

# Profile of Adverse Drug Reactions in Patients on Treatment for Drug Resistant Tuberculosis: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Tuberculosis (TB) is a communicable disease. India accounted for highest number of TB cases in the world and also share largest burden of Multidrug Drug Resistant (MDR) and Extensively Drug Resistant (XDR) TB cases. Drug Resistant Tuberculosis (DRTB) regimen contains second line anti-TB drugs which are more toxic and likely causes Adverse Drug Reaction (ADR). Severe side-effects and ADRs are one of the main reasons for non-adherence and discontinuation of drug regimen.

**Aim:** To assess the profile of the ADRs in patients on treatment for drug resistant TB.

**Materials and Methods:** The present cross-sectional study was done in DRTB ward of Respiratory Medicine, SCB MCH, Cuttack, Odisha, India. Patients were selected as per inclusion criteria. Adverse reactions were noted by detailed history, general and systemic examination with relevant Laboratory investigations. Causality assessment of ADRs was carried out using Naranjo and World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) algorithm. Severity of ADR was carried out using

Modified Hartwig and Seigel scale. Data collected was entered and analysed using IBM Statistical Package for Social Sciences (SPSS) 26, univariate analysis expressing odds ratio and 95% CI was found. Variables with a p-value < 0.05 in univariate analysis are considered significant.

**Results:** Among the 160 DRTB cases enrolled, 85 cases developed ADRs. Among the ADRs Gastrointestinal (GIT) (52.13%) was highest followed by Central Nervous System (CNS) (15.3%) and Cardiovascular System (CVS) (7.69%). Causality assessment done by Naranjo scale showed 72.6% are probable. Among the causality assessment done by WHO-UMC, majority were of possible type i.e., 51.3%. The severity assessment using Modified Hartwig and Seigel scale detected majority ADRs are mild type (63.2%).

**Conclusion:** The majority of ADRs are mild and the frequency of ADRs is low in oral bedaquiline containing regimens as compared to previous injectable containing drug resistant regimen. In this study most common ADR is of Gastro intestinal origin and serious ADRs are very rare.

**Keywords:** Communicable diseases, Drug resistance, Tuberculosis burden

## INTRODUCTION

Tuberculosis is a communicable disease. An estimated 8.2 million people were newly diagnosed with TB in 2023 globally [1]. Estimated annual number of people who developed MDR/RR TB was four lakhs. New TB cases of R-R TB were 3.2% in 2023. Previous treated case of MDRTB was 16% in 2023. A 1.4 million incidents case of isoniazid resistant TB in 2023 (including both Rifampicin sensitive and Rifampicin Resistant TB). Globally, MDR/RR TB caused an estimated 1,50,000 deaths in 2023. In the year 2023, India had largest share of the global number of people estimated to have developed, MDR/RR TB cases i.e., 27% of global drug resistant TB cases. The National Anti-TB Drug Resistance Survey (NDRS) published data about 28% of TB patients were resistant to any drugs and 6.19% had MDRTB [2]. The emergence and spread of MDRTB pose significant challenges to the control and successful eradication of TB particularly in the developing countries [3]. Drug resistant TB regimen requires a combination of a second line anti-TB drug. DRTB treatment is quite challenging owing to prolonged duration, more complex and more toxic regimens that likely cause of ADR [4].

Severe side-effects and ADRs are one of the major reasons for non-adherence and discontinuation of the drug regimen. Withdrawal of the drugs even for a short period of time can increase the resistance against the drug which may further worsen the condition [5]. The overall incidence of adverse drug events caused by anti TB medications ranges from 5.1%-83.5% in different populations [6]. ADRs contribute to increased morbidity in patients with TB [7]. As a result, it seems that it is required to recognise ADR's and to

determine the underlying connection of ADR and drugs. Diverse techniques of causality evaluation are available for determining the strength of the association between the occurrence of ADR's and drug exposure [8]. Although many studies about ADRs have been published, only a few discussed the causality assessment [9-13] and its impact on the patients. The main purpose of this research work was to characterise the pattern of ADRs, as well as to analyse the causality and severity of ADRs associated with drug resistant anti tubercular therapy.

## MATERIALS AND METHODS

The present cross-sectional study was carried out at DRTB ward of Department of Respiratory Medicine of SCB Medical College and Hospital, Cuttack, Odisha, India. for a period of May 2023 to April 2024. The sample size included all patients receiving treatment for DRTB over a period of one year. In this study, a total of 160 patients were enrolled. The Declaration of Helsinki's ethical criteria were adhered all times. The protocol of Research was submitted to the Institutional Ethics Committee of SCBMCH and was initiated after getting approval via letter no-1309/08.05.2023, Reg no-ECR/84/Inst/OR/2013/RR-20.

