily or using adjunct therapies like erythropoietin has been effective in managing anaemia while maintaining therapeutic efficacy. Similarly, optic neuritis usually manifests after 8 to 12 weeks of treatment, often requiring immediate discontinuation of linezolid to prevent permanent vision damage. Early cessation can result in partial or full recovery of vision over several months. Research indicates that dose reduction and early detection of these ADRs are crucial for preventing severe complications. There should also be emphasis on the importance of close monitoring in TB patients on long-term linezolid therapy.[27, 33]

Bedaquiline and Delamanid

Bedaquiline, a diarylquinoline, inhibits the ATP synthase, while delamanid, a nitroimidazole that inhibits mycolic acid synthesis, is are novel anti-tuberculosis (TB) drug having a distinct mechanism of action, resulting in significant advancement in the management of drug-resistant TB. Both drugs are administered orally and are generally well-tolerated.[34] In 2018, the World Health Organization (WHO) classified bedaquiline as a Group A drug, recommending its inclusion in all multidrug-resistant or rifampicin-resistant TB (MDR/RR TB) treatment regimens.[35] Recommendation for using this drug was based on evidence from meta-analyses showing that bedaquiline improves treatment success rates and reduces mortality.[36,37]

One of the main concerns with bedaquiline is QT prolongation, caused by its inhibitory effects on the hERG potassium channels in cardiac myocytes. This effect is predominantly mediated by bedaquiline's metabolites, M2 and DM-6705, which have long half-lives and lead to delayed maximal QTc effects (5–8 weeks for delamanid and up to 24 weeks for bedaquiline).[38,39] Studies have shown that QT prolongation (QTc >450 ms) occurs in 11 to 17% of patients, with severe prolongation (QTc >500 ms) reported in 2 to 3%.[6] In South African cohorts, QT prolongation was observed in 20% of patients, with 2% experiencing QTc >500 ms.[40] The risk of life-threatening arrhythmias such as torsades de pointes is low (<1%) but increases when bedaquiline is combined with other drugs like clofazimine and fluoroquinolones.[41,42] Observational studies have reported higher QTc changes than clinical trials, likely due to the exclusion of high-risk patients from trials. For example, in one study, the incidence of QTc >500 ms reached 15%, and the average increase in QTc was 49 ms.[43]

In addition to QT prolongation, hepatotoxicity is a significant adverse effect of bedaquiline, likely related to its metabolism by CYP3A4 enzymes. Liver enzyme elevations are seen in 8–12% of patients, while clinically significant hepatotoxicity (ALT/AST >3× upper limit of normal) occurs in 1 to 5%.[44] Co-administration of hepatotoxic drugs, such as pyrazinamide, further increases this risk.[45]An European multicentre study reported transaminase elevations in 10% of patients[46], while a meta-analysis of over 1,000 patients found a hepatotoxicity incidence of 15%, with pre-existing liver conditions and prolonged treatment identified as risk factors.[47]

Emerging studies highlight geographical variations in side-effect incidence. An Indian observational study reported QT prolongation and hepatotoxicity in 18% and 11% of

MDR-TB patients, respectively, with overlapping cases.[48] Similarly, a retrospective analysis from Russia observed liver toxicity in 13% and 'QT prolongation' (>450 ms) in 16% patients, particularly in those receiving concurrent fluoroquinolones or clofazimine.[49] Despite these concerns, the demonstrated mortality reduction and treatment success rates underscore bedaquiline's importance in MDR-TB regimens.[50]

To mitigate these risks, pharmacovigilance programs stress the importance of regular monitoring, including electrocardiograms (ECGs) and liver function tests. A 2022 study from Peru demonstrated that strict adherence to monitoring protocols reduced the frequency of severe adverse events by 30%, emphasizing the critical role of comprehensive care in optimizing patient safety while maintaining the benefits of bedaquiline.[51]

Fluoroquinolones (FQs)

