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Adverse Drug Reaction: A study with First- and Second-line Anti-TB Drugs at tertiary care with Nodal DRTB center.

Abstract:

Introduction: Adverse Drug Reactions (ADR) is unwanted, uncomfortable, or harmful responses to drugs, which may occur even when the drug is used at a standard therapeutic dose. In the context to tuberculosis (TB) treatment, the ADRs are a significant challenge, especially in high-burden countries like India, where drug-resistant TB (DRTB) is on the rise. The ADR is one of the major causes of treatment interruption that ultimately lead to poor outcome. The ADR management is crucial and requires know how of mechanism of the drug action, interaction, timely identification with stratification of ADR and pre existing dysfunction of the organ or system due to co-morbidities.

Results: The 13% (84/647) and three times more i.e. 40% (76/168) cases of ADR were observed among treatment with first and second line anti TB drugs respectively. Most of the ADR developed during intensive phase of treatment. The hepatotoxicity (35%) followed by peripheral neuritis and GI disturbances etc were the common ADR and recovery period and out comes remained satisfactory. However 5 % not improved from peripheral neuritis. The PZA and Linezolid remained at the top of the culprit drug list, and the COPD (43%) followed by DM (14%) and hepatic ailment (13%) etc observed as associated co morbidities.

Discussion: The TB patient with lower BMI (51%) were more vulnerable to ADR may be due to under nourishment/ malabsorption or poor immunity. Three times more ADR among SLDs could be due to use of repurposed drugs like linezolid and clofazimine, and new drugs bedaquiline and delamanid. The recovery from ADR remained satisfactory in our study but somehow 4 (5%) not recovery due to peripheral neuritis and associated co morbidity and extensive parenchyma disease. A prompt reporting or detection and quick management with drug withdrawal/ dose reduction and proper replacement of drug may improve the treatment outcomes. However there is hope that the BPaLM regimen having only four drugs for six month period with promising decreased ADR is most likely to change TB scenario in coming future. It is wise enough to carrying on with the treatment plan if the side effect is minor and not life-threatening with counseling, assurance and psychological support.

Key words: Adverse drug Event (ADE), Adverse drug Reaction (ADR), All oral longer (AOL), Anti TB Treatment (ATT), Extensive drug resistance (XDR), First line drugs **(**FLDs), Second line drugs (SLDs), Rifampin resistant TB (RRTB), Rifampin sensitive TB (RSTB).

Introduction: An Adverse Drug Reaction (ADR) refers to an unwanted, uncomfortable, adverse drug event (ADE) or a profound effect of a drug. As per the World Health Organization (WHO), an adverse drug reaction is described as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of

physiological function." The intolerance is when an individual couldn't tolerate ADR at therapeutic or sub-therapeutic doses [1]. The definitions and terminologies are updated promptly as the Pharmaco-vigilance glossary. Thus, the ADR is the undesirable interplay between human responses with the drug and drug to drug interaction on the human. ADR is classified as Type A or Type B reactions [2], with several subcategories. Although signs, symptoms, and time of onset can help differentiate these types of reactions, with some clinical overlap, it may exist. Type A reaction is most common (85-90%) and concerned with the pharmacological property (Kinetic & dynamic) of drugs, i.e., overdose, side effect, and drug interactions. Type B adverse reactions could not be explained by pharmacologic causes and include an immunologic mechanism, tend to be reproducible, and may cross-react with structurally related drugs [3]. Some of the examples of ADR induced by hypersensitivity reactions (type I anaphylaxis to type IV) are as contact dermatitis, Stevens-Johnson syndrome (SJS), drug-induced hypersensitivity syndrome (DiHS), and drug reaction with eosinophilia and systemic syndrome (DRESS). These ADR may warrant discontinuation of the culprit drug, or alteration of the regimen, lower doses/ or discard the drug as a relative/ absolute contraindication [3]. The drug interaction, drug-induced autoimmunity, and fixed drug eruption are other entities of adverse event to be identified. A centrally established State level functional pharmaco-vigilance system is mandatory for proper evaluation, monitoring and reporting [4]. However, the present study will remain précised only to the prevailing anti-TB drugs used under NTEP.

