Pharmacovigilance among patients with Multi drug resistance Tuberculosis (MDR-TB) And Extensively drug-resistant tuberculosis (XDR-TB) treatment

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Abstract

Aim: The main aim of this study is to assess adverse drug reactions among the patients treated with different regimens for MDR and XDR-TB. **Materials and Methods:** Patients who were diagnosed with MDR and XDR-TB of either gender and with an age of above 18 years were included in this study. The causality assessment of the ADRs was done by using the WHO and Naranjo's scales. The severity of ADRs in the present study was assessed by using Modified Hartwig and Siegel scale and was classified into mild, moderate and severe.

Results: Among the 508 study participants, 161 (31.69%) were observed to be with various adverse drug reactions in this study. In this study, most of the ADRs were observed to be with gastrointestinal related (29.52%) followed by nausea & vomiting (20.07%), swelling and pain at the injection site (3.54%) and ototoxicity (4.33%). According to the Naranjo's scale, the causality assessment was done and it was observed that among the 161 cases, 9(5.59) were observed to be definite, 79 (53.55) were observed to be possible ADRs 85 (46.44%) were observed to be probable ADRs and whereas the remaining 7(4.34) were observed to be doubtful ADRs. **Conclusion:** According to the Naranjo's causality assessment, most of the ADRs were possible ADRs followed by probable, most of the ADRs were observed to be with moderate severity followed by mild severity. Clinical pharmacists should take responsibility of the identification, management and prevention of adverse drug reactions especially in case of drug resistant tuberculosis patients in order to improve their health related quality of life.

Key Words: Tuberculosis, Adverse drug reactions, multidrug resistance, extensively drug resistance.

Introduction

India features among the 30 high-tuberculosis (TB) burden countries and has accounted for an estimated one-quarter (27%) of all TB cases worldwide.[1] Drug-susceptible TB (DS-TB) is treated with regimens containing multiple first-line drugs (FLDs') such as isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), whereas second-line drugs (SLDs') and few FLDs' are reserved for treatment of drug-resistant TB (DR-TB). Good bacteriological diagnosis and compliance to treatment remains two main pillars of successful treatment of TB. An adverse drug reaction (ADR) has been defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[2] Patients may encounter with a variety of ADRs' when managed with anti-TB drugs. ADRs cause significant morbidity and even sometimes mortality if not detected early.[3-5] Major concerns exist regarding treatment of DR-TB patients, especially with SLDs having lower efficacy, costly and more toxic as com- pared to FLDs. Most of ADRs are mild or minor and can be managed without discontinuation of treatment. Few ADRs can be severe or major causing life-threatening experience leading to discontinuation or modification of treatment that may require hospitalization and even mortality if unrecognized and untreated promptly. Various factors, such as timing of occurrence of ADR, pattern of illness, results of laboratory tests, Rechallenge e.g., with type, dosing or timing of drugs administration, patient age, nutritional status, the presence of preexisting diseases, or dysfunctions (such as impaired liver function, impaired kidney function and alcohol- ism), might be attributed to causality of ADRs.[6] Therefore, continued surveillance of ADRs is essential particularly in DR-TB cases where early detection and timely management of ADRs might determine successful outcome. This review aims to highlight the estimated burden and management strategies of various ADRs associated with anti-TB drugs among patients undergoing treatment of TB.

AIM AND OBJECTIVES

Aim: The main aim of the present study is to estimate the prevalence of ADRs among MDR and XDR -TB patients treated with different regimens at Damien TB centre.

Objectives:

- Identification of types and frequency of adverse drug reactions in Intensive and continuation phase.
- To evaluate the incidence of treatment discontinuation in relation to ADRs.
- To assess casualty and severity of the reported adverse drug reactions.
- To categorize the patients based on their demographic parameters.

METHODOLOGY

Study Design: It is a prospective observational cross sectional study

Study site: The present study was carried out at Damien Foundation Urban Leprosy & TB Centre, Nellore with prior approval of institutional Ethics Committee.

