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Original article

Adverse drug reaction prevalence and mechanisms of action of first-line anti-tubercular drugs

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ABSTRACT

Purpose: Understanding the appearance of anti-tubercular drug-related adverse drug reactions (ADRs) in patients receiving tuberculosis (TB) treatment is important, and may be related to morbidity and mortality if not recognized early. Here, we aimed to characterize the mechanisms underlying adverse drug reactions due to combination anti-tuberculosis therapy of the Revised National Tuberculosis Control Program (RNTCP).

Methods: This was a prospective observational study conducted in 9 DOTS centers of New Delhi, India. All enrolled TB patients receiving first-line tuberculosis treatment as per RNTCP guidelines were monitored for ADRs. All ADRs that appeared during the treatment were recorded and analyzed.

Results: The study included 1011 TB patients on anti-TB treatment under DOTS. According to Naranjo's probability scale, of a total 351 (34.72%) reported adverse events, 102 (10.09%) were definite, 59 (5.83%) probable, 123 (12.17%) possible, and 67 (6.63%) doubtful. On the Hartwig severity scale, of the 351 adverse drug events, 225 (22.26%) were mild, 105 (10.38%) were moderate, and 21 (2.08%) were severe. Out of 102 reported adverse drug reactions, 81 (79.41%) were moderate and 21 (20.59%), while 65.28% did not experience any ADRs.

Conclusions: Directly Observed Treatment (DOT) is effective and safe compared to daily treatment regimens. Patients receiving DOTS therapy needed close monitoring for adverse events. Therefore, a pharmacovigilance program should be added at the National level to accesses the adverse event incidence.

1. Introduction

Tuberculosis (TB) is a chronic granulomatous, potentially infectious disease and a major health problem in developing countries (Tripathi, 2013). One fourth of the global population is infected with *Mycobacterium tuberculosis* and is one of the world's deadliest diseases (CDC, 2017a). In 2017, 10 million people contracted TB; with India contributing 2.8 million cases and 1.3 million deaths reported from Tuberculosis worldwide. While the case rate of 2.8 out of 100,000 persons is a 2.3% decrease from 2016 (CDC, 2017a), India has suffered the topmost TB burden for the past several years, where about 1000 people die from TB every day (WHO, 2019).

In India, TB control and treatment is covered under a national program that offers free treatment to all TB patients. In 1917, the Revised National Tuberculosis Control Program (RNTCP) was organized, and developed treatment guidelines that were revised in 2010 (Tripathi, 2013). Lungs are affected in more than 85% of TB cases. This type of disease is called pulmonary tuberculosis, but *M. tuberculosis* can infect other organs of the body such as the spine, kidneys, genital organs, brain, and skin. Positive sputum smear results are an indication of a pulmonary tuberculosis infection. People who come in contact with a patient with undiagnosed or untreated infectious tuberculosis (i.e. smear positive) risk getting infected. Hence, it is very important to recognize symptoms

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of tuberculosis early in the course of the disease and ensure their treatment (RNTCP Modul 1-4, 2005).

The development of drug resistance in TB treatment and especially multidrug-resistant TB (MDR-TB) has become global public health issue in many countries and a hindrance to effective TB control (Central TB Division, 2006). Drug resistance develops either due to infection with a resistant strain or as a result of insufficient treatment like when a patient is exposed to a single drug, selective drug intake, irregular drug supply, poor drug quality, or erratic absorption of medications, which is rare (Andrews et al., 2007; Jain and Dixit, 2008; Alcaide and Santin, 2008; Jassal and Bishai, 2009).

Hospital admission is recommended for severe cases (Shabazian and Weis, 2005). First-line anti-tuberculosis drugs are components of DOTS. Anti-tuberculosis drug therapy has three categories based on the RNTCP guidelines. DOTS is the most effective strategy available for controlling TB because improvement in treatment completion rate, cure rates and decline in rates of acquired multidrug-resistant tuberculosis after implementation of the directly observed therapy.

The incidence, risk factors, morbidity, and mortality of adverse events from isoniazid (INH), particularly hepatotoxicity, have been well define (Yee et al., 2003). Noxious reactions to ethambutol (EMB) and rifampin (RIF) are well documented, although causality of these drugs is less certain because they are rarely used alone. The occurrence of major adverse reactions related to pyrazinamide (PZA) treatment is well known. However, serious adverse events (SAE) ascribable to PZA have been reported in patients treated for active disease or receiving two months of PZA and RIF for latent infection (Yee et al., 2003; Gholami et al., 2006).

First-line anti-TB drugs are mainly responsible for adverse reactions and result in discontinuation of that drug. Throughout the course of TB therapy, there may be risk of morbidity and mortality, particularly with drug-induced hepatitis. Alternative agents are often less effective and may have serious toxicity risks, so that medication must be prolonged and used with challenges to ensure compliance. As a result, the risk of treatment failure and relapse are higher (Yee et al., 2003). Hence, monitoring is crucial but costly. Familiarity with risk groups may reduce the cost as well as the occurrence of serious TB drug-related adverse effects.

2. Methods

2.1. Study design

This was an observational study to define the mechanism of adverse drug reactions in combination anti-tuberculosis therapy defined by the Revised National Tuberculosis Control Program.

