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A PROSPECTIVE OBSERVATIONAL STUDY ON ADVERSE DRUG REACTIONS TO ANTI – TUBERCULAR DOT'S THERAPY IN A SECONDARY CARE HOSPITAL AND CLINICAL PHARMACIST ROLE IN ADVERSE DRUG REACTIONS REPORTING

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ABSTRACT: ADRs constitute an enormous burden for the society. The aim of the present study was to detect, assess and report the suspected ADRS in the antitubercular DOTs therapy and explaining the clinical pharmacist role in reporting ADRs and educating the patients. Tuberculosis is an infectious, communicable bacterial disease that remains as elementary health problem caused by mycobacterium tuberculosis. This study was planned for detection, assessment, classification, casualty analysis of ADRs to anti-tubercular DOTs therapy.It was a prospective observational study conducted for 9 months in a secondary care hospital by collecting information by using WHO and HRQOL questionnaire among the TB patients who are in the study. Nearly data of 234 patients were collected which include case history, past medical history, laboratory values, and drugs prescribed with their doses and frequency of administration were collected for nine months (September 2016 – May 2017).Out of these 234 patients are willing to give information. In these 180 are males and 54 are females. ADRs are checked by using the WHO scale and Naranjo scale for ADRS. 41 ADRs are observed in 234 patients. DOTs therapy is safer. No severe life threatening ADRs are observed. If the awareness is provided to the patient and public by a clinical pharmacist, and to monitor ADRs, life style modifications and to maintain hygienic conditions to improve the patient adherence for therapeutic outcome to get relive from the disease.

KEYWORDS: Adverse drug reactions, co morbidities, DOTs, anti-tubercular's.

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1.INTRODUCTION

Tuberculosis is the most rampant, communicable infectious disease caused by mycobacterium tuberculae. The majority of cases occur in poor countries in the southern hemisphere (WHO, 2009).[1]The numbers of cases estimated to have occurred in 2008;the organism is a strict aerobe and thrives best in tissues with high oxygen tension such as in the apex of the lung [2]. WHO declares tuberculosis as a global emergency in 1993. In 1993 an increase in reported cases of TB in countries across all continents led the World Health Organization (WHO) to declare TB a global emergency. The burden of TB in many countries is compounded in those who have co-infection with the human immunodeficiency virus (HIV). [3] Of additional concern has been the increase in multidrug-resistant tuberculosis (MDR-TB), with outbreaks in different parts of the world. In 2006, the emergence of extensively drug-resistant tuberculosis (XDR-TB) was first reported. [6] About 5% of those initially infected will develop active primary disease. [5]Patients with smear-negative pulmonary disease (three sputum samples) are less infectious than those who are smear positive. The relative transmission rate from smear-negative compared with smear-positive patients has been estimated to be 0.22. [7]. Adequate and effective treatment is essential, both clinic India ranks first in estimated cases The global rate of tuberculosis is growing at approximately 1.1% per year[2]. About 1.8 million new cases of Tuberculosis are detected every year of which one fifth are extra pulmonary tubercular cases. High incidents of infection have caused a large number of morbidity and mortality. [8]. Drug treatment is the cornerstone of TB management. Mono- therapy can be used only for infected patients who do not have active TB (latent infection, as shown by a positive skin test). Once active disease is present, a minimum of two drugs, and generally three or four drugs, must be used simultaneously. [9] The duration of treatment depends on the condition of the host, extent of disease, presence of drug resistance, and tolerance of medications. The shortest duration of treatment generally is 6 months, and 2 to 3 years of treatment may be necessary for cases of multidrug-resistant TB (MDR-TB). [10] Because the duration of treatment is so long, and because many patients feel better after a few weeks of treatment, careful followup is required. [11, 12] Directly observed therapy by a healthcare worker is a cost- effective way to ensure completion of treatment. [13, 14]. .In India in 1993 as a part of revised national TB programme (NTP) DOTs therapy has been introduced. DOTs means directly observed Therapy. The drugs included in DOTS therapy are Isoniazid, Ethambutol, Rifampicin, Pyrazinamide, Streptomycin for 6-9 months. Before the advent of DOTs programme, high prevalence countries like India had a National TB programme (NTP) to combat the problem of TB, but not spectacular progress is seen. It's the most effective strategy. However, combination treatment may produce severe adverse events [15].Rifampin and isoniazid are the best drugs for prevent- ing drug resistance, followed by ethambutol, streptomycin, and pyrazinamide. [16, 17, 18]. Rifampin shows bactericidal activity against M. tuberculosis and several other

