

## Adverse effects of first line anti-tubercular drugs on patients taking directly observed treatment short course chemotherapy

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### Abstract

**Background:** The World Health Organization (WHO) TB statistics for India for 2017 gives an estimated incidence of 2.8 million cases of TB for India out of a global incidence of 9.6 million. Tuberculosis (TB) is one of the common problems in every part of the world. India is the country with the highest burden of TB. The highest burden is carried by people who already face socio-economic challenges: migrants, refugees, prisoners, miners and others working and living in risk-prone settings, and marginalized women, children and older people. Anti tuberculosis treatment (ATT) is an effective treatment strategy for TB. As with all good things comes bad, ATT is associated with adverse effects, so it is very important to identify these adverse effects at the earliest, treat them and improve compliance. Hence this study intends to find out the occurrence of side effects of anti-tuberculosis drugs in patients registered under DOTS in our hospital. The main objectives of the study was to study the adverse drug effects of first line antituberculosis drugs in patients started on DOTS under RNTCP.

**Methodology:** Pulmonary tuberculosis patients who were started on Antituberculosis drugs under DOTS were clinically observed for adverse drug reactions (ADR) during the course of the treatment.

**Results:** Out of the 50 patients selected for this study, 30 patients developed at least one or more types of ADR and a total of 9 types of adverse drug reactions were observed. The most common symptom ADR observed in this study were gastrointestinal symptoms like nausea (28%), vomiting (13%), loss of taste (11%), dyspepsia (6%) and abdominal pain (9%), diarrhea (2%), jaundice (3%), others were malaise (9%) and skin rash (1%). The mean onset of the adverse drug effects were observed within 7 days and mean duration of the adverse drug effects were seen up to 2 months after start of ATT.

**Conclusions:** This study showed that DOTS 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 treated with symptomatic medications. Gastrointestinal symptoms were the most common type of ADR and most of the symptoms subsided within the intensive phase of the treatment.

**Keywords:** Anti Tuberculosis treatment; Adverse drug reaction; Tuberculosis.

### Introduction

One of the greatest challenges facing health care systems at the dawn of the 21<sup>st</sup> century is the fight against tuberculosis. Tuberculosis (TB) continues to remain one of the most common problem affecting health care, India is the country with highest burden of TB, accounting for one-fourth of the global incidence-an estimated 2.8 million cases annually. Approximately 0.4 million people die from TB each year in India [1].

In response to the tuberculosis burden, The National Tuberculosis Programme of India (NTP) was started in 1962 which was revised in 1997 as Revised National Tuberculosis Control Programme (RNTCP) that used World Health Organisation recommended DOTS (Directly Observed Treatment, Short-course chemotherapy) strategy for TB control. Nationwide coverage was achieved in March, 2006. Since start till December 2016, more than 2 crores patients were started on treatment and more than 35 lakhs additional lives have been saved [2]. The program was considered almost successful, although it still faces many challenges.

On the basis of past history of TB, patients were divided into two categories. New patients who have not been previously treated with Anti-tuberculosis drugs are placed in category I and patients who have been treated with anti-tuberculosis drugs before for 1 month or more are placed in treatment category II and are further classified by the outcome of their most recent course of treatment into relapse/failure/Defaulter. Category I were treated with four

first line anti-tuberculosis drugs under DOTS, they are Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), Ethambutol (E) for 2 months and then with 2 drugs Isoniazid and Rifampicin for four months. Category II received five drugs (INH, RMP, PZA, E) plus Streptomycin (S) for two months, then four drugs (INH, RMP, PZA & E) for one month and three drugs (INH, RMP and E) for five months. Patients in categories I and II whose sputum smears were positive for acid fast bacilli at the end of intensive phase treatment (the first two or three months in categories I and II, respectively) received another 1 month of intensive-phase treatment. All treatment were given three times weekly. Every dose of medication in the initial phase was directly observed, either by a health worker or by a community member who was not a family member. In the four-to-five month continuation phase, when the bacterial load was far lower, at least the first of each of the thrice-weekly doses was directly observed. Medications for both phases of treatment were kept in an individual box containing the entire course of treatment for a single patient [3-5].

