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RESEARCH ARTICLE

Adverse drug reactions monitoring among TB patients on anti-tubercular drugs under RNTCP in Pondicherry.

Anusha N, Isabella Topno, Anil J Purty

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Corresponding Author

Anusha N

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Abstract

Introduction

Tuberculosis (TB) is one of the oldest diseases known to affect humans and is likely to have existed in prehominids. This disease is caused by bacteria of the Mycobacterium tuberculosis complex and usually affects the lungs. In spite of availability of effective drugs, Tuberculosis (TB) remains one of the top killers in the developing world. This is especially true in India where each year approximately 2 million new cases of TB and five lakh TB related deaths occur each year.[1] Currently available drugs are effective for treatment of the disease or latent infection, but may cause serious adverse effects.

In a report by Richard Zaleskis, it has been suggested that only a minority of patients complete their full course of anti-TB chemotherapy successfully without significant side effects. In the same report, the author concluded that the main ADRs of anti-TB drugs occur during first two to three weeks of treatment.[2]

The added problem in the treatment of TB is that a combination of drugs is used for prolonged periods of time and therefore there is likelihood of potentiating the adverse reactions of one drug by the other co-prescribed drugs.To improve adherence it is essential to know various ADRs and their management.

Worldwide, many countries have started ADR monitoring programmes with varying degree of success. In India, ADR monitoring is still in its infancy. DOTS under RNTCP has improved compliance in the last two decades.

Some common ADRs due to anti-tubercular drugs are skin rashes, gastrointestinal disturbances (nausea, vomiting, and gastritis), hypersensitivity reactions, visual disturbances, peripheral neuropathy, hepatitis, pancreatitis, ototoxicity and hyperuricaemia.[3]

Identification of ADR profile of drugs can be useful for prevention, early detection and management of ADRs. Identifying the causality and severity of ADRs is an important step in ADR monitoring programmes. Naranjo's Algorithm[4] is used to carry out the causality assessment of ADRs. For identifying severity of ADRs the Hartwig et al scale[5] is commonly used.

Till date, there are various studies on daily regimen verses DOTS, but very few studies have been done to evaluate the safety of DOTS regimen. Therefore, there is a need to study the safety aspect through monitoring of ADRs in patients on DOTS with focus on reasons for drop-outs and non-compliance for non-completion of the course of treatment. Hence, the present study was undertaken with following objectives:

Aims & Objectives:

1. To describe the socio-demographic pattern of TB patients experiencing ADRs in Pondicherry receiving DOTS.
2. To describe the pattern of ADRs caused by ATT in DOTS patients.

3. To assess the causality and severity of reported ADRs.

Methodology:

This Prospective Cohort study was started after obtaining the approval of Institutional Ethics Committee, Pondicherry Institute of Medical Sciences and RNTCP OR (operational research) committee, for a period of 12 months (January 2013 – December 2013). Fifty patients receiving DOTS under RNTCP in five DOTS centres were subjected to the study after explaining and obtaining their written informed consent.

All the patients were registered into the study during the first month of their Intensive Phase, and all the patients were followed-up for 6 months.

Patients with psychiatric disorder, pregnant patients and children upto 10 years of age were excluded.

Patients' profile: Sex, location, literacy, socio-economic status, pregnancy status and concomitant diseases like HIV and Diabetes Mellitus etc., were recorded using a pre-tested questionnaire.

Details of ADR, if detected, were recorded in the case report form and CDSCO form.

Causality assessment was done using Naranjo algorithm and severity assessment was done using Hartwig scale.

Method of analysis and Statistical tests:

Data was subjected to descriptive analysis.

Results:

Among the 50 patients who were studied, 24 of them developed at least one ADR, giving an incidence of 48%.

The following table 1 shows the baseline characteristics of the study patients.

