

# A Study on Adverse Drug Reaction Profile of 2<sup>nd</sup> Line Drugs in Multi Drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis Cases Registered under DR-TB Centre in a Tertiary Care Hospital

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## ABSTRACT

### BACKGROUND

The emergence of drug resistant mycobacterium has become a significant public health problem creating an obstacle to effective tuberculosis (TB) control. Freedom from TB is possible with timely, regular, complete treatment, with assurance, prevention and management of side effects of antitubercular drugs. Present study was conducted to evaluate common and rare adverse drug reactions (ADR) of CAT IV and CAT V to analyse demographic, radiological and bacteriological profile and treatment outcome in MDR & XDR patients. We wanted to evaluate the common and rare adverse drug reactions of intensive phase treatment of Multi Drug Resistant Tuberculosis (MDR) and Extensively Drug Resistant Tuberculosis (XDR) as per WHO-UMC Causality Assessment Scale.

### METHODS

76 patients of MDR and XDR Tuberculosis were admitted in DR-TB (Drug Resistant TB) centre, Burdwan Medical College and Hospital and the adverse drug reaction profile of 2<sup>nd</sup> line drugs were analysed during the intensive phase from April 2016 to September 2017 after fulfilling the inclusion and exclusion criteria. Treatment was given as per the guidelines of Revised National TB Control Program PMDT (Programmatic Management of Drug-Resistant TB).

### RESULTS

Adverse drug reactions on GI system were nausea 73 patients (96.10%), vomiting 70 (92.10%), acidity 41 (53.9%), and sulphurous belching and hepatitis 1 (1.31%) each. Peripheral neuropathy, hearing deficit, myopathy, skin rashes, hepatitis, nephrotoxicity, cardiac toxicity and convulsion were also observed. In psychosis, 3 (3.95%) had depression and made suicidal attempt. 1 each (1.31%) in hallucination and paranoia. 5 patients (6.58%) had blurring of vision, 2 patients (3.95%) had redness of eyes and one (1.31%) had eye irritation. Reactions were common in first 60 days of the regimen and in patients with BMI ≤18.

### CONCLUSIONS

Vigilant monitoring is required for these patients during the initial period and sputum smear and culture conversion is very well correlated with clinical and radiological improvement.

### KEY WORDS

MDR TB, XDR TB, Adverse Effects

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## BACKGROUND

*Mycobacterium tuberculosis* (*M. tuberculosis*) is an ancient human pathogen, which has plagued countless human societies despite the introduction of curative and preventive therapy in the last century. In recent years, international attention has turned toward the evolving burden of drug resistance. Multi-drug resistant tuberculosis (MDR TB) has emerged in epidemic proportions in the wake of widespread HIV infection in the world's poorest populations, including sub-Saharan Africa. Extensively drug-resistant TB (XDR TB) was first reported in 2006 but has now been documented on six continents<sup>1</sup>. These trends are critically important for global health, since drug-resistant TB mortality rates are high and second and third-line agents for the treatment of drug-resistant TB are less potent and less tolerable than first-line therapies.

Drug resistant tuberculosis (DR-TB) poses a great threat to the eradication of TB. Therefore, preventing the disease is the key to saving lives and resources. Social and behavioural variables play a big part in this prevention. It is important to determine the social factors that may lead to DR-TB in order to set up prevention programs and more efficient treatment regimens. Drug resistance in tuberculosis is a global problem and India is no exception to this. However, this rise is mainly among the previously treated cases as previous anti-tuberculosis therapy is the single most important risk factor for the development of drug resistance. The worldwide prevalence of drug resistant tuberculosis is on the rise and multiple studies give varying data regarding the adverse drug reaction of multi drug resistant tuberculosis. This study was taken up to determine the adverse drug reactions profile of a patient, previous history of anti-tubercular drug intake and pattern of drug resistant. Globally, 5% of TB cases were estimated to have had MDR-TB in 2013 (3.5% of new and 20.5% of previously treated TB cases). Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2013 and 210,000 people died. Extensively drug-resistant TB (XDR-TB) has been reported by 100 countries in 2013. On average, an estimated 9% of people with MDR-TB have XDR-TB.<sup>2</sup> WHO 2014 Global report on tuberculosis- 97,000 patients were started on MDR-TB treatment in 2013. 2<sup>nd</sup> line drugs have a lot of side effects. In India, the prevalence of multi-drug resistant TB (MDR-TB), defined as resistance to Isoniazid and Rifampicin with or without resistance to other drugs, is found to be at a low level in most of the regions. Data from several studies conducted by TRC and NTI, have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in re-treatment cases.<sup>3,4</sup> The disease is not only medical problem or a public health problem but is also a critical social problem of great magnitude. Base line and adequate information on adverse drug reactions profile of 2<sup>nd</sup> line drug in MDR and XDR TB, is required for its control and effective treatment.

