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## INCIDENCE AND COMPARATIVE ANALYSIS OF ADVERSE DRUG REACTIONS IN DOTS

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**ABSTRACT:** To assess the adverse drug reactions (ADRs) induced by antitubercular drugs used in Directly Observed Treatment Short Course (DOTS) from previously reported 8 articles from referred sources. Articles related to adverse drug reactions induced by first line anti-tuberculosis drugs in DOTS therapy published during 2002 to 2012 were searched. The incidence rate of each type of ADR from entire ADRs were analyzed and compared. The total 10083 patients from 8 studies were studied, out of those 7473 (74.11%) patients showed at least one type of ADR. The majority cases of ADRs were dermatological reactions occurred in 4389 (43.52%) patients followed by hepatotoxicity in 1634 (16.20%) patients, other reactions related to gastrointestinal (GI) in 1004 (9.95%) patients, central nervous system in 86 (0.85%) patients, peripheral nervous system in 07 (0.069%) patients, psychiatric in 03 (0.029%) patients, musculoskeletal in 166 (1.64%) patients, renal in 07 (0.069%) patients, otological in 09 (0.089%) patients, ocular in 29 (0.28%) patients, fever in 13 (0.12%) patients, breathlessness in 04 (0.039%) patients, headache in 37 (0.36%) patients and miscellaneous ADR in 659 (6.53%) patients. There were many adverse drug reactions observed during study which are needed to be monitored during DOTS therapy for prevention of serious harmful effects like leading to death.

**INTRODUCTION:** Tuberculosis (TB) an infectious disease caused by *Mycobacterium tuberculosis*, now become the second leading infectious cause of death in the world. In 2009, there were an estimated 9.4 million incident cases of TB globally that is equivalent to 137 cases per 100000 population. Most of the estimated number of cases in 2009 occurred in Asia (55%) and Africa (30%); 3 smaller proportions of cases occurred in the Eastern Mediterranean Region (7%), the European Region (4%) and the Region of the Americas (3%)<sup>1</sup>.

Before the advent of the DOTS programme, high prevalence countries like India had a National TB Programme to combat the Problem of TB. India's National Tuberculosis Programme (NTP) was started in 1962 (NTP employs a daily regimen of anti-TB drugs) as a truly integrated programme, implemented through District Tuberculosis Centers (DTCs) and peripheral health institutions.

After more than three decades, the NTP has made notable, but not spectacular progress. The overall case finding programmes are about 33% and treatment efficiency is of the same order or worse.

In order to intensify the efforts to control TB, the Government of India gradually replaced NTP by the DOTS strategy/programme in 1993 and it is now known as the Revised National Tuberculosis Programme (RNTCP).

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The objective of this revised strategy is to achieve a cure rate of 85% for infections and seriously ill patients through intermittent (three days a week) supervised short course chemotherapy or the directly observed treatment, short course (DOTS).

Under RNTCP, the doses of following first line anti-TB drugs were standardized on the basis of body weight and were given in different regimens. Ethambutol is EMB or E, isoniazid is INH or H, pyrazinamide is PZA or Z, rifampicin is RMP or R and streptomycin is S.

Antitubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time and therefore, it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the ADRs to the drugs used are one of the major reasons for the patient default for treatment.

A general knowledge of the various ADRs and their management is essential for the effective management of TB. All antitubercular drugs can cause adverse drug reactions and may result in ADRs involving almost all systems in the body, including the gastrointestinal tract, liver, skin, nervous system, oto-vestibular apparatus and the eyes<sup>2</sup>.

**TABLE 1: DATA SOURCE**<sup>1, 6, 9-14</sup>

Serial Number	Region	Country	Number of patients
1	Penang	Malaysia	653
2	Pokhara	Nepal	137
3	Sylhet Chest Disease Hospital and Sylhet Shaheed Shamsuddin Ahmed Hospital	Bangladesh	64
4	Department at Imam tertiary teaching hospital	Iran	83
5	Manipal Teaching Hospital, Pokhara	Nepal	326
6	Gangneung	Korea	57
7	Thailand	Thailand.	8714
8	New Delhi	India	185

**RESULTS:** The total 10083 patients from 8 studies were studied, out of those 7473 (74.11%) patients showed at least one type of ADR (**Fig. 1**). The majority cases of ADRs were dermatological reactions occurred in 4389 (43.52%) patients followed by hepatotoxicity in 1634 (16.20%) patients, other reactions related to gastrointestinal (GI) in 1004 (9.95%) patients, central nervous system in 86 (0.85%) patients, peripheral nervous

There are common ADRs observed in DOTS therapy such as mild gastritis, central nervous system, peripheral nervous system, hepatitis, psychiatric, dermatologic, musculoskeletal, renal, otologic, ocular, hypothyroidism, icterus, fever, breathlessness<sup>3, 4, 5</sup>.

Identification of the ADR profile of drugs can be useful for the anticipation, early detection and management of ADRs. Very few studies have been done till date to assess the ADRs of the DOTS regimen. Hence, there is a need to study the safeguard of patients on DOTS through the monitoring of ADRs. Hence, the current study was undertaken.

**MATERIAL AND METHODS:** Previously reported articles related to adverse drug reactions induced by first line anti-tuberculosis drugs in DOTS therapy during 2002 to 2012 were searched from referred sources.

