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ADVERSE DRUG REACTIONS WITH FIXED-DOSE COMBINATIONS IN TUBERCULOSIS PATIENTS

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Abstract-
Background: Government of India's National Tuberculosis Elimination Program (NTEP) has started implementing daily fixed dose combination (FDC), anti-TB treatment regimen for drug sensitive TB patients. This study was designed to assess the frequency, types and impact of adverse drug reactions (ADR) to category 1 anti-tubercular therapy using fixed drug combinations (FDC).
Methodology: This was a hospital-based observational study in the population of rural Haryana for one year from 30th September 2020 to 30th September 2021 in the SGT Medical College in the Department of Pulmonary Medicine.
Result: We encountered 384 patients who were started on ATT for the treatment of tuberculosis. Among them, 26.04% suffered from mild to life-threatening adverse drug reactions (ADR) due to the DOTS regimen. 74% of the ADR was seen in patients with pulmonary TB and the rest with extrapulmonary tuberculosis. Among the total population treated, 18.49% suffered from ADR of varying severity while being treated for pulmonary TB. Similarly, 7.55% developed ADR while being treated for extrapulmonary TB. The most common ADR encountered was hepatitis in 39% of the affected group.
Conclusion: Adverse reactions were commoner among the elderly, and were associated with prolongation and modification of anti-tuberculosis therapy but overall treatment outcomes were not adversely affected.

Key words: Tuberculosis, Fixed Drug Combinations, Adverse Reactions

INTRODUCTION-

Tuberculosis is a preventable disease and yet a burden to society. Tuberculosis is one of the deadliest communicable diseases according to the Global Tuberculosis Report 2019 of the World Health Organization (WHO) that is caused by the bacterium Mycobacterium Tuberculosis (MTB). It is still the second most frequent cause of death worldwide with 10 million new cases every year and accounting for approximately 1.5 million deaths annually.(1)

The focus from tuberculosis deviated when the world was dealing with the coronavirus Disease Pandemic (Covid 19). During this period, the disease burden, prevalence, and mortality rate due to

tuberculosis increased worldwide. A significant increase in the number of drug-resistant cases was observed from 2012 onwards, and it required equal attention as COVID-19.[2] Therefore, for the year 2022, the WHO theme for tuberculosis is "*Invest to End TB. Save Lives*". [3]

Directly observed treatment, short-course (DOTS) was introduced in India in 1993 as part of the Revised National Tuberculosis Control Programme (RNTCP).[4] The key component of DOTS therapy is the standard anti- TB short-course chemotherapy regimen, which requires continuous administration drug combinations of isoniazid (INH), rifampicin (R), pyrazinamide (PA), ethambutol (EMB), and streptomycin (SM) every other day for 6-9 months.[5] Once diagnosed, patients must undergo treatment with this regimen for an optimal outcome.

Despite positive therapeutic effects, 5% of patients on the DOTS regimen developed adverse drug reactions, which is the reason for non-adherence and treatment interruption. These undesirable reactions are hepatotoxicity, gastrointestinal disorder, allergic reaction, arthralgia, neurological disorders, hyperuricemia, and so on. [6,7]

Fixed-dose combinations (FDCs) of drugs for TB treatment have been advocated to prevent the emergence of disease resistance attributable to inappropriate drug intake.[8,9] Since FDC is used widely, these adverse effects hamper compliance and patients tend to skip treatment which is one of the reasons for treatment failure.

With this study, we wanted to have a better understanding of the adverse reactions to understand them timely and studied their impact on the treatment outcomes. The objectives of our study were to access the frequency of development of the ADRs associated with FDC of antitubercular therapy along with their frequency, severity, and management outcomes.

METHODOLOGY-

This was a hospital-based observational study in the population of rural Haryana for one year from 30th September 2020 to 30th September 2021 in the SGT Medical College in the Department of Pulmonary Medicine. Written informed consent was obtained from all participants in this study. All the patients who were confirmed with the diagnosis of tuberculosis (either microbiologically or on clinico-radiological basis) were started on a DOTS regimen with the plan of finishing the treatment in the next six months. A total of 100 patients who developed ADR due to FDC treatment of tuberculosis were included in the study.

Inclusion Criteria

1. Patients < 18 years of age following strict compliance with the ATT for pulmonary and extra pulmonary tuberculosis.
2. Newly diagnosed, Lost to follow up and recurrent tuberculosis cases.
3. All microbiologically confirmed and clinically diagnosed patients.

Exclusion Criteria

1. Patients on long term steroids or antihistaminics, with active skin disease prior to the initiation of treatment.
2. Patients with non-compliance.
3. Patients with abnormal baseline liver function tests, or alkaline aminotransferase or aspartate aminotransferase.

