WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 4, 1161-1178. Review Article ISSN 2277–7105

A STUDY ON ADVERSE DRUG REACTIONS OF ANTITUBERCULAR DRUGS IN TREATMENT OF TUBERCULOSIS: A NARRATIVE REVIEW

SK. Arshiya Kowser[1]*, B. Bhavani[1], K. Evangil[1], K. Amulya[2], M. Venkata Rao[3] and K. Padmalatha[4]

[1]V Year Pharm.D, Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, NTR District, Andhra Pradesh, India.
[2]Assistant Professor, Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, NTR District, Andhra Pradesh, India.
[3]Professor & HOD, Department of Pulmonology, Government General Hospital, Vijayawada – 520 003, NTR District, Andhra Pradesh, India.
[4]Principal, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, NTR District, Andhra Pradesh, India.

Article Received on
23 December 2024,
Revised on 13 Jan. 2025,
Accepted on 03 Feb. 2025
DOI: 10.20959/wjpr20254-35534

***Corresponding Author**
SK. Arshiya Kowser
V Year Pharm.D,
Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, NTR District, Andhra Pradesh, India.

ABSTRACT

Drug-sensitive tuberculosis (DS-TB) requires treatment with 1st-line drugs whereas drug-resistant TB (DR-TB) are treated with combination of 2nd-line drugs and fewer 1st-line drugs. Adverse drug reactions (ADRs) to these drugs are quite evident as they are being used for longer duration. The overall prevalence of ADRs with 1st-line drugs and 2nd-line drugs are estimated to vary from 8.0 - 85 and 69 - 96%, respectively. Most ADRs are observed in the intensive phase as compared to continuation phase. Major concerns exist regarding treatment of DR-TB patients, especially with 2nd- line drugs having lower efficacy more toxicity and high cost as compared to 1st-line drugs. A variety of ADRs may be produced by anti-TB drugs ranging from mild or minor to severe or major like gastrointestinal toxicity (nausea/vomiting, diarrhoea and hepatotoxicity), ototoxicity, neurotoxicity (peripheral neuropathy and seizures), nephrotoxicity, cutaneous toxicity and cardiotoxicity. Most of ADRs are minor and can be managed without discontinuation of treatment. Few ADRs' can be major causing life-threatening experience leading to either

modification or discontinuation of regimen and even mortality. A careful monitoring of ADRs during the treatment with anti-TB drugs and early recognition and appropriate management of these ADRs might improve adherence leading to favorable outcome.

KEYWORDS: Tuberculosis (TB) Adverse drug reactions (ADRs), Drug-sensitive TB (DS-TB), Drug- resistant TB (DR-TB), Anti-TB drugs; 1st-line drugs, 2nd-line drugs.

INTRODUCTION

India features among the 30 high-tuberculosis (TB) burden countries and has accounted for an estimated one-quarter (27%) of all TB cases worldwide.[1] Drug-sensitive TB (DS- TB) is treated with regimens containing multiple 1s-line drugs; such as Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E), whereas 2nd-line drugs and few 1s-line drugs are reserved for treatment of drug-resistant TB (DR-TB). Good bacteriological diagnosis and compliance to treatment remains 2 - main pillars of successful treatment of TB. An adverse drug reaction (ADRs) has been defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in human for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.[2] Patients may encounter with a variety of ADRs when managed with anti-TB drugs. ADRs cause significant morbidity and even sometimes mortality if not detected early.[3-5] Major concerns exist regarding treatment of DR-TB patients, especially with 2nd-line drugs having lower efficacy, costly and more toxic as compared to 1s-line drugs. Most of ADRs are mild or minor and can be managed without discontinuation of treatment. Few ADRs can be severe or major causing life- threatening experience leading to discontinuation or modification of treatment that may require hospitalization and even mortality if unrecognized and untreated promptly. Various factors, such as timing of occurrence of ADR, pattern of illness, results of laboratory tests, rechallenge with type, dosing or timing of drugs administration, patient age, nutritional status, the presence of preexisting diseases or dysfunctions (Such as impaired liver function, impaired kidney function, human immunodeficiency virus (HIV) coinfection and alcoholism), might be attributed to causality of ADRs.[6] Therefore, continued surveillance of ADRs is essential particularly in DR-TB cases where early detection and timely management of ADRs might determine successful outcome. This review aims to highlight the estimated burden and management strategies of various ADRs associated with anti-TB drugs among patients undergoing treatment of TB.