The currently recommended anti-tuberculosis regimen (DOTS) is based on powerful bactericidal drugs shortened the treatment duration and increased compliance and adherence with an additional advantage of lowering drug toxicity mainly because of fewer doses and less cumulative doses of drugs. Serious adverse reactions of the anti tuberculosis drugs were known to be less with intermittent therapy and is usually well tolerated [6]. However, some

patients may experience problems, usually due to the bulk of the medicines, a single day's dose consisting of 6-7 tablets. A study by Dhingra et al. reported that approximately 8.4% of the patients treated under DOTS complained of some sort of adverse drug reaction (ADR) and that most of them occurred during first four weeks in the intensive phase of treatment [7]. Medicine-related side effects can be minor or major [8]. Most of the drug reactions were not serious and were managed by symptomatic treatment. In 2-3 weeks the patients usually get adapted and adjusted to the treatment regimen [9].

Moreover, the ADR to the drugs was one of the major reasons for the patient default [10]. These events were seen to incur substantial additional economic burden because of added outpatient visits, tests, and in more serious instances hospitalizations [11].

All antitubercular drugs were known to cause ADRs and may result in ADRs involving almost all systems in the body, including the gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and the eyes [10].

### Adverse Drug Effects of First Line Anti Tuberculosis Drugs

1. Rifampicin – abdominal pain, nausea, vomiting, hepatitis, cutaneous reaction, purpura, haemolytic anaemia, flu like syndrome, acute renal failure.
2. Isoniazid – Peripheral neuropathy, skin rash, hepatitis, sleepiness and lethargy, convulsions, psychosis
3. Pyrazinamide – Nausea, vomiting, hepatitis, arthralgia, cutaneous reactions
4. Ethambutol – Optic neuritis, GI upset, hypersensitivity reactions, peripheral neuropathy, purpura
5. Streptomycin – Loss of vestibular functions, deafness, renal toxicity, cutaneous hypersensitivity, deafness, renal toxicity, cutaneous hypersensitivity, circumoral numbness [9].

Therefore, rather than concentrating only on the treatment, the adverse effects of the drugs should also be looked upon for achieving better patient compliance. Identifying the drugs causing ADRs is an important responsibility of the medical professionals and could help in educating patient along with preventing the occurrence of similar ADRs in future. It is essential for the medical professionals to educate the patients regarding the early identification of ADRs in the first few weeks. The Hartwig Scale was a commonly used scale for identifying the severity of ADR's [12].

Identification of the ADR profile of drugs is considered useful for the prevention, early detection and treatment of ADRs. Hence there is a need to study the safety profile of patients on DOTS through monitoring of ADRs in a clinical set up.

### Objectives

1. The study the ADRs in patients started on first line anti tuberculosis drugs under DOTS under RNTCP
2. To assess the severity of Side Effects of anti tuberculosis drugs using hartwig Scale.

### Methodology

A Prospective observational study was conducted among patients with newly diagnosed pulmonary or extra pulmonary tuberculosis who were started on first line anti tuberculosis drugs under DOTS in Bapuji Hospital attached to JJM Medical College, India. Total 50 tuberculosis patients aged >15 years, started on first line anti tuberculosis drugs under DOTS were selected for the study using purposive sampling technique. An ethical committee approval and a written informed consent from study subjects was obtained. Patients who had clinical jaundice, deranged platelet count, liver function test and renal function test before initiating treatment were excluded from the study.