Study Duration: The study was conducted for a period of 1 year (July 2021 to June 2022)

Research Tools:

WHO causality scale: All the suspected ADRs are categorized into six categories as per this scale Certain, Probable, Possible, Unlikely, Unclassified & Unclassifiable.

Naranjo causality scale: This scale comprises of ten (10) questions with different scores for each question and categorized into four types based on their scores as Definite ADRs (≥9), probable ADRs (5-8), possible ADRs (1-4) and doubtful ADRs (0).

Inclusion criteria

- Patient of either sex of age more than 18 years – 50 years with MDR or XDR tuberculosis.
- Patient who provide written informed consent

Exclusion criteria

- Patients receiving ART treatment
- Patients with impaired Liver and Kidney function tests.
- History of patient suffering from any other chronic disease condition requiring any concomitant medication.
- Pregnant Woman.
- Not ready to give informed consent.
- Not ready to give follow up.

Method of data collection

Patients for this study were included from Damien Foundation Urban Leprosy & TB Centre, Nellore who were diagnosed to have MDR-TB (Isoniazid and Rifampicin resistance individually or both) XDR-TB (H+R+SLD resistance) admitted in Drug Resistance Tuberculosis Centre. All study subjects were evaluated after written informed consent was obtained. Thorough detailed history was taken regarding the demographic profile, present complaints, past history of tuberculosis, history of any addiction; family history of Tuberculosis was collected using a structured patient data collection form. Detailed general and systemic examination was done to find out any abnormalities. Pre-treatment investigations done included informed consent, urine for albumin, sugar and pregnancy test for female patients (if 18 to 50 yrs. old), complete haemogram, renal and liver function test, Thyroid function test, psychiatric evaluation, Audiometry (SOS), Vision Acuity Test (SOS).

Treatment regimen

The standardized regimen consisted of an intensive phase (IP) of 6-9 months with 6 drugs, namely kanamycin (Km), Moxifloxacin (Mfx) ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and Clofazimine (Cfz) given daily. This was followed by a continuation phase (CP) of 18 months of 4 drugs, namely Lfx (levofloxacin), Eto Ethambutol and cycloserine (Cs).

At the end of 6 months of treatment, if the fourth month culture remained positive, the IP was extended for a further 3 months. Doses of the drugs were chosen according the weight range to which patient belonged.

All patients enrolled to the study were treated with a daily supervised regimen. All patients were monitored daily for adverse drug reactions after starting regimen till the patients remains admitted in hospital and later followed up personally or telephonically at regular intervals of 2 monthly bases and will be asked questions regarding possible adverse drug reactions of the drug which are prescribed to them. In between the 2 monthly follow up in OPD, telephonic questioning regarding adverse drug reactions will be asked on the any day of first week of every month. Anticipated ADRs will be identified and assessed.

The causality of adverse drug reactions will be assessed as per Naranjo’s causality assessment scale, at the end of the study, these adverse event records will be analyzed and statistically interpreted.

Statistical analysis

Prevalence of ADRs among patients treated with MDR and XDR-TB was estimated by using the formula

Prevalence = Number of cases / Population * 100

All the data analysis was done by using Microsoft excel spreadsheet, version-2009, we used descriptive statistics like, mean and simple percentage. All the demographics parameters, graphs, tables were generated using the same.

Regression analysis was used to evaluate the relationship between study participants and the occurrence of ADRs. Variables having $p < 0.05$ in univariate analysis were considered for multivariate binary logistic regression analysis to establish a possible link between the occurrence of ADRs and any affecting variable. Statistical significance was set to be $p < 0.05$.

RESULTS

The prevalence of ADRs was 31.69% among the MDR and XDR TB patients treated with different regimens.

All the study subjects were categorized based on gender and represented in table 1, among the total sample of 508 males were 362(**71.25**%) and females were (146) **28.74**%.