**Inclusion criteria:** The inclusion criteria are, all confirmed cases of DRTB of both genders undergoing treatment who gave consent for the study and aged ≥15 years are included in this study.

**Exclusion criteria:** The exclusion criteria are patients aged <15 years, pregnant females, PLHIV cases and patients not willing for treatment or giving consent are excluded.

## Study Procedure

All study subjects were evaluated after written informed consent was obtained. Thorough detailed history, general and systemic examination done. Pre-treatment investigations were done as per National Guidelines PMDT, March 2021 [14]. Cardiology, psychiatry and ophthalmic clearance were done before starting the drug therapy.

The treatment was given as per PMDT, March 2021 guidelines. All the patients enrolled in the study were monitored for ADRs during their hospital stay and later followed up personally via telephonic mode. For ADRs defined by lab values at least one documented abnormal value was considered. For those not defined by lab values, event was considered if the chest physician documented the reaction in the patient case file according to his or her clinical criteria.

causality assessment of ADRs were carried out using, Naranjo Algorithm [15] WHO-UMC (World Health Organisation-Uppsala Monitoring Centre) [16]. The severity of ADRs was carried out using Modified Hartwig and Siegel Scale [17].

**Causality assessments were carried out using Naranjo's algorithm causality assessment scale [15]:** Total scores range from -4 to +13; the reaction is considered: Definite, score- 9 or higher • Probable, score- 5 to 8 • Possible, score- 1 to 4 • Doubtful, score- 0 or less.

**WHO-UMC causality assessment [16]:** WHO-UMC classification of ADRs into following categories on the basis of causality assessment:

- Certain- Any abnormal laboratory test or clinical event and its reasonable relationship with administration of drug- not explainable by concurrent disease or drugs/chemicals.
    - De-challenge (withdrawal of drug) should be possible and clinically relevant both pharmacologically and physiologically.
    - Rechallenge information should be satisfactory.
  - Probable/likely- Any abnormal laboratory test or clinical event and its reasonable relationship with administration of drug.
    - Unlikely to be explained by concurrent diseases or drug/chemicals.
    - De challenge- clinically reasonable response.
    - Rechallenge information not required.
  - Possible- Any abnormal laboratory test or clinical event and its reasonable relationship with administration of drug.
    - Can also be explained by the ongoing disease or other drugs/chemicals.
    - De challenge- lacking or unclear.
  - Unlikely- Any abnormal laboratory test or clinical event and its improbable relationship with administration of drug.
    - Underlying diseases or drugs can provide a possible explanation.
  - Conditional/unclassified- Any abnormal laboratory test or clinical event reported as an adverse effect.
    - More data needed for proper assessment.
    - Additional data under examination.
  - Unassessable/Unclassifiable- Report as an adverse reaction.
    - Information-insufficient or contradictory so report cannot be judged.
- Severity of ADRs was assessed using Modified Hartwig and Siegel scale [17] as:
- Mild/Minor: No antidote, therapy or prolongation of hospitalisation is required.
  - Moderate: Here, it requires changes in drug therapy, specific treatment, or an increase in hospitalisation at least by a day.
  - Severe: Potentially life threatening, causing permanent damage.

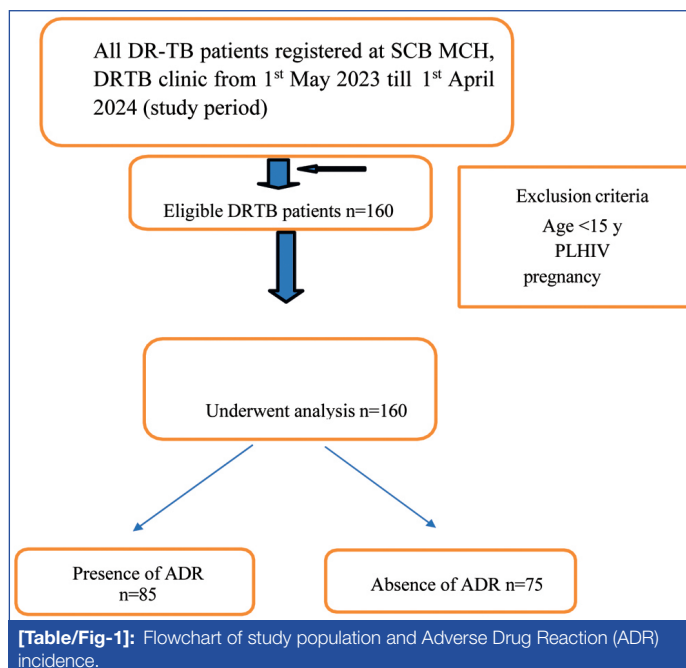
References from the concerned departments were taken for the patients with severe ADRs and were followed up regularly.