Prior to starting anti-tuberculosis treatment a detailed clinical assessment which included history and clinical examination was done and follow up clinical and hematological evaluation was done at 1<sup>st</sup> week, 1st month and 4th month of treatment. Patients were educated to report any symptoms they would experience during the course of treatment. Symptoms looked for during the follow up period were anorexia, loss of taste, nausea, vomiting, fever, bitter taste sensation, myalgia, diarrhea, abdominal pain, lethargy, jaundice, arthralgia, bleeding diathesis, itching, photosensitivity, blurring of vision, rashes, confusion, tingling and numbness, dizziness, loss of balance, convulsions, psychosis and depression. Physical examination included bleeding manifestations, skin rashes, and hypotension.

Hartwig's scale is widely used for the purpose of categorizing adverse drug reactions. This scale categorizes the reported adverse drug reaction into different levels as mild, moderate or severe. In Mild (Level 1) the ADR requires no change in the treatment with the suspected drug and Mild (Level 2) the ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay. In Moderate (Level 3) the ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required with no increase in length of stay. Moderate [Level 4 (a)] is any level 3 ADR that increases the length of stay by at least one day and in Moderate [Level 4 (b)] the ADR is the reason for admission. The Severe (Level 5) is any level 4 ADR that requires intensive medical care, Severe (Level 6) is the ADR causing permanent harm to the patient and Severe (Level 7) being the ADR either directly or indirectly leading to the death of the patient [13,14].

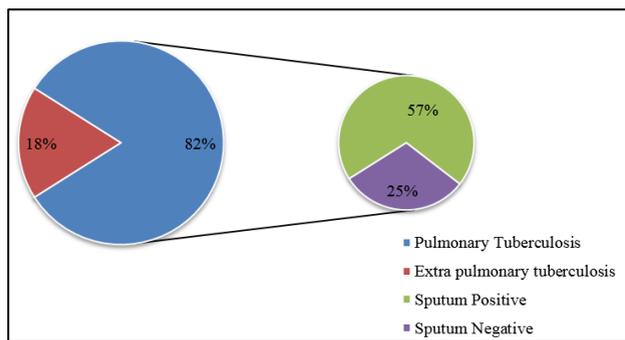
### Results

Out of the 50 patients studied majority of patients were in middle age group and majority were male (78%) as shown in Table 1. The male to female ratio was 3.5:1.

**Table 1:** Socio demographic profile of patients

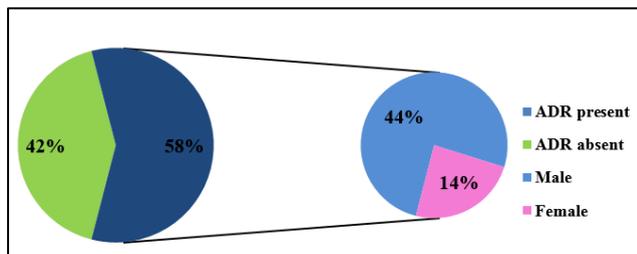
S. No.	Variables	Categories	Percentage (%)
1.	Age	16-20	4
		21-30	12
		31-40	24
		41-50	22
		51-60	20
		>60	18
2.	Sex	Male	78
		Female	22

Majority (82%) of the patients had pulmonary Tuberculosis. Out of them, 57% patients were sputum positive and 25% were sputum negative, as shown in Fig. 1.