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mycobacterial species, including M. Bovis and M. Kansasi. [19] Other nontuberculous mycobacteria, including MAC, show variable susceptibility to rifampin. Rifampin also is active against a broad array of other bacteria. Alteration of the target site on RNA polymerase, primarily through changes in the rpoB gene, leads to most forms of rifampin resistance.[15,16]. Patients with AIDS, diabetes, and other gastrointes- tinal problems appear to have difficulty absorbing rifampin after oral doses, and this has been associated with therapeutic failures in some cases. [20, 21]. DOTS—internationally recommended tuberculosis control strategy, developed in the mid-1990s and has been implemented in 182 countries. It has five essential components: political commitment, diagnosis by sputum smear microscopy, short course treatment with standard first line drug regimens, a reliable drug supply, and a recording and reporting system that allows assessment of individual patient outcomes and overall programme performance. DOTS-Plus—Strategy for management of cases with multidrug resistant tuberculosis, developed by the World Health Organization and partner agencies from 1999. It is based on the same principles as the DOTS strategy but includes use of sputum cultures and drug susceptibility tests for diagnosis and use of second line as well as first line drugs. Stop TB strategy—Developed by WHO during 2005, designed to guide tuberculosis control efforts during 2006 to 2015. It builds on the DOTS and DOTS-Plus strategies and has six major components: pursuing expansion and enhancement of DOTS; addressing tuberculosis and HIV coinfection, multidrug resistant tuberculosis, and other special challenges; helping to strengthen healthcare systems; engaging all healthcare providers; empowering patients and communities; and promoting research. The strategy underpins the second "Global Plan to Stop TB," which also covers the period 2006-15. According to WHO "Adverse drug reaction may be defined as any response to a drug which is noxious and unintended and which occurs at doses normally and used in n man for prophylaxis, diagnosis and treatment of disease or for the modification of physiological function. Most of the adverse drug reactions occur at intensive phase of treatment rather than continues phase. ADR monitoring and reporting is in its infancy stage in the developing countries. Due to lack of interest and clinical acumen, aptitude and time, many untoward adverse events pass unnoticed. Adverse drug reaction leads to decrease in patient compliance and adherence. [22, 23]According to World Health Organization (WHO) and several other studies concluded that, the poor out-come was attributed to poor patient compliance, to primary multidrug resistance and to interruption partially due to ADR (WHO 1997) and the towering incidence of TB infection has caused a high occurrence of morbidity and mortality which is partly due to serious ADRs induced by Anti- TB drugs [3].the other factors assessed. Default is a serious problem in the TB program and occurs mostly during the intensive phase. [7] So, close monitoring of adverse drug reactions is required. This study aims to observe and report the adverse drug

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reactions of antitubercular DOTs for preventing the drug resistance and counseling the patient about adverse drug reactions for better therapeutic results.

DOTS THERAPY USED IN THE HOSPITAL

DOT's Means Directly observed Therapy

The Drugs in DOTs therapy include

Isoniazid (H) – 300 mg

Rifampicin (R) – 450mg

Ethambutol (E) – 600mg

Pyrazinamide (Z) – 750mg

Streptomycin (S) – 0.75gms

Category I:-

New cases of sputum smear positive or severe pulmonary TB, or severe forms of extra pulmonary TB.

Category II:-

Defaulted, irregularly treated and relapse cases.