Epidemiology of ADRs of 1st-Line Drugs: The data on global prevalence of ADRs with 1st-line drugs is scarce. The global prevalence of ADRs is variable ranging from 8 – 85 %.[3, 7-13] The reasons for the difference in the prevalence of ADRs might be related to several possible factors, such as differences in definitions of ADRs terminologies, as adopted by physicians, whether the ADRs were 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 ADRs were studied, associated comorbidities, such as diabetes and HIV coinfection and variations in the use of specific anti-TB drugs including dosage, and also pharmacological interactions with other group of drugs comprising antiretroviral therapy (ART), oral hypoglycemic agents and also ancillary medications used for management of ADRs. A study conducted in Nigeria observed that around 14 and 13% incidences of ADRs at 6 and 8 months, respectively, among patients receiving directly observed treatment (DOTs) and short-course DOTs.[10] Brazilian National Ministry of Health reported the incidence of minor or mild ADRs in patients treated with the former 1st-line drugs to range from 5 - 20%.11 It was also observed that major or severe ADRs' were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics) and led to the discontinuation or alteration of the treatment. There was no difference in incidence of ADRs among patients having intermittent and daily intake of anti-TB drugs.[14] ADRs were more prevalent in intensive phase than continuation phase. The overall prevalence of ADRs with FLDs is estimated to vary from 2.3 - 17% in various Indian studies.[7,15-17]

A study conducted by Mehrotra observed that the prevalence of ADRs in the initial intensive phase was 17.39%.[15] Another study conducted at a tertiary institute in Calcutta observed that the overall toxicity was found in 35% cases in the daily regimen group, whereas it was found to be 27.9% in the intermittent regimen group.[18] Data regarding prevalence of ADRs are still scarce and further surveys are required from different geographical areas of India in near future.

Epidemiology of ADRs Treated with 2nd-line drugs: The management of multidrug resistant (MDR)-TB patients has been considered to be complicated and challenging because of prolonged duration of 24 - 27 months of treatment and high-toxicity profile of 2nd-line drugs. The prevalence of ADRs observed in various studies conducted worldwide ranged from 69 - 96%.[19-23] Reasons for the difference in the prevalence of ADRs are almost similar

to that of 1st-line drugs except the fact that regimens for DR-TB contains repurposed drugs like Linezolid (Lzd) and Clofazimine (Cfz), as well as newer drugs such as Bedaquiline (Bdq) and Delamanid (Dlm). The observed frequency of specific gastrointestinal (GI) ADRs (0.5–100%) followed by ototoxicity (12–70%) among patients receiving 2nd-line drugs. Tinnitus has been reported in 5 - 45% of patients whereas deafness in 6.7 - 33% patients. Ototoxicity is predominantly associated with the use of injectable aminoglycosides such as Kanamycin (Km). There is possibility of additive effects of interaction with other concomitant and potentially ototoxic drugs that were used in the regimen such as Ofloxacin (Ofx) and Cycloserine (Cs). This warrants further investigation to uncover the possibility of these interactive effects. 2nd- line drugs have reported to cause severe ADRs that have led to interruption of treatment in 19 - 60% of MDR-TB patients.[19-23] The estimated high prevalence was due to early identification and aggressive management strategies adopted by national health programs. A study from Iran reported deafness and headache/psychosis occurring due to injectable Km and Cs, respectively, as major ADRs that required frequent discontinuation and/or substitution.[23] MDR-TB patients should be managed aggressively for ADRs during therapy, especially for ototoxicity and psychiatric disorders. Very few have specifically reported frequency of ADRs in India.[19,24-28] A study conducted in Tamil Nadu reported ADRs associated with standardized treatment in 86.8% patients.[25] Severe ADRs' requiring either a reduction of dosage or termination of the offending drug(s), such as Ethionamide (Eto), Ofx, Km and Cs were observed in 58% patients. Higher incidence of ADRs associated with 2nd-line drugs has been reported in HIV patients with MDR-TB coinfection. A study conducted in Mumbai among 67 HIV and MDR-TB coinfected patients treated with anti-TB treatment, as well as ART and reported that ADRs were more frequent in this cohort with 71, 63 and 40% of patients experiencing one or more mild, moderate or severe ADRs, respectively.[26] ADRs, such as GI disturbances (45%), peripheral neuropathy (38%), hypothyroidism (32%), psychiatric symptoms (29%) and hypokalemia (23%) were reported more frequently among this cohort. Eleven patients required hospitalization and permanent discontinuation of one or more offending drugs that were observed in 40% patients. No ADRs led to indefinite suspension of an entire MDR-TB or ART regimen. A study reported 46.9% of 98 MDR-TB patients experiencing at least one ADRs.[28] ADRs observed most frequently were nausea/vomiting in 24 (24.5%) patients, hearing disturbances in 12 (12.3%) patients, dizziness/vertigo in 10 (10.2%) patients and arthralgia in 9 (9.2%) patients. Seventeen (17.4%) patients had major ADRs requiring change or stoppage of drugs that included ototoxicity (6.1%), headache and psychosis (4.1%), GI

intolerance and hypothyroidism (3.1%), as well as arthralgia and hepatitis (4.1%).[28] Agents responsible for these ADRs were Km (ototoxicity), Cs (headache/psychosis), Eto (GI tolerance/hypothyroidism) and Z (arthralgia/hepatitis). However, no mortality was observed due to occurrence of ADRs. Further studies are required for prevalence of ADRs' in near future.