**Fig. 1:** Type of tuberculosis and sputum positivity

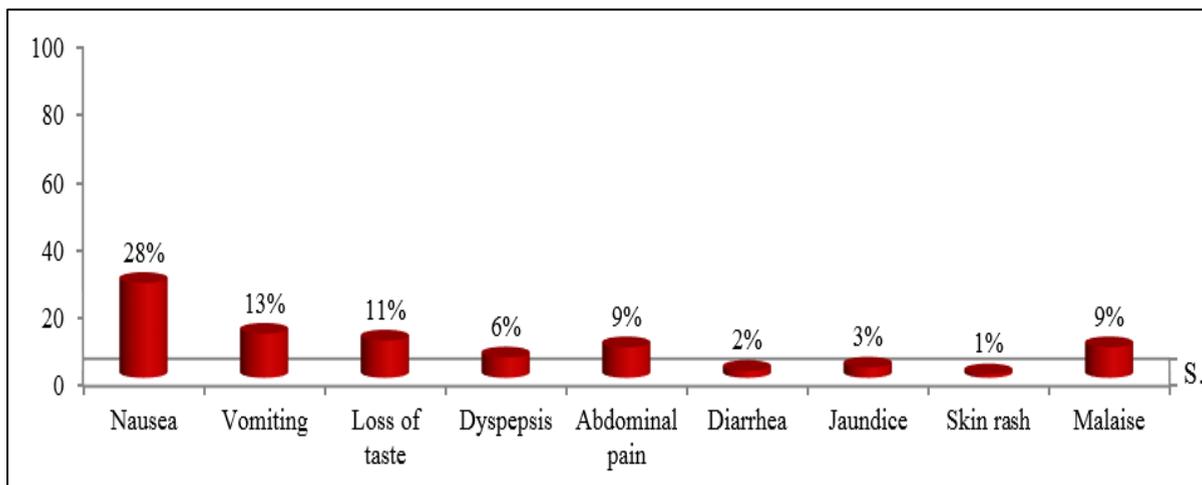
29 patients (58%) developed one or more type of an adverse drug reaction, as shown in Fig. 2. Out of which 14% were female and 44% male. ADR was seen more frequently in the age group of 31-60yrs.



**Fig. 2:** Distribution of adverse drug reaction

Mean Weight of the patients who developed ADR was 61 Kgs and mean weight of patients who did not develop ADR was 63.29 Kgs out of 29 patients who developed ADR 8(27.6%) were alcoholics. ADR was more common and severe in alcoholics than in non-alcoholics. Out 50 patients, 2 patients (4%) were HIV positive.

The most common symptom observed in this study was gastrointestinal symptoms like nausea 28%, vomiting 13%, loss of taste 11%, abdominal pain 9%, dyspepsia 6%, jaundice 3% and diarrhea 2%, and other ADRs were malaise 9% and skin rash 1%, as shown in Fig. 3.



**Fig. 3:** Observed adverse drug reactions

As shown in Fig. 4, most of the patients had observed ADR within 7 days after starting ATT and only one patient observed skin rash at 45<sup>th</sup> day of treatment. Most of the ADR subsided within 2 months of treatment course, but most patients complained of generalized weakness lasting for up to 4 months, as shown in Fig. 5.