## STATISTICAL ANALYSIS

Data collected was entered and analysed using IBM SPSS 26, univariate analysis expressing odds ratio and 95% CI was found. Variables with a p-value <0.05 in univariate analysis are considered significant. Descriptive statistics was calculated as frequency, percentage, mean and standard deviation. Kappa statistics used to identify the agreement between two scales of causality of ADRs.

## RESULTS

Flowchart of study population and Adverse Drug Reaction (ADR) incidence is shown in [Table/Fig-1]. ADR was seen in 85 (53.12%) cases out. Of 160 DRTB cases, a total of 117 kinds of ADRs were recorded.



[Table/Fig-2] shows the univariate analysis of demographic profile of ADR cases that reveals age, Body Mass Index (BMI), marital status, substance abuse, previous TB drug resistance pattern, case findings (cavitations, fibrosis, left destroyed lung and normal), type of TB and current drug regimen were significantly associated (<0.05 level of significance). There was no difference concerning sex in the odds ratio (OR 0.648, 95% CI: 0.451-0.913) p=0.961, for men compared to women. A 74.24% cases reveals bilateral cavitation and 25.75%

| Variable              | Total n (%) | Odds ratio (95% CI) | p-value |
|-----------------------|-------------|---------------------|---------|
| <b>Gender</b>         |             |                     |         |
| Female                | 25 (29.41)  | Referent            |         |
| Male                  | 60 (70.58)  | 0.648 (0.451-0.913) | 0.961   |
| <b>Age</b>            |             |                     |         |
| Total n (%)           |             |                     |         |
| 15-30                 | 41 (48.23)  | Referent            | 0.001   |
| 31-45                 | 19 (22.35%) | 0.241 (0.098-0.467) | 0.001   |
| 46-60                 | 17 (20)     | 0.348 (0.116-0.563) | 0.001   |
| 61-75                 | 8 (9.41)    | 0.147 (0.038-0.412) | 0.023   |
| <b>BMI</b>            |             |                     |         |
| Total n (%)           |             |                     |         |
| <18.5                 | 54 (63.52)  | Referent            | 0.028   |
| 18.5-24.9             | 29 (34.11)  | 1.214 (1.034-1.478) | 0.037   |
| ≥25                   | 2 (2.35)    | 1.463 (1.138-1.687) | 0.041   |
| <b>Marital status</b> |             |                     |         |
| Total n (%)           |             |                     |         |
| Married               | 57 (67.05)  | Referent            |         |
| Unmarried             | 28 (32.94)  | 2.123 (1.897-2.347) | 0.001   |

| Co-morbidity                        | Total n (%) |                     |       |
|-------------------------------------|-------------|---------------------|-------|
| Present                             | 81(95.29)   | Referent            |       |
| Absent                              | 4(4.70)     | 1.717 (1.542-1.937) | 0.089 |
| Substance abuse                     | total n (%) |                     |       |
| Smoking                             | 4 (4.70)    | Referent            | 0.001 |
| Alcohol                             | 12 (14.11)  | 0.794 (0.537-0.912) | 0.004 |
| Smoking and alcohol                 | 16(18.82)   | 0.891 (0.712-1.217) | 0.003 |
| Tobacco chewing                     | 1(1.17)     | 0.347 (0.214-0.648) | 0.001 |
| No substance abuse                  | 52 (61.17)  | 0.408 (0.217-0.736) | 0.027 |
| Previous TB treatment               | Total (%)   |                     |       |
| Present                             | 57 (67.05)  | Referent            |       |
| Absent                              | 28 (32.94)  | 0.317 (0.214-0.617) | 0.213 |
| Previous TB drug resistance pattern |             |                     |       |
| DS                                  | 46 (54.11)  | Referent            | 0.004 |
| DR                                  | 2 (2.35)    | 1.412 (0.826-2.147) | 0.021 |
| DS + DR                             | 9 (10.58)   | 1.317 (0.912-1.985) | 0.011 |
| Radiological findings               |             |                     |       |
| Infiltration                        | 17 (20)     | Referent            | 0.072 |
| Cavitation                          | 66 (77.6)   | 0.682 (0.347-0.894) | 0.037 |
| Fibrosis                            | 8 (9.4)     | 0.543 (0.341-0.912) | 0.049 |
| Left destroyed lung                 | 4 (4.7)     | 0.841 (0.417-1.212) | 0.012 |
| Effusion                            | 3 (3.5)     | 0.633 (0.342-0.937) | 0.052 |
| Normal                              | 8 (9.4)     | 0.787 (0.548-0.988) | 0.027 |
| Type of TB Total (%)                |             |                     |       |
| PTB                                 | 72 (84.7%)  | Referent            | 0.012 |
| EPTB                                | 11 (12.9)   | 1.439 (1.129-2.276) | 0.034 |
| Disseminated                        | 2 (2.4)     | 1.214 (0.989-1.642) | 0.048 |
| Type of resistance Total (%)        |             |                     |       |
| H-R                                 | 6 (7.05)    | Referent            | 0.189 |
| R-R                                 | 60 (70.5)   | 0.813 (0.314-1.761) | 0.272 |
| H-R, R-R                            | 9 (10.5)    | 1.319 (0.842-1.468) | 1.142 |
| H-R, R-R, Fq-R                      | 7 (8.2)     | 1.43 (1.102-1.788)  | 0.076 |
| R-R, Fq-R                           | 3 (3.5)     | 0.987 (0.648-1.637) | 0.127 |
| Current drug regimen total (%)      |             |                     |       |
| AOL                                 | 55 (64.7)   | Referent            | 0.011 |
| STR                                 | 24 (28.2)   | 0.783 (0.324-1.104) | 0.032 |
| H mono                              | 6 (7.1)     | 0.581 (0.286-0.881) | 0.008 |

