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# Medication Therapy Management Services and Pharmacovigilance Studies in Tuberculosis Patients: A Patient Care Aspect in the Pulmonology Department in a Tertiary Care Hospital

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## ABSTRACT

***Background:*** *Tuberculosis is fundamentally a disease of the lungs, however, it can influence any organ in the body.* ***Objectives:*** *Primary objective was to improve the patient compliance or medication adherence and to identify, detect, monitor ADRs induced by anti-tubercular drugs and report them. A secondary objective was to prevent the emergence of drug resistance and treatment of prolongation/failure in TB patients.* ***Methods:*** *A prospective, observational, cohort study was carried out for 6-months in tertiary care hospital. There were 60 patients included in the study. The data were evaluated for patients' demographic profile, type of TB, medication adherence and occurrence of ADRs. Adverse drug reactions were observed and recorded. The causality of ADRs was assessed using WHO-causality assessment scale and Naranjo causality assessment scale. The severity of ADRs was determined using Hartwig's severity assessment scale.* ***Results and Discussion:*** *Total of 60 patients were included in the study. Results showed that among 60 patients included in the study, 44 patients experienced ADRs. Among all age groups, the highest numbers of ADRs were seen in the age group 19-30 (43.1%) years. The occurrence of ADRs was noticed more in females (77.7%). The majority of ADRs occurred in patients was general (28.4%), and gastrointestinal effects (23.8%).* ***Conclusion and Scope of the Study:*** *Adherence to treatment is crucial for the cure of individual patients, controlling the spread of infection, minimizing the development of drug resistance and to reduce the chances of re-infection. Proper therapeutic monitoring of regimen, dose management, and pharmacovigilance activities are necessary. Such approaches will not only improve the treatment outcomes but also minimizes the chances of treatment prolongation/failure. All the health care professionals should interpret their responsibility in this domain of the health care profession.*

**Keywords:** Tuberculosis, Pharmacovigilance, Medication adherence, Adverse drug reactions, Morisky medication adherence scale, WHO causality assessment scale, Drug resistance

## INTRODUCTION

Tuberculosis (TB) is a standout amongst the oldest disease of humankind, with sub-atomic confirmation returning to more than 17,000 years. Despite more current modalities for finding and treatment of TB, tragically, individuals are as yet enduring, and overall it is among the top 10 executioner irresistible diseases, second just to HIV [1].

Tuberculosis is fundamentally a disease of the lungs however can influence any organ in the body. The term extra-pulmonary tuberculosis is indicated to depict the occurrence of TB at sites other than the lung. The most widely recognized sites of extra-pulmonary tuberculosis are lymph nodes, genitourinary tract, pleura, bones and joints, meninges and the focal sensory system, peritoneum and other stomach organs [2]. Total 6 nations represented 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan, and South Africa. Global advance relies upon significant processions in TB prevention and cares in these nations. Around the world, the rate of decrease in TB rate abides at just 1.5% from 2014-2015. This requirement to increase up to 4% to 5% yearly decline by 2020 to come to the first points of reference for the End TB Strategy [3]. For as far back as 5 years, it has been the main source of death from a single epidemic agent, positioning above HIV/AIDS. This is in spite of the way that, with a diagnosis at the right

time and accurate treatment, the vast majority who are affected with TB illness can be relieved. India is among the 14 countries that have a high prevalence of all 3 TB, MDR-TB and TB-HIV [4].

DOTS (directly observed treatment short course) is a standard anti-TB therapy recommended by RNTCP (Revised National Tuberculosis Control Programme) which was initiated in India in 1993. The DOTS therapy includes drug combinations of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), ethambutol (EMB), and/or streptomycin (SM) to be taken for a period of 6-9 months [5].

MTM has been defined by the pharmacy profession as "a distinct service or group of services that optimize therapeutic outcomes for individual patients that are independent of, but can occur in conjunction with, the provision of a drug product". The appropriate drug use, enhanced patient understanding of drug use, improve medication adherence, reduce risk of ADRs and reduce the cost of medications are the goals of MTM [6].

Pharmacovigilance is the set of methods, analysis, and disciplines that enable, during the commercialization phase or widespread use of a drug, to detect adverse reactions and pharmacological or therapeutic effects that were not anticipated in previous product control and evaluation phases [7]. Adverse drug reactions are thought to be the 6$^{th}$ predominant reason for death. The frequency rate evaluates roughly 2% of hospital admissions which are because of ADRs [8].