Fluoroquinolones (FQs) are broad-spectrum antibiotics that are widely used to manage a variety of bacterial infections. These are synthetic derivatives of quinolones, characterized by a fluorine atom at the 6th position of their chemical structure, which enhances their antibacterial potency and broadens their spectrum of activity.[52]

Their mechanism of action of fluoroquinolone is inhibition of bacterial DNA gyrase (topoisomerase II), an enzyme essential for DNA replication and mRNA synthesis. Despite their bacterial specificity, FQs may exert toxic effects on human musculoskeletal tissues.[53] They have been linked to tendinopathy, possibly due to their chelating properties, which impair type I collagen synthesis and promote degradation. Studies in animals have demonstrated FQ-induced cartilage damage, including chondrocyte necrosis, extracellular matrix disruption, and surface fissures, leading to contraindications for their use in children, pregnant women, and lactating individuals. In vitro studies further confirm that FQs can compromise tendon integrity, particularly in older individuals or those with pre-existing tendon injuries, as reduced matrix turnover limits repair capacity.[54] Observational studies have revealed that concurrent corticosteroid use enhances the risk of tendon rupture. A 2019 meta-analysis found an estimated incidence of tendon injury in FQ users of 1.5 to 2%, with older adults being disproportionately affected.[54] Another study reported a tendinopathy prevalence of 18.5% among participants undergoing long-term fluoroquinolone therapy for tuberculosis and highlighted that prolonged use of fluoroquinolones might enhance the risk of side effects.[55]

Clofazimine

Clofazimine is used in the treatment of 'multidrug-resistant tuberculosis' (MDR-TB), is well-known for causing skin discoloration, typically presenting as reddish-brown or dark pigmentation. This effect arises mainly due to the drug's lipophilic (fat-soluble) nature, which allows it to accumulate in lipid-rich tissues such as the skin, leading to noticeable pigmentation changes. Clofazimine also tends to bind to tissue components in the skin, forming complexes that produce the discoloration, and these complexes can persist in skin cells for extended periods. Additionally, the drug undergoes oxidative metabolism in the liver, creating metabolites that interact with cellular structures, which may contribute to the pigmentation. Although the discoloration is reversible after clofazimine is discontinued, it can persist for months due to the long half-life of the drug and its slow clearance from the body. While this side effect is generally harmless, it can be cosmetically distressing for patients, with the pigment fading gradually after treatment ends.[56,57]

Overall, clofazimine is considered a safe drug with infrequent serious adverse events (SAEs) and is well tolerated when incorporated with other MDR-TB regimens.[58] However, a study by Anderson *et al.*[59] highlighted some potential negative effects, including pro-thrombotic activity observed in human platelets. Skin discoloration is the most common adverse effect of clofazimine. Piubello *et al.*[60] reported an incidence of 3.1 %, Wang *et al.*[61] found it in 22.7%, and Dalcolmo *et al.* [62] reported an incidence of 52.1%. The different incidence rates in these studies may stem from variations in study populations or treatment regimens containing clofazimine.

In animal studies, the incorporation of clofazimine in standard second-line treatment for MDR-TB is known to result in brownish discoloration of internal organs, as in one conducted by Grosset *et al.*[63] However, clofazimine-induced skin pigmentation is a commonly occurring minor side effect; it is rarely life-threatening, as reported in a systematic review.[64] Some studies have reported an increased risk of hepatic dysfunction with the addition of clofazimine to other MDR-TB regimens. It can be a significant adverse event in patients receiving complicated treatment regimens containing clofazimine.[64,65] The risk of ADRs generally correlates with the dose and duration of treatment. Higher doses of clofazimine can lead to more severe issues and a higher chance of skin and ocular adverse effects, such as corneal deposits and possible cardiac toxicity.[66] Prolonged use, particularly in leprosy or MDR-TB treatments, which may last for several months or years, is associated with cumulative toxicity, making long-term monitoring essential. Discontinuation or dose reduction of clofazimine is often required if ADRs become severe.[67] For instance, skin pigmentation changes, though typically harmless, may lead patients to request dose reductions or discontinuation.