Specific ADRs Associated with Anti-TB Drugs

Nausea/Vomiting - GI symptoms are one of the most common ADRs seen with intake of anti-TB drugs. Its severity can range from mild symptoms like nausea and vomiting to life-threatening complications. All the 1st-line drugs can cause mild GI upsets that can be managed symptomatically without change in dosage of drugs. In a study of 893 patients by Shinde *et al.,* it was found that GI upset with nausea, vomiting and abdominal pain were the most common ADRs seen in 12.5% of patients.[29] In another prospective study from China, it was found that GI ADRs were seen in 3.74% of 4,304 patients and only 7 patients required hospital admissions.[30]

Hepatotoxicity - The clinical presentation of TB drug associated hepatitis is similar to that of acute viral hepatitis. Anti-TB drug-induced hepatotoxicity can manifest as transitory asymptomatic rise in transaminases or acute liver failure. The frequency of hepatotoxicity ranges from 2 - 39% in different countries.[31] An increased incidence of hepatotoxicity has been observed in Indian subpopulation when compared to Western population.[32,33] The occurrence of drug-induced hepatotoxicity is unpredictable though certain patients are at a relatively higher risk than other populations. The incidence has been reported to be higher in developing countries and factors, such as advanced age, acute or chronic liver disease, alcoholism, HIV, indiscriminate use of drugs, malnutrition, hypoproteinemia, hypoalbuminemia, anemia and prior history of jaundice and more advanced TB has been implicated.[34,35] Isolated H administration resulted in a 3-fold increase in alanine aminotransferase (ALT) levels over the normal in 10 - 20% of these patients.[33,36] Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occurred in 5% of patients with R. When H was used in combination with R, the incidence of hepatitis was observed to be 2.7%. Cholestatic hepatitis occurred in 2.7% of the patients receiving R in combination with H and was 1.1% when R was received in combination with TB drugs other than H.[33] Z is the most hepatotoxic drug with toxicity being either dose-dependent or idiosyncratic.[37,38] Hepatotoxicity has also been reported with 2nd-line drugs but with lesser

frequency as compared to 1st-line drugs. The incidence of hepatotoxicity is 2 - 3% with fluoroquinolones (FQs) with fulminant involvement <1%, whereas it is 1 - 2% with Eto/Prothionamide (Pto) and 0.3% with Paraamino salicylic (PAS) acid.[39,40] Hepatitis has been rarely reported with Lzd, Cfz and newer drugs such as Bdq and Dlm.[41]

Peripheral neuropathy - Peripheral neuropathy occurs in approximately 20% of patients treated with H.[42] The other anti-TB drug known to cause peripheral neuropathy is E, but very rare in comparison to H. In the existing literatures also, occurrence of peripheral neuropathy is considered rare with the recommended doses of H used in DOTS strategy. Peripheral neuropathy has also been associated with Lzd, Eto, Cs and rarely FQs.[43]

Psychiatric disorders - H-related psychiatric disorders can manifest as psychosis, obsessive- compulsive neurosis, seizure, mania, loss of memory and death.[44] The mechanism of production of H-related psychiatric disorders is not clearly known, but H is known to interfere with several metabolic processes essential for the normal functioning of the neuron. H causes deficiency of vitamin B6 by causing excessive excretion of the vitamin, which in turn leads to a disturbance of normal tryptophan metabolism. There is great variability in the clinical features of H-induced psychosis in the various reported cases. Jackson, in 1957, reported 5 - cases of H-induced psychosis that presented with excessive argumentation, mental depression, euphoria, grandiose ideas and complex delusions; none of these patients had any previous history of mental illness.[45] Cs has been associated with diverse neuro-psychiatric ADRs most common being psychosis reported in >10% patients. Other ADRs, such as anxiety, headaches and seizures, were reported in 1 - 10% of patients and insomnia, suicidal ideation in <1% of patients. Eto has reported to cause giddiness and headache in 1 - 10% of patients and rarely mental disturbances in <1% of patients. FQs has reported to cause dizziness, headaches and insomnia in 1 - 10%, whereas it can cause or lower threshold for seizures in <1% patients.[46]

Optic/Retrobulbar neuritis - E is one of the important 1st-line drugs in the treatment of TB. Retrobulbar neuritis is the most important potential ADR from E. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability, especially in the older population.[47] The reported incidence of retrobulbar neuritis when E is taken for more than 2 months is 18% in patients receiving greater than 35 mg/kg/day, 5 - 6% with 25 mg/kg/day and <1% with 15

mg/kg/day.[48] Optic neuritis is observed rarely with H and SLDs such as Lzd and Capreomycin (Cm).[49,50] Lzd induced optic neuritis is usually irreversible.

