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RESEARCH ARTICLE

Adverse Drug Reactions in Multi-Drug Resistant Tuberculosis Patients, in India, who had received DOTS Plus Treatment along with Home Care and Counselling

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ABSTRACT:

Background: Adverse drug reactions are common in MDR-TB patients on treatment. An adverse drug reaction (ADR) is defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product. Revised National Tuberculosis Control Programme used 24-months long Category IV/DOTS Plus regimen for treatment of MDR-TB.

The Community Health Department of St. Stephen's Hospital started an innovative project in 2009, in the form of Home Care for MDR Patients and it concluded with Long-term Follow-up of patients, who had received DOTS Plus Treatment along with Home Care and Counselling (2015).

Aims: To study the spectrum, severity and the risk factors for ADRs in MDR-TB patients.

Methods: In this retrospective study files of 109 MDR-TB patients who had received treatment along with home care and counselling support, were reviewed. The study was conducted between January to May 2024.

Results: Out of 109 MDR TB patients there were 68 (62%) developed one or more ADR. Joint pains 44(40.36%), was the most commonly observed ADR, followed by nausea 29(26.6%) and vomiting 25(22.93%), weakness 23(21.1%), anxiety and depression 16(14.67%), difficulty in breathing 14(12.84%), tremors 13(11.9%), giddiness 11(10.1%), skin rashes 10(9.2%).

According to Hartwig Scale mild ADRs were 58.8%, moderate 5.9% and severe 35.3%. Patients who had BMI <18.5 experienced less ADRs with an Odds Ratio =0.22; 95% CI=0.06 to 0.72, p=0.0124. Unemployment was associated with higher number of ADRs OR=3.5; 95% CI=0.99 to 12.29, p=0.05.

Sixty-two % MDR TB patients had ADRs. Our treatment outcomes showed 41(60.3) as cured, 24(35.3) died, 2(2.9) defaulted and 1(1.5) failed treatment. This was possible because healthcare teams counselled and provided all possible support to patients 24x7 thus improving adherence to therapy.

Conclusion: ADRs occurred in more than half of the cases, with joint pain being the most common. Interventions such as counselling of patients and their family on importance of adherence to drugs at the initiation of treatment, provision of nutritional support, psychological counselling and motivation, instant referral for ADRs and care of patients at referred facilities, help patients not becoming defaulters.

Keywords: Adverse Drug Reactions, DOTS Plus, Multidrug-Resistant Tuberculosis.

Introduction:

Tuberculosis is a social disease. In India its determinants are overcrowding, poor housing, malnutrition and a very large vulnerable population of elderly, children and women.[1] Many countries participating in a global survey of anti-TB drug resistance, registered cases of Multi Drug Resistant tuberculosis (MDR-TB) by mid-1990s.[2] MDR-TB is defined as disease due to *Mycobacterium tuberculosis* that is resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs.[3] An adverse drug reaction (ADR) can be defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.[4]

In 1962 Government of India (GOI) launched National TB Program (NTP) and set up District TB Centres. In 1993 World Health Organization (WHO) declared TB as a Global Emergency. In 1997 GOI revised NTP to Revised National Tuberculosis Control Programme (RNTCP) – introduction of Directly Observed Treatment Short-course (DOTS). From 2005 – 2011 Second Phase of RNTCP – Pan India coverage started. By 2011 India accounted for 24 percent of the 5.7 million new and relapse TB cases notified globally in 2010 (WHO, 2011a). It had the second highest total number of estimated MDR TB cases (99,000) in 2008, after China (100,000 cases) (WHO, 2010b). Drug resistance surveys in several states indicated that the prevalence of MDR TB in India was 2–3 percent among new cases and 12-17 percent among reinfection cases.[5]

The RNTCP used Category IV or DOTS Plus regimen as the standard regimen for treatment of MDR-TB. The programme provides a blend of institutional as well as home-based care. Category IV /DOTS Plus regimen includes: six drugs—four bactericidal: Ofloxacin (Ofx) or Levofloxacin (Lfx); Kanamycin or Capreomycin; ethionamide; pyrazinamide and two bacteriostatic drugs: Ethambutol; cycloserine (Cs) during 6–9 months of the intensive phase (IP) and four drugs: ofloxacin (levofloxacin), ethionamide, ethambutol, and cycloserine during the 18 months of the continuation phase (CP). [6]

The patients were identified at the community level, referred to the district TB officer (DTO), who sent patient's sputum sample to the culture and Drug Susceptibility Testing (DST) laboratory. On receiving the results DTO sent patient to a DOTS-Plus site for about a week for an initial workup with many blood tests, urine analysis (Urine R/M) and screening for HIV. Based on clinician judgment, audiometry and visual tests were performed for some patients. The patient then was placed on treatment at the DOTS-Plus site. After a week of treatment, the patient was referred back to the community, and the rest of the treatment was carried out on an outpatient basis. All drugs of a patient were given to DOTS Plus Centre in the form of Patient-wise box containing - IP and CP medicines.