Cycloserine

Cycloserine (4-amino-3-isoxazolidinone) is another tuberculostatic antibacterial agent which is efficacious against Mycobacterium tuberculosis and acts by inhibition of bacterial cell wall biosynthesis. It is a cyclic analogue of D-alanine that inhibits alanine racemase (Alr) and D-alanine: D-alanine ligase (Ddl), two essential enzymes involved in the

cytosolic synthesis of peptidoglycans.[68,69] L-alanine is changed into D-alanine by the first enzyme, alanine racemase, and the D-alanine-D-alanine dipeptide bond is formed by the second enzyme, which is ATP-dependent. Inhibition of both enzymes prevents the formation and linking of D-alanine residues, which ultimately disrupts peptidoglycan synthesis.[69]

WHO classified cycloserine as a second-line, group IV oral bacteriostatic drug and is a broad-spectrum antibiotic.[70] Unlike other anti-mycobacterial agents, cycloserine does not exhibit cross-resistance, making it a valuable option for treating drug-resistant tuberculosis (DR-TB).[70] Adverse effects associated with cycloserine are primarily dose-dependent and idiosyncratic. Psychiatric side effects have been seen in 9.7 to 50% of patients on cycloserine, which includes anxiety, paranoia, hallucinations, depression, euphoria, behavioural changes, and suicidal ideation, with these effects being most common during the first 12 weeks of beginning of treatment.[71]

Studies suggest that cycloserine may elevate GABA levels by inhibiting GABA transferase, potentially contributing to delirium, particularly in conditions like hepatic encephalopathy. Additionally, cycloserine interacts with AMPA/Kinase and NMDA receptors to affect glutamatergic transmission, supporting the hypothesis that, by acting on the GABA and glutamate neurotransmitter systems, it might contribute to delirium. The neurotoxic effects of cycloserine have been demonstrated in a randomized controlled trial (RCT), which showed that psychotic symptoms associated with cycloserine, mediated by the NMDA receptor pathway, worsened in schizophrenic patients. When 100 mg of cycloserine was added to typical antipsychotic treatment, it exacerbated psychosis and overall psychopathology.[72-76] Studies have shown a wide range of incidence rates for psychosis. Fatima *et al.* [77] in their study reported an incidence of 1.69% for psychosis, Singh *et al.*[78] reported the incidence to be 4.2% whereas Rathod *et al.*[79] reported the incidence at 4.90%. Studies in other countries reported a higher incidence. Ngoc *et al.*[80] in Vietnam reported an incidence of 30%. Buziashivili *et al.*[81] reported two deaths that occurred as a result of suicide due to cycloserine-induced depression and anxiety. The likelihood of psychiatric adverse drug reactions (ADRs) associated with cycloserine is generally related to both the dose and duration of treatment. Higher doses are more likely to cause severe psychiatric effects, and prolonged use increases the cumulative risk of side effects. ADRs are often observed within the first 12 weeks of treatment, particularly during the early stages when dose adjustments are typically made. If ADRs become severe, such as in the case of psychiatric symptoms or other neurotoxic effects, it may be necessary to reduce the dose or discontinue cycloserine. In cases with significant psychiatric disturbances, discontinuation of the cycloserine is recommended to mitigate the risk of further harm. Managing these side effects requires careful monitoring, dose adjustments, and, if needed, switching to alternative therapies for drug-resistant tuberculosis.[82]

Ethionamide

Ethionamide is a prodrug that is used as a second-line drug in the treatment of 'multidrug-resistant tuberculosis' (MDR-TB). Gynecomastia and gastrointestinal (GI) side effects have been associated with ethionamide and are of significant concern during multidrug-resistant tuberculosis (MDR-TB) treatment. This drug is a synthetic derivative of thiohydantoin and functions by inhibiting the InhA enzyme, which is necessary in the biosynthesis of mycolic acids, which are crucial components of the cell wall of mycobacteria. By disrupting the biosynthesis of the cell wall, ethionamide impedes the growth and replication of *Mycobacterium tuberculosis*. While effective, ethionamide is linked with a range of adverse events that can vary in severity depending on dose and duration of this drug.