Ototoxicity - Streptomycin (S) predominantly affects the vestibular system, whereas Km and Cm affects predominantly cochlear apparatus. Audiometry data suggest that the incidence of S associated ototoxicity may be as high as 25%.[51] In a large Indian study with short course chemotherapy regimes in the treatment of patients with pulmonary TB, 16.1% of the patients given S developed vertigo which was severe in 5% cases.[52] In 10% of these patients, the drug had to be stopped. Reduction of dosage was needed in about 20% cases. Ototoxicity was observed in 10.12% patients within 3.8 ± 2.6months of treatment initiation with or without audiometry assessment.[53] High prevalence of ototoxicity (27.01%) was reported in Indian patients with DR-TB treated with injectable drugs when ototoxicity was monitored regularly using pure tone audiometry.

Immunological and Hematological ADRs - R has been associated with immune mediated thrombocytopenic purpura and hemolytic anemia, especially with intermittent dosing. In a Brazilian study, R-induced thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acute interstitial nephritis and septic shock occurred in 0.1% of the patients.[33,54] However, a few Asian studies reported allergic reactions with 1st-line drugs to be between 2.02 and 2.35% and hematological ADRs to be 0.1 - 0.7%. We on hematological abnormalities during therapy found that thrombocytopenia, characterized by a rapid lowering of the platelet count in sensitive individuals was observed. Generally, the most common offending agent for the causation of thrombocytopenia secondary to anti-TB drug is R.[54,55] Isolated case reports showing thrombocytopenia following administration of Z, H and E are found in literature and are attributed to an immunological phenomenon.[54-57] S is very rarely implicated as a cause of thrombocytopenia. Lzd has reported to be associated with hematological ADRs most common being thrombocytopenia with reported incidence as high as 11.8%.[58] Other ADRs like pancytopenia and myelosuppression are less common as compared to thrombocytopenia. These hematological ADRs are dose-dependent and usually reversible with clinical management.

Arthralgia - Z and E are 2 -TB drugs that have been reported to induce hyperuricemia in non-gouty patients leading to arthralgia.[59] The metabolite Pyrazinoic acid is likely responsible for the hyperuricaemic effect. The mechanism is related to pyrazinoic acid, the principal metabolite of Z getting further oxidized by xanthine oxidase that inhibits the renal

tubular secretion of uric acid. Hyperuricemia has been reported in 43 - 100% of patients treated with Z (alone or in combination).[60] Gouty attacks have also been associated with patients taking Z and E, as this combination can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than Z alone. Arthralgia has been reported with FQs particularly Lfx and Bdq containing regimens for DR-TB.[61,62]

Renal toxicity - Aminoglycosides produce renal toxic effects due to their accumulation in the renal tubules. Such effects are more common in elderly individuals and in patients with a history of kidney disease. Prolonged use of aminoglycosides, hepatotoxicity, dehydration, hypotension and concurrent use of nephrotoxic drugs are other risk factors for renal toxicity. The risk of nephrotoxicity is less and range around 2% while using S.[63,64] Injectable drugs such as Km and Am, as well as Cm are more nephrotoxic as compared to S making treatment for DR-TB cases challenging with reported incidence of 1.2 - 6.7%.[65] E, Z and Cs have been reported to cause renal toxicity. Newer drugs such as Bdq and Dlm can be used safely in DR-TB patients with renal failure.

Cutaneous ADRs (CADRs) - Z has been described to cause various skin reactions like maculopapular rash, erythema multiforme, exfoliative dermatitis, drug rash and eosinophilia with systemic symptoms (DRESS) syndrome. Among the 1st-line drugs, Z is the commonest cause of CADRs (2.38%), followed by S (1.45%), E (1.44%), R (1.23%) and Z (0.98%).[66] It is not uncommon for exfoliative dermatitis to occur with more than 1 of the 4 - above drugs. The incidence of E-induced rash is found to be 0.5%. The author (R.P.) reported a rare occurrence of exfoliative dermatitis secondary to E and Z in an 18-year-old female.[67] Patients receiving H can develop antinuclear antibodies during the use of the drug. Less than 1% develops systemic lupus erythematosus (SLE), the incidence of which is the same in both genders. H administration can also worsen preexisting lupus. Rash has also been reported with any SLDs including newer ones Bdq and Dlm.[68]

Cardiotoxicity (QTc Prolongation) - QTc prolongation on electrocardiogram (ECG) has been reported with FQs particularly moxifloxacin (Mfx), macrolides such as Clarithromycin (Clr), Cfz, Bdq and Dlm.[69] Risk factors for QTc prolongation include elderly, female sex, underlying cardiac disorder including congenital and acquired, electrolyte imbalance and concurrent use of ancillary medications. A systematic search showed that Bdq is arelatively well-tolerated drug, as its discontinuation occurred in only 3.4 and 0.6% of

patients due to ADRs and QTc prolongation, respectively.[69]

Miscellaneous ADRs: Few case reports on H and Eto/Pto induced gynecomastia and alopecia among patients treated with TB therapy.[70] A rare occurrence of anaphylactic shock due to S was also reported.[71] Metallic taste has been reported with Eto/Pto and FQs.[33,43] Lactic acidosis has been associated with Lzd.[33,43]

Table 1: Adverse drug reactions of first line antitubercular drugs.

