A Clinical approach to the adverse drug reaction in the management of multidrug-resistant tuberculosis

Dr.R.DINESH KUMAR*[1], ASMA ABDURAHMAN[2], PIONEER E[2], SARFARAAS AHAMATH S[2]

[1]Assistant Professor, [2]Doctor of Pharmacy Students
Department of Pharmacy Practice,
The Erode College of Pharmacy and Research Institute, Erode, Tamilnadu, India

ABSTRACT

AIM AND OBJECTIVE: Multidrug Resistant Tuberculosis is considered to be a worldwide problem with notoriously difficult and challenging treatment. Antituberculosis multidrug regimens have been associated with increased incidence of adverse drug reactions (ADRs).This study have been framed to determine the incidence and associated factors of ADRs due to antituberculosis treatment.
METHOD: A search approach was used, that included the use of major electronic databases (PubMed, EMBASE, MEDLINE, library catalogues, and Google) as well as a manual search of
International journal of Tuberculosis and lung disease.
RESULT: 21 articles including 1 systemic reviews have been identified and the overall prevalence of ADRs associated with MDR-TB are estimated. The occurrence of ADRs may be influenced by multiple factors and may range from mild gastrointestinal disturbances to serious hepatotoxicity, ototoxicity, nephrotoxicity peripheral neuropathy, cutaneous ADRs etc. Agents responsible for these adverse effects were Kanamycin (ototoxicity), Cycloserine (headache/psychosis), Ethionamide (gastrointestinal tolerance/hypothyroidism) and Pyrazinamide (arthralgia/hepatitis).
CONCLUSION: Early recognition by active surveillance/reporting ADRs and appropriate management of these ADRs might improve adherence and treatment success and is a remarkable relevance to prevent emergence threat of global MDR-TB.

***KEYWORDS*: Tuberculosis, Multidrug- resistant tuberculosis, Anti-tubercular therapy, Adverse drug reactions.**

INTRODUCTION

Tuberculosis (TB) is an infectious disease usually caused by Mycobacterium tuberculosis (MTB) bacteria. It mainly affects the lungs, but it can affect any part of the body, including the kidney, glands, bones and nervous system .According to World Health Organization (WHO) TB is considered as the tenth leading cause of death worldwide and is reported that 10.4 million patients developed TB and 1.6 million patients died from TB worldwide in 2017[2].Globally, Tuberculosis (TB) continues to be a major public health concern. Multidrug-resistant TB (MDR-TB), which is defined as TB that shows resistance to both isoniazid and rifampicin, is a barrier in the treatment of TB. Approximately 3.4% of new TB patients and 20% of the patients with a history of previous treatment for TB were diagnosed with MDR-TB[1]. Many countries rely on hospital-based care during the intensive phase for the treatment of MDR-TB.As this treatment phase lasts for at least 6 months, this long period of hospitalization often leads to the problem of lack of bed capacity; introduces the risk of nosocomial reinfection with a different strain of Mycobacterium tuberculosis and is not patient friendly[9]. Directly observed therapy (DOT) is a widely recommended and promoted strategy to manage tuberculosis (TB), however, there is still disagreement about the role of DOT in TB control and the impact it has on reducing the acquisition and transmission of multi drug resistant TB[15].MDR-TB management is under Programmatic management of drug resistant tuberculosis (PMDT).The proper management of ADR can be effective in reducing the rate of mortality and morbidity and thereby increases the positive treatment outcome[8].

Patients may experience a variety of ADRs when managed with anti-tubercular drugs. Treatment with these drugs can also be associated with adverse events which is defined as any untoward medical occurrence but not necessarily have a causal relationship[13]. Adverse drug reactions represent a potential obstacle to treatment completion and could negatively affect outcome. Documenting, assessing and managing adverse drug events is important to achieve better patient compliance and improve treatment outcomes[10]. Comorbidities have a well-documented impact on drug-sensitive TB treatment, with diseases like HIV infection, diabetes mellitus (DM), chronic kidney disease (CKD), and alcohol abuse all being linked to poor treatment outcomes. Adverse medication reactions can make it difficult to complete treatment and can have a detrimental impact on the outcome[14]. To improve patient compliance and treatment outcomes, it's critical to track, monitor, and manage adverse medication events. Despite the high frequency of adverse drug reactions and long term therapy, the clinical management of MDR-TB patients in a referral centre could reach successful treatment according to WHO target, by implementing active and systematic clinical and laboratory assessment to detect, report and manage suspected and confirmed adverse drug reactions. A high death rate and default rate were important roadblocks to reaching a high cure rate[5]. MDR-TB must be diagnosed early and treated with careful clinical surveillance. The key to success is recognising adverse drug reactions and other co-morbidities, as well as their best care.

MDR-TB is lethal or deadly, but it can be treated and cured with medications that can affect people in a variety of ways. As a result, the focus of this review is mostly on how to improve the patient's quality of life or safety, as well as the epidemiology of ADRs.