Tubercular medications utilized in clinical practice like other drugs are not free from ADRs. The additional issue is that the combination of medications is constantly utilized for long duration and therefore, it is likely that the ADRs of one medication might be potentiated by the partner drugs utilized. In addition, ADRs to the medications utilized is one of the significant reasons behind the patient default for treatment. General information of the different ADRs and their administration is basic for the effective management of TB [9]. The need for utilization of multi-drug regimens has been related with expanded frequency of ADRs of anti-tuberculosis drugs. These ADRs might be mild and also fatal [10].

All in all, a patient who has minor reaction should be urged to proceed with the treatment with symptomatic measures. On the off chance that major ADR occurs, the regimen or the culpable medication, if recognized, must be ceased. Advance administration relies upon the nature of the reaction and must be done in hospital [2].

## MATERIALS AND METHODS

### Study Protocol

At the beginning of this project, a study protocol was drafted following the approval from the Institutional Review Board (IRB).

### Study Site

The study site was Out-patient department (OPD), Respiratory Intensive Care Unit (RICU) and isolation wards of Pulmonology department of a tertiary care hospital.

### Duration of Study

The duration of the study was 6-months.

### Study Type

A cohort, observational and prospective study.

### Study Criteria

The target population was tuberculosis patients undergoing anti-tubercular treatment (ATT) with DOTS therapy, age greater than 7 years, both the gender, patients with positive smear test, patients with comorbidities such as HIV, cardiovascular diseases, renal and hepatic impaired patients etc, all types of TB (pulmonary and extrapulmonary TB, MDR TB), defaulted (patients who interrupted their treatment for 2 consecutive months or more) undergoing treatment at the time of study was included.

Patients who were lost to follow-up within 1-month, uncooperative or unwilling to be enrolled, pregnant women and infants were excluded.

Verbal/written informed consent was taken from the patients before their enrollment.

**Sample Size**

A total of 60 patients were enrolled in the study after applying inclusion and exclusion criteria.

**Methodology**

The patients were given the DOTS therapy which contains an intense phase of 4 drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide/streptomycin) followed by a continuation phase of 3 drugs regimen (rifampicin, isoniazid, and ethambutol) for the period of 6-9 months. Data was collected in specially designed performa which includes name, age, sex, lifestyle factors, diagnosis, treatment, and its duration. The adherence was calculated using the Morisky scale of adherence. On an average 2 visits of patients were considered to assess the medication adherence of patients after patient education and counseling session. The medication adherence of the patients was recorded on a scale of low, medium and high adherence.

Information on any past or current occurrence of adverse effects due to the ATT drugs being administered to the patients was detected, documented in suspected adverse drug reaction reporting form by IPC, monitored and reported. The management of ADRs was done according to the clinical status of the patient. The causality assessment of ADRs was done using 2 scales: WHO causality assessment scale and Naranjo causality assessment scale. For determining the severity of ADRs Hartwig's severity assessment scale was used.

**Statistical Analysis**

Data were statistically analyzed by Graph Pad Prism software version 6.0 and was summarized by Mean ± SD for continuous data and percentages for categorical data. The association or relation between the variables was done by Chi-square test/Fisher's exact test for categorical data. All the p-values less than 0.05 were considered as statistically significant. Frequency distribution tables were prepared from the collected data.

## RESULTS AND DISCUSSION

During the study period, 60 patients who were TB positive and was ongoing anti-tubercular therapy were monitored for the period of 6-months.

From the demographic data of the sample population, Table 1 describes, the age distribution of the data which indicates that the highest number of patients were in the age group 19-30 (38.3%) years followed by age group 7-18 (16.6%) years. The gender distribution of the sample population is more in females 45 (75%) and male patients were 15 (25%) of the total sample. The occupational status of the patients varies. Most of the patients were housewives 28 (46.67%), this may be due to the reason that number of females were included in the study followed by students 19 (31.67%) as the age group distribution was highest in young adults or teen-age group. In case of addictions, very few number of patients were seen to have addictions such as pan chewing in 2 (3.33%) following which betel nut chewer, smoker (cigarette/bidi), ethanolic are seen in 1 subject (1.67%) each, whereas no addictions were seen in 54 patients i.e 90% of the total cases. Major comorbidities observed were hypertension in 15 patients (25%) followed by diabetes mellitus in 6 patients (10%). No specific comorbidities were seen in 38 patients (63.33%). The diagnostic distribution, of patients, was according to the type of TB. In pulmonary TB cases, the highest used diagnostic test is chest X-ray in 23.3% of patients and AFB in 21.67% of patients as the lungs are involved. In extrapulmonary cases, the tests were performed based on the site of infection. CT-scan was done in 11.67% of patients followed by FNAC, Mantoux test and MRI in 6.67%. Ultrasound was carried out in 3.33% of patients. CBNAAT in 13.33% of patients is performed for both pulmonary and extrapulmonary cases. It is not always positive even if the patient has TB infection so other confirmatory tests were also performed. A number of cases were seen to have pulmonary TB i.e 34 (56.6%) cases when compared to extrapulmonary TB i.e 26 (43.3%) cases.

