



Adverse Drug Reactions in Patients put on Multi Drug Resistant Tuberculosis (MDR-TB) Treatment in Seven Districts of Central Gujarat

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ABSTRACT

Aim: To study the Adverse drug reactions (ADRs) experienced by MDR TB patients put on DOTS plus regimen. **Material and Methods:** The longitudinal cohort study was conducted by following a cohort of 142 MDR TB patients registered for DOTS plus therapy in 2010 under Revised National Tuberculosis Control Programme (RNTCP). Two follow ups were taken in a cohort of 142 MDR TB patients, first at completion of 6 months of treatment and second after completion of 24 months of treatment. Subjects were interviewed to study side effects of DOTS plus regimen. **Results:** After 6 months of treatment, 48.59% (69) patients developed ADRs and between 6 months and 24 months of treatment 54.93% (78) patients developed ADRs out of total 142 at both the milestones. GI disturbances were 54.9% at 1st follow up and 46.54% at second follow up. Other side effects like headache, arthralgias, decreased hearing and skin reactions were also reported in varying frequencies. Average duration of ADRs was 60-90 days at both the follow ups. 62.68% of all ADRs were managed by symptomatic treatment and dose reduction was done in 4.47% of the patients in 2nd follow up. **Conclusion:** ADRs were experienced by more than half of the patients in the study and they increased as the duration of treatment increased. GI disturbances, Headache and Arthralgia were most common ADRs among patients. Most of them were managed by symptomatic treatment.

Key words: Adverse drug reactions, ADR management, Compliance, DOTS plus, MDR-TB, RNTCP, Treatment adherence.

INTRODUCTION

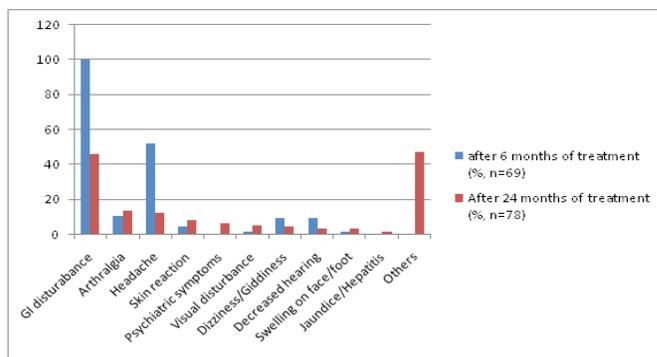
India accounts for 1/5th (21%) of global incidence of TB.^{1,2} India has second highest multidrug-resistant TB (MDR-TB) burden in the world after China.³ MDR-TB was defined in the 1990s as TB caused by *M. Tuberculosis* resistant *in vitro* to at least rifampicin and isoniazid, the two most significant drugs employed in the modern anti-TB regimens.⁴ The RNTCP in India follows the internationally recommended

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ADRs after 6 months		
Most Common	Common	Least Common
1. GI Disturbances 2. Headache	1. Arthralgia	1. Skin reactions 2. Visual disturbance 3. Dizziness/Giddiness 4. Decreased hearing 5. Swelling on face/foot



ADRs after 24 months		
Most Common	Common	Least Common
1. GI Disturbances	1. Arthralgia 2. Headache	1. Skin reactions 2. Psychiatric symptoms 3. Visual disturbance 4. Dizziness/Giddiness 5. Decreased hearing 6. Swelling on face/foot 7. Jaundice/Hepatitis

Graphical Abstract

DOTS-Plus guidelines for treatment of MDR-TB known as Category IV (Cat IV) regimen. Completing MDR TB therapy is more challenging than completing first-line TB therapy. One of the many reasons is the more toxic second-line drugs used to treat MDR TB often cause disruptive adverse reactions,⁵ which are, many a times, mentioned as obstacles in the management of MDR-TB patients. Limited evidence of ADRs in MDR TB patients is available from resource-limited settings like India. This study was taken up to evaluate frequency of occurrence of various ADRs, their duration and management in MDR-TB patients during the course of treatment.

MATERIALS AND METHODS

This DOTS Plus site is receiving the inflow of MDR-TB patients from seven districts. Treatment is provided according to Category 4 regimen under RNTCP.