Table 1: Categorization of subjects based on Gender

S. No	Gender	No. of subjects	Percentage (%)
1.	MALE	362	71.25
2.	FEMALE	146	28.74
3.	TOTAL	508	100

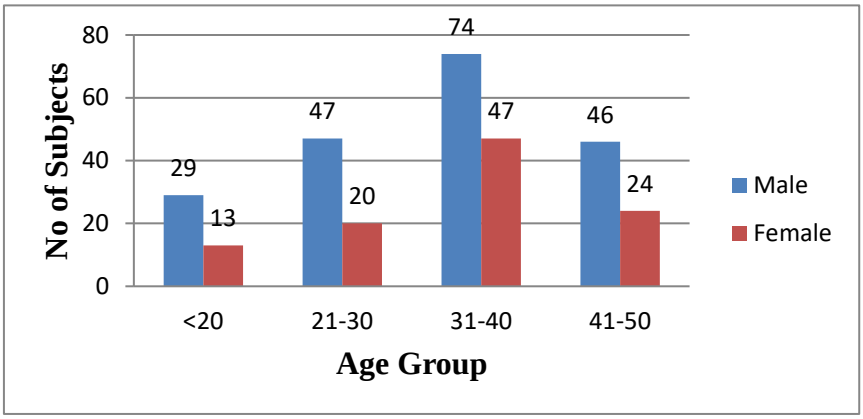
All the study subjects were categorized based on their age groups as represented in table 2, among them majority of the subjects were in the age group of 31-40 years with 35.23% followed by 41-50 years with 24.21%.

Table 2: Distribution of subjects based on age groups

S. No	Age group	Male	Female	Percentage (%)
1.	<20	69	23	18.11

2.	21-30	83	31	22.44
3.	31-40	121	58	35.23
4.	41-50	89	34	24.21
5.	TOTAL	362	146	100

Fig:1 Graphical Representation of Subjects based on age groups

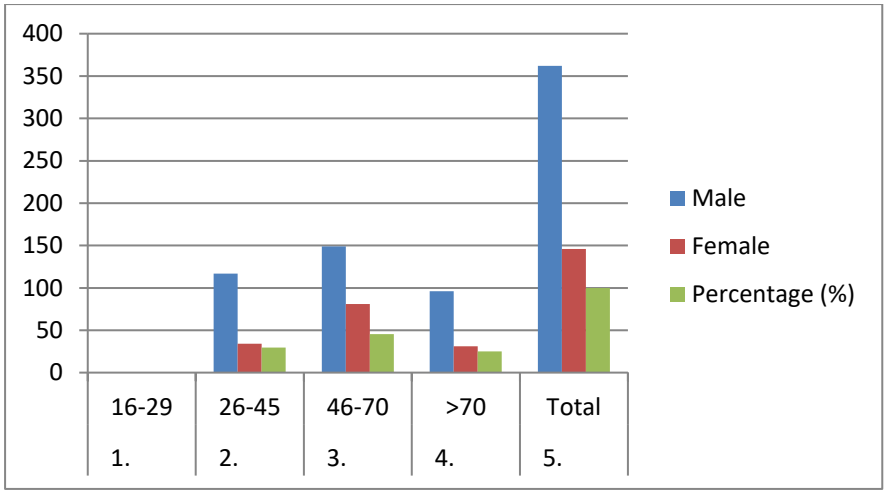


All the subjects were divided based on weight band into four categories as shown in the table 3 as the main stay in the treatment of tuberculosis is weight of the patient.

Table 3: Distribution of Subjects based on weight band

S. No	Weight (In Kg)	Male	Female	Percentage (%)
1.	16-29	00	00	00
2.	26-45	117	34	29.72
3.	46-70	149	81	45.27
4.	>70	96	31	25.00
5.	Total	362	146	100

Fig:2 Graphical Representation of Subjects based on weight band



In the present study different subjects were categorized based on the educational status shown in the table 4.