The result of each paper was carefully observed. The observed ADRs induced by first line drugs were written in table. The observed cases of each ADR were mentioned in the table. In this way the ADRs from all articles were reviewed. The incidence rate of each type of ADR from entire ADRs was analyzed and compared (**Table 1**).

system in 07 (0.069%) patients, psychiatric in 03 (0.029%) patients, musculoskeletal in 166 (1.64%) patients, renal in 07 (0.069%) patients, otological in 09 (0.089%) patients, ocular in 29 (0.28%) patients, fever in 13 (0.12%) patients, breathlessness in 04 (0.039%) patients, headache in 37 (0.36%) patients and miscellaneous ADR in 659 (6.53%) patients (**Table 2, Fig. 2**).

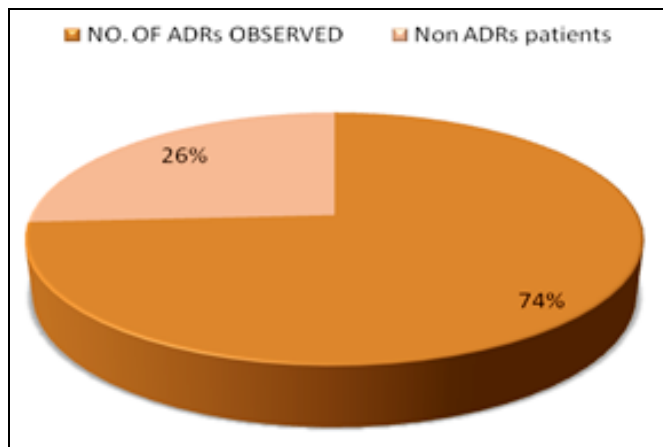


FIG. 1: COMPARATIVE ANALYSIS OF ADR AND NON ADR

TABLE 2: CLASSIFICATION OF ADR<sup>1, 6, 9-14</sup>

	Number of Patients	ADR Distribution (%)
Total	10083	
Number of ADRs Observed	7473	74.11
GI disturbance	1004	9.95
Central nervous system	86	0.85
Peripheral nervous system	07	0.069
Hepatitis	1634	16.20
Psychiatric	03	0.029
Dermatological	4389	43.52
Musculoskeletal	166	1.64
Renal	07	0.069
Otological	09	0.089
Ocular	29	0.28
Fever	13	0.12
Breathlessness	04	0.039
Headache	37	0.36
Miscellaneous	659	6.53

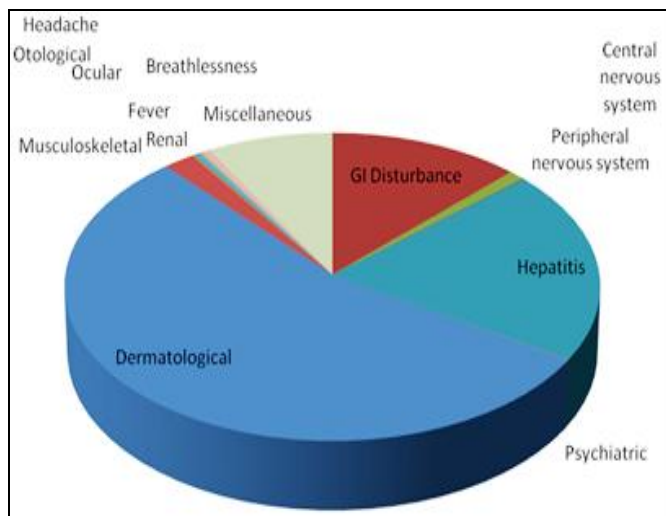


FIG. 2: ADR DISTRIBUTION IN DOTS

**DISCUSSION:** Total 10083 patients were studied; out of which 7473 patients show at least one type of ADR. The most common ADR is related to dermatological side effects. The study says that there is need of monitoring DOTS therapy in concern with ADR. Isoniazid, rifampicin, rarely in use of pyrazinamide and ethambutol are the drugs responsible for the skin reactions<sup>1</sup>. ADR occurrence in female patients was slightly more in the present study than male patients. Generally, females are considered to be more at risk of ADRs due to their smaller body size and body weight compared to the males & they pass through life stages like pregnancy, menarche etc. which modify the drug response<sup>2, 3</sup>. As the number of drugs used in regimen increases, the ADRs also increases<sup>6</sup>.

Management to ADRs occurrence mostly with add on medication, then followed by withhold the medication regimens, continue without changes and the last is change patient’s treatment regimens. Add on medication such as antiemetic for relieving patient from minor gastrointestinal reactions (nausea or vomiting) and add an antihistamine agent for reducing minor skin reactions. Gastrointestinal disorders are commonly caused by rifampicin can be reduced by restart drugs one at a time every 4 days or begin with drugs that are least likely to cause diarrhea.

Hepatotoxicity is very uncommon in children, mainly shown by isoniazid and rifampicin, isoniazid alone, pyrazinamide alone, rifampicin alone. It can be reduced by starting therapy with ethambutol and pyrazinamide. Arthralgia or gout caused due to pyrazinamide, ethambutol, and isoniazid are managed by Nonsteroidal Anti-inflammatory Drugs (NSAIDs) & colchicines. Neurotoxicity of ethambutol & isoniazid is reduced by discontinuation of the therapy. Sometimes termination of therapy is required to prevent further complications<sup>1</sup>.

In management of ADRs, the role of pharmacist is crucial. They are able to lessen the severity of ADRs by growing patient compliance by counselling.

There is need of special care to reduce further complications like hepatotoxicity and death by monitoring of DOTS therapy.

**CONCLUSION:** Various types of adverse drug reactions were observed in the current study. ADRs were needed to be monitored during DOTS therapy for the prevention of serious harmful effects like death.

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