**[Table/Fig-2]:** Univariate analysis of demographic profile of ADR cases.  
DS: Drug sensitive; DR: Drug resistant; H-R: Isoniazid resistant; R-R: Rifampicin resistant; Fq-R: Fluoroquinolone resistant; AOL: All oral longer regimen; STR: Shorter oral regimen

cases there is unilateral cavitation in CXR (PA) view. A 70.5% are Rifampicin resistance category, 10.5% cases show MDR, 8.2% Pre XDR, 7.05% with H resistance.

In BMI  $\geq 25$  group showed higher OR (OR 1.463, 95% CI: 1.138-1.687)  $p=0.041$ . [Table/Fig-3] shows the frequency of ADRs among DRTB patients having one ADR among 67(78.8%) cases, two ADR in 16 (18.8%) cases and ADR ( $\geq 3$ ) noted in 2 (2.35%) cases. [Table/Fig-4] depicts the latency of ADRs in 40 cases (47.1%) is 15 days- 3 months followed by 35 cases (41.2%) in 5-15 days and 10 cases (11.8%) after three months.

| No. of ADR | No. of patients (%) |
|------------|---------------------|
| 1          | 67 (78.8)           |
| 2          | 16 (18.8)           |
| $\geq 3$   | 2 (2.35)            |

**[Table/Fig-3]:** Frequency of ADRs among DRTB patients.

| Duration    | No. of patients (%) |
|-------------|---------------------|
| 5-15 days   | 35 (41.2)           |
| 15-3 months | 40 (47.1)           |
| >3 months   | 10 (11.8)           |

**[Table/Fig-4]:** Latency of ADRs.

[Table/Fig-5] illustrates the prevalence of Gastrointestinal Test (GIT) upset was reported in 61 (52.13%) cases among the 117 ADRs in the current study making it the most prevalent symptom. This was followed by CNS ADR in 18 (15.3%) cases, cardiovascular 9 (7.69%) cases, musculoskeletal in 7 (5.9%) cases, endocrine in 5 (4.27%) cases, psychiatric manifestations in 2 (1.70%) and others that is blurring vision in two cases and pancytopenia in one case. In [Table/Fig-6], Naranjo scale was used for causality assessment of 117 ADRs which showed majority of patients around 85 (72.6%) are probable followed by 31 (26.4%) ADRs are definite and one ADR (0.85%) are possible.

The WHO-UMC Scale was used for causality assessment of 117 ADRs which showed majority of 58 (49.5%) ADRs as possible, followed by 28 (23.9%) cases are probable and 27(23.07%) are certain.

Kappa value=0.944 (Perfect agreement between Naranjo algorithm & WHO UMC causality criteria).

Standard Error- 0.038 95% CI: 0.86- 1.0

In the above table, WHO-UMC causality criteria, shows perfect agreement with Naranjo algorithm in calculating ADRs. The confidence interval is 0.86-1.0. [Table/Fig-7] compares the Naranjo ADR scale and WHO-UMC ADR scale of causality association. It