MULTIDRUG - RESISTANT TUBERCULOSIS TREATMENT RELATED ADVERSE EFFECTS:

Without exception every MDR-TB patient experiences at least one adverse reaction (ADR) during therapy, which goes unnoticed or unreported because many of them have minor ADRs or certain ADRs occur infrequently. As a result, in order to recognise ADR and give correct care to the patient, expertise and knowledge of ADR are essential. A toxic and unanticipated response to a medicine that occurs at doses routinely used in humans to treat tuberculosis was classified as an adverse drug reaction. In contrast to an unfavourable event, an adverse drug reaction is defined by the suspicion of a causative relationship between the drug and the occurrence[8].

The causes for the disparity in the occurrence of adverse events between studies could be due to a variety of factors, including variation in demographic profiles of cohorts of patients, differences in definitions of adverse events' terminologies, as adopted by physicians, whether the adverse event was reported by patient(subjective) or detected by clinician (objective), on the basis of clinical evidence along with feasibility of monitoring with serial laboratory investigations, whether all or only the major adverse events were studied, the differences in comorbidities, such as diabetes, and other covariates, such as HIV coinfection, and variations in the use of specific antitubercular drugs, including dosage and pharmacological interactions with other drugs, such as antiretrovirals, oral hypoglycaemic agents in diabetics, and ancillary medications used to manage adverse events. The high prevalence of gastrointestinal adverse events was most likely owing to patients reporting them more frequently than other types of adverse events, resulting in subjective variation. Ototoxicity was the second most prevalent side effect. Although there is a chance of additive effects of interaction with other contemporaneous and potentially ototoxic medications used in the regimen, such as Ofloxacin and Cycloserine, ototoxicity is mostly connected with the use of injectable aminoglycosides (Kanamycin).Baghaei et al. observed that injectable Kanamycin and Cycloserine caused hearing and headache/psychosis, respectively, and that these were severe side effects that necessitated repeated discontinuation and/or substitution[5]. The most common ADRs in the MDS-TB regimen, according to Rabahi et al. 2017, include urine colour change, gastrointestinal issues, skin responses, jaundice, and joint discomfort. Only four medicines are involved: H, R, Pyrazinamide (Z), and Ethambutol (E)[16].According to Zhang et al. 2017, the most common or prominent ADRs in MDR-TB treatment were arthralgia, gastrointestinal problems, and hypothyroidism (9 percent)[11]. According to several studies, the most prevalent or relevant ADRs of MDR-TB therapy include alopecia, amylase and/or lipase elevation, allergy, arthralgia, AST and/or ALT elevations, and cardiac muscle abnormalities such as myalgia, cardiac rhythm disturbances, depression, diarrhea, dysglycaemia and hyperglycaemia, hyperuricemia, electrolyte disturbances (hypokalaemia, hypomagnesemia), flatulence, gastritis and abdominal pain, giddiness, gynecomastia, haematological abnormalities, headache, hearing loss, hepatitis, hypothyroidism, lactic acidosis, metallic taste, nausea and vomiting, nephrotoxicity, optic neuritis, peripheral neuropathy, psychotic symptoms, QT prolongation, rash, seizures, suicidal ideation, superficial fungal infection and thrush, tendonitis and tendon rupture, vestibular toxicity etc[12-14](Table 1)

ADRs are one of the leading causes of morbidity and mortality. As a result, it's critical to spot ADRs and determine if there's a link between the medicine and an adverse event. The severity of ADRs is connected to the extent to which the ADRs influence the patients' daily lives. Causality assessment of ADRs is a way for determining the strength of the relationship between drug(s) exposure and the incidence of ADRs. Anti-TB-induced ADRs have always been a source of worry due to their incidence, severity, and type[15].

Table 1: Major adverse drug reactions and causative agents.

ADR	Causative agent
Arthralgia	Pyrazinamide, Fluoroquinolones, Bedaquiline, Ethambutol
Electrolyte imbalance	Capreomycin, Kanamycin, Amikacin, Streptomycin
Gastritis and Abdominal pain	Ethionamide, Prothionamide, Para amino salicylic acid, Clofazimine, Fluoroquinolones, Isoniazid, Ethambutol, Pyrazinamide
Hematological Abnormalities	All drugs (Linezolid, Rifampicin)
Headache	Bedaquiline, Cycloserine
Hearing loss	Streptomycin, Kanamycin, Amikacin, Capreomycin
Hepatitis	Pyrazinamide, Isoniazid, Rifampicin, Prothionamide, Ethionamide, Para amino salicylic acid, Fluoroquinolones, Bedaquiline
Nausea and Vomiting	Ethionamide, Prothionamide, Para amino salicylic acid, Pyrazinamide, Ethambutol, Bedaquiline, Clofazimine, Linezolid, Amoxicillin/Clavulanic acid
Nephrotoxicity	Streptomycin, Kanamycin, Amikacin, Capreomycin, Rifampicin
Optic neuritis	Ethambutol, Linezolid, Ethionamide, Prothionamide, Clofazimine, Isoniazid, Streptomycin
Peripheral neuropathy	Cycloserine, Linezolid, Isoniazid, Streptomycin, Kanamycin, Am, Capreomycin, Fluoroquinolones, Prothionamide, Ethionamide, Ethambutol
Psychotic symptoms	Cycloserine, Isoniazid, Fluoroquinolones, Ethambutol
QT prolongation	Bedaquiline, Dlm, Fluoroquinolones, Clofazimine, Clarithromycin
Rash, allergic reaction, anaphylaxis	All drugs

*Only included main causative agents under each ADR.