India may be considered as one of the global epicentres of TB including the drug resistant one and many patients are being treated with second line anti-TB drugs. However, there is limited data of adverse drug reactions from the second line anti-TB drugs on the Indian patients. Indian patients are different from their global counterparts both by genetic structure and phenotype; hence prone to differ in anti TB drug action and pharmacokinetics also. Therefore, there is

need for more data from the Indian patients related to second line anti-TB drugs including the adverse drug reaction. Hence, the present study was planned to systemically generate and analyse the adverse drug reaction data of the second line anti TB drugs on Eastern Indian patients.

## METHODS

This cross-sectional study was designed to include all patients receiving treatment for Drug Resistant TB over a period of one year. So, there was no prespecified sample size for this study. This study was conducted at DR-TB centre, Burdwan Medical College and Hospital. Permission of Institutional Ethics Committee was obtained for the study. Written informed consents were obtained from all participating patients. 75 patients were included in the study. They were followed every month for 6 (9) months in intensive phase after the start of 2<sup>nd</sup> line drugs and adverse drug reactions were recorded, as the maximum adverse reactions usually occur in this period. Treatment was given as per guidelines by Revised National TB Control Program PMDT (programmatic management of drug-resistant TB) (erstwhile DOTS Plus).<sup>5</sup> The Drugs used in this study are Kanamycin, Tablets Levofloxacin, Ethionamide Cycloserine, Ethambutol, INH for Rifampicin Resistant TB. Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide, Ethambutol for Multi Drug Resistant TB. Capreomycin, PAS, Moxifloxacin, High dose INH, Clofazimine, Linezolid, Amoxiclav for XDR. Correlation of the adverse reactions with the offending drug was done by WHO-UMC Causality Assessment Scale. After selection of each patient on the basis of inclusion and exclusion criteria a written informed consent was taken. Data was collected using a pretested pro forma meeting the objectives of the study. Detailed history, physical examination and necessary investigations were undertaken. The purpose of the study was explained to the patient and informed consent obtained. At the end of the study the data was compiled, tabulated for analysis.

### Inclusion Criteria

1. Patient of age >18 years.
2. Both sexes.
3. Patients with proved drug resistant tuberculosis.

### Exclusion Criteria

Patients admitted <7 days in DR-TB Centre.

### Parameters Studied

1. HB%, TC, DC, ESR.
2. Blood urea, serum creatinine.
3. Liver function test.
4. FBS/ PPBS.
5. Sputum for AFB stain and gram stain.
6. Line probe assay.
7. Urine albumin, sugar and microscopy.
8. Chest X-RAY PA view.

### Statistical Analysis

All the collected data were analysed by using SPSS version 16 statistical software. Descriptive statistics were applied to the data. All data were presented as number and percent. Chi

Square Test and Fisher exact test were applied wherever applicable to find out statistical differences and p value <0.05 were considered statistically significant.