Drug	Common adverse drug reactions	Rare adverse drug reactions
Isoniazid (H)	Peripheral neuropathy, Hepatotoxicity, Cutaneous reaction, Nausea and vomiting	Anemia, Arthralgia, Dysarthria, Irritability, Seizure, Psychosis, Depression, Dysphoria, Lupoid reaction, Pellagra, Vasculitis, Thrombocytopenia, Optic neuritis,
Rifampicin (R)	Anorexia/nausea/vomiting, Hepatitis, Isolated jaundice, Sub- clinical unconjugated hyperbilirubinemia, Orange staining of body fluids.	Flu-like syndrome, Thrombocytopenia, Hemolytic anemia, Acute renal failure (majority with intermittent dosing), Pseudomembranous colitis, Pseudo adrenal crisis, Cutaneous reaction.
Ethambutol (E)	Retrobulbar/optic neuritis Nausea and vomiting	Arthralgia, Peripheral neuropathy, Thrombocytopenia, Cutaneous reaction, Acute renal failure.
Pyrazinamide (Z)	Arthralgia, Hepatotoxicity, Nausea and vomiting	Gastrointestinal reaction, Cutaneous reaction, Sideroblastic anemia, Thrombocytopenia, Photosensitivity.
Streptomycin (S)	Vestibular and auditory nerve damage, Nephrotoxicity, Cutaneous reaction, Pain, induration at site of injection.	Hypersensitivity reaction, Anaphylactic shock, Hemolytic anemia, Aplastic anemia, Agranulocytosis, Thrombocytopenia, Electrolyte abnormalities including hypokalemia, hypocalcemia and hypomagnesemia.

Management of ADRs: Management of ADRs associated with TB drugs is considered to be an essential component in order to achieve adequate adherence leading to favorable outcome particularly for DR-TB patients treated with toxic 2nd-line drugs. Principles of Pharmacovigilance (PV) have been adopted by the National TB Control Programmes all over the world. PV is defined by the World Health Organization (WHO) as the "science and activities relating to the detection, assessment, understanding and prevention of ADRs or any other drug-related problem".[72] The objective is to improve patient care by assessing both risk and benefit received from the drug. Routine surveillance of ADRs according to a framed protocol is an integral part of the National Programmes which should be performed by

symptom-based reporting followed by laboratory investigations at baseline and as when clinically indicated. Occult ADRs should be detected timely by laboratory investigations in order to prevent unrecognized serious effects. Monitoring should be frequent and more intense, particularly in high-risk groups, such as elderly, HIV or hepatitis coinfection, alcoholism, drug addiction, anemia, any preexisting illnesses, diabetes mellitus (DM), hypoalbuminemia, malnutrition, chronic kidney disease (CKD), chronic liver disease (CLD), disseminated involvement, family history of frequent ADRs or atopy/alleges and use of ancillary medications and ART or medications for treating opportunistic infections with high probability of drug interactions.

A grading system has been devised to assess severity of all types of ADRs in order to maintain accuracy and consistency in surveillance.[73]

This system includes 5 - grades as follows

Grade 1: mild symptoms requiring only observation and no intervention;

Grade 2: moderate symptoms requiring medical intervention such as ancillary drugs;

Grade 3: severe symptoms with inability to carry social or functional activities requiring medical intervention or even hospitalization;

Grade 4: life-threatening symptoms with inability to perform basic health care requiring medical intervention or hospitalization in order to prevent permanent impairment, disability or deaths; and

Grade 5: mortality associated with ADR(s).

Concept of active TB drug-safety monitoring and management (aDSM) has been introduced by WHO to provide active surveillance for detection of major or severe ADRs associated with novel DR-TB regimens and newer drugs by systematic clinical and laboratory assessment.[74, 75]

Management of ADRs in TB and HIV Co-infection - HIV patients experience more frequent ADRs to both TB and other non-TB medications for other opportunistic infections and the risk of ADRs enhances with the degree of immunosuppression.[20,21,26] Identifying one or more offending drugs responsible for ADRs in patients receiving concomitant therapy for DR-TB and HIV is very challenging. Many of the medications used to treat coinfection have overlapping or additive ADRs.[75] The typical strategy of stopping all medications and rechallenging them one by one is not possible in these patients, as the risk of emergence of

resistance, especially for ART, is very high. It should be noted that information regarding the frequency of ADRs is relatively scarce. Most of drugs have to be included in the regimens outweighing the benefit over risk despite of awareness regarding high probability of overlapping ADRs. If 2- drugs with overlapping toxicities are considered to be essential for therapy, intense monitoring of ADRs is to be considered rather than disallowing a certain combination. The treating physician, whether working in public or private sector, must notify all diagnosed cases to concerned DOTS center and can refer for further management.

