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POTENTIAL DRUG-DRUG INTERACTIONS BETWEEN ANTI–TUBERCULAR AND NON-TUBERCULAR DRUGS AMONG PATIENTS WITH PULMONARY TUBERCULOSIS IN PUDUCHERRY AND TAMIL NADU

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ABSTRACT

Tuberculosis (TB) demands a long-term multi-drug treatment. Co-infection in TB patients and concomitant noninfectious disease, particularly with an aging population, undoubtedly necessitates the use of additional drugs. This multi-drug management in a TB population increases the potential for drug interactions. The study focus is to perform a comprehensive analysis of the prevalence of and factors associated with potential interactions of first-line Anti Tubercular Therapy (ATT) drugs and concomitant medications among patients with pulmonary tuberculosis. Newly diagnosed pulmonary TB patients undergoing the standard directly observed treatment short-course (DOTS) 6-month regimen (N=205) enrolled after September 2017 were included in the study. The ATT drugs and the concomitant drugs were checked for their possible drug-drug interactions with their categorization by utilizing the IBM Micromedex solutions online database. Fifty eight patients (28.3%) were taking ATT with other concomitant medications. The most common concomitant medications were oral hypoglycemic drug metformin (75.9%) followed by glimepiride (43.1%) Prevalence of potential drug-drug interactions among the participants were 23.4% (95%CI: 17.8%-29.8%). There were 24 common drug interactions with 19 interactions having potential impact on non-ATT drugs and 5 having potential impact on ATT drugs. The majority (58.4%) of these interactions were moderate followed by major (33.3%) and minor (8.3%). Careful consideration and appropriate use of drugs, thereby avoiding the incidence of drug interactions, is an essential step in mitigation of the effects of complications.

KEYWORDS: Drug-drug Interactions, Anti-tubercular drugs, Concomitant medication, Tuberculosis, Pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases worldwide and is caused by a pathogenic bacterium, Mycobacterium tuberculosis.[1] This infection can result in chronic unexplained clinical problems such as chronic cough and weight loss. As an important public health problem, early identification and better management of the condition by medical therapy is required. TB as a disease demands a long-term multi-drug treatment.[1] Coinfection in TB patients and concomitant noninfectious disease, particularly with an aging population, undoubtedly necessitates the use of additional drugs.[2] This multi-drug management in a TB population increases the potential for drug interactions. Drug-drug interactions are one of the many factors that can alter the patient's response to TB therapy, which should be suspected whenever unexpected effects are seen.[3] Despite recent advances in identifying and reducing the risk of drug–drug interactions (DDIs) in developed countries, there are still significant challenges in managing DDIs in low-income (LICs) and developing countries worldwide.[2] A potential drug interaction refers to the possibility that one drug may alter the pharmacological effects of another drug given concomitantly.[3] The net result may be enhanced or diminished effects of one or both drugs, or the appearance of a new effect that is not seen with either drug alone. The most important adverse drug-drug

interactions occur with drugs that have serious toxicity and a narrow therapeutic index, where relatively small changes in drug level can have significant adverse consequences.[4]

Interactions may generally be categorized into pharmacokinetic ones and pharmacodynamic ones. Pharmacokinetic interactions are those which affect the drug absorption, distribution, metabolism and excretion.[4] These interactions occur as a result of increase or decrease in the concentration of the drug at the site of action. Polypharmacy, which is common in elderly patients, increases the risk substantially.[5] The mechanism most relevant to TB drugs interaction is drug metabolism.[6] Cytochrome P450 is a huge family of isoenzymes, amongst which CYP3A4 and CYP2D6 are most frequently involved in drug interactions.[6] Knowing which liver isoenzymes are concerned with metabolism of a drug is a good starting point in predicting drug interactions.

Pharmacodynamic interactions are those where the effects of one drug is changed by the presence of another drug at its site of action.[7] This includes additive or synergistic interactions, antagonistic or opposing interactions, interactions due to changes in drug transport mechanisms and interactions due to disturbances in fluid and electrolyte balance.[6] Since anti tubercular drugs are mostly given in combination, drug interactions may be of two types: between the anti-tubercular drugs themselves, and interaction with other concomitant drugs that the patient might have been administered.

