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RESEARCH ARTICLE
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A CROSS-SECTIONAL OBSERVATIONAL STUDY ON ADVERSE DRUG REACTIONS OF ANTITUBERCULAR DRUGS AT TERTIARY CARE CENTER.

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Abstract

The National Tuberculosis Elimination Programme (NTEP) in India implemented the daily weight-based Fixed Dose Combination (FDC) Anti-tuberculosis Treatment (ATT) regime to enhance compliance, and ultimately lead to better treatment outcomes. Adverse drug reactions (ADRs) are a significant element that can affect an ATT regime's treatment compliance and results. As a result, vigilant monitoring for adverse reactions in patients receiving anti-tubercular therapy (ATT) is necessary

Objectives: i) To assess the pattern and frequency of adverse drug reactions with a fixed-dose combination of anti-tubercular drugs ii) To determine the causality, severity, and factors that predispose to the development of adverse drug reactions.

Methodology: A 6-month cross-sectional observational study was undertaken at the tertiary care hospital Chandramma Dayananda Sagar Institute of Medical Education and Research (CDSIMER). 120 patients with tuberculosis were included in the study after obtaining informed consent. Data was collected and analysed on demographics, treatment regimes, and any adverse drug reactions (ADRs) experienced. The statistical analysis test chi-square aimed to identify significant factors linked to adverse drug reactions. Additionally, the WHO causality assessment scale and the modified Hartwig and Siegel scale were used to analyse the causality and severity of any reported ADRs.

Results- 43 out of 120 patients had an adverse reaction. Gastrointestinal adverse effects were most common followed by dermatological issues. According to the WHO causality scale, the majority of ADRs were probable and mild on the modified Hartwig-Siegel scale. The study found that urban, female, and employed individuals had higher rates of ADRs.

Conclusion- ATT-induced ADRs are frequent. As a result, monitoring and counselling patients about their lifestyle, as well as early diagnosis and care, will reduce the incidence of ADRs and enhance treatment adherence.

Keywords- Anti-tubercular therapy, Fixed dose combination, Adverse Drug Reaction.

Introduction-

Tuberculosis (TB) is one of the oldest diseases known to mankind and is a major cause of death worldwide. About 1/3 of the world`s population is estimated to be infected with tubercle bacilli and hence at risk of developing active disease. The Revised National TB Control Program was transformed into the National TB Elimination Program (NTEP) at the start of 2020 and added certain protocols to eliminate tuberculosis in India by 2025. TB is a major contributor to the global burden of disease, particularly in low- and middle-income countries, due to its association with the human immunodeficiency virus. [1]India is one among six- high burden nations from Southeast Asia with a high prevalence of tuberculosis (TB), accounting for almost 28% of all cases globally.[2]

Tuberculosis disease can now be treated with adequate and ongoing therapy, thanks to advances in the improvisation of dosage regimens. Treating tuberculosis (TB) requires a combination of medications taken for an extended period, often leading to ADRs. The occurrence and severity of these reactions can vary depending on several factors, including demographic characteristics, genetic makeup, nutritional status, and existing health conditions. However, if the patient takes the medicines irregularly due to ADRs of anti-tubercular treatment it leads to poor patient compliance, resistance, and may lead to poor treatment outcome such as multi-drug-resistant (MDR) tuberculosis and extensively drug-resistant tuberculosis (XDR TB). [3, 4, 5]

As a result, identifying adverse drug reactions and taking care to minimize them is critical in increasing patient compliance and decreasing the rate of drug-resistant types of tuberculosis. [6, 7] Lack of adherence to anti-tuberculosis therapy is a major factor in the re-emergence of tuberculosis, and adverse drug reactions are the major reason for poor adherence. [8, 9]

Implementing appropriate measures to minimize harm and manage ADR symptoms is crucial. In this context, Pharmacovigilance the active monitoring of medication safety becomes a critical component of global and national policies aimed at ensuring the safety of anti-tuberculosis treatment. There are very few studies and reports regarding revised regimens using fixed dose combinations (FDC). Hence, the present study was taken up.

Methods

Study Design and Population

A cross-sectional observational study was conducted between September 2022- February2023 in pulmonology department of Dr Chandramma Dayananda Sagar Institute of Medical Education And Research. The study was initiated after obtaining Institutional Ethics Committee (CDSIMER/MR/0013/IEC/2022).

Inclusion Criteria

Included in the study were: i) All patients with tuberculosis on treatment with a fixed-dose combination after 15 days of treatment. ii) Patients of either sex or all age groups diagnosed with TB.

