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EVALUATION OF INCIDENCE AND SEVERITY OF ANTI TUBERCULAR DRUGS INDUCED ADVERSE DRUG REACTIONS IN TUBERCULOSIS PATIENTS.

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ABSTRACT
Tuberculosis has been one of the common diseases of human communities. Besides of disease-related complications, there are serious adverse drug reactions due to Anti-tuberculosis drug therapy. The main objective of this study is to assess the incidence and severity of adverse drug reactions (ADRs) induced by anti tubercular drugs. All patients admitted to the general medicine department of tertiary care teaching hospital, who received anti tubercularmedications. These patients were monitored for ADRs. The causality and severity of the reactions were determined by using Naranjo, WHO-UMC scales and Hartwig questionnaire, respectively. During the study period, 96 patients received Anti-tubercular drugs; of them 55 (57.29%) developed at least one ADR. In our study mostly ADRswere observedare Gastric effects (30.90%). Our study concluded that there is need to provide information to patients regarding proper usage of medications and to reduce the ADRs.

KEYWORDS: Tuberculosis, Anti-tubercular therapy, Adverse drug reaction, Incidence and severity of ADRs.

INTRODUCTION
Evaluation is best known as the making of a judgment about the amount, number or value of something; assessment. Incidence is defined as the occurrence, rate, or frequency of a disease, crime or other undesirable thing. Severity is defined as the fact or condition of being severe. According to WHO, ADR is defined as any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[1]

According to Karch and Lasagna, ADR is defined as any response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose. For reporting purposes, FDA categorizes a serious adverse event (events relating to drugs or devices) as one in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.[2]

Causality Assessment of ADR's
Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission and even death. Henceitis essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. It is desirable that ADRs should be objectively assessed and presented based on an acceptableprobabilityscale. Many causalityassessment methods have been proposed to assess the relationship between a drug and an adverse event in a given patient. The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC) and the Naranjo Probability Scale are the generally accepted and most widely used methods for causality assessment in clinicalpractice. Along with this Modified hartwig's severity scale is also used in our study.[3]

TUBERCULOSIS
Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis, which commonly affects the lungs. India is one among the highest tuberculosis (TB) burden country in the world, accounting for nearly one-fifth of the global incidence.[4]

Global TB Statistics
- There were an estimated 9 million new cases of TB in 2013.
- There were an estimated 1.5 million deaths. Of these 1.14 million deaths were among HIV negative

people and there were a further 360,000 deaths among HIV positive people.

- There were an estimated 3.3 million cases and 510,000 TB deaths among women.
- There were also an estimated 550,000 cases of TB in children and 80,000 deaths. The estimated number of deaths among children excludes TB deaths in HIV positive children, for which estimates are not yet available.[5]

Prevalence of TB

TB prevalence in countries with a relatively high burden of TB (around 100 cases per 100 000 population or more), the prevalence of bacteriologically confirmed pulmonary TB can be directly measured in nationwide population-based surveys using large sample size. TB prevalence is estimated as 11 million in 2013, equivalent to 159 cases per 100000 populations. By 2013, the prevalence rate had fallen 41% globally since 1990.[6]

Treatment

The first line drugs are isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin.

Treatmentschedule

Category-1

- Newly diagnosed case of sputum positive indicating pulmonary tuberculosis.
- Sputumtest reporting negative pulmonary tuberculosis along with extensiveparenchymal involvement.
- Severe extra pulmonary tuberculosis.

Category-2

- Category-1 Treatment failure cases.
- Reoccurrence of TB.
- Return after interruption.

Category-3

- Sputum test reporting negative pulmonary tuberculosis with minimal involvement.
- Extra pulmonary tuberculosis but less severe.

Drug Regimen

Category- 1: 2(H3 R3 Z3 E3) 4 (H3 R3)
Category- 2: 2(S3 H3 R3 Z3 E3)+ 1(H3 R3 Z3 E3) 5 (H3 R3 E3)
Category- 3: 2(H3 R3 Z3) 4 (H3 R3)

H= INH 600mg, R= Rifampicin 450mg, Z= Pyrazinamide 1500mg, E= Ethambutol 1200mg, S= Streptomycin 750 mg.
2(H3 R3 Z3 E3) 4 (H3 R3) means first 2months of therapy with INH, Rifampicin, Pyrazinamide and Ethambutol in a thrice weekly schedule followed by INH and rifampicin for a period of 4 months in a thrice weekly schedule.