| S. No. | Type of ADR                   | No. of Patient | Drug Responsible                                            | Naranjo  |          |          |          | WHO UMC  | Hartwig  |
|--------|-------------------------------|----------------|-------------------------------------------------------------|----------|----------|----------|----------|----------|----------|
|        |                               |                |                                                             | Definite | Probable | Possible | Definite |          |          |
| 1      | <b>Gastrointestinal</b>       | <b>61</b>      | Bedaquiline, Ethionamide, Pyrazinamide, Isoniazid           |          |          |          |          |          |          |
|        | a) Nausea and vomiting        | 44             |                                                             |          | Probable |          |          | Possible | Mild     |
|        | b) Dyspepsia                  | 13             |                                                             |          | Probable |          |          | Possible | Mild     |
|        | c) Hepatotoxicity             | 4              |                                                             |          | Definite |          |          | Certain  | Moderate |
| 2      | <b>Central nervous system</b> | <b>18</b>      | Linezolid, Levofloxacin, Cycloserine, Ethambutol, Isoniazid |          |          |          |          |          |          |
|        | a) Tingling and Numbness      | 13             |                                                             |          | Definite |          |          | Certain  | Moderate |
|        | b) Burning sensation of feet  | 5              |                                                             |          | Probable |          |          | Probable | Mild     |
| 3      | <b>Musculoskeletal</b>        | <b>7</b>       | Pyrazinamide, Fluoroquinolone, Bedaquiline                  |          |          |          |          |          |          |
|        | a) Arthralgia                 | 6              |                                                             |          | Probable |          |          | Probable | Moderate |
|        | b) Myalgia                    | 1              |                                                             |          | Possible |          |          | Possible | Mild     |
| 4      | <b>Endocrine</b>              | <b>5</b>       | Ethionamide                                                 |          |          |          |          |          |          |
|        | Cold intolerance and weakness | 5              |                                                             |          | Probable |          |          | Probable | Moderate |

|   |                            |           |                                                     |          |          |                 |
|---|----------------------------|-----------|-----------------------------------------------------|----------|----------|-----------------|
| 5 | <b>Dermatology</b>         | <b>12</b> |                                                     |          |          |                 |
|   | a) Pigmentation            | 11        | Clofazimine                                         | Probable | Probable | Mild            |
|   | b) Steven Johnson Syndrome | 1         | Any drug                                            | Definite | Certain  | Severe          |
| 6 | <b>Cardiology</b>          | <b>9</b>  |                                                     |          |          |                 |
|   | QTc prolongation           |           | Bedaquiline, Delamanid, Fluroquinolone, Clofazimine | Definite | Certain  | Moderate/Severe |
| 7 | <b>Ophthalmology</b>       | <b>2</b>  |                                                     |          |          |                 |
|   | Blurring of Vision         | 2         | Linezolid, Isoniazid, Ethambutol, Ethionamide.      | Definite | Certain  | Severe          |
| 8 | <b>Pshychiatry</b>         | <b>2</b>  |                                                     |          |          |                 |
|   | a) Depression              | 1         | Cycloserine, levofloxacin                           | Probable | Probable | Moderate        |
|   | b) Suicidal Tendency       | 1         | Cycloserine                                         | Definite | Certain  | Severe          |
| 9 | <b>Hematological</b>       | <b>1</b>  |                                                     |          |          |                 |
|   | Pancytopenia               | 1         | Linezolid                                           | Definite | Certain  | Severe          |

[Table/Fig-5]: Frequency of individual ADRs.

| WHO UMC Causality criteria | Naranjo algorithm |          |
|----------------------------|-------------------|----------|
|                            | Definite          | Probable |
| Certain                    | 24                | 0        |
| Probable                   | 2                 | 65       |

[Table/Fig-6]: Comparison of Naranjo scale and WHO-UMC scale.

| Naranjo algorithm | No. of ADR | %     | WHO-UMC Causality criteria | No. of ADR | %    |
|-------------------|------------|-------|----------------------------|------------|------|
| Definite          | 31         | 26.4  | Certain                    | 27         | 23.8 |
| Probable          | 85         | 72.6  | Probable                   | 28         | 24.7 |
| Possible          | 1          | 0.85% | Possible                   | 58         | 51.3 |
|                   |            |       | Unlikely                   |            |      |
|                   |            |       | Unclassified               |            |      |

[Table/Fig-7]: Comparison of Naranjo scale &amp; WHO-UMC scale.

is seen that in Naranjo ADR scale 85 (72.6%) ADRs are probable, 31 (26.4%) ADRs are definite and 1 (0.85%) is possible where as in WHO-UMC Causality association scale shows 58(51.3%) ADRs are possible, 28 (24.7%) ADRs are probable and 27 (23.8%) ADRs are certain. The Modified Hartwig Siegel scale used for severity assessment showed maximum ADRs are 74(63.2%) which is of mild severity [Table/Fig-8].

| Severity | No. of ADRs (%) |
|----------|-----------------|
| Mild     | 74 (63.2)       |
| Moderate | 35 (29.9)       |
| Severe   | 8 (6.83)        |

[Table/Fig-8]: Severity assessment of ADRs through Modified Hartwig Siegel scale.