India is a high TB burden country. A definite diagnosis of TB is established by microscopic demonstration of Mycobacterium tuberculosis bacilli or the Genexpert technique (CBNAAT, TrueNAT Line probe assay, etc); however, the Lowenstein-Jensen solid culture is the gold standard. Unfortunately, India contributes a significant global share of MDR, pre-XDR, and XDR cases. It is estimated that out of the total detected TB cases, 3.5% and 18% of cases were diagnosed as primary and acquired drug resistant respectively. During the year 2023, a total of 2.55 million cases were diagnosed and put on treatment, and among them, drug-resistant cases were 63939 [5]. Tuberculosis broadly involves two sites, i.e., pulmonary (PTB) in 80% and the rest as an extra pulmonary tuberculosis (EPTB) involving almost all other parts of the body systems. There is hardly any difference in the treatment regimen for PTB or EPTB except the duration may be longer, especially e.g. CNS and bone tuberculosis. However, the regimen for rifampin sensitive (RSTB) and rifampin resistant (RRTB) mycobacterium disease is different. The latest trend of conventional TB treatment of RSTB includes only four drugs (RHZE) for six months, with a reported success rate of 86%, while a more enormous list of drugs is in use to formulate RRTB regimen. The main drugs used to develop a regimen for MDR, H mono, pre XDR, and XDR include certain newer drugs (i.e. Bedaquiline, Delamanid, and Pretomanid) and repurposed antibiotics (e.g. linezolid, clofazimine, etc). Most of the repurposed drugs have a track record of proven frequent ADR as compared to conventional ATT. The overall incidence of ADR among the FLDs in Indian studies varies from 2.3 to 17% while SLDs have higher cost, lower efficacy, and are more toxic [6]. The ADR is one of the significant causes of treatment interruption, nonadherence, and default that ultimately lead to poor outcome of a disease. The severity of each adverse event could be studied and assessed by the Division of AIDS (DAIDS) grading system to prioritize the action plan. Apart from the individual case profile consideration, an early detection or identification of side effects vs. ADR**,** ADE vs. ADR with stratification (mild, moderate, and severe) to necessitate hospitalization, drug history, and multi-specialty consultation (e.g., Derma and Psychiatry, etc) are crucial for the management [7]. These all may further help management in deciding if 1) the drug requires discontinuation (dechallenge) and to observe for

reduction in ADR or abated response, 2) the drug therapy is changed, or 3) the dose is modified. The appearance of ADR and its relevance to the organ or system with progression may help to differentiate in identifying the culprit drug, which enables us to proceed with a protocol for oral desensitization or rechallenge [8 - 9]. The present study is conducted for the first time at a pilgrim city, Ujjain, India, to understand ADR with FLDs and SLds ATT in the nodal DRTB center of western MP.

Material and Method: It is a prospective observational cohort study. All the cases presented with ADR and were willing to join the survey were included in the study from January 2023 to December 2023. A complete history with thorough general physical examination and Pre-treatment investigations were performed that included complete haemogram, blood sugar with HbA1c, liver, renal and thyroid function tests, pure tone audiometry (PTA) with serology testing for HBsAg, HIV and HCV, after informed consent to agree and report on follow up. A complete relevant repeat examination is performed for those reported ADR. The list of ATT drugs with common predictable ADR is summarized in (**Table 1**) [9].

Results: The study period of one year ended on 31st December 2023. A total of 84 ADR events (13%) were reported among the diagnosed 642 RSTB cases and 76 ADR (40%) among the 188 DR-TB patients admitted at Nodal Drug Resistant TB Centre. Out of 160 (84+76) cases, only 84 were considered for analysis in the present study; those reported on follow-up met the cohort criteria. Most of the ADR cases (64%) reported within the 2nd week of starting ATT and cumulative 86% within the first month, so it could be concluded that the intensive phase of treatment is the crucial period for ADR. A significant number of low BMI (51%) or malnourishment was detected among ADR cases. Associated comorbidities were observed in 37 (44%) cases, and among them, COPD (43%) remained on top (**Table 2**) followed by diabetes. (14%), hepatitis, thyroid, and HIV, etc.

Table 1: Pre/ Post Treatment Proposed Investigations

Drug/Group	Assessing
Pre Treatment Evaluation	_ Colour vision, visual acuity _ Pregnancy _ Mental health _ HIV _ LFT (ALT), creatinine, CBC _ Hepatitis serology _ HbA1c Diabetics
Post Treatment Monitoring	
Aminoglycosides (now uncommon):	Hearing, vestibular function, and Formal pure tone audiometry
ETH or PAS	Hypothyroidism
PZA	Hepatic, hyperuricemia
FQs	Arthralgia, arthritis, tendonitis, QT
CFZ	Skin ichthyosis discolouration,
DLM	Measure Albumin
LZD,	Measure CBC, Hb
BDQ, FQs, CFZ, DLM	QT prolongation Electrolytes: K/ Mg/ Ca

