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Prevalence and Determinant of Adverse Drug Reactions among MDR-TB Patients Attending St. Peter's TB Specialized Hospital, Addis Ababa, Ethiopia

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Abstract

Background: Tuberculosis is one of the major public health problems throughout the world. About 9.6 million people are estimated to have tuberculosis in 2014. From this, 480,000 cases were multidrug-resistant tuberculosis. There is a need to identify areas to be focused on and prioritized for subsequent and targeted interventions, so this study was aim to assess the prevalence and factors affecting adverse drug reactions among multidrug-resistant tuberculosis patients.

Method: Institution-based cross-sectional study design was conducted. A total of 286 patient cards were included in the study. Data abstraction form was used. The data were collected by trained nurses who are the multidrug-resistant tuberculosis ward staff. Data were entered, cleaned, and checked using Epi Data version 4.6 statistical software and analyzed by SPSS version 23. Bivariate logistic and then multivariate logistic regression analyses were done.

Result: The prevalence of Adverse Drug Reactions in this study was 169 (59.1%). Treatment outcome (AOR=10.012, 95% CI, (2.131-47.036)) and comorbidity (AOR=5.809, 95% CI (1.106-30.504)) was significantly associated with an adverse drug reaction.

Conclusion and Recommendation: There was a high prevalence of adverse drug reactions among multidrug-resistant tuberculosis patients. Comorbidity and treatment outcome were the independent determinants. Adverse drug reaction management strategies should be strengthened for better treatment outcomes.

Keywords: Adverse drug reaction; MDR-TB; Patients

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Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*; a rod-shaped bacillus called "acid-fast" due to its staining characteristics in the laboratory. Occasionally the disease can also be caused by *Mycobacterium bovis* and *Mycobacterium africanum* [1].

Tuberculosis is considered medicine-resistant (DR) when the TB causative agent (*Mycobacterium tuberculosis*) is not killed by one or more of the available anti-TB medicines. Medicine-resistant TB can be primary or secondary (acquired). Primary resistance is medicine resistance among new cases, while secondary resistance is medicine resistance among previously treated cases [1,2].

Treatment for MDR-TB is longer and requires more expensive and more toxic drugs. For most patients with MDR-TB, the current regimens recommended by WHO last 20 months, and treatment success rates are much lower [3]. In Ethiopia, MDR-TB patients are treated with a standardized second-line treatment regimen for at least 18 to 24 months. Medicine Resistance Survey (DRS) data from representative patient populations are used to design a standardized treatment regimen [2].

Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB. In 2014, an estimated 190,000 people died of MDR-TB. The number of TB deaths is unacceptably high: with a timely diagnosis and correct treatment, almost all people with TB can be cured [3].

The prevalence and mortality of Tuberculosis of all forms are estimated to be 546 and 73 per 100,000 populations respectively. In the year 2006/7 Ethiopia registered 129,743 cases of TB.

According to the latest estimates, Ethiopia standpoint on the list of high burden countries for TB. According to the MOH hospital statistics data, tuberculosis is the leading cause of morbidity, the third cause of hospital admission (after deliveries and malaria), and the second cause of death in Ethiopia, after malaria [1].DR-TB has a devastating social and financial impact on patients and the healthcare system. With a 48% success rate, MDR-TB treatment is more difficult, toxic, and ineffective, and patient mortality is higher. Additionally, MDR-TB treatment requires daily therapy for more than 20 months, which adds to the cost of care, social isolation, job loss, and other long-term socioeconomic and psychological impacts. Patients with MDR-TB take more tablets and receive more injections for a longer period, may experience more adverse effects, and require increased support to continue treatment and/or to monitor adverse effects. Detecting and controlling adverse effects promptly promotes adherence and prevents default to treatment [1,4].

Unmanaged adverse reactions greatly affect the patients' adherence to the treatment regimens, which in turn leads to the development of drug resistance [4]. This study is intended to determine the magnitude and factors associated with adverse drug reactions among MDR-TB patients on second-line anti-tuberculosis drug regimens. In addition, healthcare practitioners' knowledge and patients' understanding of their treatments will be assessed with this study.

Material and Methods

Study design and setting

An institution-based cross-sectional study was conducted at St. Peter's TB Specialized Hospital. St. Peter's has served as the only specialized TB referral hospital in Ethiopia for four decades. Afterward, by the government's decision TB treatment centers were opened in every region of the country, and that has alleviated the burden which had been laid on St. Peter's. St. Peter's is the first hospital to offer medical services to patients with drug-resistant TB. It started this service in 2008 with eight inpatients. However, 252 patients had registered and were waiting for their turn to get the medication. The hospital has 400 staff. From 2009 until June 2013, 627 MDR-TB patients were treated in this hospital.