2.2. Population selection criteria and sample size

The present study was conducted on patients receiving combination therapy for the management of tuberculosis registered at a DOTS center of the RNTCP for DOTS programs following the standard RNTCP guidelines (Gholami et al., 2006). In the present study, a total of 1011 patients across all categories (I, II and III) were screened from six centers in a defined area of RNTCP under LRS for the detection of any adverse reactions after drug administration. Out of these 1011 patients, 351 patients reported adverse events during the course of DOTS therapy.

2.3. Patient enrollment procedure

All patients visiting OPD were thoroughly examined for their health status based on physical and clinical examination, including sputum examination to confirm a tuberculosis diagnosis. On the basis of these tests and examination, patients with tuberculosis were registered for standard DOTS therapy at DOTS centers in the defined area of RNTCP under LRS Institute of Tuberculosis and Respiratory Diseases. Finally, patients were enrolled in this study between April 2008 and December 2008 (i.e. nine months) for the detection of any adverse reactions after drug administration.

2.4. Adverse events reporting

After DOTS recommendation to the patients by the physician, patients were asked to visit the nearest DOTS center to initiate DOTS therapy to ensure compliance. Patients visiting DOTS centers were assessed for the occurrence of ADR from the anti-tuberculosis therapy after every dose without any interruption in the DOTS therapy.

At the time of the visits, patients were questioned using the Naranjo probability scale and Hartwig severity scale to specify the occurrence of side effects from the DOT therapy (Naranjo et al., 1981; Hartwig et al., 1992). Baseline assessments included physical and clinical examinations, including sputum examination. Patients that experienced ADRs were evaluated on subsequent visits using specific questionnaires. Patients that developed ADRs were thoroughly checked for the CBC, uric acid and liver function, and were followed until further recovery from the ADRs. Blood samples were taken from patients who developed ADRs by a trained technician. Patients were encouraged to return at any time if new symptoms or problems arose during therapy.

2.5. Data analysis

The data were assessed using the Naranjo and Hartwig scales (Naranjo et al., 1981; Hartwig et al., 1992). The Naranjo scale measures the probability of an adverse drug reaction and was used to subjectively assess the likelihood that an observed reaction was a result of standard DOT therapy. The Naranjo criteria is an assessment of drug-induced adverse reactions based on symptom onset, course of reaction and possible drug alternatives. In assigning the phenotypes, a slow acetylator was defined as a patient whose plasma isoniazid concentration was greater than the antimode, and a fast acetylator was a patient whose plasma isoniazid concentration was less than antimode. Data were presented as incidence mean ± SD (90% C.I.) and odd ratio. Statistical analysis was conducted with Statistical Analysis Software IBM SPSS Version 0.20. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic details of patients enrolled for DOTS

The demography of patients who experienced adverse events included age, sex, weight (kg), height (cm), which and BMI are presented as mean ± SD (Table 1).

The mean age of the men varied from 28.45 (±14.873) to 34.00 (±16.405), while the mean age of the women varied from 23.00 (±11.205) to 39.14 (±25.354) years. BMI was calculated as weight (kg) divided by the square of height (meters) and were presented as the patient's mean BMI (±SD).

The overall mean ages for men and women enrolled in the present study were 30.60 (±14.435) and 27.57 (±14.485), respectively; whereas, the overall average age of all patients enrolled in the present study was 29.30 (±14.514).

Table 1
Demographic details of patients enrolled for DOTS therapy.

Patients Demography		Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	All Centers
Age (Year)	Men Mean ± (SD)	29.29 ± (15.195)	31.09 ± (13.552)	34.00 ± (16.504)	28.45 ± (14.873)	33.40 ± (15.415)	29.85 ± (8.732)	30.60 ± (14.435)
	Women Mean ± (SD)	31.89 ± (16.193)	23.00 ± (11.205)	23.14 ± (10.518)	25.00 ± (9.808)	34.62 ± (15.538)	39.14 ± (25.354)	27.57 ± (14.485)
	Average Mean ± (SD)	30.50 ± (15.700)	27.90 ± (13.209)	28.38 ± (14.665)	26.34 ± (12.973)	33.88 ± (15.231)	32.26 ± (14.875)	29.30 ± (14.514)
Weight (Kg) Mean ± (SD)		30.50 ± (15.700)	46.70 ± (10.648)	43.63 ± (10.213)	43.12 ± (10.361)	43.70 ± (9.040)	48.25 ± (10.557)	45.30 ± (10.550)
Height (cm) Mean ± (SD)		161.11 ± (5.599)	160.99 ± (13.018)	153.58 ± (19.870)	158.07 ± (12.137)	159.64 ± (14.730)	163.69 ± (7.981)	157.89 ± (7.698)
BMI (Kg/m^2) Mean ± (SD)		8.77 ± (4.13)	17.83 ± (2.915)	18.69 ± (4.674)	17.07 ± (3.011)	17.16 ± (2.916)	16.75 ± (2.920)	16.86 ± (4.160)

The overall mean weight, height and BMI of all patients enrolled in the present study were 45.30 kg (±10.550), 157.89 cm (±7.698) and 16.86 kg/m^2 (±4.160), respectively.