Category IV regimen⁶ comprises of 6 drugs- kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase and 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the Continuation Phase (for weight bands 16-

25, 26-45 and more than 45 Kgs). p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Of, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated. All patients receive drugs under direct observation on 6 days of the week. On the 7th day the oral drugs are to be administered unsupervised whereas injection kanamycin is omitted. If intolerance occurs to the drugs, ethionamide, cycloserine and PAS may be split into two dosages and the morning dose administered under DOT. The evening dose is self-administered. The empty blister packs of the self-administered doses are checked the next morning during DOT. Pyridoxine should be administered to all patients on an RNTCP Category IV regimen. Drug dosages for MDR-TB cases are decided according to the weight bands.⁶

A longitudinal cohort study was conducted by interviewing MDR TB patients of seven district of central Gujarat, registered at DOTS Plus site-SSGH, Vadodara for DOTS Plus therapy under RNTCP between February 2010 to December 2010. Patients were diagnosed to have MDR-TB if they were found resistant to Isoniazide and Rifampicin with or without resistance to other first line drugs on drug sensitivity testing (DST) results.⁴ All the patients registered during above mentioned period were included in study

(Whole universe was taken, so sample size calculation was not required). Seriously ill patients, unable to give interview and those patients who did not give consent were excluded.

Ethical clearance was obtained from Scientific Review Board (SRC) and also from Institutional Ethical Committee on Human Research (IECHR), Medical College. Data collection was done with necessary permission in writing from State TB Officer (STO), RNTCP Cell. The District Tuberculosis Officers (DTO) of the aforementioned 7 districts were also informed about this study and their cooperation was solicited. For interviewing patients admitted at the DOTS Plus site for initiation of treatment or management of adverse drug reactions, permission was obtained from the Superintendent. All patients were enrolled in the study after taking written and informed consent in the local language that the patient could understand.

Data collection was carried out from February 2010 to November 2012. The list of study subjects was obtained from DOTS Plus Site. A total of 146 patients were registered in during above mentioned period. Out of the total 146 patients, 142 could be interviewed by pretested structured questionnaire after completion of 6 months and at 24 months of DOTS plus therapy at the DOTS Centre of respective districts when they come to receive treatment or at their homes by home visit. The patients were asked questions related to various ADRs experienced in present treatment and their responses were documented. Efforts were made to get information about ADRs in deceased patients from their relatives; few of the patients who were critically ill at the time of visit were approached after their health improved. Hence the ultimate sample size for the study is 142. Rest could not be interviewed because of migration, default from treatment, refusal to give consent or death. The patient cards at DOTS Plus Site were used for

tracking the rest of the required details related to changed treatment in patients having ADRs.

The data were entered in Microsoft excel version 2007 using strict check files (data validation command) to prevent wrong data entry. Data cleaning was carried out, checked for discrepancies and rectified. Data analysis was done with Epi Info 7.0.8.0.

RESULTS

In this study, out of 142 patients, 50 were <30 years of age, 71 were in 30-50 years group and 21 were >50 years of age. Thus, most of the patients were in age group of 30-50 years. 71.83% (102) patients were males & 28.16% (40) patients were females with mean age of 34.83 ± 12.19 years at starting of study. 26.05% (37) female patients were in the reproductive age group (15-45 years). 50.71% of patients were literate, 40.84% of whom had primary education. However, 49.29% of patients were illiterate. At the time of interview, 23.24% of the patients were unemployed. Majority of the patients (46.47%) of patients had income between 1500-3000 rupees per month, while 9.85% had income of more than 5000 rupees per month.

Of the patients initiated with MDR-TB treatment, 51.03% (74) of them were due to previous treatment failure and 1.38% (2) cases were new freshly diagnosed MDR-TB cases.

Among 142 patients, 48.59% (69) patients developed ADRs at the end of 6 months of DOTS plus therapy and 54.93% (78) reported ADRs at 24 months of therapy. Distribution of ADRs among study subjects is shown in Table 1.