## DISCUSSION

In the current study, ADR was seen in 85 (53.12%) cases out of 160 cases which is similar to study by Sangolli B et al., (52.16%), Dela AI et al., (57.6%) and Panda SK et al., (39%), whereas Massud A et al., Sant'Anna FM et al., and Kaur M et al., showed 81% 78.6%, and 80%, respectively ADRs in their study [18-23]. In the current study, majority of the patients are in age group of 15-30 years (48.2%). In this study, there was no difference concerning sex in the odds ratio (OR 0.648, 95% CI: 0.451-0.913)  $p=0.961$ , for men compared to women which is in accordance to Kumari A et al., where the  $p$ -value concerning sex is 0.892 [9].

In this study, 63.5% cases were underweight (BMI <18.5 kg/m<sup>2</sup>) which is similar to the study done by Sangolli B et al., [18]. In this study, BMI  $\geq 25$  group showed higher Odd's

Ratio (OR) with  $p=0.041$  whereas in study by Sangolli B et al., BMI < 18.5 kg/m<sup>2</sup> group of ADR showed  $p$ -value < 0.05 showing significant association [18]. In the current study, 17.64% cases were associated with Type 2 DM which is similar to study by Yang TW et al., (22.6%) [24]. In this study, substance abuse in form of both alcohol and smoking in 18.82% cases. But study by Panda SK et al., 41% associated with both smoking and alcohol [20]. Co-morbidities like low BMI, Type 2 DM, smoking alcohol toxicity is associated with impaired immunity that causes increased drug toxicity by Tola H et al., [25].

In this study, in chest X-ray 74.24% cases reveals bilateral cavitation and 25.75% cases there is unilateral cavitation. Similar study by Massud A et al., 56.8% cases had bilateral cavitation and 24.7% cases had unilateral cavitation [21]. This suggests cavitory lesion is predominant in DRTB. Out of all DRTB cases, 70.5% are Rifampicin resistance category, 10.5% cases show MDR, 8.2% Pre XDR and 7.05% cases with H Mono resistance. In similar study by Waghmare MA et al., MDRTB is 30.4% cases and Pre XDR is 64% [26]. In another study, by Panda SK et al., MDR was seen in 60% cases, R-R in 35.8% and H-R in 2.10% [20].

The frequency of ADR in the current study is 53.1%. In similar study, by Swamy PN and Kumar VS is 43%, Khan FU et al., ADR occurrence is 50.8% [27,28]. The frequency of ADRs in recent studies is low due to omission of injectable drugs. In this study, with 117 ADRs, GIT toxicity was seen in 52.13% of cases similar to Khan FU et al., [28] (47.1%), Massud A et al., (66.7%) and Kaur M et al., (81.67%) of cases [21,23]. In current study, one of the reason of high GI ADR cases were most likely due to underweight They might not have tolerated the multidrug regimen. Previous studies also reported that underweight patients are more intolerant and have GI ADRs (Laghari M et al., Zhang Y et al., [7,29]). Among GI ADRs in this study, 72.13% cases have nausea and vomiting. In similar study by Panda SK et al., (19%) and Kathi B et al., (80%) cases associated with nausea and vomiting [20,30]. Similar study by Panda SK et al., (11%) and Swami PN et al., (4.65%) [20,27].

In the present study, 15.3% cases manifested as peripheral neuropathy. In similar study by Panda SK et al., (16%), Kaur M et al., (10%), Swamy PN and Kumar vs (6.20%), Kathi B et al., (2.5%) [20,23,27,30]. The higher incidence of peripheral neuropathy in may be because maximum cases are underweight in this study and suffering with malnutrition Mafukidze AT et al., [31].

The current study shows 10.25% cases have dermatological/skin manifestation in form of hyperpigmentation in (9.4%) cases. This is in accordance to Mary Prince R et al., where the incidence of hyperpigmentation is 8.77% [31]. Paikray E et al., shows the incidence of hyperpigmentation in patient under DRTB treatment was 9.3% [10]. In the current study, cardiovascular system ADR, in the form of QTc F prolongation was seen in 9 (10%) cases. Similar study by Paikray E et al., (33.7%), Kathi B et al., and Mary Prince R et al., (15.78%) showed 10% cases with QTc prolongation [10,30,32]. QTc prolongation effects are associated with use of new DRTB drugs like bedaquiline, along with fluoroquinolones and clofazamine. Electrolyte imbalance can also lead to QTc prolongation.

