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A STUDY TO ASSESS THE PREVALENCE OF ADVERSE DRUG REACTIONS AMONG PATIENTS TREATED WITH CATEGORY IV RNTCP REGIMEN AT DOTS PLUS SITE

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Abstract: India is the highest TB burden country in the world and accounts for nearly one fifth of global burden of tuberculosis. The prevalence is found to be at a low level in most of the country where it has been studied. Management of adverse drug reactions has a major role in treatment adherence and patient compliance. This was a hospital based analytical type of observational study and the confirmed cases of Multidrug Resistant Pulmonary Tuberculosis patients from various Tuberculosis Unit under PMDT site. This study was conducted using face to face administered questionnaires. Total 82.5 % patients show one or the other ADR while 17.5 % shows no ADR and average no. of events per patient=5.275. According to our findings in this prospective cohort study, there was no increased risk of TB-drug adverse events with the advancement of age. A higher percentage of female patients (91.7%) than the male (80.9%) patients experienced the ADR. study shows that DOTS Plus treatment is an effective and safe treatment strategy as most of the adverse drug reactions noted were of a mild variety and were managed with symptomatic medications.

Key Words: Prevalence, ADR, RNTCP, PMDT, DOTS

Introduction: India is the highest TB burden country in the world and accounts for nearly one fifth of global burden of tuberculosis. Every year 1.8 million person develop tuberculosis, of which. 8 million are new smear + ve highly infectious cases. Annual risk of becoming infected with TB is 1.5 % & once infected there is 10 % life time risk of developing TB disease. Patients with infectious pulmonary tuberculosis disease can infect 10-15 people in a year.[1]

A drug resistant isolate can be categorized as single or multiple drug resistant. Multiple drug resistant (MDR) is defined as resistance to Isoniazid (H) and Rifampicin(R) with or without resistance to other drugs.[2]

The term "Programmatic Management of Drug Resistant TB" (PMDT) (erstwhile DOTS Plus), refers to programme based MDR-TB diagnosis, management and treatment. These guidelines

promote full integration of basic TB control and PMDT activities under the RNTCP, so that patients with TB are evaluated for drug-resistance and placed on the appropriate treatment regimen and properly managed from the outset of treatment, or as early as possible. These guidelines also integrate the identification and treatment of more severe forms of drug resistance, such as extensively drug resistant TB.[3]

Chronic cases that have remained or have become smear positive after completing fully supervised retreatment (category II) regimens. These are most likely MDR cases and an MDR TB case whose recovered M. tuberculosis isolate is resistant to at least isoniazid, rifampicin, a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable anti TB drug (kanamycin, amikacin, or capreomycin) at a RNTCP-certified Culture & DST Laboratory.[4]

The five most common adverse events were nausea/vomiting (32.8%), diarrhoea (21.1%), arthralgia (16.4%), dizziness/vertigo (14.3%) and hearing disturbances (12%).[5]

Management of adverse drug reactions has a major role in treatment adherence and patient compliance as we all know that drug resistance has been increasing for antitubercular drugs and newer variants of drug resistant tuberculosis like XDR tuberculosis has been emerging.

Material and Methods: It was a hospital based analytical type of observational study conducted at PMDT site at Department of Respiratory Medicine, JLN Medical College and Associated Group of Hospitals, Ajmer, Rajasthan. The patients with documented evidence of sputum for Mycobacterial Culture & Sensitivity from an Intermediate Reference Laboratories were included in the study population and following methods were used for Mycobacterial Culture & Sensitivity- Conventional solid egg-based Lowenstein-Jensen (LJ) media and Molecular Line Probe Assay, at State Tuberculosis Training and Demonstration Centre Mycobacterial Culture and Drug sensitivity is done using Molecular Line Probe Assay. The negative samples from MDR suspect patients on LPA were subjected to culture on conventional solid egg-based Lowenstein-Jensen (LJ) media and DST was performed for streptomycin (S), isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). The confirmed cases of Multidrug Resistant Pulmonary Tuberculosis patients from various Tuberculosis Unit under PMDT site, Ajmer reporting to the DOTS Plus site Committee along with their DST result and PMDT referral for treatment form and after decision of DOTS Plus site Committee they were admitted for Pretreatment Evaluation in the MDR ward at the site. All these patients were clinically examined. All information to accomplish objectives was collected by personal interview of each of the study subjects for about 30 to 45 minutes at PMDT site using pre-designed Proforma.