Mild to moderate hypothyroidism is the most common and concerning side effect of ethionamide.[83] Different studies across various countries have shown differing rates of hypothyroidism among patients receiving ethionamide, such as Egypt (39.5%), Botswana (16.2%), Russia (17.2%), Peru (10%), and Lesotho (69%), showing notable incidences.[84-87]

Children and individuals with human immunodeficiency virus (HIV) are at heightened risk of developing hypothyroidism with ethionamide.[8] Prasad *et al.*[87], Hire *et al.*[88] and Fatima *et al.*[77] reported an incidence of 0.8, 0.9 and 2.96%, respectively, with this drug. Baghaei *et al.*[89] in Iran reported an incidence of 1.3% in DR-TB patients. Other studies reported a higher incidence of hypothyroidism. Chhabra N *et al.*[90] in a study from Ajmer found the incidence to be 11%. In 7.4% patients developed goitre in their study. Tola *et al.*[85] in a meta-analysis reported a pooled incidence to be 17%, Kushemererwa *et al.*[91] reported it to be 19.66%, whereas Andries *et al.*[92] reported it to be 54%.

Ethionamide-induced hypothyroidism may stem from its similarity to thioamide drugs, which inhibit thyroid hormone synthesis. The potential role of genomic pathways in this process remains unclear. Molecular docking predicts receptor-ligand interactions and ranks binding affinities, aiding in understanding mechanisms like ETH-induced hypothyroidism.[85]

Gynecomastia associated with ethionamide use is believed to result from hormonal imbalances caused by the drug's effects on the endocrine system. Ethionamide may alter testosterone metabolism or promote increased peripheral conversion of androgens to oestrogens, leading to breast tissue growth.[93] While the exact incidence is not well established, gynecomastia has been reported sporadically in clinical settings, particularly with prolonged use or higher doses. Studies have reported isolated cases of gynecomastia associated with second-line anti-TB drugs, including ethionamide.[94] One study noted gynecomastia in 1.27% of

patients attributed to ethionamide use. Resolution is generally observed after discontinuing the drug or reducing its dosage.[77]

Gastrointestinal side effects are the most commonly reported adverse reactions to ethionamide. These include nausea, vomiting, abdominal pain, anorexia, diarrhoea, and a metallic taste. The mechanism underlying these effects is largely attributed to the drug's irritative properties on the gastric mucosa. Additionally, ethionamide may alter gut motility or enzyme activity, contributing to GI discomfort. The incidence of GI side effects varies across studies, with some reporting rates as high as 40 to 60% by Wu S *et al*.[94] In a retrospective study, Sari *et al*.[95] observed that over 50% patients receiving ethionamide experiencing nausea or vomiting severe enough to warrant adjunctive antiemetic therapy.

Management strategies include administering ethionamide with food to reduce gastric irritation or using supportive therapies such as antacids and antiemetics. However, these side effects remain a leading cause of poor compliance, underscoring the need for careful monitoring and dose adjustments to maintain patient adherence.