Table 2: Patients Profile

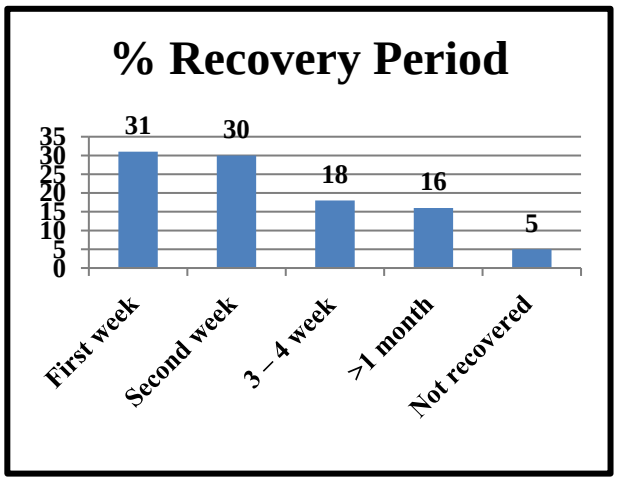
Total Patients	84 (100%)	N = 84
M: F ratio	46:38 (0.83)	
Relation to age group	Up to 20 =07 (08%) 21-40 =41 (49%) 41-60 =30 (36%) 61&More 06 (07%)	TB is also common in the productive age
Rural: Urban		
BMI	<18 =43 (51%) 18 -25 =33 (39%) >25 =08 (10%)	Lower BMI is more vulnerable to TB/ ADR
stratification Managed at	OPD =09 (11%) IPD =75 (89%)	most of the cases, hospitalization
TB case Type	PTB =64 (76%) EPTB =20 (24%)	Proportionately >20% EP cases
Microbiologic PTB N=64	RRTB 35 = 55 % RSTB 29 = 45 %	
Microbiologic EPTB N=20	RRTB 03 =15 % RSTB 17 = 85 %	
Co-morbidity N=37 (44%) System /organ involved.	COPD =43 % DM =14 % Hepatic =13 % Thyroid =08 % HIV =05 % HT =04 % Renal =03 %	DM, HIV, and COPD (steroid use) are likely to have low immunity, which may contribute to ADR.
Duration of patient presentation	1st Week 07 % 2nd Wk 64 % 3-4 Wk 15 % >1 month 14 %	most of the (>86%) patients reported during the intensive phase
Prescribed Regimen N = 84	RSTB 46 (55%) RRTB 25 (30%) PreXDR 07 (08%) Shorter 05 (06%) H mono 01 (01%)	RHZE B Lf Lzd Cfz Cs B,Dlm,Lzd,CfzCs B,L,Cfz.ZEH Eto R Z E Lfx
Outcomes of ADR	Recovered 83% Improved 12% Not recover 05%	Not recoverable due to Peripheral neuritis and co-morbidity

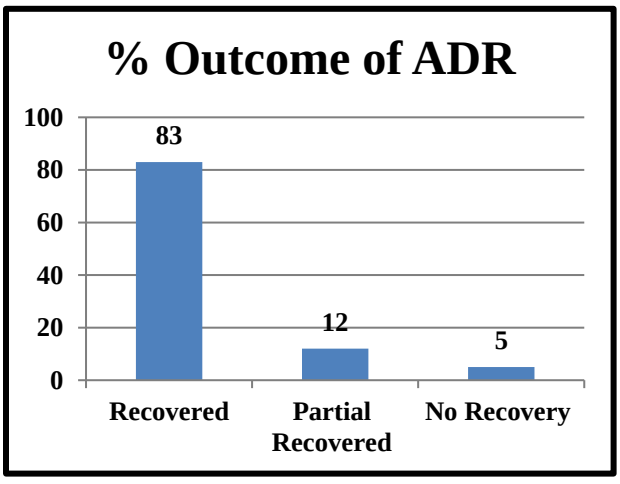
Table 3: Incidence of ADR

ADR	Percent	Causative Drugs
Hepatotoxicity	**35.3**	Z, H, R, Eto, PAS, Bdq
Peripheral neuritis	**15.3**	Lzd, Cs, H, Am, FQ, rarely Eto, E
GI	**15.3**	**Almost all of the drugs**
Psychiatric Illness	**7.1**	Cs, FQs, H, Eto
QT prolongation	**5.9**	Bdq, Mfx, Cfz, DLM
Skin reaction	**4.7**	**CFZ,**
Hearing defect	**3.5**	Aminoglycosides,
Anemia	**2.4**	**Lzd,**
Arthralgia	**2.4**	**Z,**
Visual Defect	**2.4**	**E,**
Alopecia	**1.2**	**INH**
ChestPain	**1.2**	**Z**
Renal Defects	**1.2**	Aminoglycosides.
Thrombocytopenia	**1.2**	**Lzd**
Total	**100.0**	

This study also observed various ADRs, e.g., hepatotoxicity in (35%) followed by Peripheral neuritis (15%), gastro-intestinal, QT prolongation, and dermatologic, etc, in a descending order (Table: 3). A regimen containing the drugs, especially Pyrazinamide and Linezolid, had the maximum ADR. Of all the severe forms of ADR cases, 89.3% (75/84) were admitted. Most of them recovered and responded very well; however, four patients do not recover from peripheral neuritis due to associated comorbidities.