Results:

Table 1: Prevalence of ADR based on no. of patients and gender

	Total no. of patients N (%)	**Male N (%)**	**Female N (%)**
ADR	66 (82.5)	55 (80.9)	11 (91.7)
No ADR	14 (17.5)	13 (19.1)	1 (8.3)

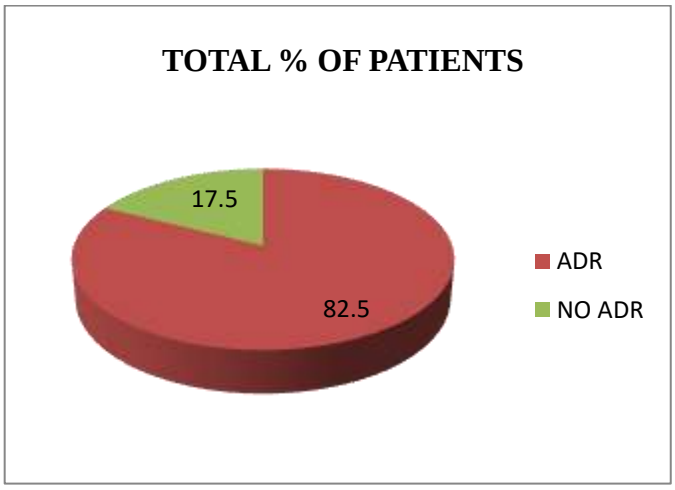

Figure 1: It shows that out of total 82.5 % patients show one or the other ADR while 17.5 % shows no ADR

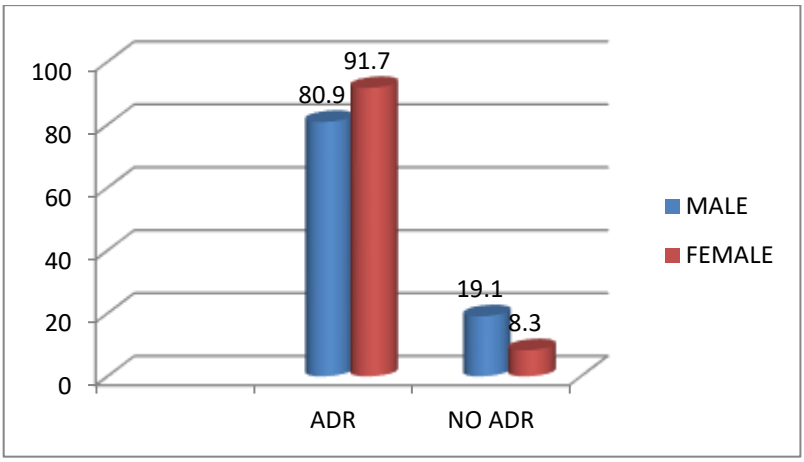

Figure 2: It shows that 80.9% males developed ADR while out of females 91.7 % developed one or the other ADR.

Table 2: Prevalence of ADR based on age

Age	With ADR	Without ADR
<=65 yrs	63	14
>65 yrs	3	0

CHI SQUARE =0.001 p VALUE > 0.05 n.s
It is found that there is no statistical difference between old age (>65 yrs) and younger age (<=65 yrs) group in ADR and without ADR.

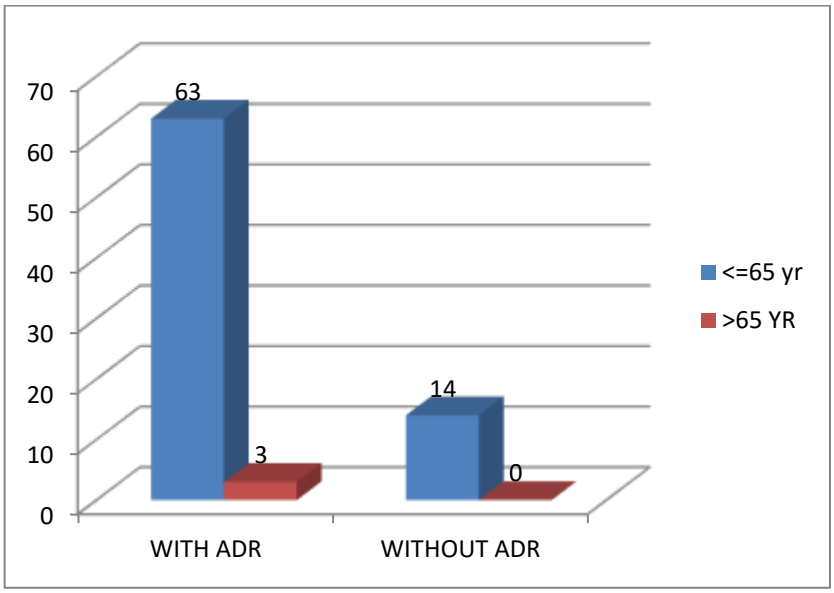

Figure 3: Age as a risk factor for ADR

Table 3: Prevalence of ADR based on age Sex

Sex	With ADR	Without ADR
Male	55	13
Female	11	1

Chi square = 0.244, p>0.05 N.S

It is found that there is no statistical difference between male and female in ADR and without ADR.