Category III:-

In sputum smear negative pulmonary To and less severe forms of extra pulmonary TB

Category IV:-

Chronic cases who remained or again become sputum smear positive after receiving fully supervised category I I treatment.

All regimens have an initial intensive phase with 4-5 drugs bringing about sputum conversion and afford fast symptomatic relief. This is followed by continuous phase during which remaining bacilli are eliminated so that relapse doesn't occur. [4]]

2. MATERIALSAND METHODS

Study site: The study was conducted in a 300 bedded secondary care hospital in a pulmonology department, anti –tubercular DOTs center, general medicine department

Study method: This was a prospective observational study conducted for 9 months in a secondary care hospital

Study procedure: The study was done by collecting information by using WHO and HRQOL questionnaire among the TB patients who are in the study. Nearly data of 234 patients were collected which include case history, past medical history, laboratory values, and drugs prescribed with their doses and frequency of administration were collected.

Study duration: The study was conducted for nine months (September 2016 – May 2017)

Assessment scales:-

***WHO** scale for assessment of ADR's

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*** Naranjo** scale

Inclusion criteria:-

***** Patients of both sexes between the ages of 20-70 years.

* Patients with ADRs to antitubercular drugs used in the inwards.

***** Patients of all categories of TB with ADRs to antitubercular visiting in DOTS centre.

***** Patients receiving minimum one anti tubercular agent.

Exclusion criteria:-

***** Pregnant ladies

* HIV $^{+ve}$ patients

* Patients below age of 20

* Patients with diabetes mellitus**.**

Aims and objectives:-

* To detect the ADRs in to anti tubercular agents used in DOTs therapy

* Causality analysis of ADRs in DOTs therapy.

* To assess the probable correlation of ADRs to age and sex of patients.

* To identify the risk of ADRs by co-morbid conditions.

* To assess and analyze the ADRs according to the demographic distribution, onset, reporting and presentation.

* To classify the severity of ADRs to anti-tubercular's into mild, moderate and severe based on the clinical feature and investigations.

* The main objective was to give the patient adherence about ADRs, comorbid conditions, for better therapeutic outcome.]

3. RESULTS AND DISCUSSION

Atotal of 242 patients who are TB suspects found +ve by diagnosis among the time period September to may, 242 patients are included for the study. Out of these 234 are willing to give the information. In these 234 patients 180 (76.9%) are males, 54 (23.07%) are females. A total of 41 (17.52%) ADRs are observed in 234 patients by the WHO assessment scale of ADRS. Most of the ADRS are observed in intensive phase of treatment because more drugs are included in this phase compared to continuous phase of therapy. Most of the ADRS are observed in males(95. 5%) than in females (5%) due to the co morbid conditions like alcohol consumption, tobacco smoking. Some other co morbid conditions are chronic lung disease, malnutrition, Diabetes, HIV $^{+ve}$ .All these conditions can double burden the disease. The ADRs observed are gastritis (4.87%), abdominal cramps (4.87%) diarrhea (2.43%) itching (4.87%) rash (4.87%), Arthralgia (19.51%), peripheralne uropathy (19.51%), psychosis (2.43%), dizziness (26.82%), Hepatitis (2. 4 3%),ototoxicity and optic problems (2.43%), syndrome (4.87%). ADRS are observed more due to Isoniazid (39%) followed

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by Rifampicin and Pyrazinamide (22%), Ethambutol (9.75%). Major ADRs aredizziness (26. 82%), Arthralgia and peripheral neuropathy (19.57%) and next was gastritis. The severity assessment of ADRS showed that majority of the ADRS are mild (53.65%) and moderate (26.82%). Severe (19.51%).The mortality rate was 3%. 60.97% of the ADRs are observed at the age group of 35-50 years. 24.39% at the age group of 20-35 years and 14.63% at the age group of 50-70 years