The presence of drug interactions among TB patients could result in low pharmacological efficiency resulting in poor treatment outcome of tuberculosis as well as in other comorbid conditions such as poor diabetic control.[6] Management of DDIs and education of healthcare providers to ensure safe and effective use of anti-tubercular drugs in developing countries like India has not gained much attention yet.[2] A study has been conducted in Africa where possible drug-drug interactions between HIV antiretroviral therapy (ART) and drugs used to treat MDR-TB patients were analyzed and possible effect on HIV treatment outcomes were evaluated.[8]

Another study has reported the simultaneous treatment of patients with anti-TB drugs and for Hepatitis C virus.[9] Though patients with infectious diseases in Low-income countries (LICs) including India are predisposed to potential drug-drug interactions, this is still a neglected topic of research in LICs. Very few studies have been done in India on drug interactions especially in TB patients. One study which was conducted in India to study DDIs among the first-line ATT drugs concluded that the four primary anti-tuberculosis drugs interacted with each other in multiple and complex ways.[10]

Hence, the focus of this study is to perform a comprehensive analysis of the prevalence of and factors associated with potential interactions of first-line ATT drugs and concomitant medications among patients with pulmonary tuberculosis in South India.

METHODS

Study setting and study population

This was conducted as a part of a large-scale observational cohort study under the Regional Prospective Observational Research for Tuberculosis (RePORT)-India consortium.[11] Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) in collaboration with the Boston Medical Center and New Jersey Medical University - Rutgers University has recruited two observational cohorts for this study (first cohort had patients with active TB and second cohort had household contacts of active TB patients). We used the cohort with active TB patients for our study.

Study enrollment started in 2014 and participants were enrolled from Puducherry and two neighboring districts in Tamil Nadu (Cuddalore and Villpuram). Newly diagnosed pulmonary TB patients (at least 1+ acid fast bacilli, culture-confirmed) undergoing the standard directly observed treatment short-course (DOTS) 6-month regimen (N=205) enrolled after September 2017 were included in the study. The ATT treatment regimen for these patients includes a 2-month intensive Phase of Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) and Ethambutol (E) daily followed by a 4-month continuation phase of Isoniazid (H) and Rifampicin (R) Ethambutol (E) daily. The ATT drugs are of fixed dose combinations. The ATT daily dose were calculated for each individual patient depending on their body weight and the drugs were prescribed as fixed dose combination (FDC) every day as per the guidelines of Revised National Tuberculosis Control Programme (RNTCP) 2017.[12] Before 2017, the ATT drugs were administered thrice weekly for both Intensive and continuous phase not based on weight of the patient.

Participants who had already completed ATT and those who have communication problems were excluded from the study. The detailed protocol of this study has been explained previously.[12-15]

Study procedure

After the process of enrollment and obtaining informed written consent from the participants, a semi-structured pre-tested questionnaire was applied to gather the participants' details. Questions were translated into Tamil (local language) and administered by well-trained and professional tamil-speaking research staffs. Questionnaire consisted of basic sociodemographic details such as age, gender, education status, employment, and and any history of comorbid conditions such as diabetes mellitus (DM) and hepatitis. The details regarding the co-morbid conditions were cross-checked with the medical reports provided by patients by

experienced research staffs. In particular, the presence of DM and hypertension were confirmed with the help of patient TB book provided by respective PHCs. We measured the anthropometric characteristics such as weight, height, and body mass index (BMI), and radiological assessment using chest X-ray. We also assessed the functional status of the participants using Karnofsky's performance scoring (KPS) system.[16]

The ATT data were collected from the DOTS card of the patients, which was provided by the respective primary health centers. The concomitant medication history taken by the patients for other comorbid conditions was collected using a specialized case report form known as "Targeted concomitant medication" which was administered as part of the RePORT study. Also, the prescriptions of patients which were filed were reviewed for prescribed medication details. To identify the presence of drug interactions, the ATT and concomitant medications should be taken by the patients at the same date and approximate time. This criterion was checked accurately using the date on DOTS card, the Concomitant medication details questionnaire and also the prescriptions of patients which was available. Depending on these criteria, the ATT drugs and the concomitant drugs were checked for their possible drug-drug interactions along with their categorization by utilizing the IBM Micromedex solutions online database.[17] The completed questionnaires were scanned and transferred to the Boston Medical Center using the Verity tele form information capture system version 10.8 (Sunnyvale, CA, USA), and it was then read into Microsoft Access database (Seattle, WA, USA).