Limitations of the study: We were limited by the reviewed studies, which presented few numerical analyses of the ADRs of TB drugs. The severity of ADRs was unreported in most studies. The few numerical analyses also limited the conclusions we could draw; the data required us to analyze ADRs at a study level rather than a patient level. Moreover, since it was not possible to ascertain how the relative contribution of ADRs in causing missed doses was calculated in all relevant studies, we were required to accept the authors finding, which may have been subjective or prone to bias. Discussions regarding ADRs and missed doses remain complex, with varying definitions and interpretations. We identify a critical knowledge gap: the absence of information regarding the patterns in which doses are missed due to ADRs. A much deeper understanding of how specific ADRs is related to drugs is needed in order to generate effective interventions. Combined with upcoming less toxic drug regimens and clinical and personal support from clinicians, these interventions will facilitate the development of targeted treatment support to improve treatment outcomes. Thus, personalized yet pragmatic patient support can be effectively and efficiently delivered.

CONCLUSION

The treatment of TB can cause a variety of ADRs. ADRs of varying severity are common during treatment of DS-TB and DR-TB, particularly in the intensive phase of therapy. Some ADRs become more prevalent in DR-TB patients coinfected with HIV. Most ADRs can be successfully managed on an outpatient basis through a community-based treatment program, even in a resource-limited setting. Concerns about severe ADRs in the management of DR-TB patients are justified; however, they should not cause delays in the urgently needed rapid scale up of SLDs. ADRs can be detected by clinical evidence in resource-limited settings. DR-TB can be cured successfully with appropriate combination of drugs if ADRs associated with them can be managed aggressively and timely. Newer and less-toxic drugs are needed to treat DR-TB patients over large scale. Accurate diagnoses and knowledge of the

pharmacological properties of the drugs involved will allow professionals to tailor their approach to each individual case in near future.

Further research

Considering that TB treatment outcomes go beyond microbiologic cure, it is essential to examine the impact of these ADRs on patients' health-related quality of life and overall treatment outcomes. Tis broader perspective will contribute to expanding the scientific community's knowledge in this field.

REFERENCES

1. World Health Organization. Global tuberculosis report, 2019. WHO, Geneva, 2019 (WHO/CDS/TB/2019.15). Available at: https://www.who.int/tb/publications/global_report/en/. Accessed June, 2020; 28.
2. World Health Organization, Requirements for Adverse Reaction Reporting. Geneva, Switzerland: World Health Organization, 1975.
3. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf, 2006; 5(2): 231–249.
4. Gülbay BE, Gürkan Ö, Yildiz Ö, *et al.*, Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. J Respir Med, 2006; 100: 1834–1842.
5. Tan WC, Ong CK, Kang SC, Razak MA. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. Med J Malaysia, 2007; 62(2): 143–146.
6. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet, 2000; 356(9237): 1255–1259.
7. Singh A, Prasad R, Balasubramanian V, Gupta N, Gupta P. Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. Clin Epidemiol Glob Health, 2015; 3: s80–s90.
8. Marra F, Marra CA, Bruchet N, *et al.*, Adverse drug reactions associated with first-line anti- tuberculosis drug regimens. Int J Tuberc Lung Dis, 2007; 11(8): 868–875.
9. Butov D, Kuzhko M, Stepanenko G, Butova T. Frequency of adverse reactions to first-line anti- tuberculosis chemotherapy in patients with relapse (RTB) and newly diagnosed tuberculosis (NDTB) European Respiratory Journal, 2018; 52(s62): PA2700.
10. Dosumu EA. Side-effects of drugs used in directly observed treatment short-course in newly diagnosed pulmonary tuberculosis subjects in Nigerians: a controlled clinical

study. Niger Postgrad Med J, 2002; 9(1): 34–37.

11. Arbex MA, Varella MdeC, Siqueira HR, Mello FA. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first-line drugs. J Bras Pneumology, 2010; 36(5): 626–640.
12. Vieira DE, Gomes M. Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. J Bras Pneumology, 2008; 34(12): 1049–1055.
13. Breen RA, Miller RF, Gorsuch T, *et al.*, Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax, 2006; 61(9): 791–794.
14. Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. Cochrane Database Syst Rev, 2001; (4): CD000970.
15. Mehrotra ML. Agra study of short course chemotherapy in pulmonary tuberculous patients. Indian J Tuberc, 1982; 29: 29–39.
16. Dedun AR, Borisagar GB, Solanki RN. Impact of adverse drug reaction of first line anti - tuberculous drugs on treatment outcome of tuberculosis under revised national tuberculosis control programme. International Journal of Advances in Medicine, 2017; 4: 645–649.
17. Naser SM, Nandy M, Banu P, *et al.*, Adverse drug reaction monitoring through active surveillance of antitubercular therapy in an urban tertiary care center. Community Acquire Infect, 2016; 3: 51–54.
18. Mandal PK, Mandal A, Bhattacharyya SK. Comparing the daily versus the intermittent regimens of the anti-tubercular chemotherapy in the initial intensive phase in non-HIV, sputum positive, pulmonary tuberculosis patients. J Clin Diagn Res, 2013; 7(2): 292–295.
19. Prasad R, Singh A, Gupta N, Giridhar BH. Epidemiology of adverse drug reaction with second line drugs among patients treated for multi- drug-resistant tuberculosis. European Journal of Biomedical and Pharmaceutical Sciences, 2015; 2: 553–561.
20. Wu S, Zhang Y, Sun F, *et al.*, Adverse events associated with the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. Am J Ther, 2016; 23(2): e521–e530.
21. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. J Antimicrob Chemother, 2017; 72(7): 1871–1879.
22. Nathanson E, Gupta R, Huamani P, *et al.*, Adverse events in the treatment of MDR-TB: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis, 2005; 9: 1027–1033.