All the patients initiated on DOTS regimen were informed regarding the side effects of drugs before the start of the treatment and were asked to follow up in pulmonary OPD as soon as they developed

them. Participants were screened for chronic disorders like diabetes, hypertension and underwent routine investigations before the start of the treatment like complete blood count, fasting blood sugar level, liver, and kidney function tests. Patients were followed up at the intervals of 1 week, 1 month, 6 months, or at any time patient experienced any symptoms that were suggestive of the development of ADR. The occurrence of ADR included any local or systemic reaction which was unfavorable and unintended. The ADR events and their frequency, severity, and impact on treatment outcomes were documented in this study.

These symptoms were categorized as minor and major reactions. The minor reactions included abdominal pain, itching of the skin, burning sensation of feet, joint pain with swelling, and flu-like symptoms. Whereas the major reactions like persistent nausea, vomiting, yellow discoloration of eyes and urine, skin rashes, deafness, dizziness, confusion, visual impairment, and features of shock.[10]

Each event was categorized on the basis of severity and intensity as mild, moderate, severe, or life-threatening. The mild events required minimal or no treatment and did not interfere with the routine activity of an individual. The moderate events caused low level inconvenience or concern with the therapeutic measurements or functioning of an individual. The severe events interrupted a patients' routine activity and may require an intervention for the correction including systemic therapy or other treatments. Severe events were usually incapacitating. Life threatening adverse drug reactions that placed an individual, in the view of an investigator, at immediate risk of death from the occurred reaction. These events were documented along with their onset, duration and intervention done for its correction.

Grade & Level	**TOXICITY**
1- Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required.
2- Moderate	Mild to moderate limitation in activity, some assistance may be needed; none or minimal medical intervention or therapy required.
3- Severe	Marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization is possible.
4- Life Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care is probable.

DISCUSSION-

In our daily clinical practice, we come across various patients who develop ADR due to FDC regimen for tuberculosis treatment. Anti-tubercular drugs are notoriously known for their variety of ADR which leads to treatment interruption and nonadherence. Various studies have been conducted and as per WHO reports, 23% of such individuals end up discontinuing the treatment. It is due to loss of compliance leading to increased morbidity and mortality along with spread of the disease. It is important to find out various ADR due to DOTS regimen and treat the same. Our study emphasized on the same and the conclusions are stated below.

The present study was performed in the population of rural Haryana for over one year. During this period, we encountered 384 patients who were started on ATT for the treatment of tuberculosis. Among them, 26.04% suffered from mild to life-threatening adverse drug reactions (ADR) due to the DOTS regimen. 74% of the ADR was seen in patients with pulmonary TB and the rest with extrapulmonary tuberculosis. Among the total population treated, 18.49% suffered from ADR of varying severity while being treated for pulmonary TB. Similarly, 7.55% developed ADR while being treated for extrapulmonary TB.

The most common ADR encountered was hepatitis in 39% of the affected group. This was a significant percentage and these patients took a longer time for the liver enzymes to reach back to the normal range. They required frequent follow up and delayed the treatment time for tuberculosis.

Next most common ADR was gastrointestinal symptoms namely loss of appetite, nausea, vomiting, diarrhea and mild to moderate abdominal pain in 30% of our study group. These were more commonly seen with rifampicin among all the drugs and were corrected with diet modification and antacids like protease inhibitors. It was one of the most common reasons of poor compliance. But due to easy correctability, with proper counselling, it had the best treatment outcome with less delay in the treatment course.

6% of the individuals displayed a cocktail of symptoms with hepatitis with gastritis.

The incidence of skin rash was found to be 22%. These patients were treated with antihistaminics and showed improvement in the majority of them. The treatment was modified for only a few cases that did not show improvement even after systemic agents.

Hyperuricemia (2%) and isoniazid toxicity (1%) were the rare ADRs noticed in our study. Patients with hyperuricemia required treatment modification with longer duration of therapy.

C. Chuchottaworn and B. Saipan in 2012 stated that the most common ADR was gastrointestinal disturbance of nausea, anorexia and vomiting after treatment with anti-tuberculosis drugs.