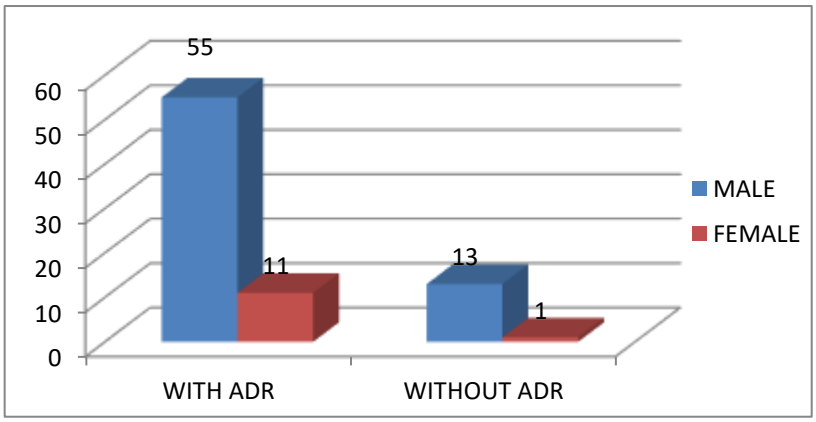

Figure 4: **Sex as a risk factor for ADR**

Table 4: Distribution of adverse events

System involved	Type of adverse drug reactions	Total No of episodes n (%)
Gastrointestinal tract (GIT)	Nausea	62(14.69)
	Heart burn	42(9.95)
	Metallic taste	37(8.77)
	Abdominal pain	26(6.16)
	Vomiting	9(2.13)
	Constipation	1(0.24)
	Total no of events	177(41.94)
Central nervous system (CNS)	Insomnia	37(8.77)
	Drowsiness	18(4.26)
	Depression(mild and moderate)	7(1.66)

	Tingling and burning	13(3.08)
	Depression severe(suicidal thoughts)	9(2.13)
	Lethargy	6(1.42)
	Headache	3(0.7)
	Psychosis(illusions, delusionsetc)	2(0.47)
	Anxiety	1(0.24)
	Total no of events	96(22.75)
Auditory and vestibular	Hearing loss	26(6.16)
	Vertigo	10(2.34)
	Tinnitus	7(1.66)
	Total no of events	43(10.19)
Visual	Decreased vision	20(4.74)
	Double vision	2(0.47)
	Total no of events	22(5.21)
Thyroid Toxicity	Hypothyroidism	1(0.24)
Other reactions	Musculoskeletal pain	46(10.9)
	Weakness and fatigue	20(4.74)
	Facial puffiness	4(0.95)
	Arthralgia	8(1.9)
	Itching	2(0.47)
	Slurred speech	2(0.47)
	Breathlessness	1(0.24)
	Total no of events	83(19.67)
	Overall total no of events	**422**