ARTHRALGIA

Antituberculous medicines Z (Pyrazinamid) and E(Ethambutol) have been shown to cause hyperuricemia in non-gouty patients, resulting in arthralgia. The hyperuricemic effect is most likely caused by the metabolite pyrazinoic acid. The mechanism is linked to pyrazinoic acid, Z's main metabolite oxidised by xanthine oxidase, which suppresses uric acid release in the renal tubules.

Hyperuricemia has been reported in 43-100% of patients treated with Z (alone or in combination).Gouty attacks have also been associated with patients taking Z. E can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than Z. . In a study by Dhingra et al on patients receiving DOTS therapy general aches and pains were complained by about 35%[9].However, in a study by Shinde et al arthralgia was seen in 0.67%which was lower in comparison to reported incidence of 2.57% in Chinese patients receiving therapy[13]. Arthralgia has been reported with FQs' particularly Lfx and Bdq containing regimens for MDR-TB.

Arthralgia is recorded in 2% of cases, therefore start with nonsteroidal anti-inflammatory medicines (indomethacin 50mg twice daily or ibuprofen 400-800 mg three times daily). When taken with an anti-inflammatory medicine, paracetamol (500-1000mg 2-3 times daily) is also beneficial. Reduce the dose if the symptoms do not go away or discontinue the suspected agent without compromising the regimen.

GASTRITIS AND ABDOMINAL PAIN

Pancreatitis, lactic acidosis, and hepatitis are all common side consequences of abdominal pain. Suspending suspected agents such PAS, Eto, Pto, Cfz, FQs, H, E, and Z and performing relevant laboratory tests to confirm the cause. Gastritis is characterised by a burning or uncomfortable sensation, a sour taste in the mouth, and stomach pain**.** If hematemesis and melena are present it indicates the threat of bleeding gastric ulcers. H-2 blockers (ranitidine 150 mg twice daily) or PPIs should be used to treat gastritis (omeprazole 20mg once daily). Stop using the suspected drug for a short time (1-7 days) if you have significant gastrointestinal pain, and avoid taking antacids with FQs because they interfere with FQ absorption. Cfz has been linked to severe gastrointestinal distress, however these cases are uncommon, and if they do occur, Cfz may be discontinued.

ELECTROLYTE IMBALANCE

Aminoglycosides, streptomycin (S), and other drugs can cause hyponatremia, hyperkalaemia, hypokalaemia, hypochloraemia, hyperammonaemia, hypomagnesemia, and hypocalcaemia, which are the most common electrolyte disturbances seen during TB treatment. According to the report, 11.4 percent of patients have electrolyte disturbances, and 25 percent of cases go unreported[15]. Capreomycin (Cm) is the most common aminoglycoside that causes this imbalance, but it is not the only one; other drugs can also cause the imbalance. It is preferable to change Cm to another aminoglycoside. When treatment is stopped, the imbalances are reversible, but supportive therapy may be required in some cases. Electrolyte imbalance can also be caused by other ADRs such as vomiting and diarrhoea, so it must be treated accordingly.

If an imbalance has occurred, a precautionary step should be taken at all times, and routine monthly electrolytes monitoring should be undertaken; if an imbalance has occurred, daily or weekly measurements are indicated, depending on the severity. Mild changes are almost always symptomless. Because potassium, magnesium, and calcium can interfere with fluoroquinolone absorption, they should be taken two hours before or four to six hours after the fluoroquinolone dose[22]. Amiloride (5–10 mg OD) or spironolactone (25 mg OD) will be used in resistant individuals to prevent potassium and magnesium wasting caused by TB medications. Encourage patients to eat foods high in potassium, such as grapefruit juice, tomatoes, and oranges. Replacement doses should be estimated using WHO recommendations, based on individual needs (Table 2).

HEMATOLOGICAL ABNORMALITIES

Anaemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, red cell aplasia, coagulation abnormalities, and eosinophilia are among the haematological abnormalities that can be diagnosed using haematological profiles such as haemoglobin, differential count, international normalised ratio, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), packed cell volume(PCV), haemoglobin distribution rate (HDW), platelets, red blood cells and white blood cells etc.