Exclusion Criteria

Patients excluded from the study were: i) multi-drug-resistant (MDR) tuberculosis; and ii) Extensively drug-resistant tuberculosis (XDR TB) patients.

After screening patients based on inclusion and exclusion criteria, written informed consent was obtained from patients. The patient's demographic information, adverse drug reaction, history of alcohol, smoking, or tobacco use, concomitant disease, and drug history were recorded in the case report form. Every patient was asked whether they had any unexpected symptoms. Further they were enquired for the following ADRs nausea, vomiting, epigastric pain, pruritis, rashes, joint pain, dizziness, numbness, visual disturbances and others if any.
If any ADR was detected it was reported to our Pharmacovigilance unit and NTEP. If they reported any of the above symptoms, detailed information about the ADRs was collected, and a correlation between the drug intake and the onset of ADRs was noted.

Analysis of ADRs
System-wise distribution of ADRs was tabulated. WHO-Uppsala Monitoring Centre (UMC) criteria were used to assess the causality of all ADRs as certain, probable or posible.[10] The modified Hartwig and Siegel scales were used to determine severity of the reaction to categorise ADR as mild, moderate and severe.[11]

Statistical Analysis
Demographic data and categorical variables obtained were analysed using latest SPSS 27 software. The categorical variables were represented using frequencies and percentages. The Chi square test used to understand the association of risk factors like demographic factor, alcohol, smoking, comorbid conditions with the adverse drug reactions.

Results
Table 1 shows out of the 120 participants in this study, the majority of participants (57.5%) of the study participants were < 50 years old. The study comprised mostly of males (65.83%) with females accounting for 34.17%. Majority were employed (77.5) and from rural area (64.2). Diabetes mellitus (12.5%) was the most prevalent comorbidity, followed by hypertension (8.3%) and systemic lupus erythematosus (0.83%).

Table -1 Demographic and clinical characteristics of study population

Characteristics		**Frequency (%)**
Age(years)	**<50**	**69(57.5)**
	51-65	**35(29.2)**
	>65	**16(13.3)**
Gender	**Male**	**79(65.83)**
	Female	**41(34.17)**
Occupation	**Employed**	**93(77.5)**
	Unemployed	**27(22.5)**
Location	**Rural**	**77(64.2)**
	Urban	**43(35.9)**
Smoking	**yes**	**40(33.3)**
	No	**80(66.7)**
Alcohol use	**yes**	**40(33.3)**
	No	**80(66.7)**
Comorbidity	**yes**	**26(21.7)**
	No	**94(78.3)**

The proportion of patients who experienced ADRs based on demographic, clinical characteristics. Female, employment level, urban area and alcoholic were shown to have a significant relationship with the development of ADRs (P<0.005) as in **Table 2**.

Table 2 Risk factors for ADRs from Antitubercular FDC medication.

Demography	**Patients With ADR(N=43) Frequency (%)**	**Patients Without ADR(N =77) Frequency (%)**	**P-value**
Age (years)			**0.175** [C]
<50	29(67.44)	40(51.94)	
51-65	11(25.58)	24(31.16)	
>65	3(6.97)	13(16.88)	
Sex			
Male	21(48.83)	58(75.32)	****0.0033** [C]
Female	22(51.16)	19(24.67)	
Employment Status			
Employed	38(88.37)	48(62.33)	****0.000793** [C]
Unemployed	5(11.63)	22(28.57)	
Location			
Rural	15(34.88)	62(80.5)	****0.00001**[C]
Urban	**28(65.1)**	**15(34.88)**	
Smoking			
yes	**12(27.90)**	**28(36.36)**	**0.3460**[C]
No	**31(72.09)**	**49(63.63)**	
Alcohol use			
yes	**11(**25.58)	**29(37.66)**	****0.178252**[C]
No	**32(74.41)**	**48(62.33)**	
Comorbidity			
yes	**11(25.58)**	**15(19.48)**	0.9124[C]
No	**32(74.41)**	**62(80.51)**	

[c] Chi-squared test- **p-value<0.05 is significant

Analysing by System wise distribution, gastrointestinal disorders were the most frequent ADR category, affecting 21 patients (17.5%). Skin and subcutaneous disorders were the second most common, affecting 16 patients (19.76%). Nervous system disorders were reported by 6 patients (6.97%). Less frequent side effects included joint pain 2(1.66%) and visual disturbance in 1(0.8%) as shown in **Table 3.**