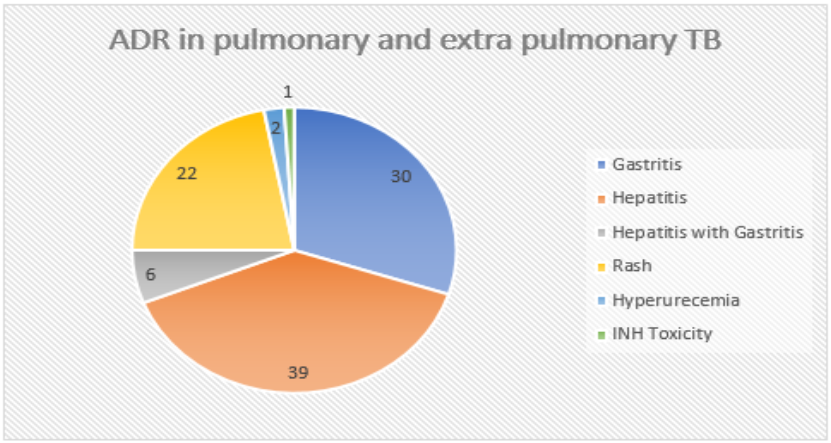
Siribaddana et al. in 2015 conducted a study in which 67 patients developed ADR out of which 12 patients developed major drug reaction and 55 patients have minor drug reaction. Most of the patients presented with hepatitis followed by itching with skin eruption.

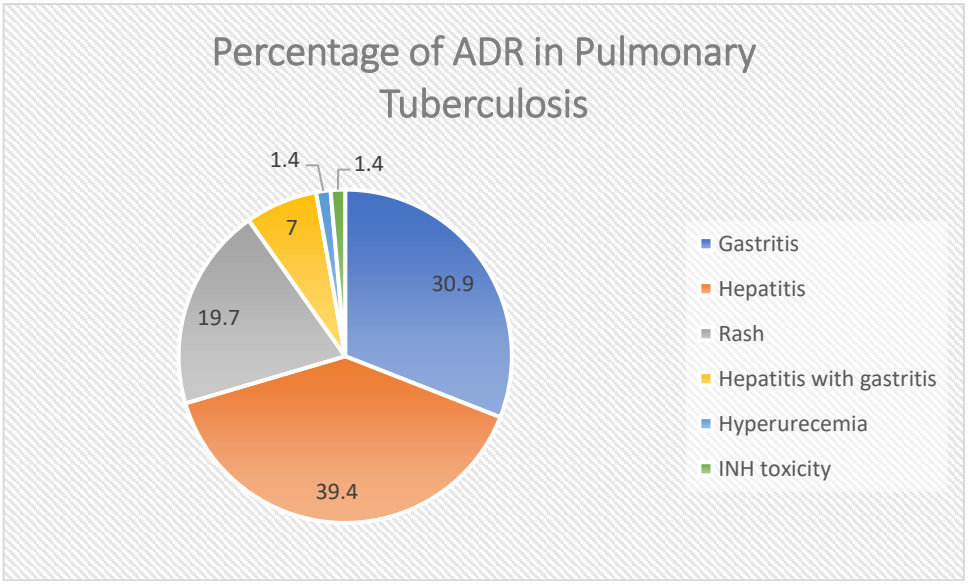
Silva VD, Mello FCQ, Figueiredo SCA in 2017 found that there is increased occurrence of cutaneous adverse effects (acne/itching) and arthralgia in patients treating with HRZE combination.

Sharma RK et al. in 2020 stated that Pulmonary TB was the most common type of TB observed in 24 (60%) patients followed by extra-pulmonary in 16 (40%) patients. Maculopapular rash was the most common (42.5%) type of cutaneous eruption.

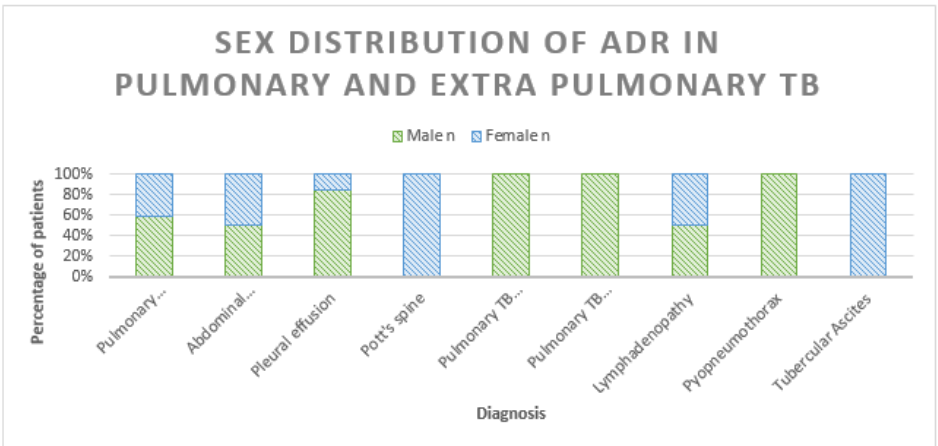
Hari Sankar KN et al. in 2021 conducted a study in which 98 patients developed ADRs, 77 (78.6%) were serious and were moderate-level 4b in severity (Hartwig and Siegel Scale), 57 (58.16%) were probably preventable (Schumock Thornton scale). Hepatitis was the most common ADR encountered followed by decrease in vision.