**Table 1 Patient's demographics, diagnosis, and type of TB infection**

| Characteristic | Type | Frequency (n) | Frequency (n)% |
|---|---|---|---|
| Age (Years) | 7-18 | 10 | 16.60% |
| | 19-30 | 23 | 38.30% |
| | 31-42 | 10 | 16.60% |
| | 43-54 | 7 | 11.60% |
| | 55-66 | 7 | 11.60% |
| | 67-78 | 1 | 1.60% |
| | 79-90 | 2 | 3.30% |

| | | | |
|---|---|---|---|
| Gender | Female | 45 | 75.00% |
| | Male | 15 | 25.00% |
| Occupation | Driver | 2 | 3.33% |
| | Employee | 2 | 3.33% |
| | Housewife | 28 | 46.67% |
| | Business | 2 | 3.33% |
| | Student | 19 | 31.67% |
| | Others | 7 | 11.67% |
| Addiction | Betel Nuts Chewer | 1 | 1.67% |
| | Bidi Smoker, Ethanolic | 1 | 1.67% |
| | Ex-Smoker | 1 | 1.67% |
| | Pan Chewer | 2 | 3.33% |
| | Smoker | 1 | 1.67% |
| | No Addiction | 54 | 90.00% |
| Co-morbidities | Diabetes Mellitus Type 2 | 6 | 10.00% |
| | HTN | 15 | 25.00% |
| | Hypothyroidism | 1 | 1.67% |
| | No co-morbidities | 38 | 63.33% |
| Diagnosis | AFB | 13 | 21.67% |
| | CBNAAT | 8 | 13.33% |
| | Chest X-ray | 14 | 23.33% |
| | CSF for AFB | 1 | 1.67% |
| | CT Scan | 7 | 11.67% |
| | FNAC | 4 | 6.67% |
| | Mantaux test | 4 | 6.67% |
| | MRI | 4 | 6.67% |
| | Pleural Pathology | 1 | 1.67% |
| | Ultrasound | 2 | 3.33% |
| | USG chest | 2 | 3.33% |
| Type of TB | Pulmonary | 34 | 56.60% |
| | Extrapulmonary | 26 | 43.30% |
| Total | - | **60** | **100.00%** |

The highest number to TB cases was seen in the age group 19-30 years i.e 24 cases, followed by the age group 7-18 years and 31-42 years i.e 10 cases each. The p-value is 0.828 which shows that there was a statistical difference between age and type of TB, shown in Table 2.

**Table 2 Association between age (in years) and type of TB**

| Age (Years) | Type of TB | | Total | p-value |
|---|---|---|---|---|
| | EPTB | PTB | | |
| 7-18 | 4 | 6 | 10 | 0.828 |
| 19-30 | 9 | 15 | 24 | |
| 31-42 | 5 | 5 | 10 | |
| 43-54 | 4 | 3 | 7 | |
| 55-66 | 1 | 6 | 7 | |
| 67-78 | 0 | 0 | 0 | |
| 79-90 | 1 | 1 | 2 | |
| Total | 26 | 34 | 60 | |

In the gender distribution more number of cases were females i.e 45 subjects and males subjects were 15. The p-value was 0.041 which indicates the statistical difference between the gender and TB cases, shown in Table 3.