Fig:3 Graphical Representation of Subjects based on Educational status

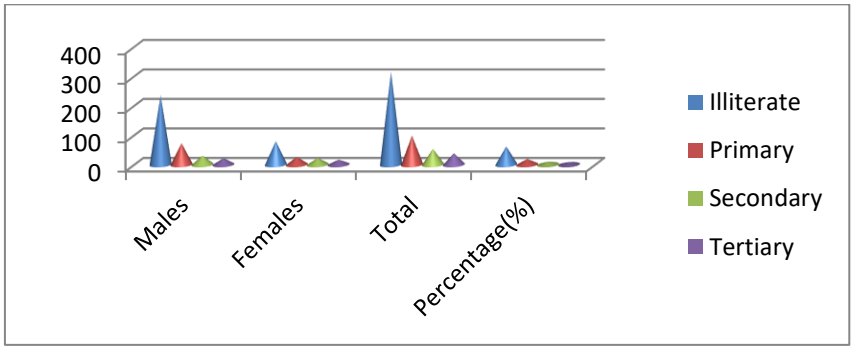


Table 4: Distribution of adverse drug reactions based on gender

Gender	**Number of Subjects**	**Percentage (%)**
Male	114	70.80
Female	47	29.19
Total	161	100

A total of 161 members got 254 Adverse drug Reactions were observed during the study period, were 114 (70.80%) of males and 47 (29.19%) females experienced ADRs.

Fig 4: Graphical Representation of Adverse drug reactions based on gender

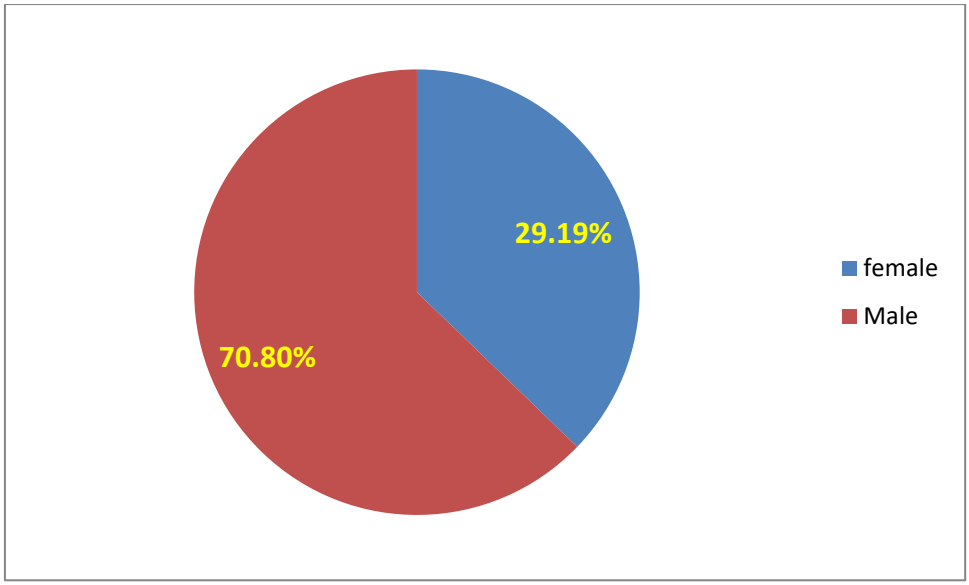


Table:5 Distribution of subjects based on drug regimens

AGE	HRZE	M,K,Eto, L,H^h, Z,E	Bdq, L,Lzd, Cf,Cs, PAS, Dlm	TOTAL
<20	1	6	00	7
21-30	6	32	3	41
31-40	13	38	11	62
41-50	8	36	7	51
TOTAL	28	112	21	161

Table 6: Incidence of ADRs in paients of MDR and XDR-TB with different anti-tuberclar regimen

S.NO	Age	Male		Female		MDR	XDR	Regimen and phases			Total AD	P Value
		Exposed	unexposed	Exposed	unexposed			IP	CP	All Oral		

											Rs	
1.	<20	6	62	01	22	91	00	11	27	0	07	
2.	21-30	32	51	09	22	107	03	18	87	03	41	
3.	31-40	41	79	21	37	174	10	34	157	10	62	P<0.0001
4.	41-50	35	56	16	18	115	08	29	124	08	51	
Total		**114**	**248**	**47**	**99**	**487**	**21**	**92**	**395**	**21**	**161**	

Abbrevations: H- Isoniazid**,** R- Rifampicin, E- Ethambutol, SLD- Second Line Drugs

All the subjects were categorized based on the common drug/s encountered for development of drug resistant tuberculosis either in single or multiple. Most common reason encountered for drug resistance is Isoniazid and rifampicin either in single or in combinations.