Even though the new programme of DOTS Plus was very well planned and had taken into consideration most of the challenges yet it had scope for innovations for improvement. The Community Health Department of St. Stephen's Hospital (CHD-SSH) started one such innovation in 2009, in the form of 'Home Care for MDR Patients'[7] and it concluded with 'Long-term Follow-up of these patients, who had received DOTS Plus Treatment along with Home Care and Counselling'.[8]

MDR tuberculosis is dangerous and extremely difficult to treat. Duration of treatment for MDR cases is two years and ADRs are much more common and unpleasant. Second line ATT are known for their Adverse Drug Reactions (ADRs). Each one of them causes some complications for weak MDR TB patients such as mentioned in **Table 1:**

Table 1: Known Adverse Drug Reactions of Second line Anti TB Drugs[9]:

Adverse Drug Reactions	Symptoms and signs	Responsible Drugs
Joints and tendons (Tendinopathy and tendinitis)	Arthalgia, pain and tenderness of joint of fingers, shoulders, knees, etc. Hyperuricaemia	*Pyrazinamide[10], Isoniazid[11], Fluorquinolones– Ofloxacin, Levofloxicin, Moxifloxacin*
Gastro-intestinal	Anorexia, nausea, vomiting, epigastric pain	*Pyrazinamide, Rifampicin, Quinolones, p-Aminosalicylic acid (PAS)*
Dermatitis	Itching, rash, hives (raised, itchy rash) with or without fever, petechial rash	*Pyrazinamide, Rifampicin, Thioacetazone*
CNS Neurotoxicity/	Headaches, dizziness, slurred speech,	*Linezolid, Fluroquinolones,*

Adverse Drug Reactions	Symptoms and signs	Responsible Drugs
Peripheral neuropathy	convulsions, tremor, and insomnia. prickling, tingling or burning sensation of the fingers and/or toes usually occurs in a stocking glove distribution. Numbness of feet/hands	*Cycloserine, Aminoglycosides, Ethionamide*
Psychiatric	Excitement, anxiety, aggression, agitation, confusion, depression, suicidal ideation, hallucination and psychosis.	*Isoniazid, Cycloserine, Ethionamide*[12]
Audio-vestibular manifestations	Ototoxicity Hearing loss, vertigo, new-onset tinnitus, Nephrotoxicity, Electrolyte imbalance.	*Injectables – Kanamycin*[13,14] */ Capreomycin, Aminoglycosides*
Optic Neuritis (vision)	blurred vision (decrease in the "sharpness" of objects), "spots" present in patient's field of vision, red/green color blindness, uveitis	*Ethambutol, Linezolid, Rifabutin, Rifapentane*
Hematological	Leucopenia, thrombocytopenia, anemia, eosinophilia	*Rifampicin, Linezolid, Isoniazid, Capreomycin*
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	*Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Fluroquinolones*
Hypothyroidism	Fatigue, weight gain	*PAS, Ethionamide*
Renal impairment	Uraemia, haematuria	*Aminoglycosides - Kanamycin, Capreomycin; Rifampicin*
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	*Fluroquinolones, Rifampicin, Pyrazinamide*
Cardiotoxicity	QT prolongation	*Quinolones*[15]

Treatment compliance of MDR is a major challenge even for a well-motivated patient. These ADRs range from disabling (irreversible hearing loss) and life-threatening reactions (renal failure, hypokalemia) to non–life-threatening effects (gastrointestinal disturbances) having serious impact on patients' quality of life.[16] Thus, it was decided to study the spectrum, severity and the risk factors of ADRs in MDR-TB patients.

AIMS AND SCOPE OF THE ARTICLE:

1. To study the spectrum of ADRs in MDR TB patients receiving DOTS Plus / Category IV regimen.
2. To assess the severity of reported ADRs.
3. To find risk factors associated with ADRs.

Methods:

STUDY DESIGN:

In this retrospective study files of 109 MDR-TB patients were reviewed. The study was conducted between January to May 2024.

THE INCLUSION CRITERIA:

Secondary data of 109 MDR TB patients who had received treatment along with home care and counselling support starting from August 2009 to August 2010, by Community Health Department (CHD) of a tertiary care hospital of Delhi and who belonged to Northeast, East, Central and West districts of Delhi. Informed consent and approval of Institutional Review Committee had been taken for those studies.