**Table 3 Association between gender and type of TB**

| Gender | Type of TB | | Total | p-value |
|---|---|---|---|---|
| | EPTB | PTB | | |

| | | | | |
|---|---|---|---|---|
| Female | 23 | 22 | 45 | 0.041 |
| Male | 3 | 12 | 15 | |
| Total | 26 | 34 | 60 | |

The adherence was calculated using the Morisky scale of adherence. On an average 2 visits of patients were considered, first and the final visit. On visits 1 of all the patients, low adherence (10%), medium adherence (68%) and high adherence (21%) were recorded. On visit 2 after educating the patients regarding the importance of adherence to the TB therapy and counseling, the patient's adherence improved showing medium adherence (5%) and high adherence (95%) of patients and none was on low adherence. As the p-value is <0.0001 there was a statistically significant difference between the 2 visits considered shown in Table 4.

**Table 4 Medication adherence distribution**

| Adherence | Distribution | No. of subjects | Percentage |
|---|---|---|---|
| Visit 1 | Low | 6 | 10.00% |
| | Medium | 41 | 68.33% |
| | High | 13 | 21.67% |
| Visit 2 | Low | 0 | 0.00% |
| | Medium | 3 | 5.00% |
| | High | 57 | 95.00% |
| Total | - | 60 | 100.00% |
| p-value | - | - | <0.0001 |

The physiologic systems affected by ADRs are highest in general (28.4%) which includes loss of appetite, fever, generalized weakness, pain and swelling of limbs, lethargy, numbness of feet, weight loss, and restlessness and gastrointestinal system (23.8%) includes nausea, diarrhea, acidity, dyspepsia, stomach upset, burning sensation in stomach and vomiting followed by neurology (10.2%) which includes vertigo, headache, abnormal mental behaviour, sleeplessness, neurologic worsening of deficits, seizures and incontinence and dermatology (10.2%) which includes itching, acne and rash. The least affected systems are respiratory, cardiology and ophthalmology (1.1%) each, depicted in Table 5.

**Table 5 Distribution of ADRs in different systems**

| System | Type of ADR | No. of ADR | Total no. of ADR (n) | Frequency (%) |
|---|---|---|---|---|
| Gastrointestinal | Epigastric pain | 1 | 21 | 23.8% |
| | Nausea | 6 | | |
| | Diarrhea | 2 | | |
| | Acidity | 1 | | |
| | Dyspepsia | 2 | | |
| | Stomach upset | 1 | | |
| | Burning sensation in the stomach | 1 | | |
| | Vomiting | 7 | | |
| Neurologic | Vertigo | 3 | 9 | 10.2% |
| | Headache | 1 | | |
| | Abnormal mental behavior | 1 | | |
| | Sleeplessness | 1 | | |
| | Neurologic worsening of deficits | 1 | | |
| | Incontinence | 1 | | |
| | Seizure | 1 | | |
| Nephrology | Interstitial nephritis | 1 | 2 | 2.2% |
| | Nephritis (Rifampicin induced) | 1 | | |
| Liver | Increased LFT/Jaundice | 5 | 6 | 6.8% |
| | Acute Hepatitis | 1 | | |
| Bones and Joints | Polyarthralgia | 8 | 8 | 9.0% |
| Hematology | Anemia | 3 | 3 | 3.4% |
| Ophthalmology | Blurred vision | 1 | 1 | 1.1% |

| | | | | |
|---|---|---|---|---|
| Dermatology | Itching | 7 | 9 | 10.2% |
| | Acne | 1 | | |
| | Rash | 1 | | |
| Urology | Hyperuricemia | 1 | 2 | 2.2% |
| | Urine discoloration | 1 | | |
| Respiratory | Cough | 1 | 1 | 1.1% |
| Cardiology | Chest pain | 1 | 1 | 1.1% |
| General/Others | Malaise | 1 | 25 | 28.4% |
| | Loss of appetite | 8 | | |
| | Fever | 4 | | |
| | Generalized weakness | 3 | | |
| | Pain and swelling of limbs | 1 | | |
| | Lethargy | 2 | | |
| | Numbness of feet | 2 | | |
| | Weight loss | 2 | | |
| | Restlessness | 2 | | |
| Total | - | - | 88 | 100% |

The ADRs were seen more in the age group 19-30 years (43.1%) followed by 31-42 (17.0%) years depicted in Table 6. Among all the cases of TB females were more to have caused ADRs i.e 34 subjects (77.7%) and male subjects were 10 (22.7%), shown in Tables 6 and 7.