R has been linked to immune-mediated thrombocytopenic purpura and haemolytic anaemia, particularly when used in a short period of time. Thrombocytopenia, leukopenia, eosinophilia, hemolytic anaemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock were all reported in 0.1 percent of R patients in a Brazilian study[11].However, according to a few Asian research, allergic responses with FLDs range from 2.02% to 2.35 percent, whereas haematological ADRs range from 0.1 to 0.7 percent[11]. In research on haematological abnormalities during therapy, the author discovered that thrombocytopenia, which is defined as a fast decrease in platelet count in susceptible individuals.R is the most common offending agent in the development of thrombocytopenia as a side effect of antitubercular medicines. Isolated case reports of thrombocytopenia following Z, H, and E administration have been reported in the literature and have been attributed to an immunological phenomena[7].S has only been linked to thrombocytopenia on a very small number of occasions.Lzd has been linked to haematological ADRs, the most prevalent of which is thrombocytopenia, which has a reported prevalence of 11.8%. Other adverse reactions, such as pancytopenia and myelosuppression, are less common than thrombocytopenia. These haematological ADRs are dose-dependent and, in most cases, reversible with proper clinical care.Intermittent usage of rifampicin has triggered the body's immune system to attack its own cells, causing thrombocytopenia purpura. In this case, the medicine should be discontinued immediately and never reintroduced, as well as therapy for shock, renal failure, and thrombocytopenia. All other disorders should be treated symptomatically, and if a severe reaction occurs, the medicine should be discontinued and never used again.

Table 2: Dosing of replacement therapy.[9]

Electrolyte✓	Level	Dosing	Frequency of monitoring
Potassium	4.0 or more	None	Monthly
	3.6–4.0	None	Monthly
	3.3–3.5	40 mEq orally daily	Monthly
	2.9–3.2	60–80 mEq orally daily	Weekly
	2.7–2.8	60 mEq orally three times a day	One to two days
	2.4–2.6	80 mEq orally every eight hours	Daily
	<2.4	10 mEq/hr IV and 80 mEq orally every six to eight hours	One hour after infusion, every six hours with IV replacement
Magnesium	2.0 or more	None	Monthly
	1.5–1.9	1000 mg–1200 mg/day	Monthly
	1.0–1.4	2000 mg/day	One to seven days
	<1.0	3000 mg–6000 mg/day	Daily
Calcium (Total nonionized Ca value adjusted for low albumin)	>8.5 mg/dl	None	
	7.5–8.4	500 mg three times a day	Monthly
	7.0–7.4	1000 mg three times a day	One to two weeks
	<7.0	Consider intravenous and taper to 1000 mg three times a day	One to four days

✓Potassium: The normal preparation of a potassium chloride infusion is 40 mEq in 200 ml of normal saline. Do not exceed an infusion rate of 20 mEq/hr (100 ml/hr). Magnesium: Quantities greater than 2000 mg are usually given by IV or intramuscular (IM). The normal preparation is magnesium sulfate 2 g in 100 ml or 4 g in 250 ml of 5% dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 ml administered over one to two hours, 4 g in 250 ml administered over two to four hours). Calcium: Normal calcium is 8.5–10.3 mg/dl (2.12–2.57 mmol/l). To adjust for low albumin in nonionized values of calcium, use this formula: Corrected calcium = 0.8 × (4.0 – measured albumin) + reported calcium. If ionized calcium is being tested, it does not need to be adjusted for low albumin and normal value is 4.5–5.6 mg/ dl (1.11–1.30 mmol/l.

HEPATOTOXICITY

Anti-tubercular drug-associated hepatitis has a similar clinical appearance to acute viral hepatitis. Hepatotoxicity caused by antitubercular drugs might appear as asymptomatic transaminase elevations or severe liver failure. Hepatotoxicity can affect anywhere from 2% to 39% of people in different nations. The clinical presentation of anti-tubercular drug associated hepatitis is similar to that of acute viral hepatitis. Antitubercular drug induced hepatotoxicity can manifest as transitory asymptomatic rise in transaminases or acute liver failure. The frequency of hepatotoxicity ranges from 2% to 39% in different countries. When compared to the Western population, the Indian sub-population has a higher rate of hepatotoxicity. Hepatotoxicity caused by drugs was found to be 11.5 percent in the Indian population. However, according to a meta-analysis published in West, the risk is 4-28 percent[9]. The occurrence of drug-induced hepatotoxicity is unpredictably high, while certain people are at a larger risk than others. Advanced age, acute or chronic liver illness, alcoholism, HIV, indiscriminate drug use, malnutrition, hypoproteinemia, hypoalbuminemia, anaemia, past history of jaundice, and more advanced TB have all been linked to a higher frequency in underdeveloped nations. In 10-20% of these patients, isolated H treatment resulted in a threefold increase in alanine aminotransferase levels over normal. In 5% of patients with R, transient and asymptomatic elevations in serum levels of bilirubin and liver enzymes occurred[12]. The incidence of hepatitis was found to be 2.7 percent when H was utilised in conjunction with R. Cholestatic hepatitis occurred in 2.7 percent of patients taking R with H and 1.1 percent of patients taking R with anti-tubercular medications other than H. Z is the most hepatotoxic medication, with dose-dependent or idiosyncratic toxicity. Hepatitis has been reported infrequently in patients taking Linezolid (Lzd), Clofazimine (Cfz), and newer drugs such as Bdq and Dlm.