Table 1: Baseline characteristics

Characteristic	n (%)
Number of patients	50 (100)
Sex	
Male	31 (62)
Female	19 (38)
Age in years	
Age categories	
1-10	0 (0)
11-20	10 (20)
21-30	14 (28)
31-40	7 (14)
41-50	10 (20)
51-60	6 (12)
61-70	2 (4)
71-80	1 (2)
Education level	
None	10 (20)
Primary school	17 (34)
High school	14 (28)
Degree	9 (18)
Socio-economic status	
Class I (Upper class)	0 (0)
Class II (Upper middle class)	0 (0)
Class III (Middle class)	7 (14)
Class IV (Upper lower class)	26 (52)
Class V (Lower class)	17 (34)
Site of disease	
Pulmonary	33 (66)
Extra pulmonary	17 (34)
Co-morbid conditions	
Diabetes	5 (10)
Hypertension	1 (2)

HIV	0 (0)
Patients exposure to first-line drug regimens	
HRZE (category I)	45 (90)
HRZES (category II)	5 (10)

Figure 1: Demography of patients on antitubercular drugs (DOTS) who developed ADR

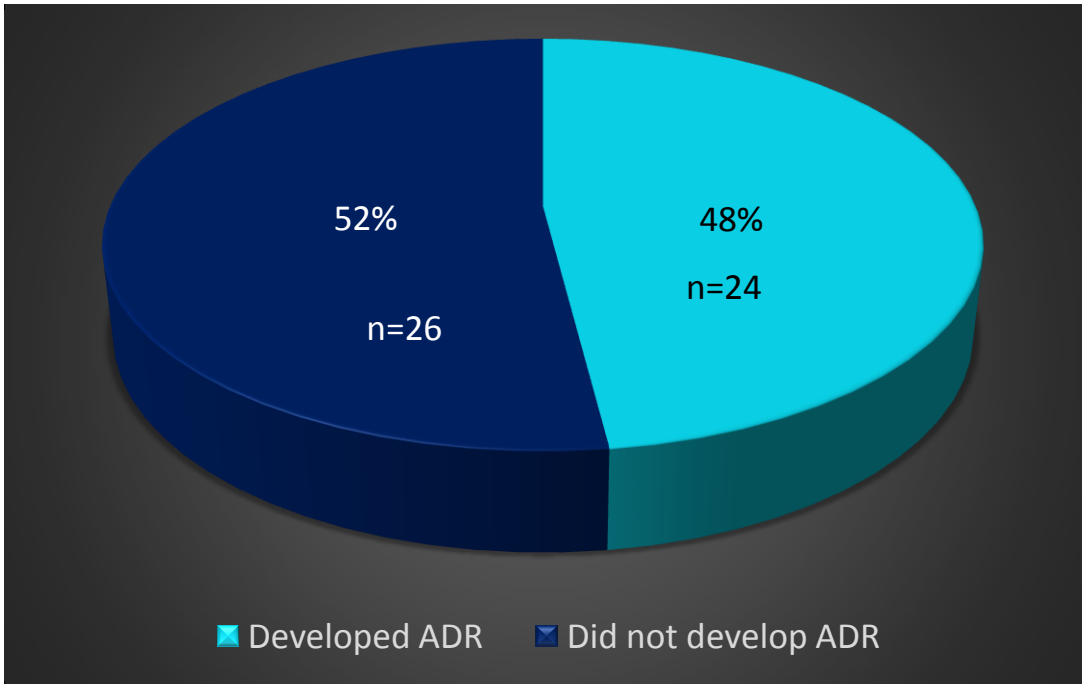

Fig. 1 shows, among the 50 patients included in the study, 24 of them developed at least one ADR giving an incidence of 48%.

Figure 2: Age distribution of patients on antitubercular drugs (DOTS) who developed ADRs