Table 3: System wise distribution of adverse drug reactions reported

Adverse Drug Reactions	**No of cases (n=43)**	**Percentage (%)**
1. Gastrointestinal system (Epigastric pain, nausea and vomiting)	**21**	**17.5**
2. Dermatological system (Pruritis and rashes)	**16**	**13.33**
3. Nervous system (Peripheral neuritis, and dizziness)	**3**	**2.5**
4. Joint pain	**2**	**1.66**
5. Visual disturbance (optic neuritis)	**1**	**0.83**
Total	**43**	**35.83**

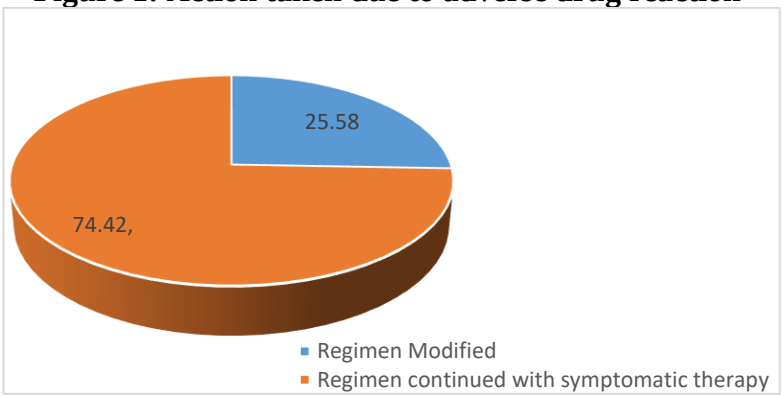
The number of ADRs were more during intensive phase when compared to continuous phase as shown in **Table 4.**

Table 4: Adverse drug reactions and phase of treatment

Adverse Drug Reactions	**Intensive Phase N(%)**	**Maintainenance Phase N(%)**
1. Gastrointestinal system (Epigastric pain, nausea and vomiting)	**18**	**3**
2. Dermatological system (Pruritis and rashes)	**16**	**0**
3. Nervous system (Peripheral neuritis, and dizziness)	**1**	**2**
4. Joint pain	**1**	**1**
5. Visual disturbance (optic neuritis)	**0**	**1**

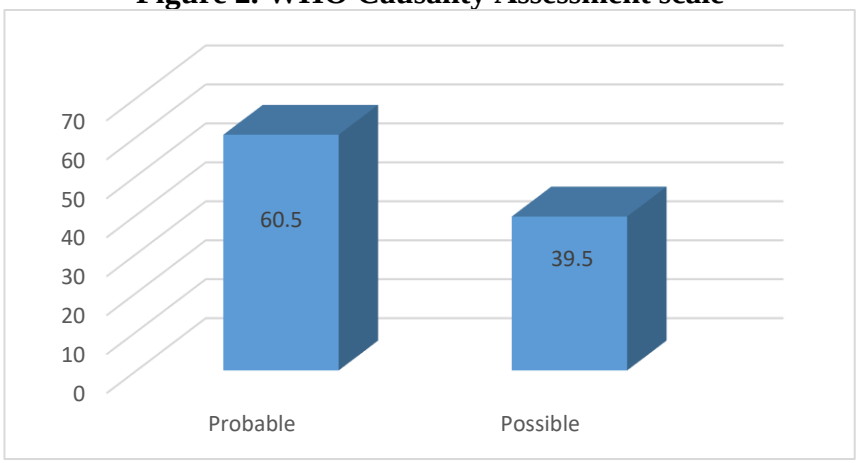
The treatment plan was modified due to ADRs in about 25.58% of cases, while the remaining 74.42% continued with symptomatic therapy shown in **Figure 1.**

Figure 1: Action taken due to adverse drug reaction



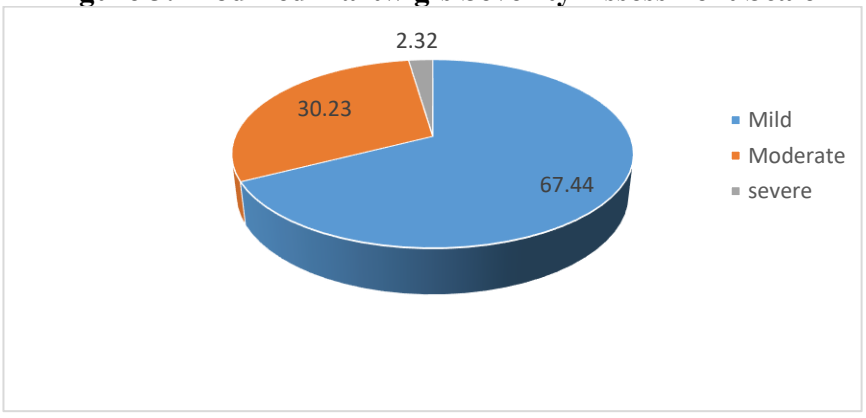
Causality assessment was done using WHO scale. The percentage of the probable and possible adverse effects was 60.5 and 39.5 respectively **(Figure 2).**