In the present study ADRs experienced by different subjects were categorized based on the anatomical site affected as shown in the table 9. The most predominant system affected was gastro intestinal tract with 29.13%.

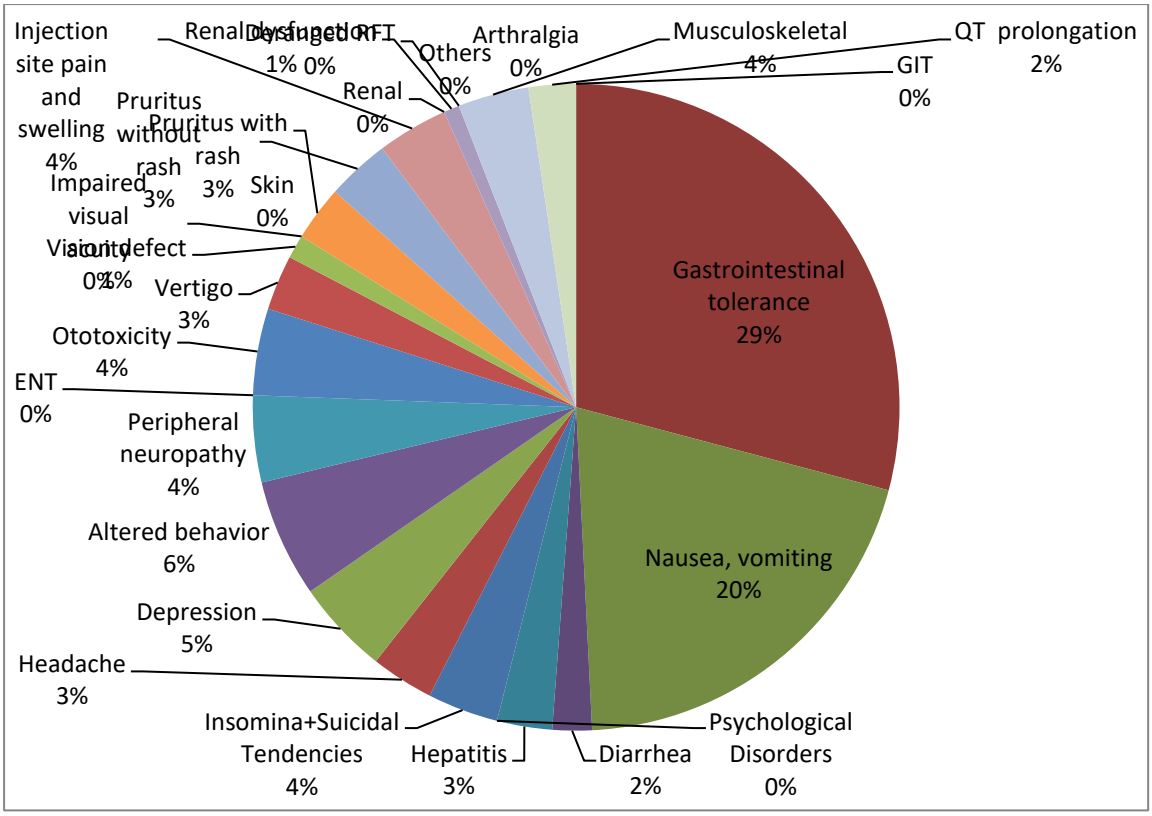
Table 7: Frequency of individual ADRs noted during treatment of MDR and XDR-TB patient.