In this study, musculoskeletal ADRs is 5.9%. The most common being arthralgia (5.12%) similar to Swamy PN and Kumar VS [27] (6.20%). Studies by Kathi B et al., [30], Paikray E et al., [10] and Mary Prince R et al., [32] shows 2.5%, 11.6% and 12.28% arthralgia cases. Pyrazinamide and quinolones are associated with arthralgia. Pyrazinamide increases the blood uric acid level and quinolones destroy cartilages. The current study showed endocrine ADRs in form of hypothyroidism in five cases (4.27%). Similar studies by Paikray E et al., [10] Massud A et al., [21] and Teshome HT et al., [33] show 1.2%, 1.84% and 1.2% incidence of hypothyroidism. The disparity in current study may be because, three cases already had hypothyroidism as Co-morbidity and so dose of thyroxine supplement increased with temporarily stopping the treatment.

In this study, psychiatry ADRs is seen in 1.70% cases. Out of which one person had depression and one person with suicidal tendency similar to Paikray E et al., (2.3%) and Swamy PN and Kumar VS 1.55% with depression and 4.65% cases with suicidal tendency [10,27]. A study by Mary Prince R et al., showed 1.75% cases with depression [32]. Depression, Psychosis and suicidal tendency are associated with cycloserine. In the current study, 1.70% cases are associated with blurring of vision and diminished vision. Similar study by Paikray E et al., had blurred vision in 1.2% cases [10]. Linezolid, ethambutol and high dose INH can cause diminished vision due to optic and retrobulbar neuritis. Linezolid especially causes irreversible optic neuritis,

In the current study, only one case (0.85%) showed pancytopenia which is suspected due to Linezolid. A similar study by Prasad R et al., suggests 1.08% cases had pancytopenia [34]. Linezolid

associated with such hematological disorders. In the current study, 78.8% cases have atleast one ADR, 18.8% cases have two ADRs and 2.35% cases have  $\geq 3$  ADRs. These findings are in consistent with a study done by Khan FU et al., where at least one ADR is in 50.8% cases have at least three ADRs [28].

In this study, 88.23% cases have latency period of ADR within three months and 11.67% cases have latency period of ADR after three months. Similarly in Anna S et al., they found latency period of ADRs in DRTB more than three months [22]. This contradictory result in this study is because in most of the cases patients are on oral bedaquiline containing regimen where ADRs are detected on early phase of treatment. In this study, in 3.41% cases dose reduction of the suspected drug was there. In 13.67% cases temporary withdrawal was there and in 11.97% cases permanent withdrawal of drugs was undertaken. In similar study by Kaur M et al., discontinuation of drug therapy was there in 34.17% cases with drug regimen modification done in 34.17% cases, permanent withdrawal of drugs done in 10.83% cases [23]. In similar study by Mishra A et al., drug withdrawal done in 63.05% with dose reduction in 5.43% cases [12].

In this study, causality assessment of ADRs according to Naranjo Scale is 72.6% under probable category and 26.4% of ADRs are under definite category. In similar study by Lakhani P et al., 37.75% ADRs are probable and 3.06% are certain [11]. In the study by Swamy PN and Kumar VS 41.08% ADRs are probable, 53.4% are possible, 3.10% ADRs are definite and 2.32% are doubtful [27]. In the current study, causality assessment of ADR according to WHO-UMC, scale is 51.3% ADRs are possible, 24.7% are probable and 23.8% cases are certain. In another study by Mishra A et al., 73.92% cases ADRs are probable and 13.04% both of certain and possible category [12]. According to Lakhani P et al., 51.02% probable and 41.83% possible category [11].

In categorisation of Severity Assessment through Modified Hartwig and Siegel scale, 63.2% ADRs are mild in nature, 29.9%, are moderate and 6.3% are severe in nature. This is in accordance to Lakhani P et al., where 57.14% ADRs are mild, 35.73% are moderate and 6.12% ADRs are severe in nature [11]. Another study by Mishra A et al., 41.30% are mild, 40.22% are moderate and 18.48% ADRs are of severe variety [Table/ Fig-9] [9-12,32].