Recommended Doses of Antitubercular Drugs

Drug	Daily Dose		3 times per week dose	
	Daily Dose(mg/kg)	Maximum Dose	Dose(mg/kg)	Maximum Dose
Isoniazid (H)	5 mg/kg (4–6 mg/kg)	300 mg	10 mg/kg (8–12 mg/kg)	900 mg
Rifampin ®	10 mg/kg (8–12 mg/kg)	600mg	10 mg/kg (8–12 mg/kg)	600mg
Pyrazinamide (Z)	25 mg/kg (20–30 mg/kg)	-	35 mg/kg (30–40 mg/kg)	-
Ethambutol(E)	15mg/kg (15–20 mg/kg)	-	30 mg/kg (25–35 mg/kg)	-
Streptomycin(S)	15 mg/kg (12–18 mg/kg)	-	15 mg/kg (12–18 mg/kg)	1000mg
Ethionamide	15 to 20 mg/kg ORALLY once daily if tolerated; divided doses if necessary; MAX 1 g/day			
Cycloserine	initial, 250 mg ORALLY every 12 h for 2 weeks, then as tolerated to 250 mg every 6 to 8 h; MAX 1 g daily			
Thiacetazone	2.5 milligrams/kilogram (mg/kg) daily.			
Capreomycin	15 mg/kg/day (maximum 1000 mg/day) IM or IV given as a single daily dose			

AIMS AND OBJECTIVES

- To improve the medication adherence of the patient by anti-tubercular drugs according to the prescribed dosage regimen.
- To improve the compliance of the patient by counselling about the importance of the treatment regimen for Tuberculosis.
- To minimize the possible ADRs by counselling to the patient.
- To maintain the patient better health care by make the patient adhere to their medications.
- To assess the severity of adverse drug reactions (ADRs) induced by anti tubercular drugs.
- To detect and report the serious and preventable suspected ADRs.

METHODOLOGY

Study design: Prospective observational study.

Study duration: The study was planned and carried out for a period of six months from February to July 2015.

Study criteria:a) Inclusion criteria

- Patients diagnosed with tuberculosis, adult patient (18 years of age and above).
- Patients who are willing to participate in the study.
- Patients with normal liver function test before start taking anti-tubercular drugs regimen.

b) Exclusion criteria

- Patients who are on alternative system(s) of medicines.
- Pediatric patient (below 18 years of age).
- Patients with serological evidence of an acute infection with hepatitis B or C.

Study procedure

The study participants who were willing to join in the study as diagnosed as either pulmonary or extra pulmonary TB in general medicine department was enrolled in the study as per inclusion and exclusion criteria. Collection of data like demographic details, social history and type of Tuberculosis (pulmonary and extra pulmonary tuberculosis) were collected in patient data collection form and evaluated for the incidence and severity of ADR's occurring due to anti tubercular drugs. The suspected or identified ADR'S were recorded in patient data collection form and ADR reporting form. Causality assessments of ADRs were performed using Naranjo's algorithm scale and WHO-UMC causality scale, and severity was done by modified Hartwig and Siegel scale.

RESULTS

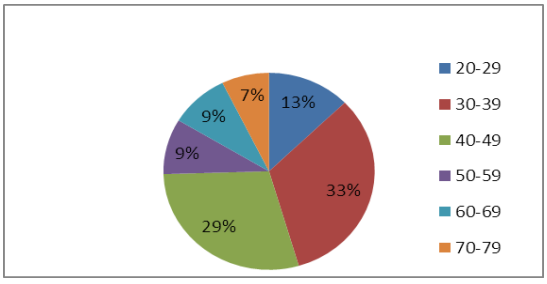
A total of 116 patients are diagnosed as TB Positive. Out of these 96 patients are involved in the study as per the inclusion and exclusion criteria.Out of that 55 (57.29%) patients were develop atleast one ADR. Here the following distributions are done only for the patients who experience ADR.

Age Wise Distribution of ADRs

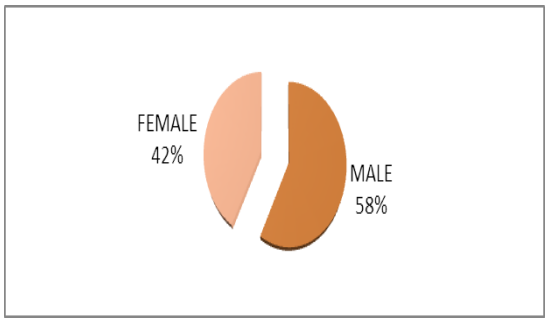
Age of the Patients(years)	No. of Participants	Frequency (%)
20-29	7	12.72
30-39	18	32.72
40-49	16	29.09
50-59	5	9.09
60-69	5	9.09
70-79	4	7.27

The table describes that the age distribution of study participants having the ADRs after taking the ATT regimen for period of time. In these maximum numbers of ADRs were seen in age group of 30-39yrs(32.72%) and minimum in 70-79yrs (7.27%). By these in our study we had seen that compare to geriatrics; adults are more prone to ADRs by the ATT regimen.