Type of ADR	**Offending Dugs**	**No. of patients**	**Percentage (%)**
GIT			
Gastrointestinal tolerance	Km/Am	74	29.13
Nausea, vomiting	H/Z/Clf	51	20.07
Diarrhea	Liz/Clf	05	1.96

Hepatitis	H/Z	07	2.75
Psychological Disorders			
Insomnia + Suicidal Tendencies	Cylo/Bdq	09	3.54
Headache	E/Cylo/Lfx	08	3.14
Depression	Cylo	12	4.72
Altered behavior	Cylo	15	5.90
Peripheral neuropathy	H/LZn	11	4.33
ENT			
Ototoxicity	Km/Am	11	4.33
Vertigo	Km/Am	07	2.75
Vision defect Impaired visual acuity	E	03	1.18
Skin			
Pruritus with rash	Clof	07	2.75
Pruritus without rash	Clof	08	3.14
Injection site pain and swelling	Km/Am	09	3.54
Renal			
Renal dysfunction Deranged RFT	Km/Am	02	0.78
Others			
Musculoskeletal Arthralgia	Z, Lfx/mfx	09	3.54
QT prolongation	Bdq, DL	06	2.36
Total		254	100

Abbrevations: H- Isoniazid**,** R- Rifampicin, E- Ethambutol,Z-Pyrazinamide, Km-Kenamicin, Am-Amikacin, Lfx-Levofloxacin, Mfx-Moxifloxacin, Clf-Clofazamine, Cly-Cycloserine, Bdq-Bedaqualine, Dl-Delamide.

Fig:5 Graphical Representation of Subjects based on Individual ADRs.



All the observed adverse drug reactions observed were assessed for causality assessment using WHO and Naranjo scale as shown in the table 6. As per the WHO and Naranjo causality scales in the present study probable and possible ADRs were commonly observed with possible ADR predominance of 65% and 49% respectively.

As per the severity assessment moderate ADRs were reported high in number. Preventability assessment revealed that 75% of ADRs in the present study can be probably prevented by clinical pharmacist interventions.

Table:8 Common adverse drug reactions, Suspected agents and Management strategies of anti tubercular drugs used in drug resistant tuberculosis

Type of ADRs	**Suspected agent**	**Clinical Pharmacist Mediated Counselling**
Gastrointestinal		
Gastritis	PAS Eto/Pto CfzAll FQs' Lzd,Bdq, Dlm	H2-blockers, proton-pump inhibitors, or other antacids Stop suspected agent(s) for short periods of time (e.g., 1–7 days) Lower dose of suspected agent, if this can be

		done without compromisingregimen Discontinue suspected agent if this can be done without compromising regimen
Nausea and vomiting	Eto/Pto PASH, E, Z Bdq Dlm	Assess for dehydration; initiate rehydration if indicated in case of severe vomiting Initiate antiemetic therapy like metoclopramide and ondansetron Changing the dose timing, splitting of dose or supplementation along with orafter food particularly for Eto, PAS
Diarrhea	PAS Eto/Pto	Reassurance and observation in mild cases Maintain hydration in severe cases Monitor electrolytes in severe cases Rule out any infectious etiology or dysentery or lactose intolerance Use of loperamide in case of non-infectious etiology
Hepatitis	Z, H, R Bdq Eto/Pto PAS FQs'	Stop all therapy pending resolution of hepatitis Switch to three drug regimen S, FQ, and Cs in critically ill or extensive disease Eliminate other potential causes of hepatitis including viral and alcoholism History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens
Tinnitus dizziness	Km Am Cm SCs FQs' Eto/Pto Lzd H	Consider using capreomycin if an aminoglycoside had been the prior injectablein regimen Consider dosing 2–3 times a week if drug is

		essential to the regimen and patientcan tolerate Discontinue suspected agent if persistence of symptoms in view of residualeffect Precaution to be taken in elderly Weekly monitoring after having symptoms
Depression and suicidalideation	CsFQ Eto/Pto H	Offer group or individual counseling Initiate antidepressant therapy Lower dose of suspected agent if this can be done without compromisingregimen Discontinue suspected agent if this can be done without compromising regimen Socioeconomic conditions and chronic illness should not be underestimated ascontributing factors to depression
Peripheral neuropathy	Lzd Cs HS Km Am Cm Eto/PtoFQs'	Increase pyridoxine to maximum daily dose (200 mg per day) Change injectable to capreomycin if patient has documented susceptibility tocapreomycin Initiate therapy with tricyclic antidepressants such as amitriptyline 25–50 mg
Ototoxicity	S Km Am, CmClr	Monitoring with audiometry every month during intensive phase when treatedwith injectable aminoglycosides - Document hearing loss and compare with baseline audiometry if Available Rule out alternative diagnoses Change parenteral treatment to capreomycin if patient has documented sus- ceptibility to capreomycin
Optic neuritis	E Eto/Pto Lzd	Visual acuity test and color vision at baseline and on occurrence of symptomswhen treated