3.2. DOTS centers for data collection and adverse events

In the present study a total of 1011 patients were screened from all six centers in the defined area of RNTCP under the LRS Institute of Tuberculosis and Respiratory Diseases for the detection of any adverse reactions after drug administration. Of these 1011 patients, 351 patients reported 714 adverse events (Table 2). One third of the screened patients reported adverse events, which may or may not have been related to medicines. Few patients experienced at least one adverse event, while the majority of patients reported more than one event during the DOT period. One patient on average reported at least 2.03 adverse events (Fig. 1).

3.3. Category based enrollment of patients and adverse events

All the patients enrolled in the present study were divided into three treatment categories (e.g. category I, II and III) based on RNTCP treatment guidelines. A total of 545 patients were enrolled as Category I for the treatment of tuberculosis. Out of these 545 patients, 186 (34.13%) patients reported adverse events among category I treatment. Whereas 225 patients enrolled as category II, only 84 (37.33%) patients reported adverse events. A total of 241 patients were enrolled as category III, of which only 81 (33.61%) patients reported adverse events (Table 3). In category II patients, a slightly higher percentage reported adverse events than categories I and III patients (Table 3).

3.4. Treatment outcome in patients receiving DOTS therapy under RNTCP

Out of 1011 patients registered in the present study, 789 (78.04%) enrolled patients as new cases receiving DOTS therapy first time, whereas 222 patients (21.96%) were receiving DOTS therapy for a second time or more due relapse, default, failure or other reasons. Among the new cases, 321 (40.68%) patients were newly positive, 119 (15.08%) were new negative and 349 (44.23%) were new extra-pulmonary patients. Among the retreated cases, 42 (18.92%) patients were relapse positive, 14 (6.31%) were failure positive, 84 (37.84%) patients were default positive and 82 (36.94%) were another category II case (Table 4). The cure rate among new pulmonary positive cases was 89.41%, whereas the treatment completion rate among new pulmonary negative and extra-pulmonary cases were 92.44% and 96.56%, respectively. The death rates among the new positive, negative and extra-pulmonary cases were 0.62%, 0.84% and 1.15%, respectively. The overall death rate among new cases was 0.89%. Treatment failure rates among the new pulmonary positive and extra-pulmonary cases were found to be 6.85% and 0.29%, respectively. The overall failure rate was 2.92%. The default rate among the new positive, negative and extra-pulmonary cases were found to be 2.49%, 6.72% and 2.01%, respectively. The overall default rate was 2.92%. The transferal rate among the new pulmonary positive patients was 0.62%.

In the retreated patients, the cure rates among relapse positive, failure positive and default positive patients were 73.81%, 42.86 and 63.10%, respectively; whereas, the death rates among relapse positive, failure positive and default positive patients were 4.76%, 7.14% and 4.76%, respectively. Failure rates among relapse positive, failure positive and default positive patients were 9.52%, 42.46% and 10.71%, respectively. Default rates among these patients were 11.91%, 7.14% and 20.24%, respectively (Table 4). In the retreated cases among other category II patients, treatment completion, failure and default rates were 89.02%, 2.44% and 7.32%, respectively (Table 4).

3.5. Number of adverse drug reactions reported during DOTS therapy

In this study, the incidence of Adverse Drug Reactions (ADRs) was very low with regimens of isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Out of 1011 tuberculosis patients

Table 2
Center patient number and recorded adverse events.

S. No.	Name of Center	No. of Patients	ADE in Patients	Total ADE
1	Bersarai DOTS Center (Center 1)	257	99	195
2	PHC DOTS Center (Center 2)	234	54	099
3	LRS Institute DOTS Center (Center 3)	127	70	150
4	Chattarpur DOTS Center (Center 4)	146	70	142
5	Fatehpur DOTS Center (Center 5)	136	32	069
6	Mahipalpur DOTS Center (Center 6)	111	26	059
	Total	1011	351	714

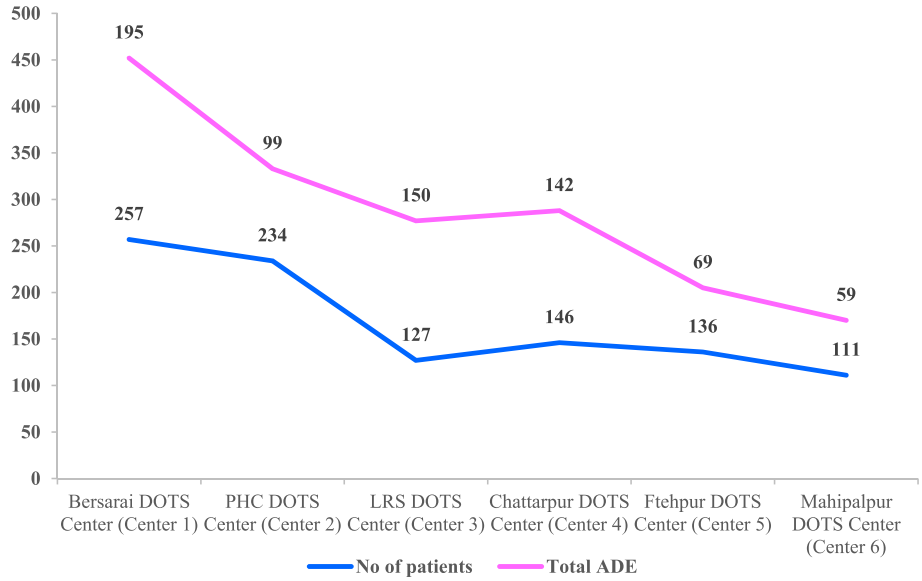

Fig. 1. Center wise number of patients and reported adverse events.