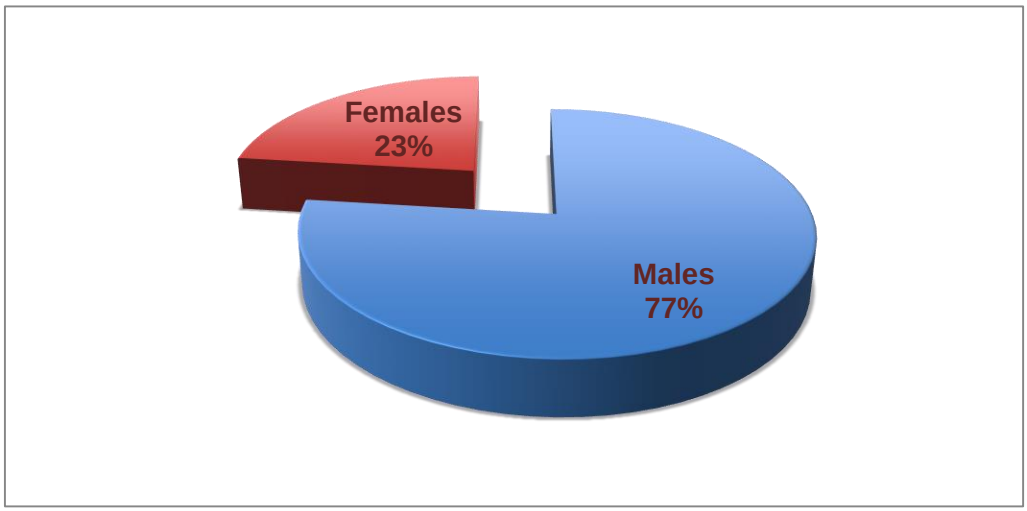

Figure 1: Demographic details of patients.

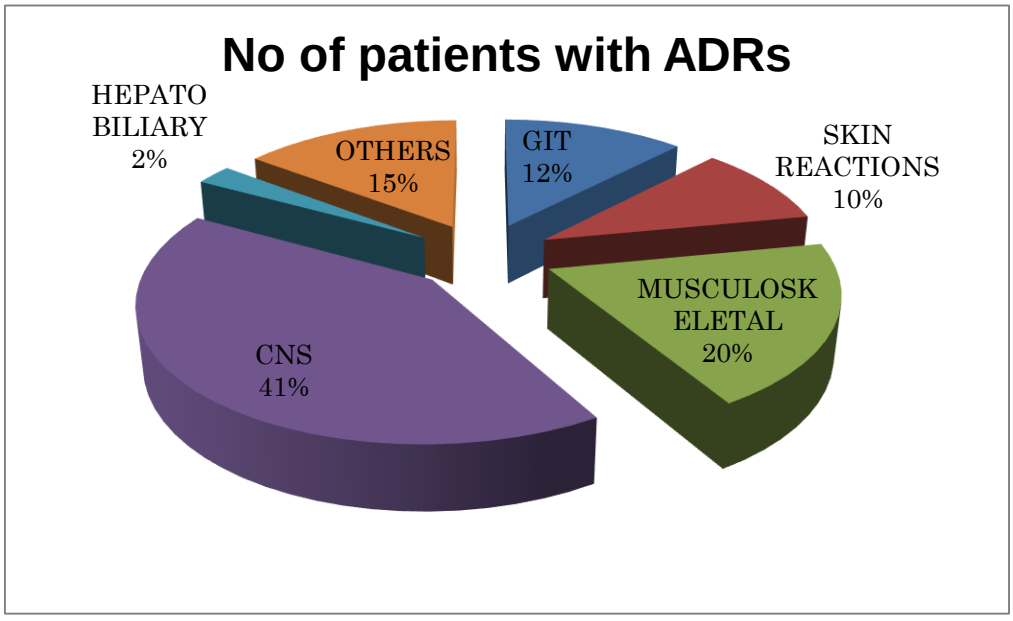

Figure 2: Systems affected due to ADR's of anti-tubercular drugs.