While on therapy, routine liver function testing is required since there may be a small transitory rise of transaminases that is normally asymptomatic, especially during the initial months of medication. A considerable increase in serum transaminases confirms the diagnosis of hepatitis, which is frequently symptomatic. Stop all anti-TB medications if liver enzymes are more than five times the upper limit of normal. If the liver enzymes continue to rise, a different reason must be considered. If the liver enzymes return to normal and the symptoms disappear, resume anti-TB treatment with the medications that are least likely to induce hepatotoxicity (Cm or aminoglycoside, FQ and Cs). The remaining hepatotoxic drugs (PAS,R, H, Z, Eto/Pto) can thereafter be continued one at a time for one week, with liver enzymes being checked at the end of each week. The problematic agent can then be identified in this manner.

NEPHROTOXICITY

The buildup of aminoglycosides in the renal tubules causes renal toxicity. Patients with a history of kidney illness and the elderly are more likely to experience such side effects. Other risk factors for renal damage include long-term use of aminoglycosides, hepatotoxicity, dehydration, hypotension, and concurrent use of nephrotoxic medications.While using S, the risk of nephrotoxicity

is low, at about 2%. Injectable medicines like Km and Am, as well as Cm, are more nephrotoxic than S, making MDRTB therapy difficult, with a reported prevalence of 1.2- 6.7 percent[13].Renal toxicity has been linked to E, Z, and Cs. In DR-TB patients with renal failure, newer medicines like Bdq and Dlm can be administered safely.

The treatment plan should be based on the advice of a nephrologist. Because of contributing factors such as diabetes, NSAIDs, and other medicines, dehydration, CHF, urinary obstruction, UTI, and prostate hypertrophy, an exact evaluation should be performed in order to confirm whether it is due to the drug or not, allowing a conclusive decision on drug discontinuation.Fluid promotion, avoidance of other nephrotoxic medicines, and other correctable risk factors can all help to lower the likelihood of toxicity.

OPTIC /RETROBULLAR NEURITIS

In the treatment of tuberculosis, E is a significant FLD. The ocular ADRs' of E treatment were first described in 1962 by Carr and Henkind et al. The most serious probable E. coli ADR is retro-bulbar neuritis.In most cases, it is reversible and is proportional to the dose and length of treatment, but it can infrequently become irreversible, resulting in permanent visual impairment, particularly in the elderly. When E is taken for more than 2 months, the reported incidence of retrobulbar neuritis is 18% in persons receiving more than 35 mg/kg/day, 5-6 percent with 25 mg/kg/day, and less than 1% with 15 mg/kg/day.H and SLDs like Lzd and capreomycin cause optic neuritis in a small number of people (Cm). Optical neuritis caused by Lzd is usually permanent. After the medicines have been withdrawn, the patient should be thoroughly checked by an ophthalmologist, and the distinction problem will be resolved. Control the glycaemic level if the patient is diabetic, as it can influence or precipitate a similar reaction.

OTOTOXICITY

The severity of hearing loss is determined by the length of therapy and the drug's dosage. Toxicity is caused by a loss of function or cellular deterioration of inner ear tissues. Many factors, such as age, dehydration, and drug-induced elimination inhibition, all raise the chance of the same, so it's important to think about them before starting any other treatment. If the treatment is not continued, the condition may deteriorate, leading to permanent hearing loss and deafness.

According to audiometry data, the rate of S-related ototoxicity could be as high as 25%.

In a cohort of 975 children treated with S sulphate for pulmonary TB, Prazic and Salaj et al discovered audiologically defined lesions in 36% of them.Infants born to tuberculosis moms who were treated with S during pregnancy have also been documented to have hearing loss[16]. There have also been reports of drug-induced toxicity running in families. In a large Indian study of patients with pulmonary TB treated with short-course chemotherapy regimens, 16.1% of those administered S had vertigo, which was severe in 5% of the cases. The drug had to be discontinued in 10% of these patients[18]. Approximately 20% of the dosage needed to be reduced. In a separate study of 1744 patients treated with various drugs, 10.3% developed S intolerance. The most common (46.8%) unfavourable reaction was involvement of the VIII cranial nerve.When ototoxicity was monitored regularly using pure tone audiometry, a high prevalence of ototoxicity (27.01%) was reported in Indian patients with DR-TB treated with injectable drugs[14].Hearing aids can be used to help patients with mild to moderate hearing loss if they benefit from them. As a last resort, cochlear transplantation can be performed to alleviate the patient's suffering. Concurrent use of loop diuretics in renally insufficient patients has also been observed to aggravate and precipitate hearing loss.

PERIPHERAL NEUROPATHY

Damage to nerves that carry messages from the brain and spinal cord to the rest of the body, or vice versa, is known as peripheral neuropathy. This can happen with a variety of antitubercular medications, but it's most prevalent with Cs, Lzd, and H, with Eto/Pto, FQ saminoglycosides, Cfz, Bdq, and E being the exceptions. After a lengthy period of use, linezolid can cause painful peripheral neuropathy and usually is non-reversible.

The depletion of pyridoxine, which is toxic to the nerve, occurs as a result of anti-TB medications' effect against Mycobacterium tuberculosis. Because isoniazid forms a compound with hydrazine and is eliminated in the urine, a relative deficit of physiologically active pyridoxine occurs. LZD induces peripheral neuropathy by disrupting mitochondrial activity in neurons and the diagnosis is based on clinical assessment.