		with E and Lzd Stop offending drug Refer patient to an ophthalmologist if persistence of symptoms Usually reverses with cessation of drug
Rash itching Allergic reaction anaphylaxis	All FLDs and SLDs	Reassurance and conservative treatment for mild dermatological reactions Exclusion of other diagnoses of skin disorders Antihistaminics and corticosteroid ointments to be used Oral steroids in refractory cases Order of reintroduction will be H, R, Z, Eto, Cs, E, PAS, FQ, and Km Discontinue offending drug responsible for severe reactions such as Steven–Johnson syndrome
Renal		
Nephrotoxicity	S Km Am Cm	Discontinue suspected agent - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine) Adjust all anti-tubercular medications according to the creatinine clearance
Heart		
QTc interval prolongation	Bdq Dlm FQs' especially Mfx Cfz Clr	Serial monitoring with ECG and look for changes If QTc interval 480–500 ms Offending drugs should be continued under serial ECG monitoring (at least twice a week)

		Exclude congenital or acquired cardiac disorders and other comorbidities.
Musculosketel		
Arthralgia	Z FQs' Bdq	Initiate therapy with nonsteroidal anti-inflammatory drugs Lower dose of suspected agent if this can be done without compromisingregimen Discontinue suspected agent if this can be done without compromising regimen.

DISCUSSION

The present observational study has evaluated a DOTS- Plus program, with special reference to Adverse Drug effects in which standard treatment of drug resistant tuberculosis cases as per RNTCP (NTEP) guidelines has been started in this DR-TB Centre. In the present study of 508 patients, the age group ranged from 18 to 50 years. Maximum number of cases was in the age group 31-40 yrs (35.33%) followed by 41-50yrs (24.00%). The median age of the patients in present study was 31.83 years, as compared to the results published by the study conducted by (Edward *et al.,* 2000),[6] was 28 years and as per the study done in Russia by (Arora VK *et al.,* 2007) was reported as 26 years .[7]

In the present study, majority of the patients were males 362 (71.25%) and Females 146 (28.74%). similar findings with higher frequency were repoted in this studies (males 65.33%and females 34.66%)(WHO, 2016)[2]. and proportion of males to females was 65.33% and 34.66% respectively(Arora VK *et al.,* 2007).[7]

In this study ADRs were observed in 31.69% patient's, a finding comparable to present study reports notified in different studies. The ADR reported in present study were, Gastrointestinal, Ototoxicity, Injection site swelling/pain, Psychiatric manifestations, Arthralgia, Skin, Renal Involvement, Vision defect, peripheral neuropathy.

Gastro intestinal symptoms were most common adverse reaction observed in this study that is 74(29.13%) similar to other studies(Rohan *et al.,* 2014),[9] (KapadiaVishakha, K *et al.,* 2013),[11]. on the contrary other studies have found observed gastrointestinal ADRs in 42%, 60% and 100% patients respectively(Arora VK *et al.,* 2007) [7] R. Singla(R.Singla *et al.,* 2009)[8] (Abhijeet Singa *et al.,* 2019)[12] (JJ Furin et al, 2001)[13]. Hepatotoxicity was noted in

7(2.75%) patients only. Similarly findings were reported other studies (KapadiaVishakha, K *et al.,* 2013),[11] (JJ Furin et al, 2001)[13]. They were mild but required immediate treatment. These gastrointestinal symptoms occurred mostly within a week of starting treatment. No patient required alteration in DOTS-Plus treatment due to gastrointestinal ADRs. Ototoxicity 11 (4.33%) was second most common ADR observed in this study of which decreased hearing 4 and tinnitus and vertigo in 2 patients These findings were similar to observations in a study which reported ototoxicity as second most common ADR after gastrointestinal ADR and frequency of ototoxicity(WHO 1975)[2], (Kapadia Vishakha K *et al.,* 2013)[11] (Kalpesh Jain et al 2013)[14]. Singh R *et al* in 2007 reported ototoxicity in 5.92% patients(Abhijeet Singa *et al.,* 2019)[12]. Kanamycin was withdrawn in 80% of these patients and substituted with PAS (p-amino salicylic acid).

