Causality And Severity AssesmentOf Adverse Drug Reactions Among Mdr-Tb And Xdr-Tb Patients Treated With Different Anti Tubercular Regimens

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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 bedefinite,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.

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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),andethambutol(E),whereas second-linedrugs (SLDs') and few FLDs' are reserved for treatment ofdrug-resistant TB (DR-TB).

Goodbacteriologicaldiagnosis and compliance to treatment remains two main pillars ofsuccessful treatment of TB. An adverse drug reaction (ADR)has been defined as "a response to a drug which is noxiousand unintended and which occurs at doses normally used inhuman for the prophylaxis, diagnosis, or therapy of disease,or for the modification of physiological function.[2] Patientsmay encounter with a variety of ADRs' when managed withanti-

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TB drugs. ADRs cause significant morbidity and evensometimes mortality if not detected early.[3-5] Major concernsexistregardingtreatmentofDR-TBpatients,especiallywith SLDs having lower efficacy, costly and more toxic as com-pared to FLDs. Most of ADRs are mild or minor and can bemanaged without discontinuation of treatment. Few ADRscan be severe or major causing life-threatening experienceleading to disconti-nuation or modification of treatment thatmayrequirehospitalizationandevenmortality ifunrecognized and untreated promptly. Various factors, such astiming of occurrence of ADR, pattern of illness, results oflaboratory tests, Rechallenge e.g., with type, dosing or timing ofdrugsadmini-stration,patientage,nutritionalstatus,thepres ence of preexisting diseases, or dysfun-ctions (such asimpaired liver function,impaired kidney function andalcohol-ism), might be attributed to causality of ADRs.[6] Therefore,continued surveillance of ADRs is essential particularly inDR-TB cases where early detection and timely managementof ADRs might determine successful outcome. This reviewaims to highlight the estimated burden and managementstrategies 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:

1. Identification of types and frequency of adverse drug reactions in Intensive and continuation phase.
2. To evaluate the incidence of treatment discontinuation in relation to ADRs.
3. To assess casualty and severity of the reported adverse drug reactions.
4. 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 concomitantmedication.
- PregnantWoman.
- 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 individuallyor 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 andcycloserine(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 generatedusing 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 508males 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

In the present study different subjects were categorized based on the educational status shown in the table 3.

Table 3: Educational status & Place of Living

Educational status	Males	Females	Total	Percentage(%)	P value
Illiterate	236	80	316	62.20	P<0.004
Primary	73	26	99	19.48	
Secondary	31	23	54	10.62	
Tertiary	22	17	39	7.67	
Place of Living					
Rural	248	95	343	67.51	P<0.03
Urban	114	51	165	32.48	

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.

Table: 6 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 7: Incidence of ADRs in paientsof MDR and XDR-TB with different anti-tuberclar regimen

S.NO	Age	Male		Female		MDR	XDR	Regimen and phases			Total ADRs	P Value
		Exposed	unexposed	Exposed	unexposed			IP	CP	All Oral		
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	
4.	41-50	35	56	16	18	115	08	29	124	08	51	
Total		**114**	**248**	**47**	**99**	**487**	**21**	**92**	**395**	**21**	**161**	P<0.0001

Table 8: Drug Resistance Profile of Patients

Drug resistance	Male	Female	Total	Percentage
H	49	17	66	12.99
H+R	265	113	378	74.40
H+R+E	28	15	43	8.46
H+R+SLD	20	01	21	4.13
Total	362	146	508	99.98

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 9: Frequency of individual ADRs noted during treatment of MDRand 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.

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:10 Analysis of ADRs by different scales

Analysis of ADRs	No.of patients	Percentage
Causality assessment (WHO Scale)		
Certain	11	6.83
Probable	52	38.50
Possible	85	65.21
Unlikely	10	6.21
Unclassified	2	1.24
Unclassifiable	1	0.62
Naranjo's Scale		
Definite	9	5.59
Probable	66	40.99
Possible	79	49.06
Doubtful	07	4.34
Severity assessment (Hartwig Scale and siegel Scale)		
Mild		
LEVEL 1	19	11.80
LEVEL 2	21	13.04
Moderate		
LEVEL 3	51	31.67
LEVEL 4	47	29.19
Severe		
LEVEL 5	15	9.31
LEVEL 6	04	2.48
LEVEL 7	04	2.48
Preventability Assessment (Schumock and Thomton Scale)		
Definitely Preventable	25	15.52
Probably Preventable	121	75.15
Not Preventable	15	9.31