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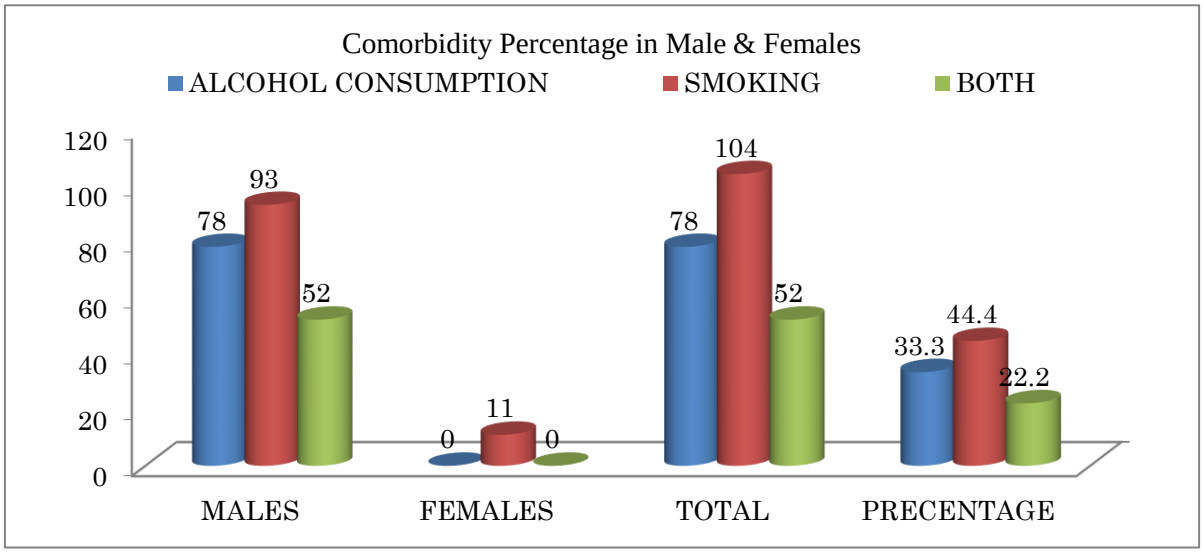

Figure 3: Co morbid conditions of people suffering with tuberculosis.

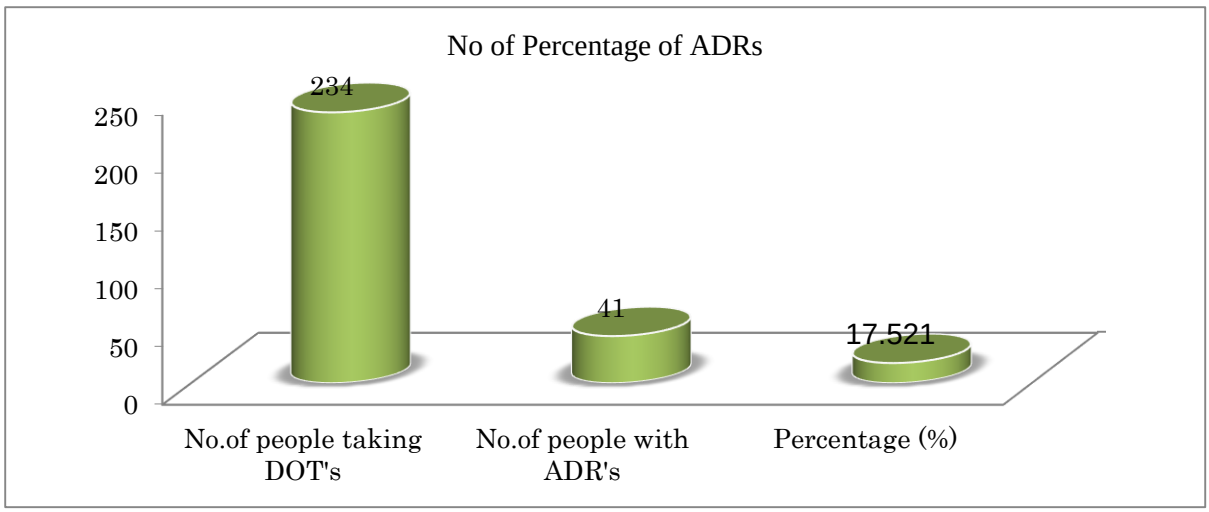

Figure 4: Number of ADR's and the system which is affecting through the TB drugs.