**RESULTS**

In our study among the 76 cases, most of them were pulmonary Tuberculosis (96%) whereas only 4% were Extra Pulmonary Tuberculosis. Majority were from age group 21-30 (44%), that is, the most productive age group of life. Majority 64% either studied up to 5<sup>th</sup> standard or are illiterate (fig. 1). Majority (95%) live in a Kuchcha house. 32% of patients were farmers, 23% were housewives and 12% were labourers. Most of them (84.2%) had no co morbidities but among the rest a significant number of patients (6.6%) had Diabetes Mellitus. In our study 50 patients are Rifampicin Resistant (RR), 25 patients are MDR, 1 patient is XDR. Majority 67 out of 76 had a history of incomplete ATD intake (88.2%). Biological specimen: sputum CBNAAT/ LPA/ DST MTB detected, Rif resistant was found in 71 patients, MTB detected, Rif resistant by CBNAAT in FNAC of lymph node for 3 patients and both sputum & pleural fluid CBNAAT MTB detected, Rif Resistant for 2 patients. Chest X-Ray features showed that a majority: 41 patients had bilateral consolidation and 21 patients had cavitary lesion. Overall compliance in IP: 63 patients had taken regular medication and 13 patients took irregular treatment or were lost to follow up. 3 patients died in each, regular and irregular treatment.

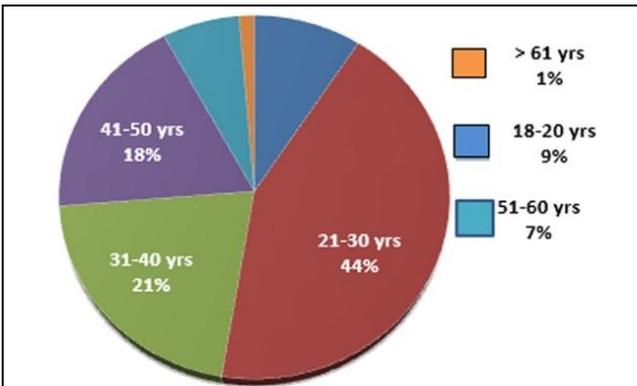


Figure 1. Age Distribution of MDR and XDR TB Patients

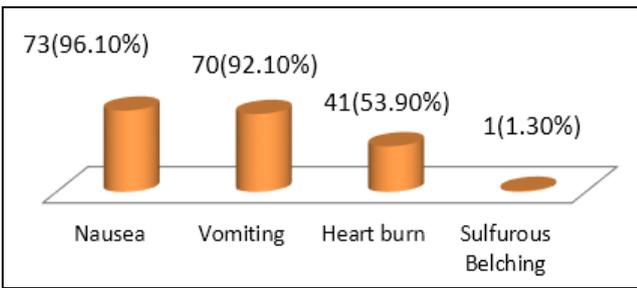


Figure 2. Gastrointestinal System Related ADRs

Adverse drug reactions related to Gastrointestinal system like nausea, vomiting, heart burn and sulphurous belching were noted in most of the patients and these were more common after initiation of treatment (fig 2). Among the GI

related symptoms, incidences of emesis (nausea & vomiting) were higher than even cumulative of all other GI related ADRs and the difference was statistically significant (p, <0.0001).

The patients developed a number of neurological & musculoskeletal ADRs during the treatment with the second line drugs (fig 3). Arthralgia was significantly higher than peripheral neuropathy (p, 0.0003). However, many patients experienced ADRs involving other systems or organs e.g. liver, kidney, heart, eye, skin and others (fig 4). Incidentally, patients with low BMI were more prone to develop adverse drug reactions.