AGE WISE DISTRIBUTION OF ADRs



GENDER WISE DISTRIBUTION OF ADRs



GENDER WISE DISTRIBUTION OFADRs

Gender	No. of Participants	Frequency (%)
MALE	32	58.18
FEMALE	23	41.81

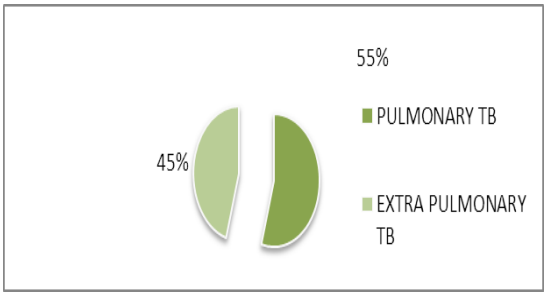
The table reveales that total of 55 patients were prone to ADRs. Out of these 32 are male and 23 are females. So that in our study males are (58.18%) more susceptible to the ADRs by ATT drugs compare to the females (41.81%).

TYPE OF TUBERCULOSIS AMONG ADR PATIENTS

Type of Tuberculosis	No. of Participants	Frequency (%)
PULMONARY TB	30	54.54
EXTRA PULMONARY TB	25	45.45

The table describes that among 55 patients were developed ADRs. In these 30 patients was diagnosed as pulmonary TB and 25patients extra pulmonary TB like TB Meningitis, TB Abdomen and TB Lymphadenitis.

TYPE OF TUBERCULOSIS AMONG ADR OBSERVED PATIENTS

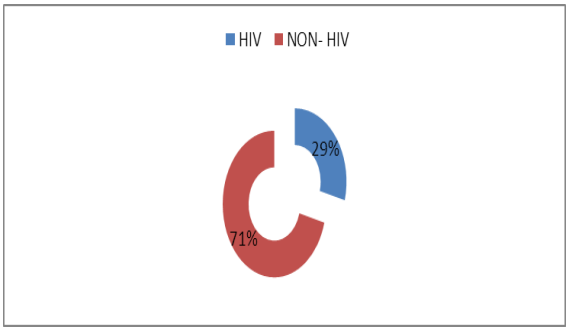


COMORBIDITIES ASSOCIATED WITH PATIENTS WHO EXPERIENCE ADRs

Comorbidity	No. of Participants	Frequency (%)
HIV	16	29.09
NON- HIV	39	70.90

This table states that among 55 patients who develop ADR 16 are suffering TB with HIV and 39 were diagnosed as TB but free from HIV.

COMORBIDITIES ASSOCIATED WITH PATIENTS WHO EXPERIENCE ADRs

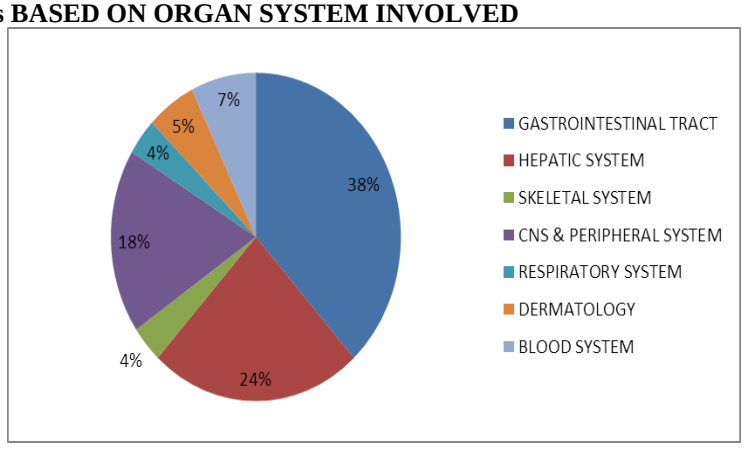


INCIDENCE OF ADRs BASED ON ORGAN SYSTEM INVOLVED

System Involved	No. of Participants	Frequency (%)
GASTROINTESTINAL TRACT	21	38.18
HEPATIC SYSTEM	13	23.63
SKELETAL SYSTEM	2	3.63
CNS & PERIPHERAL SYSTEM	10	18.18
RESPIRATORY SYSTEM	2	3.63
DERMATOLOGY	3	5.45
BLOOD	4	7.27

This table deals with site of occurrence of ADR, the most commonly involved body system is gastrointestinal tract system (38.18%), followed by hepatic system (23.63%), CNS & Peripheral system (18.18%), Blood (7.27%), dermatology (5.45%), skeletal system (3.63%) and respiratory system (3.62%).