Table 1: shows that number of patients on ADR's and number of people on DOT's therapy.

System	ADR'S	H	R	Z	E	S	TOTAL	%
GIT	Gastritis, vomiting	1	0	0	1	0	2	4.878049
	Abdominal cramps	0	2	0	0	0	2	4.878049
	Diarrohea	0	0	1	0	0	1	2.439024
SKIN	Itching	2	0	0	0	0	2	4.878049
	Rash	1	0	1	0	0	2	4.878049
musculo skeletal system	Arthralgia	2	0	6	0	0	8	19.5122

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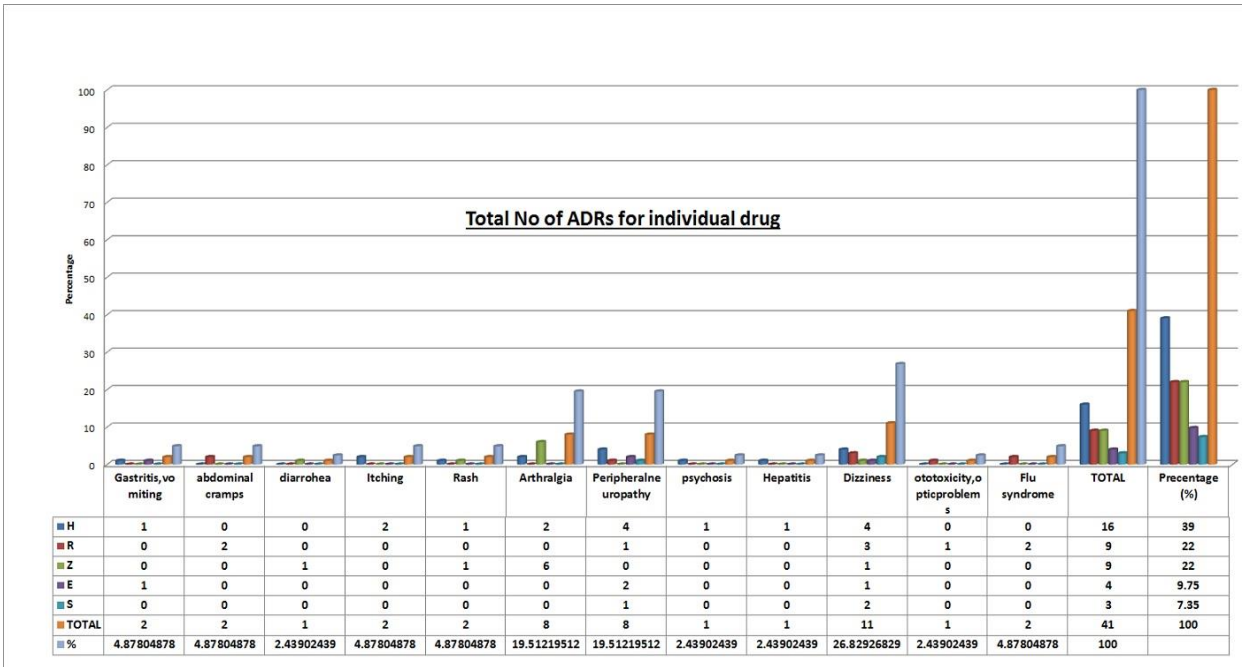
CNS	Peripheral neuropathy	4	1	0	2	1	8	19.5122
	psychosis	1	0	0	0	0	1	2.439024
Hepato biliary	Hepatitis	1	0	0	0	0	1	2.439024
Others	Dizziness	4	3	1	1	2	11	26.82927
	ototoxicity,opticproblems	0	1	0	0	0	1	2.439024
	Flu syndrome	0	2	0	0	0	2	4.878049
	TOTAL	16	9	9	4	3	41	100
	Percentage (%)	39	22	22	9.75	7.35	100	