As it is shown in Table 1, the most common side effect reported at 6th month and 24th month of therapy was GI disturbances, Headache and Arthralgias. Other side

Adverse Drug Reactions	After 6 months of treatment (N=69)		After 24 months of treatment (N=78)	
	Frequency	%	Frequency	%
GI Disturbances	69	100	36	46.15
Arthralgia	7	10.14	10	12.82
Headache	36	52.17	9	11.54
Skin reactions	3	4.35	6	7.69
Psychiatric symptoms	0	0.00	5	6.41
Visual disturbance	1	1.44	4	5.13
Dizziness/Giddiness	6	8.70	3	3.85
Decreased hearing	6	8.70	2	2.56
Swelling on face/foot	1	1.44	2	2.56
Jaundice/Hepatitis	0	0.00	1	1.28
Others	0	0.00	37	47.43

*Multiple responses possible

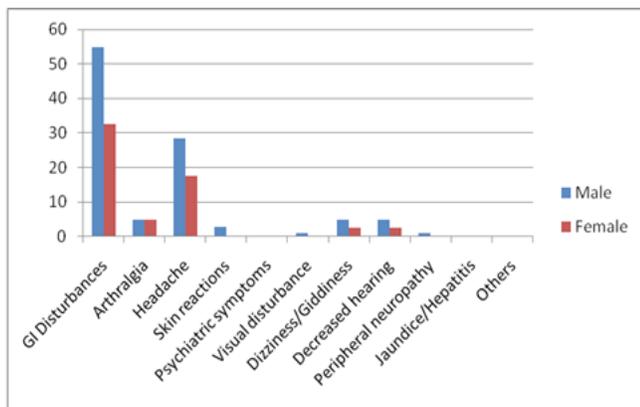


Figure 1: Gender wise distribution of ADRs after 6 months of DOTS plus therapy

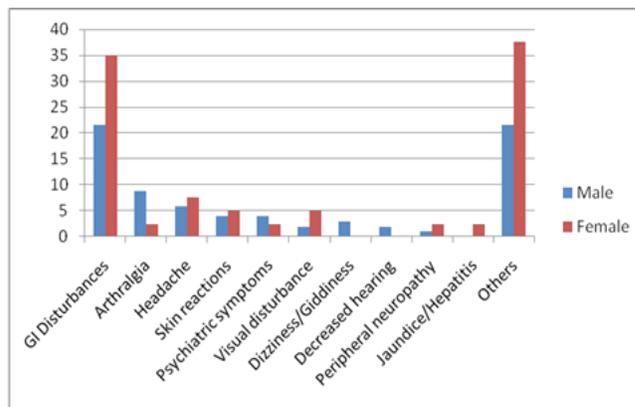


Figure 2: Gender wise distribution of ADRs after 24 months of DOTS plus therapy

Adverse Drug Reactions	Median duration of ADR (in days)	
	After 6 months	After 24 months
GI Disturbances	60	15
Arthralgia	80	5
Skin reactions	50	4
Peripheral neuropathy	120	17
Decreased hearing	135	315
Dizziness/Giddiness	90	100
Psychiatric symptoms	0	13
Jaundice/Hepatitis	0	There is only one patient
Visual disturbance	135	30
Headache	45	15

z	After 6 month of Treatment (%) (N=69)	After 24 months of Treatment (%) (N=78)
Symptomatic treatment	85	62.68
Stopped one or more drug	4	13.43
Specific treatment	1.16	13.43
Refer to DOTS plus site & treatment change	9.84	5.97
Reduce drug dosage	0	4.47

effects commonly seen included breathlessness, chest pain, hematemesis, weakness, pimples on face and pain and swelling at injection site. GI disturbances, Headache and dizziness/giddiness which were reported at 1st follow up were reduced in later part of treatment when 2nd follow up was taken. Complaints of Arthralgias, Skin reactions, Visual disturbance and swelling on face/foot were increased in later part of treatment. Treatment change was advised in patients with complaint of decreased hearing, so that complaint was reported less during 2nd follow up. Psychiatric symptoms, Jaundice/Hepatitis and other side effects were reported in later part of course of treatment.

Most of the ADRs were noted more in males at first follow up (Figure 1). While during 2nd follow up it was found that all the side effects were more in females except for arthralgias and psychiatric symptoms (Figure 2).