Statistical analysis

Data was extracted from the RePORT India project database and performed analysis using the Stata version 14.2 software. Descriptive statistic used to summarize continuous variables were mean and standard deviation (SD) and categorical variables were proportions. Prevalence of potential drug-drug interactions were reported with 95% confidence interval (CI). Subgroup analysis of these potential drug-drug interactions were performed based on their severity and appropriate clinical recommendations were provided. Chi-square test was done to assess the factors associated with the potential drug-drug interactions among the study participants. Multivariable logistic regression was performed with factors having p-value up to 0.20 in the univariable analysis. Adjusted odds ratio (aOR) with 95%CI was reported. Variables with p value less than 0.05 were considered statistically significant.

Ethical considerations

Approval was obtained from the scientific advisory and institutional ethics committee (IEC) of JIPMER and institutional review boards (IRB) at Boston Medical Center and New Jersey Medical University - Rutgers University.

RESULTS

In total, 205 participants with TB were assessed for the targeted concomitant medication intake during the study period. Sociodemographic details of these participants are as follows. About 7.3% of the participants belonged to elderly age group (60 years and above); more than three-fourth (78%) were males; almost two-third (64%) had no formal education; more than three-fourth (77%) were employed. About 53.2% of the participants were classified as underweight based on Asia-Pacific guidelines for BMI classification. Treatment outcome of the participants shows that a majority of them (71.25%) were bacteriologically cured followed by those participants who were lost to follow-up (12.19%) and 5.85% had bacteriologic status which was indeterminate (**Table-1**). DM (52.7%) was the most common comorbidity among the participants followed by Hepatitis (22.4%) **(Figure-1a)**. Almost three-fourth (72.2%) of the participants had some form of functional impairment. Chest X-ray findings showed that 72% of the participants had their lung affected.

Table 1: Socio-demographic characteristics of the study participants (N=205).

Sr.No.	Characteristics	No. of patients (%)
1.	**Age group**	
	<60 years	190 (92.7)
	≥60 years	15 (7.3)
2.	**Gender**	
	Male	160 (78.0)
	Female	45 (22.0)
3.	**Occupational status**	
	Employed	157 (76.6)
	Unemployed	38 (18.5)

	Others		10 (4.9)
4.	**Status of lung (N=168)**		
	Affected		121 (72.0)
	Not affected		47 (28.0)
5.	**Functional status of the patients**		
	Normal		57 (27.8)
	Impaired		148 (72.2)
6.	**Co-morbidity status**		
	Diabetes mellitus		108 (56.7)
	Hepatitis		46 (22.4)
	Cancer		3 (1.5)
7.	**BMI Status**		
	Underweight		110 (53.7)
	Normal		63 (30.7)
	Overweight/Obese		32 (15.6)
8.	**ATT dose schedule (Revised RNTCP regimen since 2017)**		
	Weight band (kg)	**FDC (pills/day)**	
	25-39 kg	2	26 (12.7)
	40-54 kg	3	117 (57.1)
	55-69 kg	4	48 (23.4)
	≥70 kg	5	14 (6.8)
9.	**Treatment Outcome**		
	Bacteriologic cure		146 (71.21)
	Bacteriologic failure		4 (1.95)
	Bacteriologic status indeterminate		12 (5.85)
	Death		5 (2.43)
	Emerging resistance		1 (0.48)
	Lost to follow-up		25 (12.19)
	NA		6 (2.92)

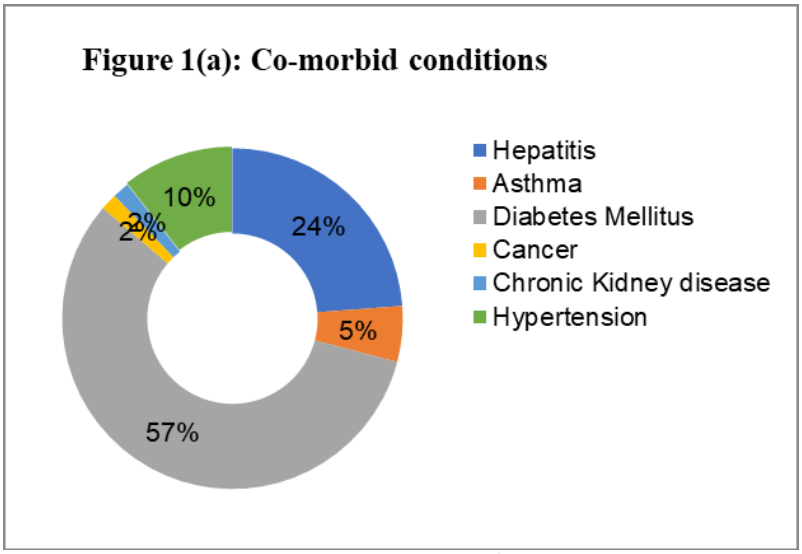

Fig. 1(a): Prevalence of Co-morbid conditions[a] present in patients with PTB
[a]Diabetes mellitus was the most prevalent co-morbidity in the study population followed by hepatitis

In total, 58 patients (28.3%) were taking ATT along with other concomitant medications. A patient might have one or more comorbid conditions which necessitates the use of one or more drugs. The most common concomitant medications taken were oral hypoglycemic drug metformin (75.9%) followed by glimepiride (43.1%) **(Table-2 and Figure-1b)**.