During the entire event there was one mortality in the patient with isoniazid toxicity. The patient was 67 years old and required intense ICU care. Treatment with DOTS was withheld and treatment modification was planned after recovery. But during the hospital stay, patient went into acute renal failure and after 12 days of ICU admission there was mortality of the patient.



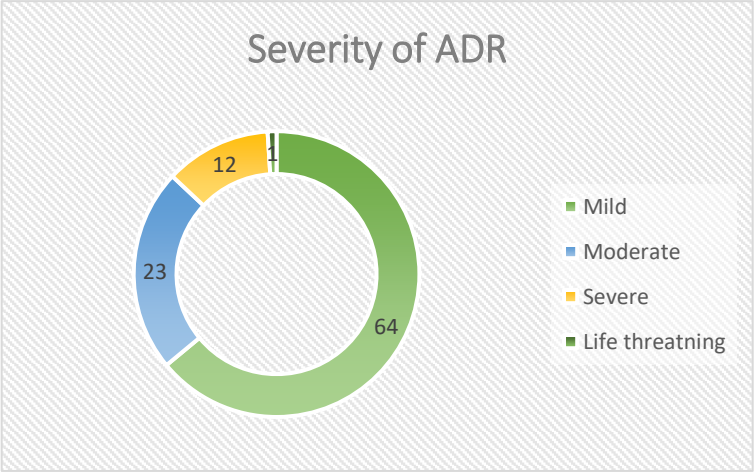


Sociodemographic distribution of the study- In the sample population, 64% of males and 56% of females developed ADR for which intervention was done and the data was compiled. The mean age of the sample population that developed ADR with the DOTS regimen was 46.97 years. There was not much difference between the same among men and women as the mean age for women was calculated to be 45.95 years, whereas the same for men was calculated as 45.40 years. Among the population who developed ADR, 71% of them were being treated for pulmonary TB (42 males and 29 females) and the rest were extrapulmonary TB. Among the extrapulmonary TB patients who suffered from ADR, the following data was compiled. The following table explains the distribution of data with a gender distribution of ADR due to DOTS in pulmonary and extrapulmonary TB.



During our study, we encountered various ADRs due to the DOTS regimen with varying degrees of severity starting from gastritis managed on a daycare basis to life-threatening conditions like isoniazid toxicity. Among the sample population, hepatitis was the most common ADR encountered with an incidence of 39% followed by gastritis among 30% of the population. Hepatitis along with gastritis was recorded in combination with 6% of individuals and out of which 40% required modification of ATT. Rash was another encountered entity more common among middle-aged women comprising 22% of our sample size. Rarely hyperuricemia (2%) and isoniazid toxicity (1%) were addressed which made us worrisome as the treating physicians. Hyperuricemia was one of the reasons we had to modify the ATT, and once developed took 3-4 weeks to revert to normal values. Isoniazid toxicity was encountered in one of our patients, which lead to neurological changes and ultimately was labeled as life-threatening. The patient developed anuria for 2 days and the cause of death was found to be chronic renal disorder.
Of the severity of ADR among the sample population, 64% of them had mild symptoms and required minimal or no interference. They were only admitted on a daycare basis for observation and were discharged after monitoring. 23% had an inconvenience and they were classified as moderate ADR. Most of them suffered from rash and hepatitis and therefore needed modification of ATT.

12% of people after taking ATT for 4-5 days developed persistent nausea, and lethargy leading to hampered day-to-day activities. These patients required systemic intervention after admission. The majority of patients required change or modification of ATT and the symptoms were resolved with intervention. Out of which 1% had a life-threatening complication due to chronic renal disease. Most of the patients had a fair outcome with either continuation or modification of ATT. The ADR was resolved for almost all of them (except for one mortality).



CONCLUSION

The present study showed that various adverse drug reactions due to the DOTS regimen were associated with prolongation of treatment. In such cases with proper counselling and timely intervention, led us to good compliance of the affected patients. Adverse effects were more common among older patients with above 50 years of age and did not show any gender discrepancy. Proper follow up, timely intervention and counselling will help us reduce ADR events especially mild variety. The above complied data was found comparable to the data researched globally.

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