THE EXCLUSION CRITERIA:

MDR TB patients from other districts than the four mentioned above.

HELP OF HOME CARE SUPPORT TEAMS:

Two experienced mobile multi-disciplinary teams of home care providers - Health educator cum care giver and a team assistant helped investigators in reaching ex-MDR patients' houses for collection of data. These teams were the ones that had actually done 'Home Care for MDR Patients' project from 2009 - 2014.

In those home visits 'Home Care' in the form of physical and mental support had been given through counselling about disease, hygiene and nutrition counselling, nursing care, and support at the time of Adverse Drug Reactions (ADRs). The teams had also helped these depressed, and weak MDR patients by providing psychosocial support and encouraging them to do some work. The result was that the patients had re-started earning. School/college drop-out student patients were also supported psychologically and motivated so that they had got re-admitted into schools/ colleges.

Teams got ex-patients registered under a Govt. TB Scheme which they were ignorant about. This scheme provided Rs. 300 per patient per month. Though this was a small amount yet it helped patients financially. Under the project there was provision for one egg and 250 gm of milk per patient per day for the whole course of treatment. This was arranged through a local shop.

In Intensive Phase: teams visited fortnightly - total visits 12 in 6 months
In Continuation Phase: visits were made in 45 days - total visits 12 in 18 months.
Teams recorded every home visit details in the 17-page 'Patient-wise files'.

SUPPORT AT THE TIME OF ADRS:
Support at the time of ADRs was provided. The teams took the patients in confidence and gave them their mobile telephone numbers so that patients could get help of teams 24x7. Once the team members got any information about early warning symptoms or ADR, they informed the consultant of study institution. The consultant then contacted nodal TB officers of either of the two Govt. hospitals involved in this project and asked teams to refer/take patients to general government hospitals or Institute of Human Behaviour and Allied Sciences (IHBAS) for ADRs as per the instructions of nodal officers. In the government hospitals nodal TB officers took prompt action and patient got special attention for her/his health problems. This increased the motivation and compliance. In this way a lot of patients were prevented from becoming defaulters.

NURSING CARE:
Massage for joint pain and application of cold compresses or dressing for injection site was provided at home to patients who required it.

STATISTICAL ANALYSIS:
The data from 109 'Patient-wise files' was searched. Patients having ADRs were selected. This

data was cleaned and tabulated with frequency tables and percentages using MS-Excel. Data was subjected to descriptive analysis. Severity assessment of ADRs was done by using Hartwig scale.[17] The patients with ADRs were further divided into two groups. Odds Ratio (between Group I and Group II) with 95% confidence intervals was calculated by using MedCalc Statistical Software version 19.2.6.[18] A statistical test was considered significant when the P value was <0.05.

Results:

A. Socio-demographic and clinical profile of 109:
Among the 109 MDR patients there were 63 (57.8%) males and 46 (42.2%) females. Ninety-nine (90.8%) study subjects were adult (age >=18 years), rest 10 (9.2%) were children. Mean age of adult study subjects was 33.8 (SD 13.38) years (range 18 to 65 years). Mean age of children was 16.0 (SD 1.18) years (range 14 to 17 years). There were 91(83.48) Hindus and 17(15.59) Muslims and 1(0.92) Sikh. Table 2

A little more than half ie 55(50.4%) patients were either educated up to Primary school or were illiterate. Unemployed and unskilled patients together were 56(51.36%). Patients who earned below Rs 7323 per month were 82(76.1%).

The mean body weight of patients 43±7.73 Kg (range, 22 to 67 kg) and body mass index (BMI) <18.5=73 (66.97%). Concomitant medical diseases were present in 20(18.35%) patients. These included Chronic Obstructive Pulmonary Disease in 7(6.4%), Thirteen (11.9%) patients were immunocompromised, of which 2(1.8%) were HIV positive and 11(10.0%) were diabetic. Addiction to tobacco (smoking and chewing) and alcohol was seen in 30(27.5%) and 21 (19.3%) cases respectively.