Table 2: Distribution of study participants based on the type of concomitant medications intake (N=58 participants).

Sr. No	Name of the drug	Pharmacological classification	No. of patients (%)
1.	Insulin	Anti-diabetic	15 (25.9)
2.	Metformin	Anti-diabetic	44 (75.9)
3.	Glimepiride	Sulphonyl ureas (Anti-diabetic)	25 (43.1)
4.	Glibenclamide		1 (1.7)
5.	Pioglitazone	Thioglitazones (Anti-diabetic)	3 (5.2)
6.	Tenegliptin	Gliptins (Anti-diabetic)	2 (3.4)
7.	Linagliptin		1 (1.7)
8.	Atorvastatin	Statins (Anti-hyperlipidemic)	5 (8.6)
9.	Theophylline	Bronchodilator	1 (1.7)
10.	Ranitidine	H2 receptor antagonists	2 (3.4)
11.	Esomeprazole	Proton pump inhibitors	1 (1.7)
12.	Omeprazole		1 (1.7)
13.	Sodium bicarbonate	Antacid	1 (1.7)
14.	Aluminium hydroxide		1 (1.7)
15.	Methyl prednisolone	Corticosteroids	1 (1.7)
16.	Hyoscine butylbromide	Anti-cholinergic	1 (1.7)
17.	Vitamins and minerals	Multivitamins	1 (1.7)

18.	Enalapril	Anti-hypertensives	1 (1.7)
19.	Telmisartan		1 (1.7)
20.	Metoprolol		1 (1.7)
21.	Propranolol		1 (1.7)
22.	Amlodipine		4 (6.9)
23.	Verapamil		2 (3.4)
24.	Doxycycline	Antibiotics	2 (3.4)
25.	Azithromycin		1 (1.7)
26.	Cefotaxime		1 (1.7)
27.	Trimethoprin		1 (1.7)
28.	Sulphamethoxazole		1 (1.7)
29.	Chlorpheniramine maleate	Anti-histaminic	1 (1.7)
30.	Aspirin	Anti-platelet drug	2 (3.4)
31.	Clopidogrel		1 (1.7)
32.	Isosorbide mononitrate	Anti-anginal	1 (1.7)
33.	Aceclofenac	Non-steroidal Anti-inflammatory drugs (NSAIDs)	1 (1.7)
34.	Acetaminophen		1 (1.7)
35.	Bromhexine, guaiphenesin, terbutaline	Anti-tussive	1 (1.7)
36.	Domperidone	Anti– emetic	1 (1.7)

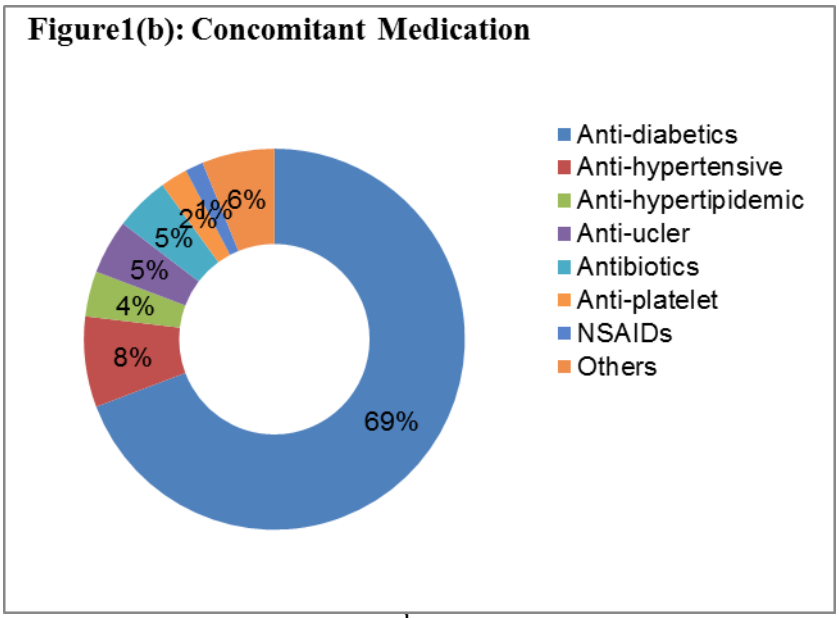

Fig. 1(b): List of concomitant medications[b] taken on simultaneous date as that of ATT.