Amikacin/Kanamycin

Aminoglycosides are broad-spectrum antibiotics used for MDR-TB. Nephrotoxicity and ototoxicity are two main side effects of concern after administration of aminoglycosides.[96] Ototoxicity caused by aminoglycosides is irreversible. Free radicals are generated by aminoglycosides within the inner ear, which cause injury to sensory cells and neurons in the inner ear, resulting in permanent hearing loss. Permanent hearing impairment is due to the cochlear damage, while ataxia, dizziness and/or nystagmus are due to damage to the vestibular apparatus. Nephrotoxicity is another major toxicity limiting the use of aminoglycosides. Drug-induced nephrotoxicity is defined as two consecutive increases in blood creatinine level by 0.5 mg/dl or 50% from the baseline, whichever is higher, during the course of treatment or up to one week after the end of treatment.[97] Studies on both humans and animals have shown a connection between the buildup of aminoglycosides in the renal cortex and their nephrotoxic effects.[98-100]

Duggal P *et al*.[101] investigated the association of hearing impairment in MDR-TB patients with use of intravenous second-line aminoglycosides, specifically kanamycin, amikacin and capreomycin. They reported that about 18.75% of MDR-TB patients had hearing loss receiving a single second-line aminoglycoside. Among them, 6.25% of patients experienced hearing loss, which started with high frequencies (4000–8000 Hz) and progressed to lower frequencies (500, 1000, 2000, and 3000 Hz). It affected the patient's ability to comprehend speech. Hearing loss in the 4000 Hz range can also impair speech understanding, which can have a negative impact on communication, particularly in settings with background noise. None of the individuals in their research exhibited any improvement after stopping the drug, which has been determined to be irreversible once it has started. Ototoxicity is assessed by comparing the outcomes of follow-up monitoring tests with baseline data, ideally acquired before the administration of an ototoxic substance. The best way to identify ototoxic hearing loss is to use serial audiograms to directly detect changes in pure tone thresholds, especially when ultra-high frequency thresholds are present. For patients taking ototoxic antibiotics, it has been advised to monitor audiological assessments 1-2 times per week following baseline evaluations. The range of MDR-TB patients experiencing hearing loss as an adverse event ranges between 6–18% as reported in several studies. Most studies reveal that higher frequencies are affected before the lower ones, which could give us time to stop and minimize irreversible communication problems in individuals getting aminoglycoside therapy and serve as a monitoring technique for ototoxicity diagnosis. The aminoglycoside can be discontinued in all patients exhibiting hearing loss, and a different second-line medication can be started instead. The incidence of hearing loss can be significantly reduced by the termination of aminoglycoside use immediately at the onset of ototoxicity and replacing it with any of the other second-line drugs. Other authors also discussed switching to different second-line medications and finishing the entire course of treatment.[102,103]

Recent evidence in aminoglycosides kinetics hints that renal accumulation of aminoglycosides is related to the dosing schedule. Studies show that if larger doses of the drug are administered at less frequency, it may decrease the drug concentration in renal tissue and thereby be associated with reduced potential for nephrotoxicity.[101] This finding has changed the conventional practice of multiple daily dosing and has been replaced by once daily dosing of aminoglycosides. Meta-analysis of randomized clinical trials shows once a day dosing has diminished[104] or comparable [105-108] nephrotoxicity rates, better[105,106] or comparable efficacy and comparable ototoxicity compared to multiple daily dosing.

Reduced toxicity has been linked to personalized aminoglycoside dosing based on patients' individual pharmacokinetic factors and standard equations, as well as targeted peak and trough concentrations in the serum.[109] Patients receiving aminoglycoside treatment have shown a correlation between ototoxicity and nephrotoxicity as well as an increased mean trough aminoglycoside blood level.[110]

Para-amino salicylic acid (PAS)

Para-amino salicylic acid (PAS), a second-line anti-tuberculosis drug, is frequently associated with hypothyroidism and hepatotoxicity, both of which may impact patient adherence and treatment success. Hypothyroidism is a well-recognized side effect of PAS, specifically when used in conjunction with other drugs such as ethionamide or prothionamide, which also impair thyroid function. PAS is believed to disrupt thyroid hormone synthesis by interfering with iodine uptake or its incorporation into thyroid hormones. Fatigue, weight