Table 3
Category of treatment and adverse events.

S. No.	Treatment Category	Name of Drugs	Patient enrollment	Adverse events	% ADEs
1	I	Isoniazid Rifampicin Pyrazinamide Ethambutol	545	186	34.13
2	II	Isoniazid Rifampicin Pyrazinamide Ethambutol Streptomycin	225	84	37.33
3	III	Isoniazid Rifampicin Pyrazinamide	241	81	33.61
Total			1011	351	

Table 4
Treatment outcome in patients receiving DOTS therapy.

Patients Registered	Type of Patient	Cured (%)	TC (%)	Died (%)	Failure (%)	Default (%)	Transferred (%)	Total (%)
New Pulmonary and Extra-pulmonary Patients								
321	Positive	287 (89.41)	0	2 (0.62)	22 (6.85)	8 (2.49)	2 (0.62)	321 (40.68)
119	Negative	0 (00)	110 (92.44)	1 (0.84)	0 (00)	8 (6.72)	0 (00)	119 (15.08)
349	Extra-pulmonary	0 (00)	337 (96.56)	4 (1.15)	1 (0.29)	7 (2.01)	0 (00)	349 (44.23)
789	Total	287 (36.38)	447 (56.65)	7 (0.89)	23 (2.92)	23 (2.92)	2 (0.25)	789 (100)
Retreated Patients								
42	Relapse Positive	31 (73.81)	0 (00)	2 (4.76)	4 (9.52)	5 (11.91)	0 (00)	42 (18.92)
14	Failure Positive	6 (42.86)	0 (00)	1 (7.14)	6 (42.86)	1 (7.14)	0 (00)	14 (6.31)
84	Default Positive	53 (63.10)	0 (00)	4 (4.76)	9 (10.71)	17 (20.24)	1 (1.19)	84 (37.84)
82	Other CAT-II	0 (00)	73 (89.02)	0 (00)	2 (2.44)	6 (7.32)	1 (1.22)	82 36.94)
222	Total	90 (40.54)	73 (32.88)	7 (3.15)	21 (9.46)	29 (13.06)	2 (0.09)	222 (100)

*TC = Treatment control.

enrolled in DOTS for treatment, only 102 (10.09%) patients reported adverse drug reactions during their therapy (Table 5).

3.5.1. Hepatotoxicity

Isoniazid, pyrazinamide and rifampicin are the most common drugs that potentially cause hepatic injury. In the present study, the most common drug that removed from the treatment regimen due to hepatotoxicity was rifampicin, followed by isoniazid. Hepatotoxicity was reported in 22 (2.58%) patients who discontinued one of these anti-tuberculosis drugs. Isoniazid was discontinued in 10 (0.99%) patients, while rifampicin was discontinued in 12 (1.19%) patients.

3.5.2. Hyperuricemia

It is well known that anti-TB therapy with pyrazinamide and ethambutol affects uric acid level and leads to polyarthralgia. Only

Table 5
Number of severe adverse drug reactions during DOTS.

S. No	ADRs	INH n (%)	RIF n (%)	PYZ n (%)	SM n (%)	EMB n (%)	Total n (%)
1	Hepatotoxicity	10 (0.99)	12 (1.19)	–	–	–	22 (2.58)
2	Hyperuricemia	02 (0.18)	–	02 (0.18)	–	07 (0.69)	11 (1.08)
3	Peripheral neuritis	08 (0.79)	–	–	–	03 (0.30)	11 (1.08)
4	Hypersensitivity	05 (0.49)	06 (0.59)	03 (0.30)	–	–	14 (1.38)
5	Visual Toxicity	–	–	–	–	03 (0.30)	03 (0.30)
6	Cutaneous reactions	03 (0.30)	07 (0.69)	03 (0.30)	–	–	13 (1.29)
7	Flu-like syndrome	–	11 (1.08)	–	–	–	11 (1.08)
8	Ototoxicity	01 (0.09)	–	–	04 (0.40)	–	05 (0.49)
9	Fever	09 (0.89)	–	–	01 (0.09)	–	10 (0.99)
10	Psychiatric changes	02 (0.18)	–	–	–	–	02 (0.18)
	Total	40	36	8	5	13	102

11 (1.08%) patients reported hyperuricemia, which lead to the discontinuation of one of the prescribed anti-tuberculosis drugs. Isoniazid and pyrazinamide were discontinued in two (0.18%) patients each whereas ethambutol was discontinued in seven (0.69%) patients.