[b]Anti-diabetic drugs were the most common drugs taken by the population. The least common drugs prevalent include anti-tussives, anti-emetics, multivitamins, anti-anginal, corticosteroids, anti-cholinergic, bronchodilators and anti-histamines which was placed in the category "others".

Prevalence of potential drug-drug interactions among the study participants were 23.4% (95%CI: 17.8%-29.8%). We found 24 common drug interactions with 19 interactions having potential impact on non-ATT drugs and 5 having potential impact on ATT drugs. Severity of these interactions were classified as major, moderate and minor. The majority (58.4%) of these interactions were moderate followed by major (33.3%) and minor (8.3%). Classification of these interactions based on their impact on ATT and non-ATT drugs, possible mechanism of action and clinical recommendations for the same were provided in **Table-3 & 4.**

Table 3: Drug-drug interactions between Non-TB drugs and ATT*.

Sr.No	Non ATT Drugs	ATT drugs	
		Rifampicin	Isoniazid
1.	Acetaminophen		
2.	Aluminium hydroxide		
3.	Amlodipine		
4.	Atorvastatin		
5.	Clopidogrel		
6.	Domperidone		
7.	Doxycycline		
8.	Enalapril		
9.	Esomeprazole		
10.	Glimepiride		
11.	Linagliptin		
12.	Metformin		
13.	Methyl prednisolone		
14.	Metoprolol		
15.	Omeprazole		
16.	Pioglitazone		
17.	Propranolol		
18.	Sodium bicarbonate		
19.	Theophylline		
20.	Verapamil		

*** The ATT drugs taken by the study population are fixed dose combinations of Rifampicin, Isoniazid , Ethambutol and Pyrazinamide. In our study, only the first line ATT drugs (Rifampicin &Isoniazid) were found to have potential interactions with the other non-TB drugs ; red, showing major severity where caution should be present and monitoring is required; yellow, showing moderate severity where dosage adjustments might be required ; green, showing minor severity.**

Table. 4: Common potential drug-drug interactions classified based on their impact on ATT and non-ATT drugs, possible mechanism of action and clinical recommendations (N=205).

Sr. No	Name of the Interacting drugs	Effect	Severity	Probable Mechanism	Inference (Clinical management recommendations)	No. of patients (%)
INTERACTION WITH IMPACT ON NON-ATT DRUGS						
1.	Amlodipine + Rifampicin	Concurrent use may result in reduced amlodipine efficacy	Major	Induction of CYP-mediated metabolism of amlodipine in GIT by rifampicin	Monitor BP when amlodipine is co administered with CYP3A inducers. Dosages of drug metabolized by these enzymes may require dosage adjustment when starting or stopping rifampicin.	3 (1.5)
2.	Glimepiride + Isoniazid	Concurrent use may result in increased glimepiride exposure and risk of hypoglycemia.	Major	Inhibition of CYP2C9 mediated glimepiride metabolism by isoniazid	Monitor for signs of hypoglycemia	23 (11.2)
3.	Acetaminophen + Isoniazid	Concurrent use may result in an increased risk of hepatotoxicity	Major	Initial inhibition of CYP2E1-mediated metabolism of acetaminophen by isoniazid; induction of CYP2E1- mediated metabolism of acetaminophen by isoniazid	Use caution. Acetaminophen use should be avoided or limited in patients taking isoniazid.	1 (0.5)
4.	Domperidone + Isoniazid	Concurrent use may result in increased domperidone exposure and an increased risk of QT Prolongation leading to serious cardiac effects.	Major	Inhibition of CYP3A4- mediated domperidone metabolism.	Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizures.	1 (0.5)
5.	Linagliptin + Rifampicin	Concurrent use may result in reduced linagliptin exposure	Major	Induction of CYP3A4 mediated linagliptin metabolism and P-glycoprotein mediated linagliptin efflux transport	Selection of an alternative to CYP3A4 and P-gp inducer with no or minimal enzyme induction potential or use of an alternative treatment recommended	1 (0.5)
6.	Metoprolol succinate + Rifampicin	Concurrent use may result in reduced metoprolol efficacy	Major	Induction od CYP mediated metabolism of metoprolol by rifampicin	Consider monitoring BP to ensure continued antihypertensive efficacy or use an alternative to rifampicin if possible	1 (0.5)
7.	Clopidogrel +	Concurrent use may result in reduced	Moderate	Inhibition of CYP2C9 mediated	Caution is recommended.	1 (0.5)