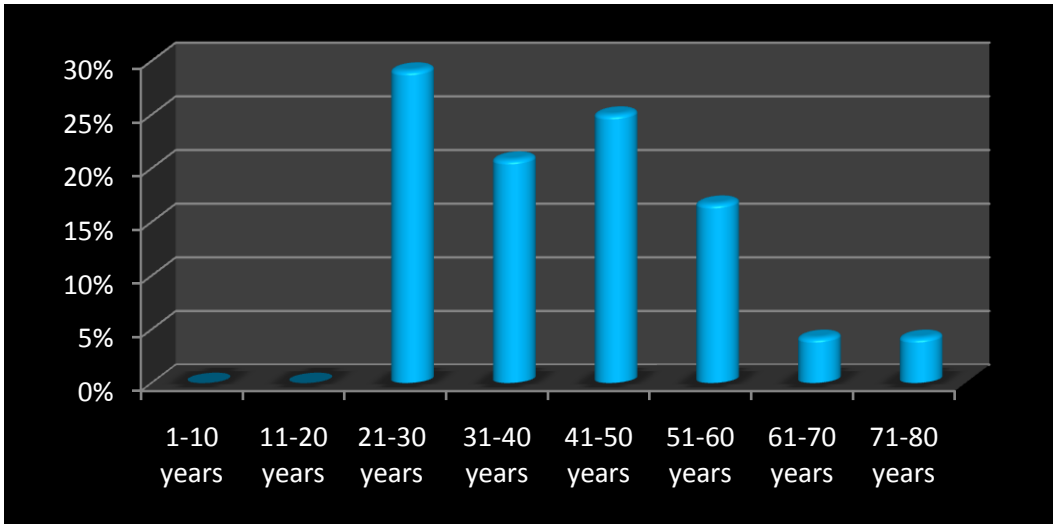

Fig. 2 shows the age distribution of the patients who developed ADRs. The mean age of the patients who developed ADR was 41.3 years. 29.1% of the ADRs were reported in the age group of 21-30 years.

Figure 3: Sex wise distribution of patients on antitubercular drugs (DOTS) who developed ADRs

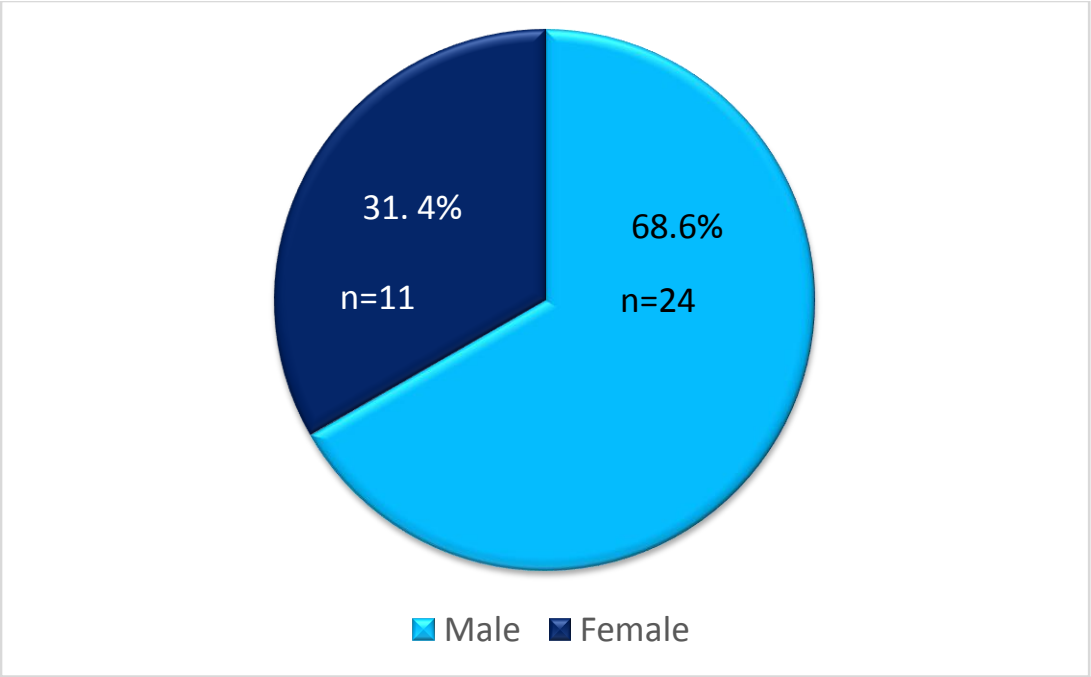

Fig. 3 shows the sex distribution of the patients who developed ADRs. The occurrence of ADR among males was 68.6% and among females was 31.4%.