Table 2: Age & sex wise distribution of 109 patients

Age & sex	**Male (n & %)**	**Female (n &%)**	**Total (n & %)**
>10 - 20	9(14.28)	16(34.78)	25 (22.93)
>20 - 30	20(31.74)	16(34.78)	36(33.02)
>30 - 40	13(20.63)	7 (15.21)	20(18.34)
>40 - 50	9(14.28)	4 (8.69)	13(11.92)
>50 - 60	11 (17.46)	1 (2.17)	12 (11.0)
>60 - 70	1 (1.58)	4 (8.69)	3(2.75)
	63(100.0%)	**46(100.0%)**	**109(100%)**
Religion			
Hindu	53(84.12)	38 (82.6)	91 (83.48)
Muslims	10 (15.87)	7 (15.21)	17 (15.59)
Sikhs		1 (2.17)	1 (0.92)

B. Socio-demographic and clinical profile of 68 patients with ADRs:

Among 109 patients there were 68 (62.39%) who developed one or more ADR. Out of these there were 35(51.5) were males and 33(48.5) females. The patients with ADRs were further divided into two groups. Group I, having 1 to 5 ADRs (52 patients) and Group II having 6 to 20 ADRs (16 patients). In Group I The mean age was smaller ie < 34 years, and there were more males 29(55.8), BMI <18.5 in 38(73.07), more smokers 7(70%) and more who took alcohol 10(90.9%) in comparison to Group II. Table 3.

Table 3: Socio-demographic and clinical profile and treatment outcome in patients with ADRs

	Group I (1 to 5 ADRs) **n=52**	**Group II** (6 to 20 ADRs) **n=16**	**Total**
MEAN AGE	34	37	
Males	**29(55.8)**	6(37.5)	35(51.5)
Females	23(44.2)	**10(62.5)**	33(48.5)
TOTAL	52(76.5)	16(23.5)	68(100.0)
Caste			
Scheduled Caste	10(19.23)	5(31.25)	15(22.05)
Scheduled Tribe	10(19.23)	5(31.25)	15(22.05)
Other Backward Classes	5(9.61)		5(7.35)
General/Others	24(46.15)	5(31.25)	29(42.65)
Caste not remembered	3(5.77)	1(6.25)	4(5.88)
Education of head of family			
Postgraduate/Graduate	5(9.61)	1(6.25)	6(8.82)
Intermediate	6(11.54)	1(6.25)	7(10.29)
High School	8(15.38)	3(18.75)	11(16.18)
Secondary	10(19.23)	1(6.25)	11(16.18)
Primary	8(15.38)	3(18.75)	11(16.18)
Illiterate	15(28.85)	7(43.75)	22(32.35)
Occupation of head of family			
Clerk/Shop/Farmer	1(1.92)		1(1.47)
Skilled	9(17.3)		9(13.23)
Semi-skilled	11(21.15)	2(12.5)	13(19.12)
Unskilled	7(13.46)	2(12.5)	9(13.23)
Unemployed	24(46.15)	12(75.0)	36(52.94)
Family income in Rupees			
>19575	1(1.92)		1(1.47)
9788 to 19574	7(13.46)	1(6.25)	8(11.76)
7323 to 9787	3(5.77)	1(6.25)	4(5.88)
4894 to 7322	7(13.46)	3(18.75)	10(14.70)
2936 to 4893	18(34.61)	7(43.75)	25(36.76)
980 to 2935	9(17.3)	3(18.75)	12(17.65)
979 to Nil	7(13.46)	1(6.25)	8(11.76)
Comorbidities			
Diabetes	2(50)	2(50)	4(100.0)
COPD	1(50)	1(50)	2(100.0)
Substance abuse			
Smoking	**7(70)**	3(30)	10(100.0)
Chewing	4(80)	1(20)	5(100.0)
Alcohol	**10(90.9)**	1(9.1)	11(100.0)
Body Mass Index (BMI)			
<18.5	**38(73.07)**	6(37.5)	44(64.70)
>18.5 to 24.9	9(17.3)	9(56.25)	18(26.47)
>24.9	1(1.92)		1(1.47)
Not Known as Dead	4(7.69)	1(6.25)	5(7.35)
OUTCOME			
Cured	30(57.7)	11(68.8)	41(60.3)
Died	20(38.5)	4(25)	24(35.3)
Defaulted	1(1.9)	1(6.2)	2(2.9)
Failure & XDR	1(1.9)	0	1(1.5)

C. *Various types of ADRs:*

Out of various ADRs the most common ones were related to musculoskeletal system and gastro-intestinal system Table 4.