Average No. of Events Per Patient=5.275

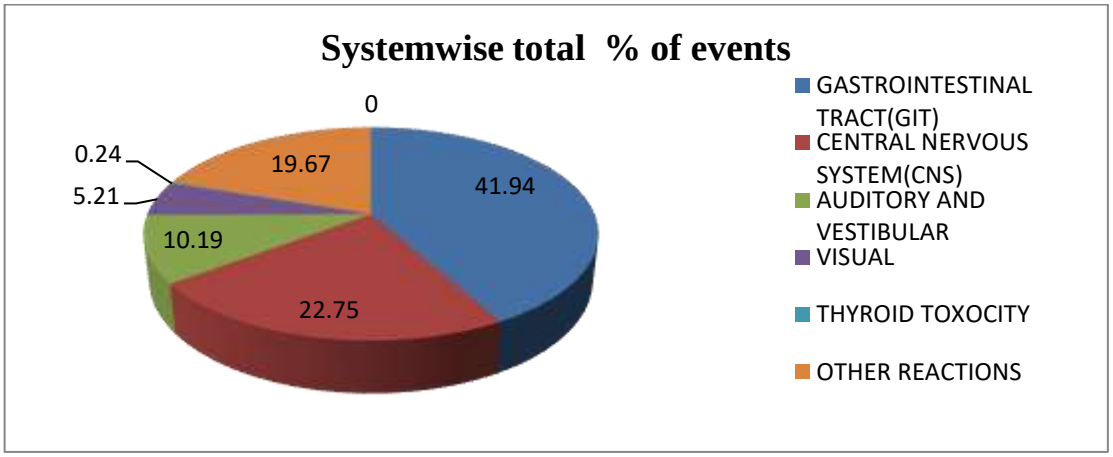

Figure 5: Distribution of Adverse Events

Discussion:

Management of adverse drug reactions has a major role in treatment adherence and patient compliance as we all know that drug resistance has been increasing for antitubercular drugs and newer variants of drug resistant tuberculosis like XDR tuberculosis has been emerging. In this study a total of 86 patients were enrolled in the study of which 6 lost to follow up so excluded from study and among 80 patients 66 (82.5%) developed ADRs. Our study considers the all possible risk factors for ADR and their statistical significance of association with the ADR account the prevalence of adverse drug reactions among patients treated with category IV RNTCP regimen at Dots Plus site.[6]

In a study among urban residents of New York City, tuberculin positivity was present in 5.5% in the area of highest socio-economic status versus 22.4% in the lowest.[73] According

to our findings in this prospective cohort study, there is no increased risk of TB-drug adverse events when age increases. In previous reports, the occurrence of any major side effect has been associated with age, especially amongst the elderly. The frequency of adverse reactions has shown to increase in a progressive and direct form in relationship to age.[7, 8]

Overall, vulnerability to adverse reactions are more probable at older ages-especially hepatotoxicity-due to a significant reduction in clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution, as well as other factors affecting liver function.[9, 10] In our study this insignificance of age can be due to disproportionately more number of patients in the age group below 65 as compared to age group more than 65.

Percentage of female patients experiencing ADRs are found to be more in our study than the male patients but the association is not found to be statistically significant.[11,12] Considered female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs. Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to males. In our study numbers of females are relatively very less as compared to these studies so this can be the reason for this disproportion. In the present study side effects were noted in 66 out of 80 patients (83%) and treatment had to be modified due to side effects in 14 (21%), which is higher than previously recorded in the literature.[13]

Gastrointestinal (GI) side effects were common but mostly were mild in severity and does not result in change in TB treatment. In addition, neuro-psychiatric toxicities were next commonly observed system wise adverse effects and most common adverse effects which required frequent changes in DOTS-Plus regimens**.** Fluoroquinolones are very effective and are central to MDR-TB treatment regimens.[14] however we attributed drowsiness in 11 and arthralgia to OFX in 11 cases. Different studies have reported hearing loss as an adverse drug reaction in patients of MDR-TB ranging from 6–18% [15] In our study ototoxicity was observed in 20 out of 80 patients (25%) with events ranging from hearing loss, vertigo and tinnitus in decreasing no of frequencies. In our study visual side effects were observed in 18 out of 80 (22.5%) patients of which decreased vision was most common adverse event with 20 episodes and out of them 80 % of episodes were observed at 6 months after the start of treatment which was attributed to ethambutol. Hepatotoxicity and nephrotoxicity was not reported in our study by any patient, these symptoms develop relatively late in treatment. Generally, our findings are similar to the findings of[16] that adverse events of the anti-TB medicines were bearable and did not cause discontinuation of the treatment apart from the occasional suspension of an offending agent in 11.7% of the patients.[17]

Conclusion:

A total of 80 patients were selected for this study out of which 85% were males and 15 % were females, and maximum distribution of 64% was seen in the age group of 31-50 yrs. Most people had poor socioeconomic status. Only 2 (2.5%) out of 80 patients had salary more than ten thousand rupees. Most of them were farmers (31.25%) by occupation, illiterate (51.25%) and unemployed (50%). Overall ADR was prevalent in 83% of patients. 81 % of males had ADR while 92 % of females show one or the other symptoms of ADR. According to our findings in this prospective cohort study, there was no increased risk of TB-drug adverse events with the advancement of age. A higher percentage of female patients (91.7%) than the male (80.9%) patients experienced the ADR but, there was no statistically significant association of sex with the incidence of ADRs. This study shows that DOTS Plus treatment is an effective and safe treatment strategy as most of the adverse drug reactions noted were of a mild variety (Hartwig's scale level 1) and were managed with symptomatic medications.

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