Figure 4: Socio-economic status and prevalence of ADR among the study patients on antitubercular drugs (DOTS)

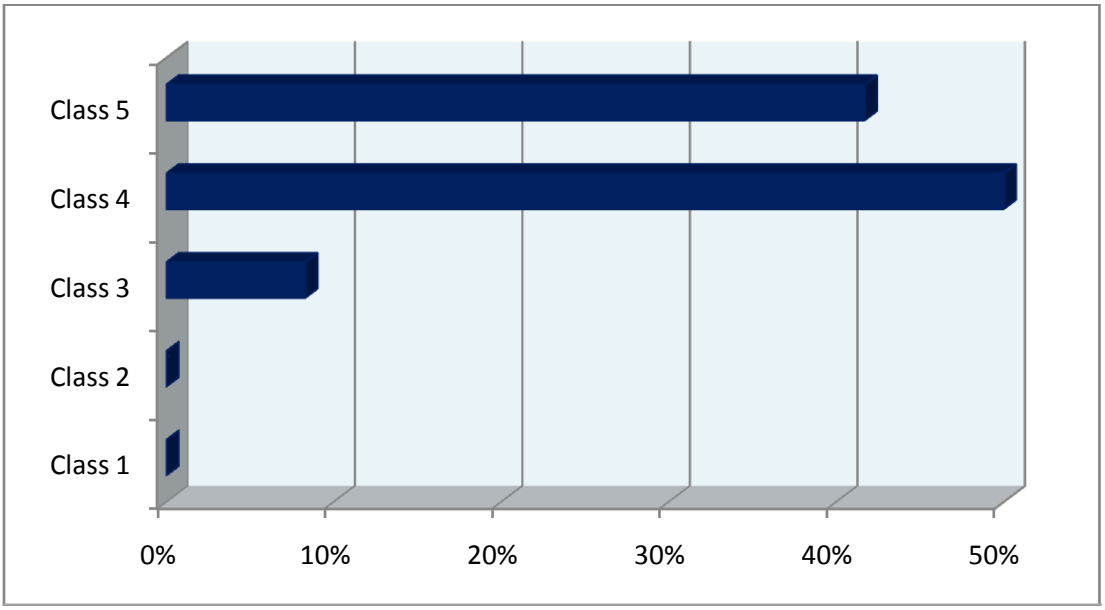

Fig. 4 shows the socio-economic pattern of patients who developed ADRs. Patients in Class 4 category of socioeconomic status showed 50% of the ADRs.

Known allergy:
Among the 24 patients, 3 patients were category II patients, 2 of them had relapse and 1 patient had treatment failure. The 3 patients had a previous history of similar ADR to the drugs. The treatment failure patient had nausea and vomiting during his previous anti-tubercular chemotherapy. One of the relapse patient had nausea and the other had nausea and giddiness during their previous anti-tubercular regimen.

Table 2: Types of ADRs experienced by the patients on antitubercular drugs (DOTS) (n=24)

Type of ADR	No. of reports (n)	Percentage (%)
Nausea	17	70.8
Epigastric pain	7	29.2
Giddiness	5	20.8
Vomiting	3	12.5
Pruritus	2	8.3
Dyspnea	1	4.2

A total of 35 ADRs were reported among the 24 patients who developed ADR. The most common was nausea, which was observed in 17 patients, followed by epigastric pain in 7 patients, giddiness in 5 patients, vomiting in 3 patients, pruritus in 2 patients and dyspnea in 1 patient. Some patients have had more than one ADR.

Figure 5: System-wise ADRs affected in patients on antitubercular drugs (DOTS)