The incidence is roughly 1.1 % in the general population, but it is 6% in the elderly, and all patients should receive pyridoxine daily to prevent peripheral neuropathy. Pyridoxine prophylaxis is usually 50 mg daily (for every 250 mg of Cs) in all patients taking Cs and Lzd, and 10 mg in patients receiving H who are at risk of peripheral neuropathy. Lzd is the most common offending substance, with 60-70% of patients taking 600 mg/day developing PN, while pyridoxine has no effect in preventing Lzd-induced PN. As a result, if H is being used, it should be discontinued and, if possible, the aminoglycoside switched to Cm. Reduce the dose of Cs without jeopardising the regimen. Other contributing factors, such as diabetes or malnutrition, should be considered, as well as physical treatment, which may be beneficial to the patient.

Begin medical treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol. If the symptoms persist, begin with 25 mg of amitriptyline at night for one week, then 50 mg HS the following week, and gradually increase to a maximum of 150 mg per day. SSRIs and TCI antidepressant medications are not advised. In extreme situations, carbamazepine can be started at 200 mg once daily for one week, then 200 mg BD for one week, and finally 200 mg three times a day. Only if an alternative treatment is available and the regimen is not jeopardised may the prescription be stopped.

PSYCHOTIC SYMPTOMS

Isoniazid, cycloserine, ethambutol, and fluoroquinolones can all cause psychosis. Ethambutol-induced psychosis is uncommon. Visual or auditory hallucinations, delusions, paranoia, and strange thoughts are common symptoms. Caregivers should be familiar with these symptoms in order to detect them early.

The modulation of N-methyl-D-aspartate receptor (NMDAR) antagonists and partial agonism by the drug at the NMDAR associated glycine site is one possible mechanism for cycloserine-induced psychosis. Isoniazid causes vitamin B6 deficiency, which disrupts normal tryptophan metabolism. Ethambutol also inhibits the activity of pyridoxal-5-phosphate, resulting in a depletion of GABA and other synaptic transmitters, leading in psychotic symptoms. The specific mechanism of ethambutol-induced psychosis is unknown at this time.

Psychosis affects roughly 12% of people, and while having a history of psychiatric disease is not a contraindication to using the above drugs, it does raise the risk of acquiring psychotic symptoms during treatment.Always monitor the patient's creatinine level while taking Cs, as a loss in renal function can lead to toxic Cs levels, which can lead to psychosis. To avoid neurological symptoms, pyridoxine should be taken in a daily dose of no more than 200 mg.

QT PROLONGATION/CARDIACTOXICITY

QT prolongation on electrocardiogram (ECG) has been reported with FQs, particularly moxifloxacin (Mfx), macrolides such as Clarithromycin (Clr), Cfz, Bdq, and Dlm. Elderly, female sex, underlying cardiac disorder (both congenital and acquired), electrolyte imbalance, and concurrent use of ancillary medications are all risk factors for QTc prolongation. Bdq is a reasonably well-tolerated medicine, according to a systematic search, since it was discontinued in just 3.4% and 0.6% of patients, respectively, due to ADRs and QTc prolongation[17].

Stop all suspicious medicines and confirm the QT prolongation with an ECG if the QTc value is >500ms. In an increased state, keep serum electrolytes within normal limits. Check to see whether any additional supportive therapy medicines have a QT-prolonging effect; if so, cease taking them and assess your renal and hepatic function. The ECG should be observed before treatment, and if any QT prolongation medicines are given for the first four weeks, the ECG should be evaluated monthly. Many psychotic medicines, prokinetics, 5-HT3 receptor antagonists, antifungals, and other drugs will induce and trigger the reaction, therefore try to avoid taking them together. Also, rule out any other possible reasons of the reaction and treat them as needed.

RASH, ALLERGIC REACTION AND ANAPHYLAXIS

Any of the anti-tubercular medications can cause hypersensitivity reactions. Isoniazid (H), rifampicin (R), and pyrazinamide (P) are the most prevalent agents that can induce allergic responses (Z). Reactions occur at a rate of 4–6% of the time. An allergic reaction such as pruritus, flu-like syndrome, angioedema, urticaria, shock, and shortness of breath are common symptoms of hypersensitivity reactions.

Antibody-mediated immune reactions, also known as type B reactions, are the mechanism at work. They are dose-dependent and can occur at any point during treatment.

INH and R cause allergic reactions because of their metabolites (monoacetyl hydrazine and desacetyl rifampicin).

Antihistamines are commonly used to treat these responses, which occur 61.5% of the time. It can be treated symptomatically in mild cases. However, in the case of severe allergic responses, rule out any other possible causes that aren't related to medications. All therapy will be stopped if there is no evident explanation, and an antihistamine will be given up to 3-4 times daily.

A parenteral corticosteroid (dexamethasone IM or IV 2-4mg 4 times daily) may be given in the case of a severe widespread rash. The flushing reaction to R or Z is typically modest and goes away with time. Hydrocortisone cream for localised rash and prednisone in a low dose of 10-20 mg/day for several weeks may also be used to treat minor dermatological responses. Tyramine-containing foods (cheese, red wine) can cause hot flushes and itchiness. Any medicine that causes Steve Johnson syndrome should never be used again, not even as a test. Table 3 shows the TB drug's most demanding dose.