INCIDENCE OF ADRs BASED ON ORGAN SYSTEM INVOLVED



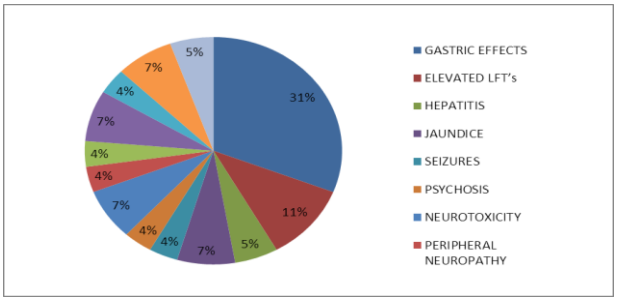
TYPE OF ADR DETECTED

ADRs	No. of Participants	Frequency (%)
GASTRIC EFFECTS	17	30.90
ELEVATED LFT's	6	10.90
HEPATITIS	3	5.45
JAUNDICE	4	7.27
SEIZURES	2	3.63
PSYCHOSIS	2	3.63
NEUROTOXICITY	4	7.27

PERIPHERAL NEUROPATHY	2	3.63
RESPIRATORY EFFETCS	2	3.63
ANAEMIA	4	7.27
ARTHRALGIA	2	3.63
DIARRHOEA	4	7.27
RASH	3	5.45

This table states that most common ADRs were observed as Gastric effects (30.90%) followed by Elevated LFT's (10.90%) and less commonly observed ADRs were Seizures, Psychosis, Peripheral neuropathy, Respiratory effects and Arthralgia. In our study the less commonly observed ADRs were all had the same incidence of 3.63%.

TYPE OF ADR DETECTED

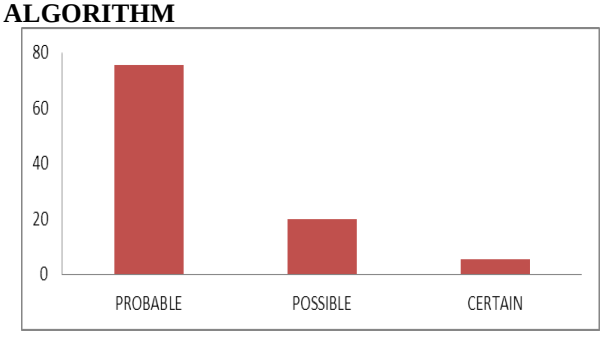


CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO NARANJO ALGORITHM

Scale	No. of Participants	Frequency (%)
PROBABLE	41	75.54
POSSIBLE	11	20.00
CERTAIN	3	5.45

The causality assessment of ADRs according to Naranjo's scale revealed that 41 (75.54%) cases were detected as probable, 11 (20.00%) as possible reactions and 3 (5.45%) as certain reactions.

CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO NARANJO ALGORITHM



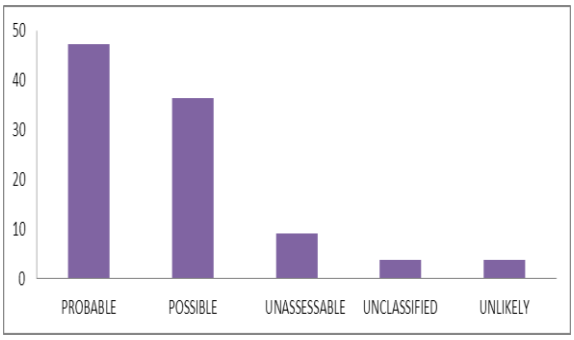
CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO WHO-UMC

Scale	No. of Participants	Frequency (%)
PROBABLE	26	47.27
POSSIBLE	20	36.36
UNASSESSABLE	5	9.09
UNCLASSIFIED	2	3.63
UNLIKELY	2	3.63

The causality assessment of ADRs according to WHO assessment scale revealed that 26 (47.27%) cases were detected as Probable, 20 (36.36%) as possible reactions, 5 (9.09%) as Unassessable reaction, 2 (3.63%) as Unclassified and 2(3.63%) as Unlikely.

CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO WHO-UMC

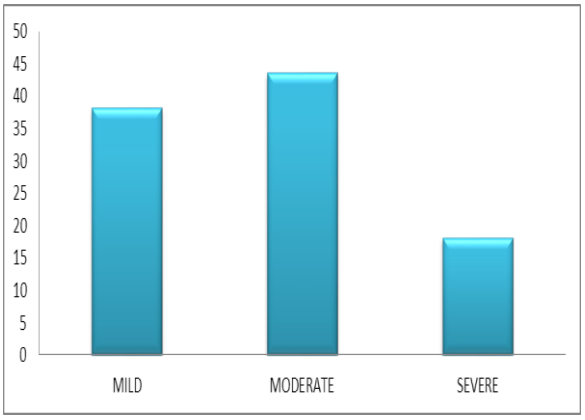
CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO HARTWEIG'S SEVERITY ASSESSMENT SCALE



Scale	No. of Participants	Frequency (%)
MILD	21	38.18
MODERATE	25	43.63
SEVERE	10	18.18

According to Hartweig's severity assessment scale shows that 21 (38.18%) cases were detected as Mild, 25(43.63%) as Moderate and 10 (18.18%) as severe.

CAUSALITY OF ADRS INDUCED BY ANTI-TB DRUGS ACCORDING TO HARTWEIG'S SEVERITY ASSESSMENT SCALE



DISCUSSION

Among 116 patients were involved in the study, 55(57.29%) patients showed at least one adverse reaction. This relatively high incidence of adverse reactions indicates that there is a need for more evaluation of susceptibility of patients for developing Anti-TB induced ADRs.

Nemagouda, conducted a study to determine the incidence of adverse effects and the risk factors for developing side effects against anti-TB drugs. They evaluated 50 newly diagnosed tuberculosis patients taking Anti-tuberculosis treatment during the time period from 14th may 2012 -14th July 2012. The results revealed that 48% of ADRs incidence is observed in their study. The occurrence of ADR in the study was higher in females. The association of incidence of ADR and different parameters is studied and possible predisposing factors found were age (the age group 41-60) years was seen to have maximum incidence of ADR (45.83%) and the age group (0-20) years had lowest reported incidence.

In our study ADR incidence high in the age group (30-39) where as low in the age group (70-79). Usually ADR incidence increases in association to age but vice versa happens in this study. Likewise seen in the study conducted by K.V. Ramanath et al, in Adichunchanagiri Institute of Medical Sciences and Research Centre, B G Nagara and RNTCP/DOTS centres within the TB unit of Mysore city (8 centres) over a period of 9 months. We observed that different types of ADRs who are under TB treatment with a complete follow-up was done through phone calls and Few of them are among those ADRs most frequently occurred were gastrointestinal system disorders (38.18%) and was followed by hepatic system (23.63%) similar results seen in Nishant P. Dalal et al, conducted prospective, observational study at DOTS centre of tertiary care hospital, Pune were 19 patients out of 35 developed GI effects with an incidence of 12.67%.

CONCLUSION

Our study concluded that there is need to provide information to patients regarding proper usage of medications for tuberculosis treatment and to reduce the ADRs by tubercular regimen. This type of studies will be more and continuous to aware and reduce the ADRs by the anti tubercular medications and completely fallen the mortality rates occur due to tubercular medications usage. Also the government of India to be organised RNTCP programmes most frequently for the prevention of tuberculosis disease also needed to available the tubercular medications at urban level and whole over the country to reduce the mortality rates of tuberculosis.

ABBREVIATIONS

ADR-Adverse drug reaction
AEs-Adverse events
AIDS-Acquired immunodeficiency syndrome
ART-Anti-retroviral therapy
BMI-Body mass index
CI-Confidence interval
CNS-Central nervous system
DM-Diabetes mellitus
DOTS-Direct Observational Therapy shortcourse
FDA-Food and Drug Administration
GIT-Gastro intestinal tract
INH-Isoniazid
LD-Lipodystrophy
LFTs-Liver function tests
MDR-TB-Multidrug resistant Tuberculosis
NSAIDs-Non-steroidal anti-inflammatory drugs
NSP-New sputum positive
OPDs-Out –patient days
PN- peripheral neuropathy
RNTCP-Revised National Tuberculosis Control Program
RTC-Regional Tuberculosis centre
SH-skin hypersensitivity
SIDA-Swedish international development agency
SPSS-Statistical package for social sciences
TB-Tuberculosis
WHO-UMC-World health organization-Uppsala monitoring centre
WHO-World health organization.

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