3.5.3. Peripheral neuritis

Peripheral neuropathy occurs due to nerve damage characterized by numbness and pricking pain in the hands or feet. Symptoms of peripheral neuropathy include pain, numbness, tingling, weakness, loss of muscle control, burning sensation, and loss of feeling. These also symptoms are reported more in patients suffering from nutritional deficiency. In the present study, a total of 11 (1.08%) patients reported peripheral neuropathy, among which with (0.79%) and three (0.30%) patients reported peripheral neuritis due to isoniazid and ethambutol treatment, respectively.

3.5.4. Hypersensitivity

A total of 14 (1.38%) patients reported hypersensitivity during DOTS therapy under RNTCP. Hypersensitivity was reported with isoniazid, rifampicin and pyrazinamide in five (0.49%), six (0.59%) and three (0.30%) patients, respectively.

3.5.5. Visual toxicity

The most serious potential adverse effect of ethambutol is ocular toxicity, which is manifested by optic or *retro*-bulbar neuritis that may affect one or both eyes. In the present study, three (0.30%) patients reported visual toxicity due to ethambutol treatment, which was then discontinued from their therapeutic regimen.

3.5.6. Cutaneous reaction

Cutaneous reactions were reported in 13 (1.29%) patients receiving DOTS therapy under RNTCP and their drug therapy of one or more drugs were discontinued. In the current study, cutaneous reactions were reported with rifampicin, isoniazid and pyrazinamide in three (0.30%), seven (0.69%) patients and three (0.30%) patients, respectively. Due to the inhibitory effect of rifampicin on cellular immunity, it may interfere with cutaneous reactivity in intradermal tuberculosis.

3.5.7. Flu-like syndrome

Flu-like syndrome was reported in 11 (1.08%) patients treated with rifampicin.

3.5.8. Ototoxicity

Ototoxicity was the most significant adverse reaction reported by patients taking streptomycin. Ototoxicity such as tinnitus, balance disturbance, ear pain, vertigo, and dizziness. In the present study, ototoxicity was reported in five (0.49%) patients who omitted the drug from their treatment protocol. Isoniazid was stopped due to ototoxicity in one (0.09%) patient, whereas streptomycin was stopped in four (0.40%) patients.

3.5.9. Fever

Fever was the most common reported adverse drug event due to anti-tuberculosis therapy but discontinuation of the offending drugs were required in only special cases. In the present study, isoniazid was discontinued in nine (0.89%) patients due to fever, whereas streptomycin was discontinued in only one (0.09%) patient.

3.5.10. Psychiatric changes

Some of the patients had psychiatric behaviors including hallucination, abnormal behavior and psychosis during their anti-tuberculosis therapy, which required of the prescribed drugs or some modification in the treatment regimen to prevent development of neuroticism (i.e. psychological illness). In the current study, only two (0.18%) patients reported psychological illness due to isoniazid.

3.6. Correlation of ADR with monitoring indices and their possible mechanism

3.6.1. Hepatotoxicity

In the current study the most common drugs discontinued due to hepatotoxicity was rifampicin and isoniazid (Table 6). Hepatotoxicity was reported in 22 (2.58%) patients receiving DOTS therapy in the present study. Severe hepatotoxicity can lead to the discontinuation of at least one of the three standard drugs used in DOTS therapy, or sometimes all three drugs are omitted from treatment for few weeks to allow liver enzyme function to return to normal or near to normal before they are reintroduced back into therapy. Severe hepatotoxicity was more frequent among younger and older patients. There was no significance difference between patient genders in those who developed hepatotoxicity compared with those who did not. Liver enzymes were found to be elevated in patients with and without symptoms. Hepatotoxicity in patients receiving anti-tuberculosis therapy may be due to the formation of toxic metabolites. Rifampicin may cause liver dysfunction because of cholestasis at both the sinusoids and canaliculi of the liver due its uptake by hepatocytes and corresponding effect on excretion. In contrast, isoniazid-induced hepatitis is caused by the formation of the toxic metabolite, monoacetyl hydrazine, which covalently binds to liver proteins. The major path of isoniazid metabolism is hepatic acetylation by N-acetyl transferase to generate acetylisoniazid, which is further hydrolyzed to isonicotinic acid and acetylhydrazine and excreted in the urine. In some patients, hepatitis due to an allergic reaction has also been proposed. Acylation of hepatic macromolecules by acetyl hydrazine may lead to the release of antigenic macromolecules that induce the formation of antibodies that act against the liver.

Table 6
Correlation of ADR with monitoring indices and their possible mechanisms.