Table 3: Dose of Rechallenging.10

Drug	Day 1	Day 2	Day 3
H	50 mg	Full dose	
R	75 mg	300 mg	
Z	250 mg	1000 mg	
Eto/Pto	125 mg	250 mg	
FQ	50 mg	200-250 mg	Full dose
Cs	125 mg	250 mg	
E	100 mg	500 mg	
PAS	1 g	4 g	
Cm, Am, Km	125 mg	500 mg	

OTHERS

Hyperthyroidism, myalgia, pancreatitis, and other ADRs can occur as a result of DR-TB treatment. To determine the efficacy and safety of medications, continuous monitoring and evaluation should be carried out in all cases. This will aid in determining the occurrence, cause, drug identification, and, ultimately, prevention.Treatment should be controlled correctly based on the induced ADR.

In some circumstances, the medicine should be stopped or withdrawn, while in others, it may be continued.

Table 4: Basic management of ADR.

ADR	Management
Arthralgia	Lower the dose or discontinue the suspected agent
Electrolyte imbalance	Withhold; supportive therapy
Gastritis and Abdominal pain	Withheld
Haematological Abnormalities	Stop drug in severe cases; No reintroduction; Supportive therapy
Hearing loss	Withheld/adjust/stop accordingly; substitution; hearing aid, surgery
Hepatitis	Stop the drugs
Nephrotoxicity	Withheld/adjust/stop accordingly; substitution
Optic neuritis	Stop the drug; Resolved when drug stops; ophthalmologist consultation
Peripheral neuropathy	Correct the vitamin deficiencies
Psychotic symptoms	Stop the suspected drug for a short period
QT prolongation	Maintain electrolytes; If QTc > 500ms stop the drug; Hospitalisation
Rash, allergic reaction, Anaphylaxis	Rechallenge and dechallenge the drugs to identify the offending agent.

Table 5: Some of the Recommended Drugs for the ADR Management.

ADR	Suggested Drugs for Management
Arthralgia	NSAIDs, Codeine
Electrolyte imbalance	Electrolyte supplement- oral/IV/ diet- Amiloride, spironolactone
Gastritis and Abdominal pain	H-2 blockers, PPIs, Avoid antacids
Hematological Abnormalities	Supplements
Headache	Ibuprofen or paracetamol
Hepatitis	Supportive therapy
Nausea and Vomiting	Fluid intake, Domperidone, omeprazole, Ondansetron, metoclopramide, prochlorperazine, promethazine
Peripheral neuropathy	Pyridoxine(neurological prophylaxis); amitriptyline
Psychotic symptoms	Antipsychotic therapy
Rash, allergic reaction, anaphylaxis, itching, hypersensitivity	Anti-histamines, hydrocortisone cream, calamine lotions, corticosteroids

Many therapies have failed owing to ADR, necessitating thorough education and knowledge transfer to patients about ADR in TB, which will undoubtedly aid in the disease's spread and control.To further limit the risk of tuberculosis, both patients and treatment providers should be informed of this basic therapy pattern.

Tables 4 and 5 provide a summary of therapy and medicines that can be used to treat some ADRs. Even if there are numerous management policies, all ADR should be addressed based on the characteristics of each patient (age,comorbidities, gender, other medications, etc.)

CONCLUSION

One of the most pressing and difficult concerns facing global TB control is the spread of MDR-TB. Anti-TB drug related adverse events (ADRs) might be lethal if not appropriately treated. The ADRs will reduce both treatment compliance and success rates. Adverse reactions can be identified and managed more effectively when patients are monitored on a regular basis.The management is based on individual ADR, can treat symptomatically, withhold the drug or withdraw the drugs.

ABBREVIATIONS

H: Isoniazid; E: Ethambutol; Z: Pyrazinamide; R: Rifampicin; S: Streptomycin; Km: Kanamycin; Am:Amikacin; Cm: Capreomycin; FQs: Fluoroquinolones;Bdq: Bedaquiline; Dlm: Delamanid; Lzd: Linezolid;Cs: Cycloserine; Cfz: Clofazimine; PAS: Para amino salicylic acid; Eto: Ethionamide; Pto: Prothionamide;TB: Tuberculosis; LTBI: Latent TB infection; DR:Drug-resistant; XDR: Extensive drug-resistant; ADR:Adverse drug reaction; MDR: Multidrug resistant tuberculosis; NMDAR: N-methyl-D-Aspartate receptors;PMDT: Programmatic management of drug-resistant tuberculosis; ATT: Antituberculous therapy; Gfx:Gatifloxacin; OD: Once daily; BD: Twice daily; PO: Per oral; PN: Peripheral neuropathy; Amx/Clv: Amoxicillin/Clavulanic acid; Amk: Amikacin; HS: At bed time; Cl:
Clarithromycin; SSRIs: Selective serotonin reuptake inhibitors.