Table:11 Common adverse drug reactions, Suspected agents and Management strategies of antitubercular 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-pumpinhibitors,orotherantacids Stop suspectedagent(s)forshortperiodsoftime(e.g.,1–7days) Lowerdoseofsuspectedagent,ifthiscanbedonewithoutcompromisingregimen Discontinuesuspectedagentifthiscanbedonewithoutcompromisingregimen Severegastritis,asmanifestedbyhematemesis,melenaorhematochezia,israre Dosing of antacids should be carefully timed so as to not interfere with theabsorptionofanti-tuberculardrugslikeFQs'andBdq(take2hoursbeforeor3hoursaftermedications) Reversibleupondiscontinuationofsuspectedagent(s) LzdandBdqcancausepancreatitisandworkuprequiredifsuspected Severe abdominal distress and acute abdomen have been reported with the useofclofazimine Althoughthesereportsarerare,ifthiseffectoccurs,clofazimineshouldbe Suspended
Nauseaandvomiting	Eto/PtoPASH,E,Z BdqDlm	Assessfordehydration;initiaterehydrationifindicatedincaseofseverevomiting Initiateantiemetictherapylikemetoclopramideandondansetron Changing the dosetiming, splittingof doseor supplementationalong withorafterfoodparticularlyforEto,PAS Lowerdoseofsuspectedagentifthiscanbedonewithoutcompromisingregimen Discontinuesuspectedagentifthiscanbedonewithoutcompromisingregimenrarelynecessary Nauseaandvomitingfrequentlyobservedinearlyweeksoftherapybutabatewithtimeontreatmentandadjunctivetherapy AvoidondansetroninpatientstakingMfx,Bdq,andDlminviewofQTprolongation
Diarrhea	PAS Eto/Pto	Reassurance andobservationinmildcases Maintainhydrationinseverecases Monitorelectrolytesinseverecases Ruleoutanyinfectiousetiologyordysenteryorlactoseintolerance Useofloperamideincaseofnon-infectiousetiology
Hepatitis	Z,H,R BdqEto/PtoPASFQs'	Stopalltherapypendingresolutionofhepatitis Switchto threedrug regimen S, FQ,and Cs incritically ill or extensivedisease Eliminateotherpotentialcausesofhepatitisincludingviralandalcoholism History of previous hepatitis should be carefully analyzed to determine mostlikelycausativeagent(s);theseshouldbeavoidedinfutureregimens Conditions to stop therapy: AST or ALT elevation ≥5 times ULN with normal bil-irubin/AST or ALT elevation ≥3 times ULN with bilirubin ≥2 times ULN or symptomsofjaundice/isolatedtotalbilirubin≥2timesULN Considersuspendingmostlikelyagentpermanently(H,Eto,Z,FQs'incaseofshorterregimenandEto,Z,Bdq,FQs'incaseoflongerregimens) ReintroduceremainingdrugswhenASTandALTelevation<2timesULN,oneatatimewhilemonitoring liverfunctionevery3daysinthefollowingsequence(FQs',Eto,H,Zincaseofshorterregimenand FQs',Bdq,Eto,Zincaseoflongerregimens) Generallyreversibleupondiscontinuationofsuspectedagent N-acetylcysteinecanbeprescribedbutevidenceisuncertain Gastroenterologistconsultincomplicatedcasessuchashepaticencephalopathyorportalhypertension
Psychological Disorders		
Tinnitusdizziness	KmAmCmSCs FQs'Eto/PtoLzdH	Considerusingcapreomycinifanaminoglycosidehadbeenthepriorinjectableinregimen Considerdosing2–3timesaweekifdrugisessentialtotheregimenandpatientcantolerate Discontinuesuspectedagentifpersistenceofsymptomsinviewofresidualeffect Precautiontobetakeninelderly Weeklymonitoringafterhavingsymptoms
Depression andsuicidalideation	CsFQ Eto/PtoH	Offergrouporindividualcounseling Initiateantidepressanttherapy Lowerdoseofsuspectedagentifthiscanbedonewithoutcompromisingregimen Discontinuesuspectedagentifthiscanbedonewithoutcompromisingregimen Socioeconomicconditionsandchronicillnessshouldnotbeunderestimatedascontributingfactorstodepression Depressivesymptomsmayfluctuateduringtherapyandmayimproveasillnessissuccessfullytreated