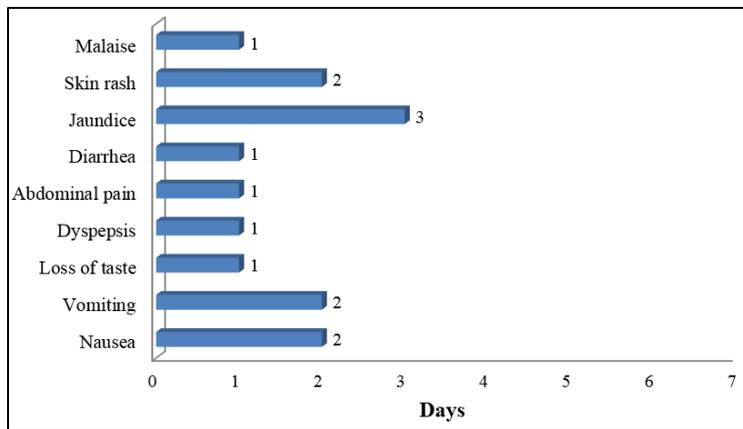


Fig. 4: Median time of onset of ADR's

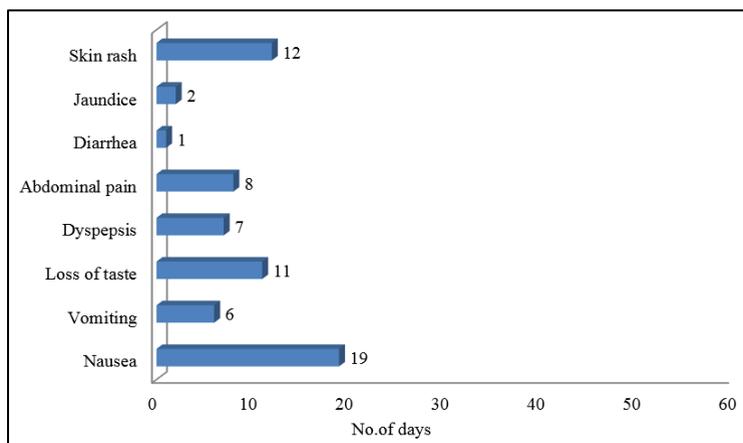


Fig. 5: Maximum duration of ADR's

Out of the 29 patients who developed ADRs, 22(75.9%) patients required symptomatic treatment on outpatient basis with medications like antacids, antiemetic, antihistamines in order to continue ATT and 6(20.7%) patients required hospitalization. Of the 22(75.9%) patients who required symptomatic treatment, 12(54.5%) patients had 1 OPD visit, 9(40.9%) patients had 2 OPD visits, and 1(4.5%) patient had 4 OPD visits. The reasons noted for increasing OPD visits

and hospitalization were increase in severity of GI intolerance and jaundice. Of the 29 patients, 4(13.8%) patients discontinued treatment as they could not tolerate the ADRs, of which 1 patient stopped the treatment due to skin rash, 3 patients due to severe GI intolerance.

Hartwig's scale was used to assess the severity of ADR. Majority of patients (65.5%) developed level 3 reactions, 24.1% patients developed level 1 reactions and 10.4% developed level 4B reactions, as shown in Fig. 6.

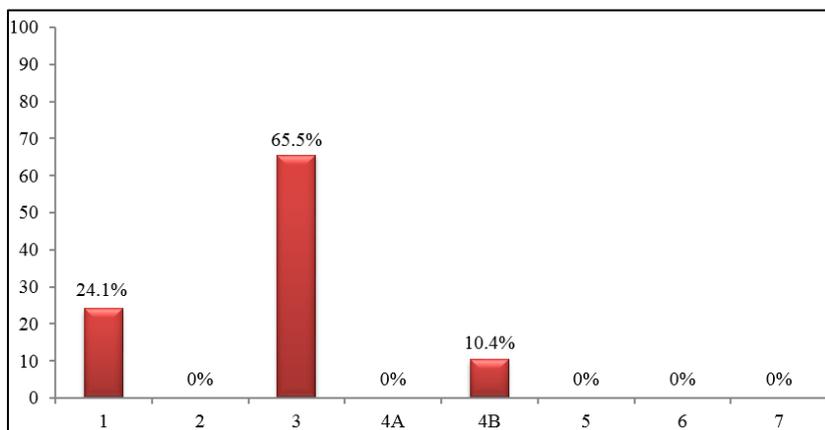


Fig. 6: Severity of ADR on Hartwig's Scale

## Discussion

Identifying adverse drug reactions to ATT, treating them and improving compliance is a very important aspect in the treatment of tuberculosis. Directly observed treatment, short-course (DOTS) is a very effective treatment strategy adopted by Revised National Tuberculosis Control Programme (RNTCP).

In the study, it was noted that out of the 50 patients studied, 29 patients (58%) developed one or more types ADR; 22 were male and 7 female patients. ADR was found in more number of male patients as our study group consisted of predominantly male patients. However, incidence of ADR was more among female i.e., 63% of female patients suffered ADR and 56% of male patients had ADR which is similar to many studies. A total of 9 types of adverse drug reactions were observed. ADR was found to be more common in female gender and patients who consumed alcohol.

In a study by Yee et al., in Montreal 9% patients developed serious adverse side effects. Occurrence of any major side effect was associated with female sex, age over 60 years [14].