S. No.	Type of ADRs	Number of Patients	Monitoring Indices	Possible Mechanism
1	Hepatotoxicity	22	↑ALT (SGOT)↑AST (SGPT)	Due to formation of toxic metabolites
2	Hyperuricemia	11	↑Uric acid level	Decrease uric acid excretion
3	Peripheral neuritis	11	Tingling, pricking pain, numbness.	Slow INH metabolism
4	Hypersensitivity	14	Nausea, vomiting, abdominal pain, dizziness, itching.	Unpredictable Type-B reactions.
5	Visual Toxicity	03	Visual disturbance	Optic neuritis
6	Cutaneous reactions	13	Skin rashes, itching, dermatitis.	Decreased platelet count
7	Flu-like syndrome	11	Fever, itching	Drug allergic reaction
8	Ototoxicity	05	Hearing loss, tinnitus, balance disturbance	Primarily due lesion in the vestibular sensory epithelium.
9	Fever	10	Rise of body temperature	Immunological reaction
10	Psychiatric changes	02	Hallucination, abnormal behavior	Due to deficiency of Vit - B6
	Total	102		

Hepatotoxicity developed in patients after 18 ± 7.773 days (95% CI 12–28 days) of treatment. Liver enzyme levels resumed normal activity in all patients when treatment was stopped. After laboratory results indicated the DOTS therapy was resumed, the order of re-challenge was conducted according the RNTCP guidelines. Isoniazid was the first of the drugs to be re-challenged, followed by rifampicin and pyrazinamide with daily monitoring of the patients' clinical conditions and liver functions. The median interval between the detection of hepatotoxicity and restart of the therapy was 15 ± 3.247 days (7–42 days, 95% CI 10–21 days).

3.6.2. Hyperuricemia

In the current study, a total of 11 patients reported raised blood uric acid levels (i.e. hyperuricemia). Clinically, patients were examined for hyperuricemia through the measurement of blood uric acid levels. In patients who reported polyarthralgia and/or joint pain, blood biochemistry revealed high serum uric acid levels. Clinical examination and biochemical parameters indicated a correlation between monitoring indices and hyperuricemia. Hyperuricemia due to ethambutol and isoniazid treatment was confirmed by discontinuation and re-challenge information. This may be because of reduced renal clearance of urate and acute gout triggered in patients with prior experience of gout or diminished renal function. There were no significance differences in the age ($p = 0.142$) or gender (OR 0.652; 95% CI 0.421–0.869; $p = 0.642$) of patients who did or did not develop hyperuricemia.

3.6.3. Peripheral neuritis

A total of 11 patients reported peripheral neuritis; in eight patients this was due to isoniazid and ethambutol. These drugs induce pharmacological changes in pyridoxine metabolism and consequently, the reduction in pyridoxine and pyridoxal phosphate inhibits the formation of the inhibitory neurotransmitter, gamma aminobutyric acid (GABA). Peripheral neuropathy was secondary to chronic exposure due to pyridoxine and pyridoxal phosphate deficiency.

3.6.4. Hypersensitivity

We report a total of 14 (1.38%) patients with hypersensitivity during DOTS therapy under RNTCP. Hypersensitivity was reported in patients treated with isoniazid, rifampicin and pyrazinamide and all anti-tuberculosis drugs were contraindicated in known cases of hypersensitivity. Hypersensitivity reactions may occur and are often characterized by an allergic reaction like pruritis, urticaria, angioedema, flu-like syndrome, shock, and shortness of breath after intermittent therapy. This has been attributed to antibody-mediated immune reactions or type-B reactions, which are dose-independent and can happen at any time during therapy. It has also been recommended that some adverse effects associated with isoniazid and rifampicin may be attributed to its metabolite monoacetyl hydrazine and desacetyl rifampicin, respectively. Various exanthemas, Stevens-Johnson syndrome, "toxic" epidermal necrolysis, purpura-like vasculitis, acute thrombopenic purpura, joint pain, drug fever, and leukopenia have been attributed to hypersensitivity. These reactions may arise during combined treatment with other tuberculostatics and it is therefore difficult to determine which drug is responsible for these side effects.

Visual toxicity: In the present study, only three (0.30%) patients reported visual toxicity and needed to adjust their drug regimen. Ethambutol may cause reduction in visual acuity, which appears to be caused by optic neuritis related to dose and duration of treatment. Optic neuropathy is virtually unknown or uncommon with doses of 15 mg/kg body weight and is rare at doses of up to 25 mg/kg. Reduction in visual acuity by ethambutol treatment was reversible when drug administration was discontinued. Many patients reported visual defects with ethambutol treatment had displayed subjective visual symptoms before or simultaneously with decreased visual keenness. Therefore, all patients receiving ethambutol as treatment should be questioned periodically about blurred vision and other subjective eye symptoms. If careful evaluation confirms the magnitude of visual change and fails to reveal another cause, ethambutol therapy should be discontinued, and the patient reevaluated at frequent intervals. Recovery of visual acuity generally occurs over a period of weeks or months after a drug is omitted from their treatment. The underlying cause of visual impairment appears to be from a metabolic disturbance due to depletion of copper and zinc, which serve as prosthetic group for many enzymes. The eye normally contains a considerable store of zinc, amounting to 0.5% of the weight of the eyeball. Much of the zinc is in the pigmented cells of the outer zone of the retina, where it serves as a metal prosthetic group for retinol (alcohol) dehydrogenase. Ethambutol may produce constriction of the visual field, central and peripheral scotoma, and green-red color blindness associated with retrobulbar neuritis. Visual evoked potential testing is considered to be the most reliable method for early detection of ocular abnormalities.