Discussion: Tuberculosis is a global problem and an infectious disease that spreads/is transmitted mainly through aerosols produced by the pulmonary TB patient during coughing or sneezing. Multiple drugs are used to constitute a regimen for drug-resistant mycobacteria. These drugs act together at different sites or systems of the mycobacterium metabolism to effectively disrupt/disestablish them. A Fixed Dose Combination (FDC) of ATT drugs pack is provided under NTEP, according to weight band, but somehow a marginal overdose of any of the single drug may be likely to increase ADR. Hence, the drug logistics should take care of an adequate stock of loose medicines for customized therapy; otherwise, a lower weight band FDC remains the choice with reduced doses. There is nothing significant to comment about age, sex, and occupation of the participant in the present study. Still, the ADR remained highly prevalent (>50%) with low BMI (<18) could be due to comorbidity, lower socio-economic strata, malnutrition, or poor GI absorption. The Nikshya Poshahar





Yojana started by NTEP India may help to improve BMI.

It is wise enough to carry on with the treatment plan if the side effect is minor and not life-threatening with counseling, assurance, and psychological support. Managing side effects might involve stopping or lowering the dosage of the culprit/ troublesome medication, compromising the treatment outcome. An observational study by Cai Shi et al. mentioned 30.77% (440/1430) of cases in which ADR was experienced at least once during treatment for TB [10]. Rajendra Pd et al in a review article mentioned ADRs with FLDs and SLDs are estimated to vary from 8.0% to 85% and 69% to 96%, respectively. He further noted that most Indian studies reported 2.3 to 17 % ADRs among FLDs [6]. Kumari A. et al [11] had reported 87% ADR in their research with MDR TB cases and most common ADR observed were Gastritis (65%) followed by arthralgia (60%) and hyperuricemia (30.8%) etc during the period 2012-13 with conventional 18-24 months treatment. So the difference in ADR percentage and pattern depends on the drugs/ regimen used [11]. Similarly, our study reported 13% and 40% of ADR with FLDs (e.g. RHZE) and SLDs (used for RRTB) respectively. The majority of ADR observed were hepatic toxicity in 35% of cases, followed by 15% each as peripheral neuritis and gastro-intestinal disorders (Table 2).

The present study also observed three times more ADRs with SLDs than the FLDs. The reasons for this different incidence of ADR could be the fact that the repurposed drugs like linezolid (Lzd) and clofazimine (Cfz), as well as newer drugs such as bedaquiline (Bdq) and delamanid (Dlm) were used [6]. These SLDs are one of the significant causes of default from treatment. At present two regimen in Indian context are proposed under NTEP for MDR/RRTB treatment; first is 'All Oral Longer' with five drugs (Bdq, Lfx, Lzd, Cfz, Cs) with 18 months of treatment and the second one is 'Shorter' with seven drugs (Bdq Moxi, Cfz, Z, E, H^h, Eto) with duration of 9-11 months. We preferred the AOL regimen to minimize ADR with a limited number of drugs. Thus, an increase in the number of drugs, which translates to more chances of adverse drug reactions.

At present, limited ATT drugs are available; and somehow, the MTB is notorious for developing resistance against antibiotics or chemotherapeutic agents. The duration of treatment is also prolonged, thus the invention or discovery of newer potent, efficacious, nontoxic, cost-effective, and short duration of treatment is an urgent need. Globally, the cure rate (near 60%) of DRTB cases is not satisfactory, and we have to use the repurposed drugs, i.e., linezolid (Lzd) and clofazimine (Cfz), etc, which are more likely to fuel the ADR. However, the BPaLM regimen having four drugs (Bdq, Pretomanid, Lzd, Mfx) is most likely under process to be launched throughout India for drug-resistant TB. This newer BPaLM regimen has included only the pretomanid for the first time and shown the most promising outcome (although not included in the present study) with a success rate near 90% in various clinical trials.