23. Baghaei P, Tabarsi P, Dorriz D, *et al.*, Adverse effects of multidrug-resistant tuberculosis treatment with a standardized regimen: a report from Iran. Am J Ther, 2011; 18: e29–e34.
24. Singla R, Sarin R, Khalid UK, *et al.*, Seven-year DOTS-Plus pilot experience in India: results, constraints and issues. Int J Tuberc Lung Dis, 2009; 13(8): 976–981.
25. Joseph P, Desai VB, Mohan NS, *et al.*, Outcome of standardized treatment for patients with MDR- TB from Tamil Nadu, India. Indian J Med Res, 2011; 133: 529–534.
26. Isaakidis P, Varghese B, Mansoor H, *et al.*, Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One, 2012; 7(7): e40781.
27. Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: a 4-year retrospective study. Lung India, 2017; 34(6): 522–526.
28. Prasad R, Singh A, Srivastava R, *et al.*, Adverse drug reaction in the treatment of multi drug resistant tuberculosis. Indian J Tuberc, 2013; 144(4): 390A.
29. Shinde KM, Pore SM, Bapat TR. Adverse reactions to first-line anti-tuberculous agents in hospitalized patients: pattern, causality, severity and risk factors. Indian J Med Spec, 2013; 4: 1–4.
30. Lv X, Tang S, Xia Y, *et al.*, Adverse reactions due to directly observed treatment strategy therapy in Chinese tuberculosis patients: a prospective study. PLoS One, 2013; 8(6): e65037.
31. Anand AC, Seth AK, Paul M, Puri P. Risk factors of hepatotoxicity during anti-tuberculosis treatment. Med J Armed Forces India, 2006; 62(1): 45–49.
32. Parthasarathy R, Sarma GR, Janardhanam B, *et al.*, Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing Isoniazid, Rifampicin and Pyrazinamide. Tubercle 1986; 67(2): 99–108.
33. Blumberg HM, Burman WJ, Chaisson RE, *et al.*, American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med, 2003; 167(4): 603–662.
34. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest, 1991; 99(2): 465–471.
35. Pande JN, Singh SPN, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax, 1996; 51(2): 132–136.

36. Baghaei P, Tabarsi P, Chitsaz E, *et al.*, Incidence, clinical and epidemiological risk factors and outcome of drug-induced hepatitis due to antituberculous agents in new tuberculosis cases. Am J Ther, 2010; 17(1): 17–22.
37. Prasad R, Verma SK, Chowdhury SR, Chandra M. Predisposing factors in hepatitis induced by anti-tuberculosis regimens containing Isoniazid, Rifampicin and Pyrazinamide: a case control study. JIMI, 2006; 9: 73–78.
38. 38 Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with Rifampin and Pyrazinamide for the treatment of latent tuberculosis infection: experience from 3- public health tuberculosis clinics. Int J Tuberc Lung Dis, 2002; 6(11): 995–1000.
39. Kumar R, Bhatia V, Khanal S, *et al.*, Shalimar. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis and predictors of outcome. Hepatology, 2010; 51(5): 1665–1674.
40. British Thoracic Association. A comparison of the toxicity of Prothionamide and Ethionamide: a report from the research committee of the British Tuberculosis Association. Tubercle, 1968; 49(2): 125–135.
41. DR-TB STAT (Drug-Resistant TB Scale-Up Treatment Action Team). Treatment of Drug- Resistant TB with New and Re-Purposed Medications: a Field Guide. Cleveland, DR-TB STAT, 2018; 1-55. Accessed at: http://drtb-stat.org/
42. Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. Study of adverse drug reactions caused by first line anti-tubercular drugs used in directly observed treatment, short course (DOTS) therapy in Western Nepal, Pokhara. J Pak Med Assoc, 2008; 58(10): 531–536.
43. Philadelphia Tuberculosis Control Program. Guidelines for the Management of Adverse Drug Effects of Antimycobacterial Agents. Available at: https://medbox.org/ pdf/5e148832db60a2044c2d3f51. Accessed December, 2020; 11.
44. Prasad R, Garg R, Verma SK. Isoniazid- and ethambutol-induced psychosis. Ann Thorac Med, 2008; 3(4): 149–151.
45. Jackson SL. Psychosis due to isoniazid. BMJ, 1957; 2(5047): 743–746.
46. Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. CNS Drugs, 2010; 24(8): 655–667.
47. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther, 1997; 13(5): 473–477.
48. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. Ann N Y Acad Sci,

1966; 135(2): 904–909.