Figure 2. WHO Causality Assessment scale



The severity of adverse drug reactions was assessed using the Modified Hartwig and Siegel Scale. Out of the 120 patients evaluated, 67.44% were categorized as mild, requiring no changes in medication. Additionally, 30.23% fell into the moderate category, and only 2.32% needed intensive medical care, belonging to the severe class as in **figure 3.**

Figure 3: Modified Hartwig's Severity Assessment Scale



Discussion

There are many publications on ADRs to anti-tubercular medication. However very few have reported ADRs to FDCs. There is need to be explained in detail as all of medications are consumed at a given time and hence ADRs. The bioavailability of each drugs is unknown in the formulation. The current regimen also is based on body weight range and not individualized per kg body weight. Therefore there is likelihood of over dosage.

Our study aimed to identify and analyse the ADRs associated with the daily use of combination medications (FDC) in the NTEP's treatment plan. The percentage of ADRs among patients with pulmonary tuberculosis at our hospital throughout the research period was found to be 35.83% (Table 2). This is comparable to earlier studies that found a similar rate of 36.17%. [12]

Our study revealed that among various patient demographic characteristics only females, employed individuals, those residing in urban areas, and alcoholic patients exhibited a statistically significant association with an increased risk of developing ADRs. Females were more susceptible to ADRs with a rate of 51.16%, which aligns with study by Cheah et al.[13] This increased risk in females could be attributed to hormonal fluctuations, particularly during pregnancy and menstruation. Additionally, potential interactions between anti-tuberculosis medications and birth control pills might further contribute to a higher incidence of ADRs in this group.[14, 15] These results point to the necessity of extra safety measures, medication counselling, and closer observation in cases where anti-TB drugs are prescribed to female patients. Individuals living in urban areas and those who are employed report more ADRs compared to their rural or unemployed counterparts. This could be due to greater access to healthcare information and resources. This increased access might lead them to be more aware of potential side effects and therefore report them more frequently. However, other studies haven't shown the same significant difference. [5] Our findings align with those of Kurniawati et al., who observed a higher prevalence of ADRs in individuals with a history of alcohol consumption compared to those without.[16] Alcohol can interact with anti-TB medications and increase the risk of ADRs.

The Gastrointestinal (GI) symptom were the most common ADRs, with nausea, epigastric pain, and vomiting. This finding aligns with a prior study by Kiran et al. (26.7%) highlighting the known GI intolerance associated with first-line ATT drugs.[6] Dermatological adverse effects, including purities (itching) and rashes, emerged as the second most common category of reported ADRs, accounting for 37.2% of all cases. [6] Among these, maculopapular rash was the most frequently observed.[16]

This study identified a higher prevalence of ADRs during the intensive treatment phase, similar to previous research where a peak was observed within the first two months of anti-TB therapy.[17] This knowledge emphasizes the importance of early detection and intervention for ADRs. Consequently, healthcare professionals should actively counsel patients about the potential for ADRs during the intensive phase, specifically focusing on the mentioned signs and symptoms (nausea, vomiting, rashes, etc.). Furthermore, implementing routine monitoring practices during this critical phase is crucial for the timely identification and management of ADRs.

Our study found that the majority (60.5%) of reported ADRs fell under the "probable" category according to the World Health Organization (WHO) causality scale.[6]

ADRs may cause patients to stop the drug, hospitalization, or occasionally even death. A modified Hartwig-Siegel scale was employed to evaluate the severity of the reaction that had occurred. 67.4% of ADRs were minor, and only one patient needed critical care, which was similar to the Maqusood M et al. study. [18]

A limitation of this study is the relatively small sample size. While our findings suggest potential associations between certain factors and adverse drug reactions, the generalizability of these results to the broader population may be limited.

Conclusion

While ATT-related ADRs are frequent, their potential to lead to treatment interruption and drug resistance necessitates proactive measures. Early detection and management of these reactions, coupled with patient counselling on lifestyle adjustments and potential ADRs, can significantly improve adherence and treatment success. This multi-pronged approach holds the key to minimizing the impact of ADRs and ensuring optimal outcomes for patients undergoing TB treatment

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