Linezolid belongs to the oxazolidinone group, is an integral part of the bidaquiline-based regimen that disrupts mitochondrial protein synthesis with dysfunction in metabolically active cells, resulting in ADRs such as lactic acidosis and peripheral neuropathy. The optic neuritis, myelosuppression, e.g., thrombocytopenia and anaemia, are also reported [12]. The toxic effect of linezolid is dose and time related; however, severe and life-threatening neuropathy warrants permanent discontinuation, and in early mild to moderate cases, a reduction in doses from 600 to 300 mg may be worth a trial as also been done in our study. In the present study, linezolid as a part of the AOL regimen (N=25) was discontinued and replaced with Delamanid in 37.5% of cases, and doses were reduced in 12.5% of cases due to ADR.

Gyanshankar Mishra et al reported linezolid dose reduction in 17 (37.78%) and entire withdrawal in 19 (42.22%) with predominance of younger aged and female patients [12].

The Clofazimine (Hydrophobic riminophenazine group) induced orange to brownish skin pigmentation, which is the most frequent ADE and occurs within a few weeks. The QTcF prolongation is the most severe ADR that needs temporary drug discontinuation, and other types of anaemia [13]. A counseling with or without antihistamines was sufficient to continue clofazimine in our study.

Levofloxacin (fluoroquinolones group) is the most common ADR, including gastrointestinal disturbances, hepatotoxicity, headache, and dizziness. The prolongation of QT interval on ECG and psychiatric disorders has also been stated by Grosu-Creangă et al. [12]. A significant QT prolongation in five cases was also observed in our study in combination with another QT-prolonging agent (e.g. Bdq, DLM or Cfz). All efforts were sought, including infection, electrolyte correction, and cardiologist opinion. However, due to persistent QTc prolongation, the second line drugs had to be withdrawn/ replaced, thus weakening the regimen. The stopped drugs introduced with normalization of QT interval in reduced or full doses as per PMDT guideline [14].

Bedaquiline (BDQ) is the most potent, newer anti-TB drug, introduced after a long period of nearly 50 years. It belongs to the diarylquinoline category and has a lipophilic property that allows it to penetrate more efficiently the cell membrane of mycobacterium with a novel mechanism of action by inhibiting adenosine triphosphate (ATP) synthesis in bacterial microenvironments, thus disrupting bacterial energy metabolism [15]. An approved BDQ-containing regimen is recommended, with an initial 400 mg daily for 2 weeks as a loading dose, and then 200 mg three times a week until 6 months. BDQ can cause various side effects, such as QT interval prolongation, cardiac arrhythmias on ECG, gastrointestinal disorders, joint and muscle pain. Nabilah A. Nihlah et al [15] mentioned that BDQ provides good synergy when combined with other anti-TB antibiotics, e.g., 1) BDQ, pretomanid, and linezolid showed high culture conversion rates and low relapse rates for extensively resistant TB. 2) BDQ and pretomanid have a strong synergistic effect on MDR TB. 3) BDQ and delamanid (Dlm): shown promising results for MDR/XDR TB patients, but with higher cardiac toxicity. In addition, BDQ may also cause nausea, vomiting, headache, limb pain, bilateral hearing loss, acne as well as elevated liver enzymes. A regular monitoring of liver function, electrolytes, and ECG is recommended.

Delamanid (group of Nitro-dihydro-imidazo-oxazole): Its use remained limited in our study, as a replacement drug in AOL/ Shorter regimen. The QT prolongation is the most severe ADR and requires frequent monitoring. The other frequent ADR with Dlm includes nausea, vomiting, and dizziness.

Pretomanid (PA) is the most potent and promising newer drug, although it has not been used in the present study. It is a prodrug and needs activation by Mycobacterium tuberculosis. The intake of this drug with food, especially a high-fat and high-calorie meal, enhances the solubility of the tablets and the gastrointestinal absorption. The PA has a broader spectrum, and clinically, it is active against replicating and non-replicating bacilli. Most commonly adverse effects related to PA administration reported in trials were: gastrointestinal (GI) symptoms (28,4%), hepatic disorders (25,5%) with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation (19,2%), skin or subcutaneous tissue disorders (166%), headache (11,0%) [16].

Conclusion: ADR is an untoward/unwanted/ or undesirable exaggerated drug action so it becomes mandatory to understand about 1) Common producible symptoms 2) Pharmacokinetic and dynamic action of individual drug in use 3) Drug interaction 4) Existing comorbidities and 5) immunological status of the host. Hence, for better patient care and safety with ADR, it requires systematic screening, with meticulous record keeping, and comprehensive reporting mechanisms, along with health education and awareness among the patient and the health worker.

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