		Historyofpreviousdepressionisnotacontraindicationtotheuseoftheagents listedbutmayincreasethelikelihoodofdepressiondevelopingduringtreatment
Peripheralneuropathy	LzdCsHSKm Am CmEto/PtoFQs'	Increasepyridoxinetomaximumdailydose(200mgperday) Change injectable tocapreomycin if patienthas documented susceptibilitytocapreomycin Initiatetherapywithtricyclicantidepressantssuchasamitriptyline25–50mg Nonsteroidalanti-inflammatorydrugsoracetaminophenmayhelpalleviatesymptoms Lowerdoseofsuspectedagent,ifthiscanbedonewithoutcompromisingregimen Discontinuesuspectedagentifthiscanbedonewithoutcompromisingregimen Neuropathymaybeirreversible;however,somepatientsmayexperience improvementwhenoffendingagentsaresuspended
ENT		
Ototoxicity	SKm Am,CmClr	Monitoringwithaudiometryeverymonthduringintensivephasewhentreatedwithinjectableaminoglycosides -Documenthearinglossandcomparewithbaselineaudiometryif Available Ruleoutalternativediagnoses Change parenteral treatment to capreomycin if patient has documented susceptibilitytocapreomycin Decreasefrequencyand/orlowerdoseofsuspectedagentifthiscanbedonewithout compromising the regimen (consider administration three times perweek) Discontinue suspected agent if this can be done without compromising theregimen Theriskoffurtherhearinglossmustbeweighedagainstthe risksofstoppingtheinjectableinthetreatmentregimen Whilethebenefitofhearingaidsisminimaltomoderateinauditory Toxicity,consideratrialusetodetermineifapatientwithhearinglosscanben-efitfromtheiruse
Opticneuritis	EEto/PtoLzd	VisualacuitytestandcolorvisionatbaselineandonoccurrenceofsymptomswhentreatedwithEandLzd Stopoffendingdrug Referpatienttoanophthalmologistifpersistenceofsymptoms Usually reverses withcessationof drug
Skin		
Rash itchingAllergic reactionanaphylaxis	AllFLDsandSLDs	Reassuranceandconservativetreatmentformilddermatologicalreactions Exclusionofotherdiagnosesofskindisorders Antihistaminicsandcorticosteroidointmentstobeused Oral steroidsinrefractorycases Orderofreintroductionwillbe H,R,Z,Eto,Cs,E,PAS,FQ,andKm Discontinueoffendingdrugresponsibleforsevere reactionssuchasSteven–Johnsonsyndrome
Renal		
Nephrotoxicity	SKm Am Cm	Discontinuesuspectedagent -Considerusingcapreomycinifanaminoglycosidehadbeentheprior injectableinregimen Considerdosing2–3timesaweekifdrugisessentialtotheregimenandpatientcantolerate(closemonitoringofcreatinine) Adjustallanti-tubercularmedicationsaccordingtothecreatinineclearance Renalimpairmentmaybepermanent CreatininemonitoringeverymonthforfirstthreemonthsandtheneverythreemonthswhenSLIDcontinuedduringintensivephase Creatininemonitoringevery1to3weeksincaseofHIV,DMandotherhighrisk Cases
Heart		
QTcintervalprolongation	BdqDlmFQs' especiallyMfxCfzClr	SerialmonitoringwithECGandlookforchanges IfQTcinterval480–500ms Offendingdrugsshouldbecontinuedunderserial ECGmonitoring(atleasttwiceaweek) Excludecongenitaloracquiredcardiacdisordersandothercomorbidities Monitorelectrolytes(Na,K,Ca,andMg)andcreatinineroutinely -PrecautionswhenusedwithCm,Am,orotherancillarymedications Suchasdiuretics/macrolideantibiotics Iflowelectrolytes,discontinuedrugtemporarilytilllevelsgetcorrected IfQTcinterval≥500ms Offendingdrugsshouldbeimmediatelystoppedtemporarilytillintervalgoes <470ms MfxshouldbereplacedwithLfxpreferably Subsequently,CfzthenBdqandDlmifthereispersistentprolongation AvoidBdqandDlmcombinationcontainingregimensifthereiscardiotoxicity ReintroductioninfollowingsequencetillthereisQTinterval<470ms-

		Bdq,MfxincaseofLfxresistance,Cfz,andDlm
Musculosketel		
Arthralgia	ZFQs' Bdq	Initiatetherapywithnonsteroidalanti-inflammatorydrugs,LowerdoseofsuspectedagentifthiscanbedonewithoutompromisingregimenDiscontinuesuspectedagentifthiscanbedonewithoutcompromisingregimen Symptomsofarthralgiagenerallydiminishovertime,evenwithoutinterventionUricacidlevelsmaybeelevatedinpatientsonZAllopurinolappearsnottocorrecttheuricacidlevelsinsuchcases

Abbrevation :

ALT- alanine transaminase, AST- aspartate transminase, Am- amokacin, Bdq- bedaqualine, Cfz-clofazimine,Clr-clarithromycin,Cm-Capr-eomycin, Cs- cycloserin,
Dlm- delamanid, DR-TB- drug resistence tuberculosis, E- ethambutol, ECG- electo cardiogram, E- ethionamide, FLD- first line drugs, FQ- flucroquinolones, Gfx- gatifloxacin, Km- kanamycin, H- isoniazid, Lfx- levofloxacin, Lzd- linezolid, Mfx- moxifloxacin, NSAID-nonsteriodial anti- inflammatory drug, PAS-para amino salicylic acid, Pto- prothionamide , QD- once daily, R- rifampicin, S- streoptomycin, SLD- second line drugs, Z-pyrazinamide

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 31-40yrs (35.33%) followed by 41-50yrs (24.00%).Themedianageofthepatientsinpresentstudy was31.83years,ascomparedtotheresults published by the study conducted by (Edward *et al.,* 2000),[6] was 28 years and as per the study done in Russia by (AroraVK *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(AroraVK *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, Gastroi-ntestinal, 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%and100% patients respectively(AroraVK *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%.(AroraVK *et al.,* 2007)[7] and 15% (Bloss E st al2010).[15] in other studies. Allpatients 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%.(AroraVK *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 pharma-cological,nonpharmacological, and psycho-logical 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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