Table 4: ADRs in 68 MDR-TB patients on DOTS Plus regimen

	Males n & %	**Female n & %**	**Total n & %**
Nausea	14(22.22)	15(32.60)	29(26.6)
Vomiting	13(20.63)	12(26.08)	25(22.93)
Hiccups	1(1.59)	0(0)	1(0.92)
Abdominal Pain	5(7.93)	5(10.86)	10(9.2)
Black stools	1(1.7)	1(2.4)	2(1.8)
Loss of appetite	2(3.17)	1(2.17)	3(2.75)
Ringing in the ears	5(7.93)	4(8.69)	9(8.25)
Hearing Loss	1(1.59)	0(0)	1(0.92)
Headache	2(3.17)	**6(13.94)**	8(7.34)
Giddiness	3(4.76)	**8(17.39)**	11(10.1)
Difficulty in breathing	4(6.34)	**10(21.73)**	14(12.84)
Burning in micturition	2(3.17)	1(2.17)	3(2.75)
Swelling of face & the feet	1(1.59)	4(8.69)	5(4.58)
Sleeplessness (insomnia)	2(3.17)	1(2.17)	3(2.75)
Anxiety	8(12.69)	8(17.39)	16(14.67)
Depression	6(9.52)	**10(21.73)**	16(14.67)
Altered Behaviour	0(0)	1(2.17)	1(0.92)
Angry	0(0)	1(2.17)	1(0.92)
Suicidal tendencies	0(0)	0(0)	0(0)
Psychiatric problem	3(4.76)	4(8.69)	7(6.42)
Tremors	4(6.34)	**9(19.56)**	13(11.9)
Blurring of vision	5(7.93)	5(10.86)	10(9.2)
Unusual bruising or Haemoptysis (bleeding)	4(6.34)	4(8.69)	8(7.34)
Joint pains	22(34.92)	22(47.82)	44(40.36)
Dark coloured urine	2(3.17)	2(4.34)	4(3.67)
Jaundice	0(0)	0(0)	0(0)
Skin rashes	3(4.76)	**7(15.21)**	10(9.2)
Cough	3(4.76)	4(8.69)	7(6.42)
Weakness	9(14.28)	**14(30.43)**	23(21.1)
Body Pain	4(6.34)	3(6.52)	7(6.42)
Tingling	1(1.59)	2(4.34)	3(2.75)

D. *Serious and long lasting ADRs:*

There were some serious ADRs observed, such as 'Unusual bruising or Bleeding', 'Hearing Loss and 'Psychiatric Problems'. Some ADRs lasted for $\geq$ 6 months. Table 5.

Table 5: Serious and/or long-lasting ADRs

	T. Male =35 (n & %)	**T. Female =33 (n &%)**	**G. Total 68 (n & %)**
Unusual bruising/ haemoptysis	3 (8.57)	3(9.0)	6(8.8)
Hearing Loss	1 (2.86)	0(0)	1(1.47)
Psychiatric Problems	3 (8.57)	4(12.12)	7(10.3)
Breathlessness $\geq$1 month	4(11.43)	10(30.30)	14(20.58)
Blurring of vision $\geq$1 month	3 (8.57)	3(9.0)	6(8.8)
Ringing in the ears $\geq$1 month	4(11.43)	2(6.06)	6(8.8)
Swelling of face and feet >1 month	1 (2.86)	2(6.06)	3(4.41)
Giddiness >1 month	3(4.76)	5 (15.15)	8(11.76)
Headache $\geq$1 month	2(5.71)	6(18.18)	8(11.76)
Vomiting $\geq$3 months	7(20.0)	7(21.21)	14(20.58)
Depression >3 months	4(11.43)	6(18.18)	10(14.71)
Anxiety >3 months	4(11.43)	6(18.18)	10(14.71)
Tremors $\geq$3 months	2(5.71)	6(18.18)	8(11.76)
Skin rashes $\geq$3 months		4(12.12)	4(5.88)
Joint Pains $\geq$6 months	7(20.0)	11(33.33)	**18(26.47)**
Weakness $\geq$6 months	2(5.71)	1 (3.03)	3(4.41)

E. Admissions to hospitals for ADRs.:
Fifteen patients required admission in Lok Nayak Jai Prakash (LNJP) Hospital/Guru Teg Bahadur (GTBH) Hospital/Rajan Babu Tuberculosis (RBTB) Hospital/Institute of Human Behaviour and Allied Sciences (IHBAS) in Delhi:

1. 52 years old male for hiccups, vomiting, no appetite – (Died in 8 months of starting treatment)
2. 48 years old female for haemoptysis – (Died in 3 months of starting treatment)
3. 40 years old female for cough – (Died in 9 months of starting treatment) XDR?
4. 38 years old male with joint pain, haemoptysis, weakness and complications.
5. 27 years old male required modification of drugs due to joint pain.
6. 23 years old male required admission for ringing in the ears – (Died in less than 2 months of starting treatment)
7. 18 years old male required admission for nausea, headache.
8. 17 years old female required admission for headache, cough, blue patch on face.
9. 19 years old male required admission for joint pain and complications. (Died after 15 months of starting treatment)
10. 18 years old female required admission for breathlessness – (Died in 9 months of starting treatment)
11. 65 years old female had epigastric pain PAS was stopped at G.B. Pant Hosp due to its complications.
12. 35 years old male admitted for vomiting, hiccups, no appetite (Died after 21 months of treatment)
13. 22 years old female admitted for cough, joint pain. (Died after 14 months of treatment)
14. 48 years old male for joint pain
15. 40 years old male, a known case of HIV for loss of appetite, cough and weakness