	Gastritis,vomiting	abdominal cramps	diarrohea	Itching	Rash	Arthralgia	Peripheralneuropathy	psychosis	Hepatitis	Dizziness	ototoxicity,opticproblems	Flu syndrome	TOTAL	Precentage (%)
H	1	0	0	2	1	2	4	1	1	4	0	0	16	39
R	0	2	0	0	0	0	1	0	0	3	1	2	9	22
Z	0	0	1	0	1	6	0	0	0	1	0	0	9	22
E	1	0	0	0	0	0	2	0	0	1	0	0	4	9.75
S	0	0	0	0	0	0	1	0	0	2	0	0	3	7.35
TOTAL	2	2	1	2	2	8	8	1	1	11	1	2	41	100
%	4.87804878	4.87804878	2.43902439	4.87804878	4.87804878	19.51219512	19.51219512	2.43902439	2.43902439	26.82926829	2.43902439	4.87804878	100	

Figure 5: Total number of ADR's present for each drug with percentage.

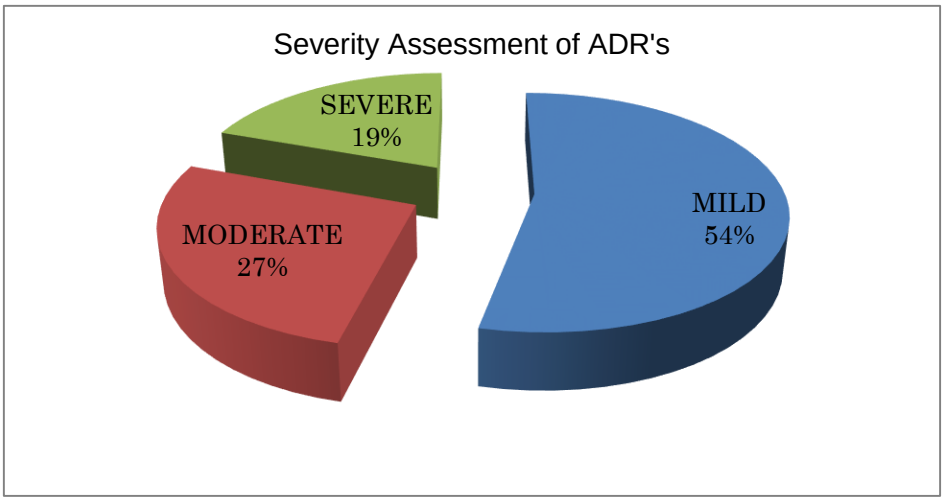


Figure 6: Severity of ADR's for anti tubercular drugs.