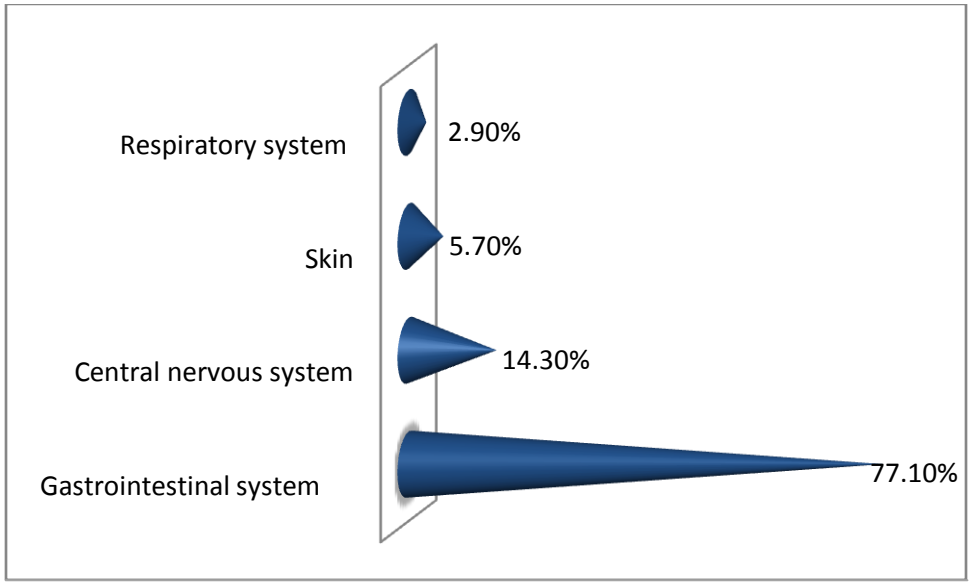

Fig. 5 shows the various systems affected by the ADRs. Gastrointestinal system was the most commonly affected system by ADR, which was 77.1%, followed by CNS 14.3%, skin 5.7%, and respiratory system 2.9%.

Onset of ADR:
Hundred percent of the ADRs were observed during the initial intensive phase of anti-tubercular therapy.

Figure 6: Treatment category of patients on antitubercular drugs (DOTS) who developed ADR

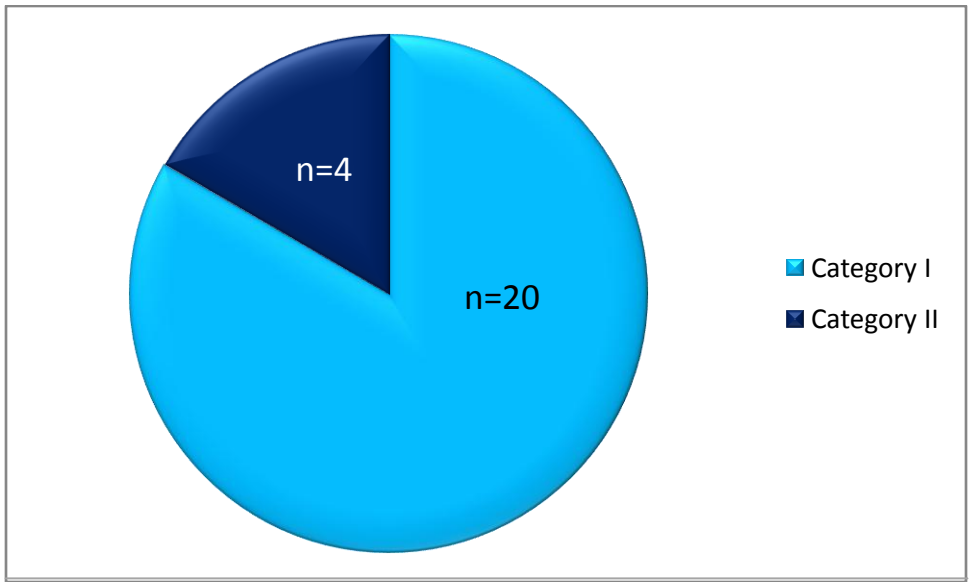

Fig. 6 shows the treatment category of the patients who developed ADRs. Among the 24 patients 20 of them received Category I and 4 patients received Category II.

Management of ADRs:

Among the patients who developed ADR, 6 (25%) needed symptomatic treatment. Treatment was not needed for 18 (75%) patients.
Nausea – T. Domperidone 10 mg
Epigastric pain – T. Ranitidine 150 mg
Giddiness – T. Vertin 8 mg (Betahistine)
Pruritus – T. Avil 25 mg (Pheniramine)

Outcome of ADRs:
Hundred percent of the patients recovered from the ADR.