Table 2 shows that the average duration for most of ADR after the initiation of category IV treatment was 2-3 months (60-90 days). Decreased hearing, Peripheral neuropathy and Decreased vision were seen between 3-5 months (90-150 days) after initiation of cat IV treatment.

According to guidelines, symptomatic and specific treatment was given and complaint stopped in most of patients. Some of the patients with complaint of decreased vision, dizziness and psychiatric symptoms required change in treating drugs and reference to special departments through the DOTS Plus Site (Table 3).

DISCUSSION

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem, with most cases arising from a mixture of physician error and patient non-compliance during treatment of susceptible TB. The disease is not only a medical problem or a public health problem but also a

critical social problem of great magnitude. DOTS-Plus is more complex than the basic DOTS strategy. Baseline information and adequate information on epidemiological factors, various side effects of drugs is required for effective treatment. For DOTS-Plus to be successful, special attention is needed for adherence to difficult-to-take regimens for longer period and side-effect management.

The present study was conducted among the cohort of the year 2010 put on MDR TB treatment registered for DOTS Plus therapy under RNTCP of Vadodara Region. Out of the total 146 patients, data for 142 was obtained.

According to our study, mean age of 35.01 ± 12.25 years favours the argument that the disease was common in economically productive age group compared to older age group, indicating an exposure to drug resistant cases in the last two decades. Similar finding was shown in a study done by Bhatt GS *et al.*, (2010) in Ahmedabad, Gujarat where the mean age was 33.64 ± 11.03 years.⁷ Similar result was seen in a study by Datta *et al.*, in Kashmir in 2010, where the mean age was 39 ± 4.7 years.⁸ However, study done by Cavanaugh *et al.*, in Russia during 2002-2005 has shown that mean ages were 42 years.⁹ Similar result were shown in study of Masjedi *et al.*, during 2002-2006 in Iran, mean ages were 44.38 ± 19.05 years.¹⁰

In this study, there were 102 males (71.8%) and 40 females (28.2%), thereby showing higher occurrence of MDR-TB in males as compared to female patients. The male to female ratio in this study was 2:1, similar results were also shown in study done by Cavanaugh *et al.*, in Russia which showed that 83% were male and 18% were female.⁹ In a study by Chiang *et al.*, in Taiwan, 71.9% were males and 28.1% females (36) and in study of Eker *et al.*, in Germany during 2004-2006, 24% patients were female (median age 28 years), and 76% were male (median age 39 years).¹¹ But in study of Datta *et al.*, in Kashmir showed that Ratio of male to female was 29:23.⁷ and study of Masjedi *et al.*, in Iran showed that out of these 43, 27 (62.8%) were male and 16 (37.2%) female.¹⁰

In the present study, almost half of the patients, i.e. 48.59% (69) at 6th month and 54.9% (78) at 24th month experienced one or the other ADRs of drugs in different frequencies and for different durations as shown in Table 1 and 2. Most patients faced problems mainly after 2-3 months of treatment initiation. Most of these ADRs, in 85% and 62.68% (42) were managed by symptomatic treatment. While according to guidelines; skin reaction, psychiatric symptoms dizziness/giddiness, visual disturbance, swelling of face/foot, jaundice/hepatitis—

were ADRs that required hospitalization and change in treatment regimen. Similar finding were seen in study done by Bhatt GS *et al.*⁷

Nathanson E *et al.*, conducted study in five DOTS-Plus sites and the five most common adverse reactions observed were nausea/vomiting, diarrhoea, arthralgia, dizziness/vertigo and hearing disturbances.¹²

In Tamilnadu Pauline J *et al.*, found that the main side effects were GI Disturbances, Giddiness, Arthralgia, insomnia, Swelling/pain at injection site, Skin lesions, Depression, Jaundice, Convulsion, Impaired hearing, Impotence and Visual problems.¹³

In contrast to our finding, Masjedi *et al.*, in Iran found that the most common ADR was hearing loss (46%), followed by hepatitis (9.2%), psychosis/ suicide attempts (6.9%) and tinnitus (2.3%).¹⁰