3.6.5. Cutaneous reaction

Cutaneous reactions were reported in 13 (1.29%) patients receiving DOTS therapy under RNTCP and required discontinuation of one of the affecting drugs. In the current study, cutaneous reactions were reported with isoniazid, rifampicin and pyrazinamide in three (0.30%), seven (0.69%) and three (0.30%) patients, respectively. Rifampicin has an inhibitory effect of rifampicin on cellular immunity that may interfere with cutaneous reactivity to intradermal tuberculosis. Eczematous patches, crusted plaques and flaccid bullae on the skin are flexible when rifampicin was discontinued.

3.6.6. Flu-like syndrome

Flu-like syndrome was reported in 11 (1.08%) patients treated with rifampicin. Flu-like symptoms, thrombocytopenia, hemolytic anemia, leukopenia, bleeding and eosinophilia were reported in these patients. Intermittent therapy with rifampicin is a common denominator for inducing renal failure (i.e. acute hemolysis and shock), as in acute interstitial nephritis that is usually preceded by fever and flu-like symptoms.

3.6.7. Ototoxicity

Ototoxicity was reported in five (0.49%) patients who needed to discontinue one of the drugs promoting this condition. Patients presenting ototoxic adverse effects after treatment with anti-tuberculosis therapy were evaluated for various clinical conditions for monitoring indices. Ototoxicity was the most important adverse reaction reported with streptomycin treatment, which included tinnitus, vertigo, balance disturbance, pain in the ear and dizziness. These conditions may be primarily due to lesions in the vestibular sensory epithelium, rather than the organ of Corti and changes in vestibular nerves and central vestibular nuclei are secondary to this effect, resulting from increased atrophy.

3.6.8. Fever

Fever was the most commonly reported adverse drug event due to anti-tuberculosis therapy but discontinuation of one of the affecting drugs was needed in only special cases. In the present study, isoniazid was discontinued in nine (0.89%) patients due to fever, whereas streptomycin was discontinued in only one (0.09%) patient due to an immunological reaction.

3.6.9. Psychiatric changes

We reported only two patients with psychiatric changes over the course of DOTS therapy. The precipitating mechanism of the psychiatric changes (i.e. seizures) is not exactly known but it may be related to the INH-induced deficiency of pyridoxine. INH induces pharmacological changes in pyridoxine metabolism because of increased renal excretion of pyridoxine through the formation of INH-pyridoxine hydrazones. The hydrazones competitively inhibit pyridoxine kinase, which triggers the change of pyridoxine to the physiologically active pyridoxal phosphate, as well as inactivation of pyridoxal containing enzymes. The subsequent reduction in pyridoxine and pyridoxal phosphate inhibits the formation of the neurotransmitter, gamma aminobutyric acid (GABA). Therefore, a possible mechanism of psychiatric changes like seizures in patients with INH toxicity may be the reduction in GABA levels.

3.7. Classification of ADRs using Naranjo's probability scale

Naranjo's probability scale are used to measure the probability of an adverse drug reaction and then to subjectively assess the likelihood that the observed reaction was a result of the prescribed regimen. A total of 351 patients reported adverse events that were classified as definite ADRs, probable ADRs, possible ADRs and doubtful ADRs according to Naranjo's probability scale. Out of 351 (34.72%) reported adverse events, 102 (10.09%) were definite, 59 (5.83%) probable, 123 (12.17%) possible and 67 (6.63%) doubtful.

3.8. Classification of ADEs and ADRs severity according to Hartwig scales

Severity of drug related adverse events was measured using Hartwig severity scales. A total of 351 adverse drug events were reported in the present study, of which 225 (22.26%) ADEs were mild, 105 (10.38%) were moderate and 21 (2.08%) were severe. Out of 102 reported adverse drug reactions, 81 (79.41%) ADRs were moderate and 21 (20.59%) were severe (Table 7).

4. Discussion

More men than women are suffer from tuberculosis worldwide. In our study, there were more male cases of tuberculosis than females and males had higher incidences of adverse events than female patients. Other studies in India ((Arora and Bedi, 1989; Gaur et al., 2004) and abroad (Alvarez et al., 1987; Umeki, 1989; Dutt and Stead, 1993; Korezeniewska-Kosela et al., 1994; Perez-Guzman et al., 1999) have also reported male predominance of tuberculosis, which was similar to the male prevalence observed in young adults and elderly patients in our study. One possible explanation for this male predominance may be that in most countries, young men usually have more social- and labor-based activities than women that favor the transmission of the disease. It matches with earlier reports that suggest responses to TB differ between men and women. Early detection and treatment of TB may also be more difficult for women than for men (Holmes et al., 1998). A study conducted by Sharma et al. (2007) reported the incidence of TB was higher among males as compared to females because males are more likely to also smoke and have alcohol and drug addictions compared to females, which increase their risk of contracting tuberculosis (Leung et al., 2004; Lonroth et al., 2008). Smoking accounted for a 32.8% higher risk of tuberculosis among males, but females have only an 8.6% greater risk of pulmonary tuberculosis compared to males (Leung et al., 2004).

We found that a highest number of male patients who also experienced adverse events belonged to the productive age group (i.e. 20–29 years), while the lowermost percentage of adverse events were reported in the youngest patients (i.e. <15 years). According to a study conducted by Sharma et al. (2010), tuberculosis is more prevalent in the productive age group population and the impact of the disease is felt by their children and families. In addition, progression from TB infection to disease may be faster in women of reproductive age than men of the same age (Murray, 1991). Nonetheless, there is an estimated 2:1 male: female ratio in the number of TB cases reported to public health authorities.