Figure 7: Causality assessment of ADRs using Naranjo algorithm

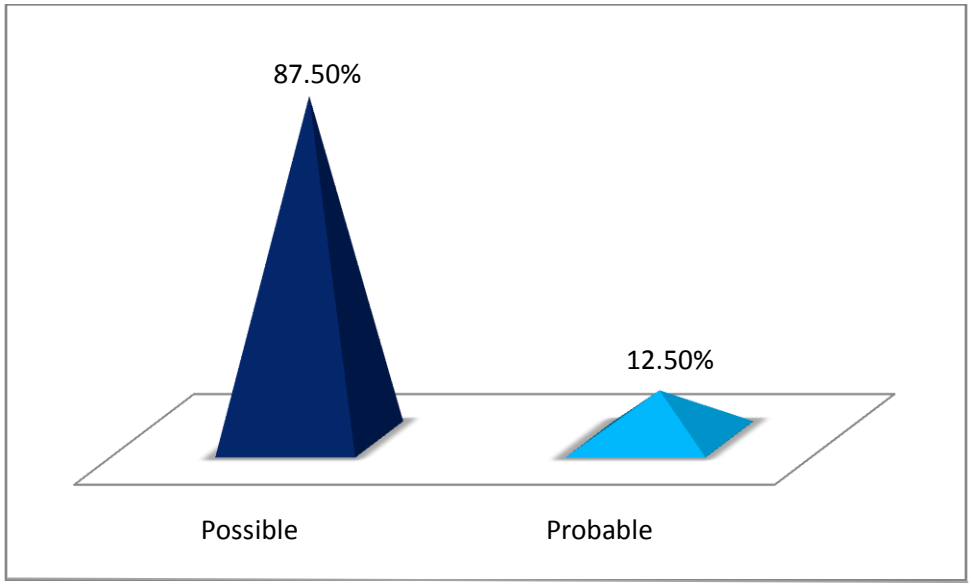

Fig.7.The causality assessment ADRs done by Naranjo algorithm showed that 87.5% (21) of the ADRs were possible and 12.5% (3) were probable.

Figure 8: Severity assessment of ADRs using Hartwig Scale

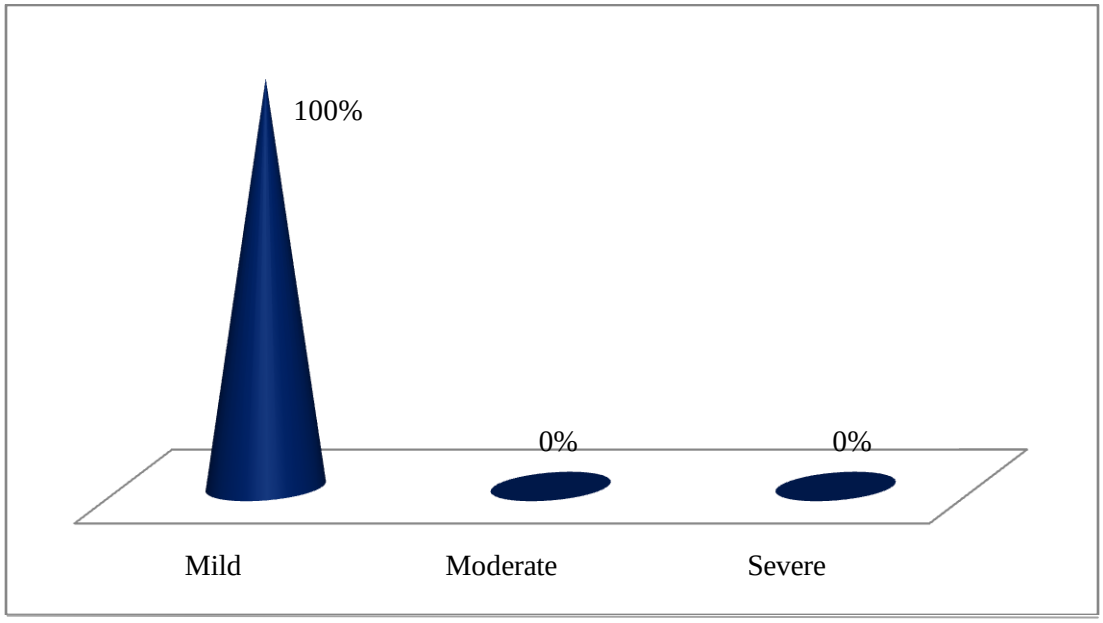

Fig. 8.The severity assessment of the ADRs using Hartwig scale. It was found that 100% of the ADRs were mild category (Level 1).
Level 1 – An ADR occurred but required no change in the treatment with the suspected drug