	Isoniazid	antiplatelet activity of clopidogrel		clopidogrel metabolism to active metabolite by isoniazid		
8.	Enalapril maleate + Rifampicin	Concurrent use may result in decreased enalapril effectiveness	Moderate	Increased metabolism of enalapril	Monitor for continuing BP control after the addition or withdrawal of rifampicin, adjusting the enalapril dose to regain control. Substitution of an alternative ACE inhibitor or a different class of antihypertensive agent may be required	1 (0.5)
9.	Pioglitazone HCL + Rifampicin	Concurrent use may result in decreased pioglitazone exposure.	Moderate	Induction of CYP2C8 mediated pioglitazone metabolism	Use caution and adjust pioglitazone dosage based on clinical response however do not exceed the maximum recommended daily dose of 45mg.	3 (1.5)
10.	Rifampicin + Metformin	Concurrent use may result in increased metformin plasma concentrations; enhanced glucose lowering effects of metformin.	Moderate	Increased OCT1 expression and hepatic uptake of metformin	Consider monitoring patients for increased metformin adverse effects and also monitor blood glucose levels and for signs and symptoms of hypoglycemia on concurrent use.	44 (21.5)
11.	Rifampicin + Omeprazole	Concurrent use may result in decreased omeprazole plasma concentration.	Moderate	Induction of CYP 2C19 & CYP3A4 mediated omeprazole metabolism by rifampicin	Concomitant use should be avoided.	1 (0.5)
12.	Rifampicin+ Propranolol HCL	Concurrent use may result in decreased propranolol effectiveness	Moderate	Increased propranolol metabolism	If concurrent therapy required monitor BP carefully. A higher dose of propranolol may be required in patients receiving rifampicin for longer than ½ weeks. Beta blockers less likely to be affected include atenolol, nadolol & timolol	1 (0.5)
13.	Rifampicin + Doxycycline	Concurrent use may result in reduced doxycycline serum concentrations and potential loss of doxycycline efficacy	Moderate	Increased doxycycline clearance induced by rifampin	Monitor patient response to combined rifampin and doxycycline treatment as lowered doxycycline effectiveness should be anticipated. Alternatively, consider administering doxycycline in combination with streptomycin	2 (1.0)

14.	Rifampicin + Atorvastatin	Concurrent use may result in decreased atorvastatin concentration when administered separately after rifampin or increased atorvastatin exposure when administered simultaneously with rifampin.	Moderate	Induction of CYP3A4 metabolism of atorvastatin by rifampin; inhibition of organic anion-transporting polypeptide (OATP1B1) – mediated atorvastatin hepatic reuptake by rifampin	If concurrent therapy is needed, simultaneous co-administration of the two drugs is recommended; when atorvastatin administration is delayed after rifampin administration, a significant de crease in atorvastatin exposure may occur.	5 (2.4)
15.	Rifampicin+ Theophylline	Concurrent use may result in decreased theophylline effectiveness	Moderate	Increased theophylline metabolism	Dosage adjustments of theophylline may be necessary	1 (0.5)
16.	Rifampicin + Verapamil	Concurrent use may result in decreased verapamil effectiveness	Moderate	Induction of CYP450 3A4 mediated verapamil metabolism	Monitor patients for loss of calcium channel blocker effects. Dose increases may be required	2 (1.0)
17.	Rifampicin Glimepiride	Concurrent use may result in decreases glimepiride plasma concentrations	Moderate	Induction of CYP 4502C9 mediated biotransformation of glimepiride by rifampicin	Use caution and monitor blood glucose or Use therapeutic alternative	25 (12.2)
18.	Isoniazid +Theophylline	Concurrent use may result in theophylline toxicity	Moderate	Alterations in theophylline metabolism	Theophylline levels should be closely monitored when isoniazid therapy is initiated or changed or discontinued.	1 (0.5)
19.	Rifampicin + Esomeprazole	Concurrent use may result in decreased esomeprazole plasma concentrations.	Moderate	Induction of CYP2C19- and CYP3A4-mediated esomeprazole metabolism by revampin.	Use should be avoided	1 (0.5)
INTERACTION WITH IMPACT ON ATT DRUGS						
20.	Rifampicin + Isoniazid	Concurrent use may result in hepatotoxicity	Major	Increased isoniazid metabolism	Monitor LFT, especially in children and in adults with predisposing risk factors. Monitor the patient for clinical symptoms of liver toxicity	205 (100)
21.	Rifampicin + Pyrazinamide	Concurrent use may result in severe hepatic injury	Major	Unknown	Monitor throughout the entire course of therapy since a majority of patients have onset of symptoms of liver injury after the fourth week of therapy.	205 (100)
22.	Rifampicin + Sodium bicarbonate	Concurrent use may result in decreased rifampicin exposure	Moderate	Reduced absorption of rifampicin	Daily doses of rifampicin should be administered at least 1 hour before antacid	1 (0.5)