Psychiatric 43 (16.92%) manifestations were the third most common adverse reaction in this study of which insomnia was the most common followed by suicidal tendency, depression and altered behavior in descending order. Psychiatric ADRs were less common in this study as compared to 15.9%.(Arora VK *et al.,* 2007)[7] and 15% (Bloss E st al2010).[15] in other studies. All patients with psychiatric manifestation required withdrawal of cycloserine which was replaced with PAS (P-amino salicylic acid).

Injection site swelling/pain 9 (3.54%) was fourth common ADR observed in this study. In contrast, it was reported in a study that injection site swelling/pain seen in 21.05% patients[8]. None of the patients required withdrawal of injection Kanamycin. Arthralgia 9 (3.54%) was fifth common ADR observed in this study. Similar observation was seen in 4.5% and 7.94% respectively. (Rohan *et al.,* 2014),[9] (Kapadia Vishakha K *et al.,* 2013)[11] In contrast, it was observed in the studies that arthralgia was seen in 31% and 23.68% patients.[8,14] Skin Adverse drug reactions ADR observed in this study was 7 (2.75%) of which pruritus without rash in and pruritus with rash in 8 (3.14%) patient. Frequency of skin reaction found in this study is similar 4%, 1.58% and 4.5%.(Arora VK *et al.,* 2007)[7](Kapadia Vishakha K *et al.,* 2013)[11] (Torun T et al 2005)[16] On the one of the study reported cutaneous reactions in 43.3% patients (JJ Furin et al, 2001)[13].

Renal involvement was seen 2(0.78%) patients in this study which is our findings are consistent with the studies reporting other studies 1.58%, 2.7% and 2% respectively. (Rohan *et al.,* 2014),[9] (Kapadia Vishakha K *et al.,* 2013)[11] (Abhijeet Singa *et al.,* 2019)[12] Renal involvements were seen in the form of borderline derangement of serum creatinine (2mg%) which improved in few weeks and none required withdrawal of injection kanamycin. Other

ADR including Visual defect in 3 (1.18%), Peripheral Neuropathy 11(4.33%). our findings seen in a study with frequency of visual disturbance 1(0.9%) and peripheral neuropathy 11 (3.87%) (Rohan *et al.*, 2014),[9].

In present study Causality assessment of 161 members got 254 ADRs was done by Naranjo's Causality Scale, According to the Naranjo's scale, the causality assessment was done and it was observed that among the 161 cases, 9(5.59) were observed to be definite, 79 (53.55) were observed to be possible ADRs 85 (46.44%) were observed to be probable ADRs and where as the remaining 7(4.34) were observed to be doubtful ADRs.. The distribution of 254 ADRs as Mild 24.84%, moderate 60.86% and sever 14.05%, as the study population the patients was hospitalized for ADRs, higher number of ADRs belonged to "Moderate "grade.

Conclusion

ADRs were extremely common in the current study, however the majority of them were handled with little success using pharmacological, nonpharmacological, and psychological techniques mediated by clinical pharmacist changes to the treatment strategy was done. Our study showed that the prevalence of GI adverse effects, psychosis were more common and could be controlled symptomatically. The majority of ADRs were mild, avoidable, and may have been related to the implicated medicines. Although ADRs were commonly reported, the majority of patients continued their therapy by either stopping the offending medication or receiving supportive care, as we were able to see in our study.

In order to resolve the problem and assist in improving patient compliance, which enables them to tolerate adverse effects, resulting in a decrease in the default rate, routinely monitoring the predictability of ADRs with pertinent clinical parameters and close attention to patient complaints are both necessary.

It emphasizes the significance of tailored and ongoing monitoring during the course of therapy among MDR and XDR tuberculosis patients.

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