Discussion:

Tuberculosis is a highly prevalent disease. In spite of implementation of DOTS under RNTCP, it still remains to be a major health concern. Among the various problems associated with the disease per se like cough, dyspnoea,

evening rise of temperature, anorexia, loss of weight, chest pain, hemoptysis, the toxicity arising due to the ATT drugs is a major concern.[6]

The present study was able to identify the pattern and type of ADR and also analyze the causality and severity of ADRs in patients on ATT under RNTCP in Pondicherry to some extent.

A total of 50 patients were enrolled in the study among which 24 (48%) patients developed ADRs. A study from Nepal reported an incidence of 12.37%, Kishore et al, 2008.[6] Another study by Xiaozhen Lv et al, 2013 from China, reported an incidence of 15.08%.[7] Anupa Khatri Chhetri et al from Nepal, in her study in 2008 reported a similar incidence of ADR which was 54.74%. [8] Another study by F. Marra et al from Canada in 2007 reported an incidence of 30% ADRs.[9] Two studies from Russia reported a much higher incidence of 72.8% Chukanov et al, 2004[10] and 60.2% Tashpulatova, 2003[11] than the present study.The difference in the results between the previous studies and the present study could have been due to the difference in the genetic, demographic and nutritional status in the different population groups.

In the present study majority of the ADRs were reported by the age group 21-30 years. This is similar to a study by Anupa Khatri Chhetri et al, 2008[8] where the incidence was high in the same age group due to ATT. In another study by Shakya et al, 2004[12] younger age group 18-20 years were found to have more incidence of ADRs. The results of the present study could be because the age group of 21-30 years included the majority (28%) of patients undergoing treatment under RNTCP in Pondicherry.

Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to males.[8] A study by Yee et al,[13] and Shakya et al[12] considered female gender as a risk factor for the occurrence of ADRs due to anti-TB drugs. In the present study male patients were found to have more incidences of ADRs 68.6% than female patients 31.4%. The reason for this could be that the present study had more number of male patients 62% than female patients 38%.

The most common system affected by ADR is gastrointestinal system 77.14%, highest was nausea 70.83%, which is similar to a study conducted by Dhingra et al, 2004[14] where it was 53%.

Onset of ADR is an important factor helpful in early detection of ADR.[6] In the present study most of all the ADRs occurred within 30 days of initiation of ATT. In the study conducted by Dhingra et al, 2004[14] 67% of ADRs occurred in the first 4 weeks of treatment.

It is essential for the health care professionals to counsel the patients regarding the early identification of ADRs in the first few weeks. Regular monitoring of the patients during these initial weeks might be essential for early detection of ADRs.[6] It will also be helpful in assuring the compliance of the patients who are getting ATT.

In the present study, majority of ADRs 87.5% had a possible relationship with the suspected drugs and only 12.5% of the ADRs had a probable relationship with the suspected drugs. No dechallenge or rechallenge was done to establish the causative agent, placebo effect was not studied, and no laboratory investigations were done to determine the concentration of drug in body fluids or tissue. Owing to the lack of all these parameters, none of the reported ADRs could be classified as 'definite' attributed to the suspected drugs.

In the present study, 100% of the ADRs were of Mild [Level (1)] type. In most of these patients, adverse effects were seen to abate spontaneously over a period of time.

Conclusion:

The present study was able to identify the pattern and type of ADR, analyze the causality and severity of ADRs and also assess if there is a relationship between ADRs and the number of drop-outs in patients on ATT under RNTCP (DOTS) in Pondicherry to some extent. ADRs encountered in the study like nausea, dizziness, etc., are in concurrence with the established ADRs. ADRs like hepatotoxicity, peripheral neuropathy, optic neuritis, etc., were not observed possibly because of the small sample size of the present study. Further studies with larger sample size are required to ascertain the same.

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