23.	Isoniazid + Prednisolone	Concurrent use may result in decreased isoniazid effectiveness.	Minor	Increased metabolism/ clearance	Monitor patients for a decreased response to isoniazid. Dosage adjustments of one or both drugs may be necessary.	2 (1.0)
24.	Isoniazid + Aluminum hydroxide	Concurrent use may result in decreased isoniazid effectiveness	Minor	Decreased isoniazid absorption	Do not administer antacids concurrently with isoniazid. Recommend taking antacids at least two hours after taking isoniazid.	(0.5)

Table-5 shows the factors associated with potential drug-drug interactions among the study participants. In the univariable analysis, BMI category and DM status had significant association with potential drug-drug association. Apart from these variables, age category and Karnofsky score was also included in the final multivariable model as these variables had p value less than 0.2. Multivariable logistic regression has found that participants who were overweight/obese had 7.87 times more odds of having potential drug-drug interaction (aPR=7.87; 95%CI: 2.60-23.83) when compared to those belonging to underweight category after adjusting for other potential confounders. The adjusted model also revealed that participants with DM had 7.75 times higher odds of having potential drug-drug interaction (aPR=7.75; 95%CI: 2.48-24.25) compared to those without DM.

Table 5: Factors associated with potential drug-drug interaction among the TB patients in Puducherry and Tamil Nadu (N=205).

Sr.No	Characteristics	Total	Potential drug-drug interaction n=48 (%)	Chi square p-value	Adjusted Odds Ratio (95% CI)	Adjusted p-value
1.	**Age group**					
	<60 years	190	42 (22.1)	0.11	1	-
	≥60 years	15	6 (40.0)		1.08 (0.29-4.11)	0.90
2.	**Gender**					
	Male	160	38 (23.7)	0.83	{Not included in the model}	
	Female	45	10 (22.2)			
3.	**Functional status**					
	Normal	57	9 (15.8)	0.11	1	
	Impaired	148	39 (26.3)		1.45 (0.57-3.65)	0.43
4.	**BMI Category[#]**					
	Underweight	110	8 (7.3)	<0.001*	1	-
	Normal	63	21 (33.3)		3.48 (1.33-9.07)	0.01*
	Overweight/Obese	32	19 (59.4)		7.88 (2.60-23.83)	<0.001*
5.	**Diabetes Mellitus**					
	Present	108	44 (40.7)	<0.001*	7.75 (2.48–24.25)	<0.001*
	Absent	97	4 (4.1)		1	-

p value statistically significant (<0.05)
[#]***Asia Pacific guidelines for BMI classification***

DISCUSSION

Avoidance of Drug interactions is a small, yet an essential step in mitigating the effects of TB. Drug-drug interactions are clinically important if the disease being treated with the drug is serious or potentially fatal if left untreated. Ignorance of such interactions in pharmacotherapy might result in precipitation of toxicity and reduction in the therapeutic efficacy of the drugs. The systematic knowledge of drug interaction, which includes absorption, elimination, and transport and drug metabolism may help to prevent such adverse effects.[18]

Appropriateness of drugs taken by the patients must be evaluated to avoid these undesirable effects. A study conducted by Cascorbi et al on elderly population has shown that 36% of the drugs were unnecessary and 30% were inappropriate for elderly people.[19] This could also be the situation among TB patients with other co-morbidities. This scenario can be avoided if the physicians prescribe only the essential and appropriate drugs to the patients. Utilizing tools such as MAI (Medication appropriateness index) tool and Beer's criteria as seen in a cross-sectional study conducted by Hasan et al could minimize the number of drugs used in patients, thereby avoiding the drug interactions.[20]

Amongst the first-line ATT drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin), Rifampicin is most likely to cause clinically significant drug interactions as it is a potent inducer of cytochrome