In our study, 4% patient at 6th month of treatment and 2.56% patients at 24th month of treatment with complaint of decreased hearing were put on Para-amino Salicylic acid (PAS) instead of Injection Kanamycin. Arora VK *et al.*, in New Delhi also observed that Injection Kanamycin was stopped in 5% patients due to hearing loss/giddiness.¹⁴

In our study 5% patient at 6th month and 12.82% patients at 24th month who had complaint of joint pain (arthralgia) were prescribed Tablet Paracetamol (500 mg TDS) initially for a week. After review, if there was no improvement, the dose was increased up to 1000 mg TDS for a week. Whereas, in a study done by Nathanson E *et al.* 11% had minor joint pain which was managed by symptomatic treatment.¹² In a study done by Datta *et al.*, (2010) in Kashmir, 13.4% patients developed arthralgia attributed to pyrazinamide, which was relieved by non-steroidal anti-inflammatory drugs in most of the cases.⁸

Patient with complaint of symptoms suggestive of peripheral neuropathy (pins and needles sensation, numbness or pain in the hands or feet with or without signs), Tablet Pyridoxine (20 mg once a day) was prescribed for 2 weeks and the patient reviewed at weekly intervals.

In the current study, specific treatments were required in 1.16% cases noted in 1st follow up and 13.43% patients in second follow up while change of drug regimen were required in 9.84% at first follow up and 5.97% at second follow up and in 4.47% patients noted at 24th month of treatment, dose of drugs were reduced.

A study done by Joseph *et al*, in Tamil nadu reported that 58% patients required dose reduction or termination of the offending drug.¹³ Whereas, in Taiwan Chiang *et al* study, 21.4% patients had adverse drug reactions that required medication to be stopped.¹⁵ Another study by Isakidis *et al*, in Mumbai also noticed that 45% experienced adverse events, of which only 20% required change of regimen.¹⁶

There are several possible explanations for the differences in the number of patients requiring drugs to be removed from the regimen due to ADRs in this study and other studies. These include differences in training, their different experiences with a variety of patients, variation in health care workers ability to detect ADRs and their management.

The time-lag between present treatment ADRs and interview was more which could have resulted in a recall bias.

There is a need for counselling before initiation of treatment, which is again reinforced during treatment. These initiatives can lead to better compliance and minimizing default rate.

CONCLUSION

ADRs were experienced by more than half of the patients in the study and they increased as the duration of treatment increased. GI disturbances, Headache and Arthalgia were most common ADRs among patients. Most of them were managed by symptomatic treatment.

Highlights of Paper

- Almost half of the patients in the present study experienced one or the other ADRs of drugs, gastrointestinal symptoms were most common among them. Nearly 2/3rd of the patients with ADRs were managed by symptomatic treatment and a few of them required either change of drug, reduction in the dose of drug or stopping the treatment.

Author Profile



- **Dr. Sangita Patel:** Is an Associate Professor in the Department of PSM, Medical College Baroda and a passionate teacher with 19 years of teaching experience. She did her MD in PSM from M. S. University in 1999. She did her diploma in Industrial health from M. S. University in 2002. She did her graduate certificate course on clinical research methodology from University of South Florida. She has done several research projects funded by NIH UNICEF, WHO, ICMR, Population council and UNFPA. Her Research interests include HIV, Maternal and child health and tuberculosis. She has published more than 60 papers in international and national journals.



- **Dr. Kapil Bhikhubhai Nimavat:** M.D. PSM, has had wide experience of Revised National TB control Programme for 13 years. He has been working in the field of public Health since 2002; and has been In-charge Superintendent at Community Health Center for 4 years. He has earlier worked as Senior Medical Officers at District TB center Rajkot for 3 years.

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ABBREVIATION

MDR-TB:	Multi drug resistant tuberculosis
ADRs:	Adverse drug reactions
RNTCP:	Revised National Tuberculosis Program
SSGH:	Sir Sayajirao General Hospital
PAS:	p-aminosalicylic acid
SRC:	Scientific Review committee
IECHR:	Institutional Ethical Committee on Human Research
STO:	State TB Officer
TDS:	Three times a day

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