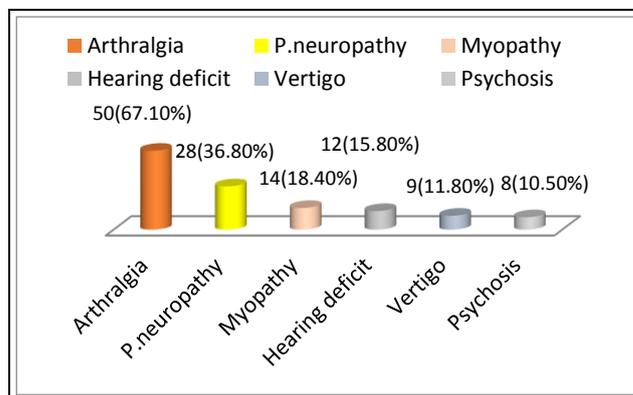


Figure 3. Common Neurological ADRs of 2<sup>nd</sup> Line Anti-Tubercular Drugs

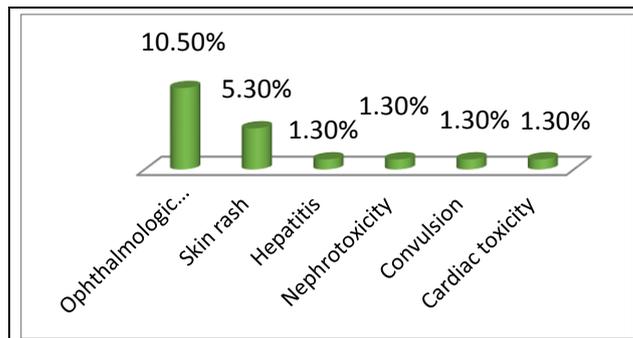


Figure 4. Less Common ADRs of 2<sup>nd</sup> Line Anti Tubercular Drugs Involving Different Systems

**DISCUSSION**

The present study has found that the second line anti-TB drugs are prone to produce adverse drug reactions in almost every patient. There was clustering of Gastrointestinal ADRs in the initial phases of treatment. However, in the later phase many patients suffered from neurological ADR. There were also reports of involvement of eye, liver, kidney, heart or skin in a number of patients. Most of the patients in the present study had suffered from Gastrointestinal related ADRs. This is corroborated with the other studies like Sangeta V et al,<sup>6</sup> Rohan Hire et al,<sup>7</sup> Dela AI.<sup>8</sup>

A large number of patients in the present study (67%) had complaint of arthralgia. This was in contrast to previous studies done by Nathanson et al,<sup>9</sup> Sangeta et al,<sup>6</sup> Hire et al<sup>7</sup> and Dela AI<sup>8</sup> where only few patients experienced minor joint pain. In our study hearing deficit, psychosis, vertigo and

ophthalmological problem were detected in some patients whereas in the study by Sangeta V et al<sup>6</sup> hearing deficit, vertigo and ophthalmological problem was found in fewer patients and psychosis was not reported. In the study by Hire et al<sup>7</sup> arthralgia, vertigo, psychosis ophthalmological problem was reported in fewer patients and hearing deficit was not reported. In the study by Dela AI<sup>8</sup> arthralgia and psychosis were reported in fewer patients, hearing deficit, vertigo, ophthalmological problem were not reported. Renal impairment in our study was found to be less than in the study by Hire et al.<sup>7</sup> (table 1)

Names of ADRs	Our Study (n=76) (%)	Sangeta V et al (Baroda, n=142) <sup>6</sup> %	Rohan Hire et al (Central India, n=110) <sup>7</sup> %	Dela AI (Gujarat, India n=72) <sup>8</sup> %
GI related ADRs	96	100	30	24.5
Arthralgia	67	10.14	4.5	14.38
Hearing deficit	15.8	8.7	--	--
Vertigo	11.8	8.7	1.8	--
Psychosis	10.5	--	4.5	14.38
Ophthalmological problem	10.5	1.44	0.9	--
Renal impairment	1.3	--	2.7	--

**Table 1. Comparison of Various Studies Related to ADRs of 2<sup>nd</sup> Line Anti Tubercular Drugs**

Drugs were stopped or withdrawn in a number of patients. There are several possible explanations for the differences in the number of patients requiring drugs to be removed from the regimen due to ADRs. These include genetic and phenotypic differences of the patients of Eastern India as well as variation in ability of the health care workers to detect ADRs and provide management.

The major strength of the study was complete follow up of the patients for a long duration. The study also utilized the standard tools like WHO-Uppsala Monitoring Center tool for causality assessment which is simple and widely used worldwide. However, there were few weaknesses in the study. These include limited sample size, no formal sample size pre-estimation and possibility of under-reporting of ADRs. As the patients were assessed periodically, and reports of the symptoms were mostly dependent on the capacity of the patients to recall the ADRs, there remained the chances of recall bias and underreporting of non-serious ADRs.

## CONCLUSIONS

Adverse Drug Reactions are common findings with second-line anti TB drugs. Almost all major systems are affected by the ADRs due to these drugs though the large proportion is non-serious and self-limiting. Gastrointestinal ADRs usually cluster around the initiation of treatment whereas neurological and other systems get involved with continuation of treatment. Patients with low BMI are more

prone to develop ADRs. However, there is a need for further studies to explore the serious ADRs and validation of the present findings in larger sample population.

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