One patient had hypothyroidism after commencement of therapy and Ethionamide was discontinued. There were 2 patients who completed their treatment but didn't get last sputum culture done. Five had no response, as shown by continually positive cultures. They were suspected XDR cases.

Management of ADRs by Home care teams under 'Home Care Project':

Our project also involved Home Care for patients therefore we could do much more for them:

	Male	**Female**	**Total**
Psychosocial support to patients and their family members especially the caretaker through counselling	63	46	109
Nursing care	7	8	15
Care for mental problems	4	6	10
Support in Hospital Admissions	9	6	15
Nutritional support provided	48	35	83
Support in getting Govt. TB Scheme money of Rs. 300/per month	14	14	28
Support in getting employment	10	0	10
Support provided in bringing back to school/college	1	6	7

Severity assessment of ADRs by Hartwig Scale:
Maximum number of MDR TB patients had mild ADRs 40(58.8%). Under moderate severity were 4(5.9%) resulting in patient transfer to higher level of care and 24 (35.3%) patients died and according to Hartwig Scale, ADRs directly or indirectly resulting in patient death are severe ADRs. (Figure 1).

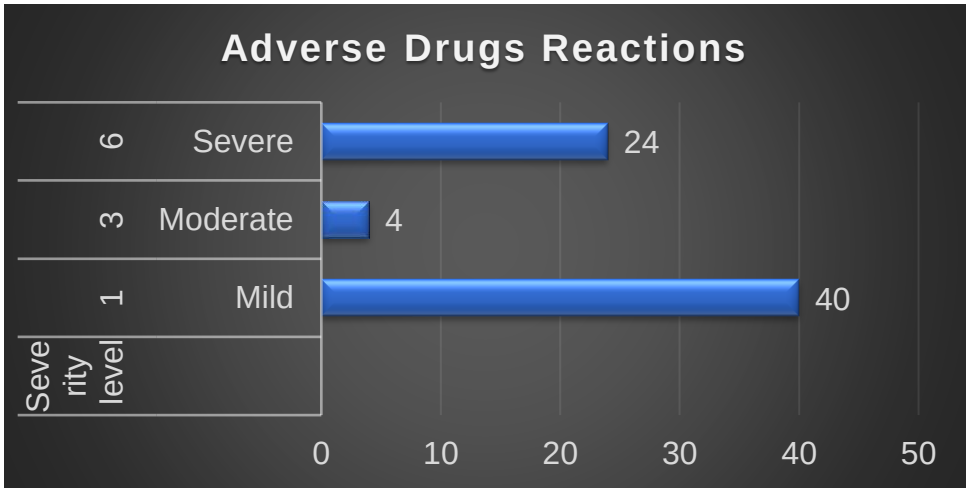

Figure 1: Severity assessment of ADRs using Hartwig Scale

F. Risk factors associated with ADRs:

On comparing the 2 groups it was found that the difference for BMI <18.5 and unemployment, Odds Ratio =0.22; 95% CI=0.06 to 0.72 and p=0.0124 and OR=3.5; 95% CI=0.99 to 12.29 and p=0.05 respectively, were statistically significant. Table 6.

Table 6.: Comparison of two ADR groups

		Group I (1 to 5 ADRs)	**Group II** (6 to 20 ADRs)	**Total**	**Odds Ratio [95% CI]**	**P-value**
BMI <18.5	Yes	38	6	44	0.2211	**0.0124**
	No	14	10	24	0.0677 to 0.7217	
		52	**16**	**68**		
Schedule Caste & Sch. Tribe	Yes	20	10	30	2.6667	0.0963
	No	32	6	38	0.8392 to 8.4733	
Illiterate	Yes	15	7	22	3.1975	0.0634
	No	37	9	46	0.9371 to 10.9102	
Unemployed	Yes	24	12	36	**3.5**	**0.0506**
	No	28	4	32	0.9967 to 12.2910	

G. Outcome in patients with ADRs:

Though 62% MDR TB patients had ADRs yet our treatment outcomes for patients with ADRs were good and showed 41(60.3) cured, 24(35.3) died, 2(2.9) defaulted and 1(1.5) failed treatment.