REFERENCEs

[1] Centers for Disease Control and Prevention. Tuberculosis: Basic TB facts. 2012 Waghmare MA, Utpat K, Joshi JM. Treatment outcomes of drug-resistant pulmonary tuberculosis under programmatic management of multidrugresistant tuberculosis, at tertiary care center in Mumbai. Medical Journal of Dr.DY Patil University.2017;10(1):41.

[2] World Health Organization. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Geneva, Switzerland: WHO.2012.

[3] Wilke RA, Lin DW, Roden DM, Watkins PB, Flockhart D, Zineh I, Giacomini KM, Krauss RM. Identifying genetic risk factors for serious adverse drug reactions: Current progress and challenges. Nature Reviews Drug Discovery.2007;6(11):904-16.

[4] Adverse Drug Reactions in Drug-Resistant Tuberculosis Management: A Clinical Approach Leya P Babu, Johnson V Babu, Shaji George, Nimmy Robin, Joicy Jose

[5] Putting in harm to cure: Drug related adverse events do not affect outcome of patients receiving treatment for multidrug-resistant Tuberculosis. Experience from a tertiary hospital in Italy
Gina Gualano,Paola Mencarini, Maria Musso,Silvia Mosti, Laura Santangelo,Silvia Murachelli, Angela Cannas, Antonino Di Caro,Assunta Navarra,Enrico Girard,Fabrizio Palmieri, Delia Goletti

[6] Incidence and predictors of major adverse drug events among drug-resistant tuberculosis patients on second-line antituberculosis treatment in Amhara regional state public hospitals; Ethiopia: a retrospective cohort study Mehari Woldemariam Merid, Lemma Derseh Gezie, Getahun Molla Kassa, Atalay Goshu Muluneh,Temesgen Yihunie Akalu and Melaku Kindie Yenit

[7] Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis Kathryn Schnippe,Cynthia Firnhaber,Rebecca Berhanu,Liesl Page-Shippand Edina Sinanovic

[8] Adverse drug reactions in tuberculosis management
Rajendra Prasad, Abhijeet Singh, Nikhil Gupta

[9] Treatment outcomes and adverse reactions in patients with multi drug-resistant tuberculosis managed by ambulatory or hospitalized care from 2010-2011 in Tashkent, Uzbekistan Lola Kalandarov, Mirzagaleb Tillashaikhov,Nargiza Parpieva,Shoiba Saidova,Natavan Alikhanova, Rony Zachariah,Davron Mukhtarov, Sarvar Alidjanov, Jamshid Gadoev,Anthony D Harries

[10] Adverse Drug Reaction in Treatment of Multidrug Resistant Tuberculosis Rajendra Prasad, DSc; Abhijeet Singh, MD; Rahul Srivastava, MD; Ramawadhsingh Kushwaha, MD; Rajiv Garg, MD; Giridhar Belur Hosmane, MD; Amita Jain, MD

[11] Adverse Reactions to Antituberculosis Drugs in Iranian Tuberculosis PatientsAliasghar Farazi, Masoomeh Sofian,Mansoureh Jabbariasl,and Sara Keshavarz

[12] Assessment of incidence and severity of adverse drug reactions in multidrug resistant tuberculosis patients G.Akhil, T.Hussain Naik Authors Dr P.Manjula,G. Nikhitha

[13] Ambispective study of adverse drug reactions in multi-drug resistant tuberculosis patients in Warangal, Telangana *Safurah Fatima, Maria Fatima Syeda, Nagesh Adla, Rama Devi*

[14] Management of multidrug resistant tuberculosis (MDR-TB) – Monitoring is the key to successful Outcome J.S. Akshata ,Anushree Chakrabarthy

[15] Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis Rajendra Prasad,Abhijeet Singh, Rahul Srivastava, Giridhar B. Hosmane,Ram Awadh Singh Kushwahaa, Amita Jain B

[16] Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis
Kwonjune J. Seung, Salmaan Keshavjee, and Michael L. Rich

[17] Mandovra NP, Lele TT, Vaidya PJ, Chavhan VB, Leuppi-Taegtmeyer AB, Leuppi JD, et al. High Incidence of New-Onset Joint Pain in Patients on Fluoroquinolones as Antituberculous Treatment. Respiration. 2020. 17.

[18] Diagnosis and treatment of multidrug-resistant tuberculosis
Jong Geol Jang, Jin Hong Chung

[19] Multidrug-resistant tuberculosis (MDR-TB):epidemiology, prevention and treatmentL. P. Ormerod.

[20] Does directly observed therapy (DOT) reduce drug resistant tuberculosis? Patrick K Moonan, Teresa N Quitugua,Janice M Pogoda, Gary Woo, Gerry Drewyer,Denise Dunbar, Kenneth C Jost Jr,Charles Wallace, Stephen E Weis, Behzad Sahbazian

[21] Tuberculosis: A disease without boundaries Nicole Fogel

[22] Adverse Drug Reactions of Anti‐Tuberculosis Treatment among Children with Tuberculosis Madeeha Laghari,Bandeh Ali Talpur,Syed Azhar Syed Sulaiman,Amer Hayat Khan, Zohra