| Sl. No. | Author's name & year          | Place of study                                                | Population studied | Patients developed ADRs | Type of ADRs                                                                                                                                                                                                                                                                                                             | Causality assessment of ADR acc. to WHO-UMC                                                                                                      | Causality assessment through Naranjo algorithm | Severity assessment through Modified Hartwig & Siegel scale                                                                               |
|---------|-------------------------------|---------------------------------------------------------------|--------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 1       | Paikray E et al., (2022) [10] | SCB Medical College & Hospital., Cuttack                      | 86                 | 86                      | Most frequent is QTcF prolongation 33.7%, f/b vomiting (26.7%), vertigo (12.8%), arthralgia (11.6%), weakness (11.6%), hyper pigmentation (9.3%), itching (2.3%), hypothyroid (1.2%), depression /suicidal (2.3%) each, & blurred vision (1.2%). Majority ADRs were mild and possible relationship with suspected drugs. | In Bedaquiline group-possible (68%); certain (18.6%); probable (13.4%)<br>In Delaminid group-possible (57.3%); certain (10.3%); probable (32.4%) | Not done                                       | In Bedaquiline group-mild (61.5%); Moderate (26.1%); severe (12.3%).<br>In Delaminid group-mild (71.4%); moderate (14.3%); severe (14.3%) |
| 2       | Kumari A et al., (2018) [9]   | Prasad R Government Medical College, Kangra, Himachal Pradesh | 104                | 104                     | Details not studied                                                                                                                                                                                                                                                                                                      | Possible (82%); certain (4%); probable (1%)                                                                                                      | Not done                                       | Mild (21%); moderate (49%); severe (17%)                                                                                                  |
| 3       | Mishra A et al., (2022) [12]  | Jawaharlal Nehru Medical College, Ajmer, Rajasthan            | 92                 | 68                      | ADRs are GI (6.52%), hepatitis (3.26%), pshychiatry (11.96%), pshychosis (4.35%), musculoskeletal (18.48%) in form of joint pain; peripheral neuropathy (4.35%); itching (4.35%) ophthalmic (3.26%); pancytopenia (1.08%)                                                                                                | Probable (73.92%);certain (13.04%); possible (13.04%)                                                                                            | Not done                                       | Mild (41.3%); moderate (40.22%); severe (18.48%)                                                                                          |

|   |                                   |                                                                      |     |    |                                                                                                                                                                                                                                         |                                                                              |                                                       |                                                  |
|---|-----------------------------------|----------------------------------------------------------------------|-----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------|
| 4 | Mary Prince R et al., (2023) [32] | Department of Respiratory Medicine, Government Medical College, Kota | 62  | 57 | Systemic ADRs-Electrolyte imbalance (40%); gastric intolerance (38%); hepatic derangement (17%) Arthralgia (12.28%); QTc prolongation (15.78%); hyperpigmentation (8.77%); depression (1.75%); anaemia 2 cases                          | Not done                                                                     | Not done                                              | Not done                                         |
| 5 | Lakhani P et al., (2019) [11]     | King George's Medical College, Lucknow, Uttar Pradesh                | 115 | 98 | Gastrointestinal (GIT) -nausea/vomiting/epigastric pain (38.76%); CNS (21.24%); Impaired hearing (7.14%); Dermatology (6.12%); Arthralgia (5.10%); Hypothyroid (2.04%); Ophthalmology (blurred vision) (2.04%) Renal impairment (3.06%) | Probable (51.02%); Possible (41.83%); Unlikely (6.12%); Unclassified (1.02%) | Probable (37.75%); possible (58.18%); certain (3.06%) | Mild (57.14%); Moderate (35.73%); Severe (6.12%) |
| 6 | Present (2024)                    | SCB Medical College, Cuttack (dept. of Respiratory medicine)         | 160 | 85 | Among the ADRs Gastrointestinal (GIT) (52.13%) was highest followed by Central Nervous System (CNS) (15.3%) and Cardiovascular System (CVS) (7.69%)                                                                                     | Possible (49.5%); probable (23.9%); Certain (23.07%)                         | Probable (72.6%); Definite (31%); Possible (0.85%)    | Mild (63.2%); moderate (29.9%); Severe (6.83%)   |

[Table/Fig-9]: Comparison of Adverse Drug Reactions (ADRs) in DRTB patients across different studies [9-12,32].

## Limitation(s)

It is a single center study and may be associated with a selection bias. There is no randomised control group for comparison. There might be some discordance between physicians and patients about certain ADRs leading to under reporting of ADRs like bodyache, dizziness nausea and headache in the current study. The current study lacks laboratory investigations like plasma or tissue drug concentration investigations for causality assessment.

## CONCLUSION(S)

The DRTB treatment is a major challenge due to the long duration of treatment and multiple drugs used in the regimen. The wide spectrum of potential ADR reactions further escalates this challenge. The majority of ADRs is mild and may have been related to implicated medicines. Although ADRs were commonly reported, the majority of the patient continued therapy by either receiving supportive care or by stopping offending medication, as we are able to see in this study. Serious adverse reactions are rare in the current study. Bedaquiline coupled with other active medications reduce adverse drug events in MDRTB patients as compared to previous injectable drug regimen for DRTB. As a result, Bedaquiline usage in DRTB patients should be promoted.

In order to resolve the problem, associated with ADR prompt identification and management of ADRs holds the key to successful outcome. Under programmatic condition, training of the primary health care worker, development of management protocol feasible at peripheral centre and prompt referral to higher centre if required can have a major impact on treating the adverse reactions and hence the management of drug resistant TB.

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