Discussion:

Treatment of drug-resistant tuberculosis (TB) involves the use of multiple medications, and most patients experience difficulty tolerating them. The response of an individual patient, however, cannot be predicted. Medications should not be withheld because of fear of a reaction. Patients should be well-informed, about the benefits and the possible side effects and toxicities of therapy, prior to initiating a treatment regimen. The present study was able to study the spectrum, assess severity and find some risk factors of ADRs in MDR TB patients receiving DOTS Plus regimen.

A total of 109 patients were studied in the study among which 68 (62.39%) patients developed ADRs out of which 10 (9.2%) were children (0-17 years). In a study by V.K. Arora et al out of 66 MDR TB patients 33 (50%) developed ADR.[19] Kapadia et al found 50(52.94%) patients experienced adverse drug reactions and 42 of them required drug modifications.[20] Kushemererwa O et al reported an incidence of 67.48% ADRs. [21] Another study reported an incidence of 72.4% ADRs.

I. Spectrum of ADRs:

We studied the spectrum of ADRs. The most common was related to *musculoskeletal system:* There is pain and tenderness of joints: fingers, shoulders, knees, etc. (usually mild) but at times it could be severe and quite debilitating for the patient. Pyrazinamide and Quinolones are the drugs that can cause joint pains. Quinolones are associated with a two - to fourfold increased risk of acute tendinopathy (defined as pain or reduced function without rupture) and tendon rupture.[22] In a Ugandan study joint pain was (244/369, or 66%),

most frequently reported adverse effect.[23] Another Uganda study mentioned that first of the five most commonly reported specific ADRs was arthralgia (44, 24.72%). We observed joint pain in 40.3%, weakness in 21.1% and body pain in 6.4%. In our study joint pains lasted for >6 months for 18(26.47%). Out of these 5 had to be admitted. Their Pyrazinamide was discontinued. But two 22 years young patients who also had cough died at 3 and 14 months. Three patients experienced severe weakness lasting for more than 6 months. Whereas weakness was found in (10 cases, 11.6%) by Paikray E in their study of 86 MDR TB cases.[24]

Gastro-intestinal system: Ethionamide and Quinolones are to be blamed for this. Nausea, vomiting, diarrhoea and taste disturbance have been reported to occur in up to 20% of patients treated with fluoroquinolones.[25] Common ADRs with ethionamide/prothionamide are gastrointestinal upset, anorexia, and hepatotoxicity. Sometimes taking medicines after breakfast helps. If nausea-vomiting is moderate to severe we may have to do liver function tests (LFT) to rule out drug induced hepatic dysfunction. We observed nausea in 26.6%, vomiting 22.9%, abdominal pain 9.2%, hiccups 1.8% and black stools 1.8%. Four patients with gastro-intestinal symptoms were admitted. Three patients' Pyrazinamide and one patient's PAS was discontinued as they had vomiting and epigastric pain respectively. Two of the admitted middle-aged males 35 years and 52 years, having hiccups with vomiting died at 21 months and 8 months respectively. In Lativia the most commonly reported events were nausea (58%), vomiting (39%). Ategyeka PM found vomiting (58/369, or 16%) was quite frequent. In a Systematic Review it was found that out of 3 most common side effects gastrointestinal disorders (32.1%) were the most.[26]

Dermal: Pyrazinamide is to be blamed for it. In our study skin rashes were found in 9.2% so their Pyrazinamide was stopped for 7-10 days and gradually re-started gradually. But 4 females continued having rashes for more than 3 months.

CNS/peripheral neuropathy: Fluorquinolones/Cycloserine/Aminoglycosides can cause headache, giddiness, tremors and tingling. In our study headache was observed in 7.3%, giddiness 10.1%, tremors 11.9% and tingling in 2.7%. Two young patients 17 and 18 years old were admitted for headache. Headache and other side effects … may also occur in some patients.[27] In a study less frequently reported ADRs were ototoxicity (4.1%), blurring of vision (4.1%), headache (4.1%) ….[28]

Psychiatric problems: Cycloserine is an oral bacteriostatic drug and a Group B drug as per WHO 2019 guidelines.[29] It leads to confusion, depression, altered behavior, and suicidal tendency and Ethionamide can cause hallucination and depression. Symptoms usually improve when the dose of cycloserine is decreased.[30] We found insomnia in 2.7%, anxiety & depression in 14.6%, altered behaviour and anger each in 0.9%. Four males and 6 females were given care for mental problems. Three males and 4 females were shown at IBHAS Hospital and their Cycloserine was stopped. Three patients including 1 male and 2 females expired. One of these female patients was admitted as she had multiple ADRs (haemoptysis, nausea, vomiting, headache, giddiness, difficulty in breathing, joint pain, anxiety depression and sleeplessness). She succumbed to her problems and died. Psychiatric disorders were found in 13.2% out of 2602 patients in the Systematic Review mentioned earlier.