**Table 6 Association between age and ADRs**

| Age (in years) | Total | Percentage |
|---|---|---|
| 7-18 | 13 | 14.70% |
| 19-30 | 38 | 43.10% |
| 31-42 | 15 | 17.00% |
| 43-54 | 9 | 10.20% |
| 55-66 | 9 | 10.20% |
| 67-78 | 0 | 0.00% |
| 79-90 | 4 | 4.50% |
| Total | 88 | 100% |

**Table 7 Association between gender and ADRs**

| Gender | No. of subjects with ADRs | Percentage |
|---|---|---|
| Male | 10 | 22.70% |
| Female | 34 | 77.70% |
| Total | 44 | 100.00% |

The causality assessment of ADRs was done using WHO-UMC causality assessment scale and Naranjo causality assessment scale, shown in Table 8. According to the WHO scale highest is probable i.e 38 (43.1%) ADRs followed by possible i.e 35 (39.7%). And as per Naranjo scale, highest is probably 60 (68.1%) ADRs followed by possible 18 (20.4%).

**Table 8 Causality assessment**

| Gender | No. of subjects with ADRs | Percentage |
|---|---|---|
| Male | 10 | 22.70% |
| Female | 34 | 77.70% |
| Total | 44 | 100.00% |

The severity of ADRs was calculated using Hartwig's severity assessment scale and it was found to have a number of mild i.e 45 (51.1%) ADRs followed by moderate i.e 43 (48.8%) ADRs, shown in Table 9. No severe ADRs were recorded.

**Table 9 Severity of ADRs using Hartwig's severity assessment scale**

| Scale | Frequency (n) | Frequency (%) |
|---|---|---|
| Mild | 45 | 51.1% |
| Moderate | 43 | 48.8% |
| Severe | 0 | 0.0% |
| Total | 88 | 100.0% |

The management of ADRs was done by either adding on the medication according to the patients' clinical status in 51 (57.9%) patients like in case of loss of rash or itching; an anti-histaminic is given, and for vomiting antiemetic drug was given. Withhold treatment was done in 4 (4.5%) patients in case of increased LFT and Jaundice. Continued medication without a change in 29 (32.9%) patients and changed regimen in 4 (4.5%) patients, which is given in Table 10.

**Table 10 Management of ADRs**

| Action Taken | No. of ADRs | Percentage |
|---|---|---|
| Add on medication | 51 | 57.9% |
| Withhold treatment | 4 | 4.5% |
| Continue medication without change | 29 | 32.9% |
| Change regimen | 4 | 4.5% |
| Total | 88 | 100.0% |

Pharmacovigilance activities conducted and ADRs are reported by the pharmacy practice department. Total of 44 cases out of 60 subjects was detected and managed in TB cases in the pulmonology department. These cases were identified, assessed as per WHO-UMC scale and Naranjo causality assessment scale. The individual case safety reports (ICSRs) documented was sent to NCC. The status of these voluntary reports is being acknowledged for our participation in the pharmacovigilance program in NCC, Pv-Pi, IPC; Ghaziabad, India.

## CONCLUSION AND SCOPE OF THE STUDY

Adherence to treatment is crucial for the cure of individual patients, controlling the spread of infection, minimizing the development of drug resistance. It is the duty of clinical pharmacist and other health care professionals to educate patients regarding TB infection and medication adherence in an approach to reduce the TB burden. The required measures to be taken by all the health care professionals such as conducting patient counseling sessions, following up the patient's therapy throughout the recommended duration and proper therapeutic monitoring of regimen will be beneficial. In our study, the improvement was observed upon proper counseling and education regarding disease and its management to the patients. The improvement in medication adherence was encouraged and the positive results were seen in the therapeutic effects and cure of TB infection.

A significantly high incidence of ADRs has been reported (73.3%) which shows not only geriatrics but also that the adults were more inclined to have ADRs. As the regimen contains a number of drugs the chances of getting ADRs was also increased. Most common systems involved are general and GIT. The highest incidence of ADRs was seen in adult patients. ADRs will lead to discontinuation of drugs, development of drug resistance and treatment failure/ prolongation. Persistent activities of Pharmacovigilance are necessary for detecting, monitoring, managing and reporting of ADRs. Such approaches will not only improve the treatment outcomes but also minimizes the chances of treatment prolongation/failure.

It is one of the major inadequacies of spontaneous reporting program that health care fails to identify and report ADRs. Clinical pharmacists play a major role in promoting Pharmacovigilance activities among other health care professionals by educating them regarding detection and ADR reporting procedure by conducting seminars or workshops and integrating a Pharmacovigilance system as public health care. All health care professionals should interpret their responsibilities in this domain of the health care profession.

## DECLARATIONS

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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