In another study by Koju et al., 80% of the total number of patients reported at least one type of side effect. Female gender (38.10%), alcoholics (38.89%) and sputum-smear positive (32.14%) were associated with increased occurrence of major side effects [15].

Also in another studies from India – Dhingra et al., [7] 67% of the ADRs occurred in the first four weeks. Females had a higher incidence of ADRs. In a study at the DOTS center Kasturba Hospital, Manipal, and at the DOTS Centre, Udupi, by Tak et al., [10]. The incidence of ADRs was 17.02%. Old age and alcoholism were found to be the predisposing factors.

The high incidence of ADR seen in our study could be probably due to inclusion of even very minor symptoms like loss of taste, appetite and nausea. Whereas, other studies mentioned above have considered only major adverse drug reactions.

Adverse Drug Reactions (ADRs) to ATT is one of the major reasons for the default for treatment. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations. As a result the risk of treatment failure and relapse are higher. The currently recommended antituberculosis regimens are usually well tolerated. In general, a patient who has minor side effects should be encouraged to continue the treatment with symptomatic measures such as antacids, antihistamines, antiemetics, multivitamins and analgesic. If major side effects occur, the regimen, or the offending drug if identified, must be stopped. Further management depends on the nature of side effects and may have to be done in a hospital.

It is important to detect ADR as early as possible in the initial phase, in order to reduce the default and treatment failure rate. It is essential for the healthcare 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 is essential for early detection of ADR's.

In our study, among the 29 patients who developed ADR, 75.9% required symptomatic treatment. Hartwig's scale was used to assess the severity of ADR. Majority of patients (65.5%) developed level 3 reactions, 24.1% patients developed level 1 reaction. The mean onset time of the adverse drug effects were observed within 7 days and mean duration time of the adverse drug effects were seen up to 2 months after start of ATT. The most common being involvement of the gastrointestinal system that is nausea (28%), vomiting (13%), loss of taste (11%), dyspepsia (6%), abdominal pain (9%), jaundice(3%), diarrhea (2%) and others were skin rash (1%) and malaise (9%). Patients with minor adverse effects improved with symptomatic medications like antacids, antihistamines and antiemetics and could continue the treatment.

In the study by Tak et al., [10]. Gastritis was the most common ADR and multiple drug therapy was the major predisposing factor. In 87.1% of the cases, the suspected drug was continued in spite of the ADR, without any complications. The severity assessment of ADRs showed that 31(51%) reactions were moderate and 30 (49%) were of the mild nature and found DOTS therapy to be safer and showed that regular monitoring is required for ADRs, so that certain percentage of ADRs can be prevented. Outcome of the ADR in 13(61.90%) cases, the patients recovered from ADRs without any complications and in 6(28.57%) cases, the reactions continued on discharge and there was no fatal reactions during the study period.

A study conducted by Daphne [16] showed that the most common ADR was gastritis, the second most common reaction was skin reaction, whose occurrence was comparable to that found in the study conducted by Dhingra et al., [7] and Zierski [17], where it was found to be around 17%.

In a study conducted at the Regional Tuberculosis Center (RTC) in Pokhara, Western Nepal in patients undergoing DOTS treatment during the 5 month study period it was seen that the ADR's were classified as mild (level 1). The most commonly reported ADR was tingling and burning sensation in hands and feet experienced by 32(11.03%) patients.

## Conclusions

This study shows that treatment given under RNTCP is an effective and safe treatment strategy as most of the adverse drug reactions seen were of a mild variety (Hartwig's scale level 1) and were managed with symptomatic medications. Gastrointestinal symptoms were the most common observed symptoms and most of the symptoms subsided within the intensive phase of the treatment. The health care professionals have to be vigilant during the intensive phase of the treatment, identify symptoms at the earliest and hence help in minimizing morbidity and default rate.

**Conflicts of interests:** None declared

**Acknowledgements:** None.

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