Respiratory system: In our study 2.7% experienced difficulty in breathing, cough in 6.4% and haemoptysis in 7.3%, so 6 patients required admission in government hospitals. One 48 years old female with haemoptysis succumbed to it and died in 3 months of starting treatment. Another 18 years old female with breathlessness died in 9 months of starting treatment.

Oto-vestibular system: Aminoglycosides are ototoxic drugs because they have the ability to destroy the inner ear structures irreversibly. They are used to treat Gram-negative bacterial infections that are aerobic and as a second-line treatment for tuberculosis.[31] Ringing in the ears was found by us in 8.2% and hearing loss in 0.9%.

Ocular: One serious and vision threatening side effect of EMB is ethambutol-induced optic neuropathy (EON). The prevalence of EON in patients treated for tuberculosis is estimated to be 1-2%. [32] Optic neuropathy - blurring of vision was found in 9.2% of cases in our study. In a study by Dela et al. among all the ADRs in treatment of DR-TB, ethambutol was the most common drug responsible for visual impairment (4%).[33]

Endocrine System: Ethionamide is an antimycobacterial drug used as a second-line agent in the treatment of multidrug-resistant tuberculosis. It has been shown to inhibit thyroid hormone synthesis, and is reported to cause

hypothyroidism.[34] Hypothyroidism was observed in 1(0.92%) of our female patient so Ethionamide was discontinued.

II. Assessment of severity of reported ADRs:
According to Hartwig Scale mild ADRs were 58.8%, moderate 5.9% and severe 35.3%.

III. Risk factors associated with ADRs:
For risk factors subgroup analyses based on characteristic such as Schedule Caste & Schedule Tribe, illiteracy, Body Mass Index <18.5 and unemployment was done. The last two showed significant difference between groups.

Patients who were having BMI <18.5 were likely to experience less ADRs with an Odds Ratio =0.22; 95% CI=0.06 to 0.72, p=0.0124. Uganda study also mentions that patients who were underweight (adjusted odds ratio = 0.34 (0.16, 0.69 at 95% confidence interval) were less likely to experience an adverse drug reaction. Nutritional support in the form of one egg and 250 gram of milk per day was provided for our patients. Ategyeka et al mentioned in their study that patients who received food supplies (adj. PR = 0.61, 95%; 0.51, 0.71) were less likely to suffer from AEs.

In our study unemployment was another risk factor that was associated with higher number of ADRs OR=3.5; 95% CI=0.99 to 12.29, p=0.05.

IV. Outcome in ADR patients:
Though 62% MDR TB patients had ADRs yet our treatment outcomes for ADR patients were good and showed 41(60.3) as cured, 24(35.3) died, 2(2.9) defaulted and 1(1.5) failed treatment. This was possible because health care teams were present for patients 24x7 and counselled and provided all possible support to them thus improving adherence to therapy. Our cure rate is comparable to studies from Korea, Vietnam and Turkey.[35'36'37]

Conclusions:

Our study found ADRs are common among MDR-TB patients, occurring in 62% of cases, with joint pain being the most common, with little more than one fifth (22%) requiring admission in hospitals for care of ADR complications. The information from our study will help in planning and implementation of services to reduce MDR morbidity and prevent MDR mortality due to ADRs.

RECOMMENDATIONS:
Health education and IEC activities for general public: This should aim at educating about symptoms of TB, need for early registration at DOTS center (more awareness on availability and accessibility of free services), need to get sputum and other tests done as prescribed at DOTS center, and in case of positive reports, starting treatment.

Motivation and psychological counselling of Tb patients especially MDR TB patients and their family: importance of taking regular DOTS Plus treatment, MDR TB treatment related complications and yet adherence to drugs, importance of balanced diet.

Provision of Health services: provision of nutritional requirements during the treatment and afterwards, instant referral for ADRs and care of patients at referred facilities (delay in receiving timely and appropriate care at the time of ADRs and their complications may result in mortality). These definitely help in preventing patients from becoming defaulters.

Limitations of the study: It includes sample size from only 4 districts of Delhi, which limits the generalizability of this study. As our home care teams visited patients at home and had developed very good rapport with them the internal validity of the study is good.

Conflict of Interest: The authors have no conflict of interest to declare.

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