P450 enzyme group (CYP2C8, CYP2C9 CYP3A). It is involved in the metabolism of many drugs, particularly OCPs, corticosteroids and oral anticoagulants.[21] This happens either by enhancing their rate of synthesis or by reducing their rate of degradation. The ATT amongst itself will induce interactions altering the therapeutic efficacy. Pyrazinamide increases the serum concentration of isoniazid, whereas decreases the serum concentration of rifampicin.[22] In a randomized, cross-over study, 16 patients with untreated pulmonary tuberculosis were administered rifampicin 450 mg + INH 300 mg.[23] It was observed that AUC of rifampicin is decreased while its clearance is increased. However, keeping in mind the risk benefit ratio, the regimen has been designed.

In our study, more than half of the patients were on anti-diabetic medications, which necessitates an understanding about the relationship between these conditions and regimens. Both these diseases do not coexist incidentally, but rather diabetes predisposes to the development of TB and vice–versa. Coming to the regimen, Patients on glimepiride and taking isoniazid may have excess risk of hypoglycemia compared to when taking glimepiride alone. It was the most common form of potential drug-drug interaction found with isoniazid in our study. A case report done by Boglou et al also explains the need of caution while prescribing isoniazid in DM patients receiving glimepiride to avoid excess hypoglycemia risk.[24] Another anti-diabetic drug having clinically significant interaction is Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. Linagliptin when given along with rifampicin may lead to reduced linagliptin exposure which occurs by induction of CYP3A4 mediated linagliptin metabolism and P-glycoprotein mediated linagliptin efflux transport. Other possible drug-drug interaction found in our study population is the combination of Isoniazid and Prednisolone. When Isoniazid was taken as a fixed dose combination with Prednisolone, it decreases the isoniazid concentrations leading to lower exposure and half-life of isoniazid in both slow and rapid acetylators. This could have been caused by an enhanced acetylation or renal clearance or even by an increase in the total body water of isoniazid as found in a study conducted by Sarma et al.[25] Isoniazid effectiveness will be reduced when given with antacids such as aluminum hydroxide. Previous evidences have also suggested that the aluminum hydroxide decreases the bioavailability of isoniazid.[26] Although didanosine tablets contain antacids in the formulation, it has been shown that it is too little to affect the bioavailability of INH if given concurrently.

In our study, we found that almost one-fourth of the participants had hepatitis. This might be drug–induced hepatitis (DIH), one of the major complications amongst the patients receiving ATT. The liver plays a major role in the drug metabolism and detoxification. Saukkonen et al, in their study said that drug-induced liver injury (DILI) is a problem of increasing significance, but has been a long-standing concern in the treatment of TB.[27] Management of hepatitis remains a crucial factor for improving treatment outcomes of TB patients. The importance of this was illustrated by Shamaei et al, saying that drug induced liver injury can complicate treatment regimen and causes prolonged hospital stay.[28]

The study has certain strengths. It adds to the limited literature available on the epidemiology of potential drug-drug interaction among TB patients in Indian setting. Data quality assurance through double data entry & validation are added advantages of the study. However, our study should be interpreted with caution owing to its limitations. TB patients included in our study were selected from three districts in South India, limiting the generalizability of study results. Only the patients diagnosed in public sector were included in our study. Hence, our study sample may not be representative as the patients receiving drugs from private sector might have higher risk of taking inappropriate or unwanted drugs. This leads to potential drug-drug interaction and adverse clinical consequences.

The limitation of the study is that there is no information on actual clinical occurrence, severity and outcomes of these drug-drug interactions.

Therapeutic drug monitoring (TDM) plays an essential role in some TB patients who respond slowly to treatment, have drug-resistant TB, are at risk of drug-drug interactions or have concurrent disease states that significantly complicate the clinical situation.[29] TDM often is the best available tool for sorting out drug interactions and providing the patient only necessary doses. TDM combined with clinical and bacteriological data, can be a decisive tool, allowing the health care professionals to successfully treat even the most complicated TB patients.

CONCLUSION

Tuberculosis warrants medication intake on a daily basis. The intake of concomitant medications taken for other co-morbidities in such patients heightens the risk of polypharmacy which may result in drug interactions. Careful consideration and appropriate use of drugs, thereby avoiding the incidence of drug interactions, is an essential step in the mitigation of the effects of this complication. When an interaction is discovered, it is possible that the interacting drugs may be used effectively with adjustment of dosage or other therapeutic modifications.

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