49. Tang S, Yao L, Hao X, *et al.*, Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J, 2015; 45(1): 161–170.
50. Moore RD, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. J Infect Dis, 1984; 149(1): 23–30.
51. Prazić M, Salaj B. Ototoxicity with children caused by streptomycin. Audiology, 1975; 14(2): 173– 176.
52. Berte SJ, Dimase JD, Christianson CS. Isoniazid, para-aminosalicylic acid and streptomycin intolerance in 1,744 patients. An analysis of reactions to single drugs and drug groups plus data on multiple reactions, type and time of reactions, and desensitization. Am Rev Respir Dis, 1964; 90: 598– 606.
53. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrobe Agents Chemotherapy, 1999; 43(7): 1549–1555.
54. Garg R, Gupta V, Mehra S, Singh R, Prasad R. Rifampicin induced thrombocytopenia. Indian J Tuberc, 2007; 54(2): 94–96.
55. Prasad R, Mukerji PK. Rifampicin induced thrombocytopenia. Indian J Tuberc, 1989; 36: 171– 175.
56. Prasad R, Mukerji PK. Ethambutol-induced thrombocytopaenia. Tubercle, 1989; 70(3): 211–212.
57. Kant S, Verma SK, Gupta V, Anand SC, Prasad R. Pyrazinamide induced thrombocytopenia. Indian J Pharmacol, 2010; 42(2): 108–109.
58. Sotgiu G, Centis R, D'Ambrosio L, *et al.*, Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J, 2012; 40(6): 1430–1442.
59. Gerdan V, Akkoc N, Ucan ES, Bulac Kir S. Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricaemia. Singapore Med J, 2013; 54(6): e125–e126.
60. Postlethwaite AE, Bartel AG, Kelley WN. Hyperuricemia due to ethambutol. N Engl J Med, 1972; 286(14): 761–762.
61. Kang BH, Jo KW, Shim TS. Current status of fluoroquinolone uses for treatment of tuberculosis in a tertiary care hospital in Korea. Tuberc Respir Dis (Seoul), 2017; 80(2): 143–152.

62. Pym AS, Diacon AH, Tang SJ, *et al.*, TMC207-C209 Study Group. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J, 2016; 47(2): 564–574.
63. Rougier F, Claude D, Maurin M, *et al.*, Aminoglycoside nephrotoxicity: modeling, simulation, and control. Antimicrobe Agents Chemotherapy, 2003; 47(3): 1010–1016.
64. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis, 2002; 6(7): 622–627.
65. Yang TW, Park HO, Jang HN, *et al.*, Side effects associated with the treatment of multidrug- resistant tuberculosis at a tuberculosis referral hospital in South Korea: A retrospective study. Medicine (Baltimore), 2017; 96(28): e7482.
66. Tawanda G. Chemotherapy of tuberculosis, Mycobacterium avium complex disease and leprosy. In: Brunton LL, Chabner BA, Knollman B, eds. Goodman and Gilman's: The Pharmacological Basis of the Therapeutics. New York, USA: McGraw Hill Med, 2011; 12: 1559.
67. Garg R, Verma S, Mahajan V, Prasad R. Exfoliative dermatitis secondary to ethambutol and pyrazinamide. Internet J Pulm Med, 2008; 9(1): 1–4. Doi: 10.5580/c9f.
68. Potter JL, Capstick T, Ricketts WM, Whitehead N, Kon OM. A UK-based resource to support the monitoring and safe use of anti-TB drugs and second-line treatment of multidrug-resistant TB. Thorax, 2015; 703, 297: 29- 8.
69. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J, 2017; 50(5): 1701462.
70. Garg R, Vaibhav, Mehra S, Prasad R. Isoniazid induced gynecomastia: a case report. Indian J Tuberc, 2009; 56(1): 51–54.
71. Prasad R. Anaphylactic shock due to streptomycin sulphate. J Indian Med Assoc, 1984; 82(7): 254– 255.
72. WHO. A Practical Handbook on the Pharmacovigilance of Medicines Used in the Treatment of Tuberculosis. Available at: https://www.who.int/docs/default-source/documents/ tuberculosis/a- practical-handbook-on-the-pharmacovigilance-of-medicines-used-in-the-treatment-of-tuberculosis. pdf?sfvrsn=6e5fc0cf_5. Accessed December, 2020; 11.
73. Division of AIDS, National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected version

74. 2.1. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed December, 2020; 11.
75. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Available at: https:// apps.who.int/iris/bitstream/handle/10665/311389/97892415 50529- eng.pdf?ua=1. Accessed December, 2020; 11.
76. Prasad R, Gupta N, Handbook on Adverse Drug Reactions in TB treatment. 1st ed. Delhi, India: Jaypee Brothers Medical Publishers, 2019.