According to RNTCP guidelines, the cure rate of TB is expected to be >85%. We report a cure rate among new pulmonary positive patients of 89.41%, whereas the treatment completion rate among new pulmonary negative and extra-pulmonary cases were 92.44% and 96.56%, respectively. A previous study reported a cure rate of 91% in category I patients and 73.3% in category II patients (Chadha and Bhagi, 2000). Similar findings were also reported by several other published studies, suggesting that TB patients can improve their quality of life and reduce further infection with proper treatment regimens (Arora et al., 2003; Gaur et al., 2004; Filho et al., 2007; Pardeshi and Deshmukh, 2007).

Treatment failure rate among the new pulmonary positive and extra-pulmonary cases were 6.85% and 0.29%, respectively, and the overall failure rate was 2.92%. According to the RNTCP guidelines, the expected failure rate should be <4%, which is consistent with our findings. In the present study, the failure rate in new pulmonary positive patients was slightly higher than expected but the overall failure rates among the new pulmonary tuberculosis and

Table 7
Hartwig scale classification of ADEs and ADRs severity.

Severity	Adverse Drug Events (%)		Adverse Drug Reactions (%)	
	Number	Percent	Number	Percent
Mild	225	64.10	0	0.00
Moderate	105	29.91	81	79.41
Severe	21	05.99	21	20.59
Total	351	100	102	100

extra-pulmonary tuberculosis patients was significantly lower than the expected failure rate (Central TB Division, 2009).

In the retreated patients, the cure rate among relapse positive, failure positive and default positive patients were 73.81%, 42.86 and 63.10%, respectively; whereas, death rate among relapse positive, failure positive and default positive patients were 4.76%, 7.14% and 4.76%, respectively. Failure rates among relapse positive, failure positive and default positive patients were 9.52%, 42.46% and 10.71%, respectively. Default rates among relapse positive, failure positive and default positive patients were 11.91%, 7.14% and 20.24%, respectively. In the retreated other category II patients, the treatment completion rate, failure rate and default rate were 89.02%, 2.44% and 7.32%, respectively.

In the present study, we demonstrate that the ADR incidence was low with regimens that contained isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Out of 1011 tuberculosis patients enrolled under DOTS for treatment, only 102 (10.09%) patients reported adverse drug reactions during the DOTS therapy.

The Naranjo's probability scale is used for measuring the probability of an adverse drug reaction, to subjectively assess the likelihood that observed reactions were the result of the prescribed regimen. A total of 351 patients reported adverse events that were classified as definite, probable, possible and doubtful ADRs according to the Naranjo's probability scale. Out of 351 (34.72%) reported adverse events, 102 (10.09%) were definite, 59 (5.83%) probable, 123 (12.17%) possible and 67 (6.63%) doubtful. We reported a case of maculopapular rash in patients receiving standard DOTS therapy and the adverse reaction was categorized as a probable ADR (Khayyam et al., 2010).

The Hartwig preventability scale is generally used to measure the preventable and non-preventable nature of adverse events. In the present study, a total of 37 (36.27%) adverse events were non-preventable, while 65 (63.73%) were preventable in nature. We have reported a case of maculopapular rash in patients receiving standard DOT therapy and the adverse reaction was non-preventable (Khayyam et al., 2010).

Severity of drug-related adverse events were measured according to the Hartwig severity scale. A total of 351 adverse drug events were reported in the present study, of which 225 (22.26%) were mild, 105 (10.38%) moderate and 21 (2.08%) were severe ADEs. We have reported a case of maculopapular rash in patients receiving standard DOT therapy and the adverse reaction was categorized as moderate of level 3 (Khayyam et al., 2010).

5. Conclusion

The incidence of adverse drug reactions associated with DOTS therapy was very low but is still a serious problem in India because of the high TB burden in the country. Therefore, monitoring for possible adverse drug reactions, especially in patients at risk for TB, should be routinely conducted. Our findings show that all the components of the DOTS therapy were associated with a low prevalence of adverse events. This suggests that DOTS is effective and safe compared to daily treatment regimens, but an increased incidence of tuberculosis increases the number of patients at risk of these adverse events. Patients receiving DOTS therapy require close monitoring for these adverse events and therefore, a pharmacovigilance program should be added at the national level to assess changes in the incidences of these adverse events.

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Author contributions

FI, MS, and KUK conceptualized the analysis, analyzed the data and drafted the manuscript. MKR, MDA, AY, MSA and WQ assisted in the analysis and contributed to the interpretation of the results, as well as manuscript preparation.

Declaration of Competing Interest

Faisal Imam, Manju Sharma, Khalid Umer Khayyam, Mohd. Khan Rashid, Mohammad Daud Ali, Ayaz Ahmad and Md. Sarfaraz Alam report no conflicts of interest that are directly relevant to the content of this study.

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Ethical approval

Ethical approval was obtained from the L.R.S. Institute of Tuberculosis and Respiratory Diseases New Delhi, Human Research Ethics Committee with reference AMS/EC/2008/12038.

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