Table 3: Summary of adverse effects and incidences

Drug	*Adverse effect*	*Incidence*	*Reference number*
Linezolid	Peripheral Neuropathy	13–93.3%	16, 17, 18, 19, 110, 21, 22, 23, 24
	Anaemia	4.44–42%	17, 18, 20, 24, 27
	Optic neuropathy	1.3–13.2%	28, 29, 30, 31
Fluoroquinolones	Tendinopathy	1.5–2% (higher in older adults and those on corticosteroids)	54 (Meta-analysis)
	FQ resistance in MDR-TB	20–60% (increasing over time, higher resistance in untreated cases)	55
Bedaquiline	QT prolongation	11–20% (QTc >450 ms), 2–3% (QTc >500 ms)	40, 41, 42, 43
	Hepatotoxicity	8–12% (elevation in liver enzymes), 1% - 5% (clinically significant hepatotoxicity)	48, 49, 50
Clofazimine	Skin discoloration	3.1–52.1%	60, 61, 62
	Hepatic Dysfunction	Higher doses and prolonged use increase the likelihood of hepatic issues	60, 63
	Cardiac Toxicity	Potential increase in toxicity with prolonged use or combined therapy	60, 62, 63
Cycloserine	Psychosis & Psychiatric Disorders	9.7–50% (higher in early treatment)	77, 78, 79, 80, 81
	Seizures	Variable (incidence not clearly defined)	77, 78, 79
Ethionamide	Hypothyroidism	0.8–54% (variable across studies)	77, 85, 87, 88, 89, 90, 91, 92
	Gynecomastia	~1.27%	77, 93
	Gastrointestinal Side Effects	40–60%	94, 95
Para-aminosalicylic Acid (PAS)	Hypothyroidism	10–32%	111, 112
	Hepatitis	5–15%	94, 112, 113
Amikacin	Nephrotoxicity	10–25% (higher in patients with renal impairment)	98, 99, 100
	Ototoxicity	3–10%	101

gain, cold intolerance, and dry skin are some common clinical manifestations. The incidence of hypothyroidism during PAS therapy has been reported to range between 10 and 20%, with some studies citing rates as high as 32% in patients on prolonged therapy or combination regimens.[111,112] Thyroid dysfunction is particularly notable in regimens involving MDR-TB treatment, where regular thyroid function monitoring is essential to prevent complications and enable timely intervention with levothyroxine.

Hepatitis, another significant adverse effect of PAS, typically results from direct hepatocyte toxicity or immune-mediated reactions to PAS metabolites. Symptoms such as jaundice, anorexia, fatigue, and elevated liver enzymes (ALT, AST) can develop, with an incidence reported between 5 and 15% in different cohorts.[94,113] A prospective study observed hepatotoxicity in approximately 12% of patients receiving PAS, particularly in those having pre-existing hepatic conditions or concurrent use of other liver-toxic drugs.[94] Similarly, another study reported that hepatotoxicity often necessitated dose adjustments or discontinuation of PAS in around 10% of patients, with most cases being reversible upon cessation.[112] Rare but severe cases of fulminant hepatitis underscore the need for vigilant liver function monitoring during therapy.

Both hypothyroidism and hepatotoxicity emphasize the importance of individualized treatment and regular monitoring during PAS use. 'Thyroid function tests' (TSH, T3, T4) and 'liver function tests' (LFTs) should be done periodically, particularly in those at high high-risk. Effective management strategies, including dose reduction, supportive care, and thyroid hormone replacement, can help mitigate these risks, ensuring better patient compliance and treatment outcomes in MDR-TB cases.

Table 3 summarizes adverse effects and their incidence with various drugs used in the management of drug resistant tuberculosis.

Conclusion

The management of patients having drug-resistant tuberculosis (DR-TB) is still challenging in view of the high prevalence of adverse drug reactions (ADRs) that are associated with second-line treatment regimens. These ADRs, ranging from mild to severe, can negatively impact patient compliance, prolong treatment duration, and compromise treatment

success rates. Identifying and managing ADRs effectively is critical to improving treatment outcomes in patients with MDR-TB and XDR-TB.

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