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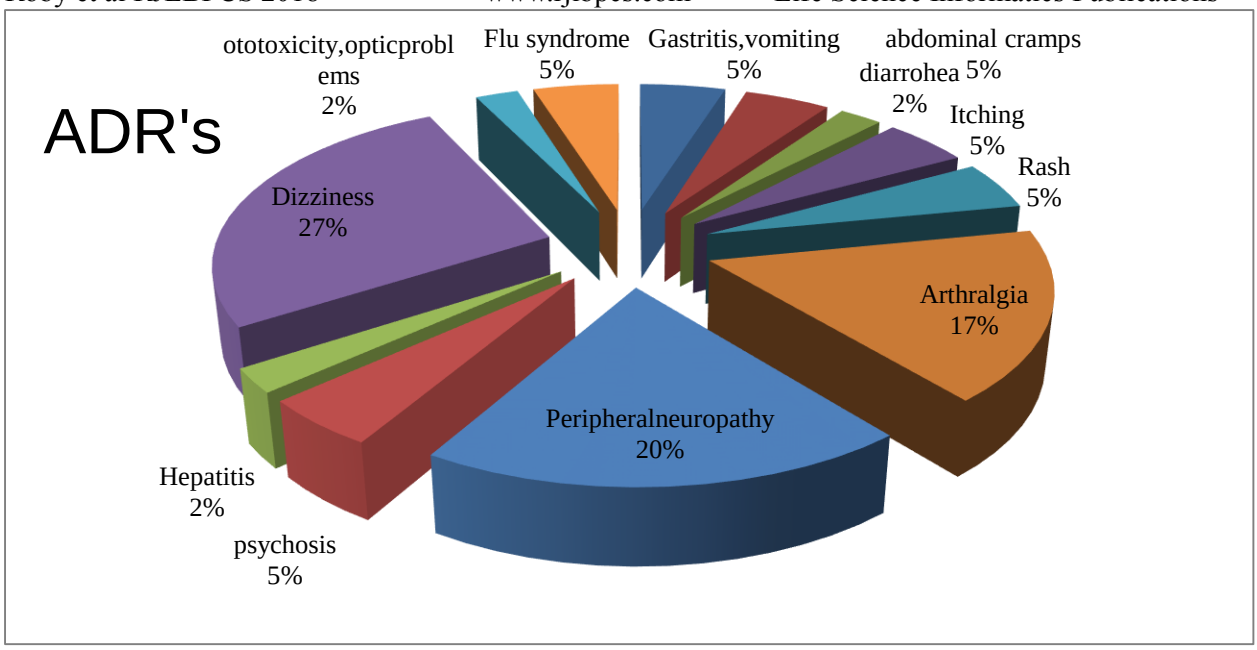

Figure 7: Percentage of ADR's observed in the hospital using DOT's therapy

A total of 242 patients who were taking DOTS therapy were included for the study. Out of this 234 are willing to give the information. Among these 234 patients 180 are males and 54 are females. By checking the ADRs using WHO scale for ADRs, 95% of ADRs are observed in males due to co morbid conditions and remaining 5% in females. Majority of the ADRS (39%) are due to Isoniazid. Majority of the ADRs observed are dizziness (26.82%), followed by Arthralgia and peripheral neuropathy (19.51%) and next was gastritis(4.87%).Remaining were observed in less no: of patients. Majority of the ADRs are mild (53. 65%) and moderate (26. 82%). Severe (19.51%). The mortality rate was 3% .60.97% of ADRs is observed at the age group of 35-50 years and 14.63% are at the age group of 50-70. Its association with drug resistance causing MDRTB and XDR -TB is making the disease difficult to treat day by day.

4. CONCLUSION

DOTs therapy is safer. No severe life threatening ADRs are observed. If the awareness is provided to the patient and public by a clinical pharmacist, to monitor ADRs, life style modifications and to maintain hygienic conditions to improve the patient adherence for therapeutic outcome to get relive from the disease. This study strongly suggests that there is a greater need for streamlining the of ADR reporting and monitoring system to create awareness and to promote the reporting of ADR by all health care professionals should be undertaken to ensure patients safety and adherence[5]. Our study evaluated and assessed that it may be better to have hands of well-trained and highly specialized clinical pharmacist to counsel the patient to provide better health. Our great success will probably come from the efforts to enhance the awareness of the consequences to avoid indiscriminate consequences.

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Role of clinical pharmacist in ADR reporting: -ADRs are a major cause of patient related morbidity and mortality.

*Reporting of ADRs is considered to be an important step in maintaining and achieving a safe drug therapy.

*Monitoring of ADRs in each and every patient.

*Empowerment of people with TB and communities, through advocacy, communication and social mobilization as well as patient and community participation in TB care are important in facilitating treatment adherence using DOTs approach.]

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