Study participants and sampling procedures

All MDR-TB patients who were treated with anti-TB drugs at St. Peter's TB Specialized Hospital were the source population. Whereas all patients attending St. Peter's TB Specialized Hospital who are MDR-TB patients receiving second-line anti-TB treatment and aged 18 and above were the study population. All records of patients who have been on treatment from January 01st, 2009, to December 31st, 2019, in St. Peter's TB Specialized Hospital were reviewed, and 286 patients' profile cards that fulfill the inclusion criteria were included in the study (Figure 1).

Data collection instruments and methods

A data abstraction form was developed to meet the objectives of this study. It was used to obtain the required information from the patient's medical chart. The form consisted of questions regarding sociodemographic characteristics, clinical characteristics, treatment regimens, adverse drug reactions, and ADR management. The list of patients needed for the study was obtained from the hospital's database. After getting the list of the patients, their charts were retrieved from the record and documentation office. A data abstraction format was used to record the necessary information from patients' charts. The data were collected by trained nurses who are staff of the MDR-TB ward.

Variables of the study

The dependent variables of the study are adverse drug reactions. Whereas the independent variables include age, sex, marital status, educational status, occupational status, comorbidity, MI, site of TB, anti-TB drugs, treatment outcome, history of smoking, history of alcohol use, and drug abuse history.

Measurements

New: A patient who has received no or less than one month of anti-tuberculosis treatment.

Relapse: A patient who was previously treated for TB and whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with a recurrence episode of TB.

Treatment after being lost to follow-up: A patient after taking treatment for more than one month who returns to treatment following interruption of treatment for two or more consecutive months.

Treatment after the failure of a new TB regimen: A patient who has received d new regimen for TB and in whom treatment has failed. Failure is defined as sputum smear/culture positive at five months or later during treatment.

Treatment after the failure of retreatment regimen: A patient who has received a retreatment regimen for TB and in whom treatment has failed. Failure is defined as sputum smear/culture positive at five months or later during treatment.

Transfer in: A patient who has been transferred from another TIC to continue MDR-TB treatment.

Other: Refers to any DR-TB patient who does not fit into any of the above categories.

Cured: Treatment completed according to national recommendation without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment completed: Treatment completed according to national recommendation without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of; lack of conversion by the end of the intensive phase, a bacteriological reversion in the continuation phase after conversion to negative after in the sensitive phase, or evidence of additional acquired resistance to fluoroquinolone second-line injectable drugs, or adverse drug reactions.

Lost to follow-up (LFTU): A patient whose treatment was interrupted for two consecutive months or more.

Died: A patient who dies for any reason during the course of treatment.

ADR: A response to a medicine that is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or the modification of

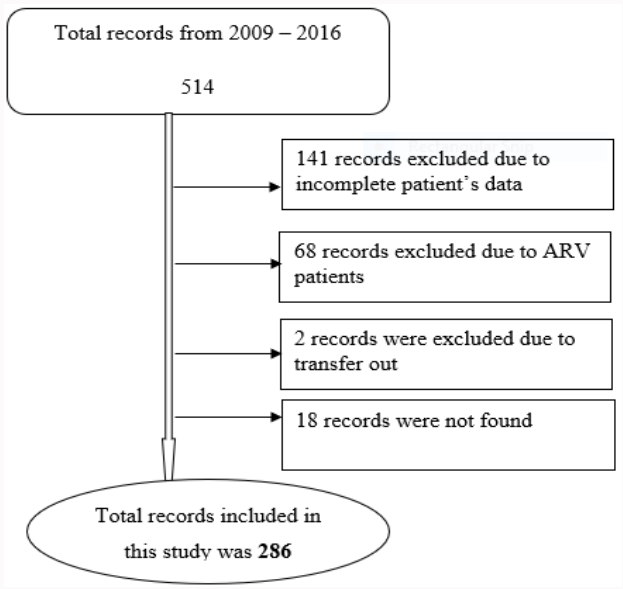

Figure 1: Schematic representation of a selection of patient profile cards among the patients attending St. Peter Hospital, Addis Ababa, 2009-2016.

physiological function.

Side effects: An expected, well-known reaction resulting in little or no change in patient management.

Data quality control

Four data collectors (Diploma nurses) were trained on the content of the questionnaire and the objective of the study for 03 days. A pre-test was done at 5% of the sample size, at Black Lion Hospital before the actual data collection. The supervisor and the investigator checked the data for completeness, missing, and unwanted filling daily. Epi data manager version 4.6.0.4 was used for data entry. SPSS version 23 was used for the analysis.

Ethical consideration

Ethical clearance was obtained from the ethics review committee of Addis Ababa College of Health Sciences, School of Pharmacy. In addition, permission was requested from the hospital's medical director. To ensure confidentiality, the name and other identifiers of the patients are not recorded on the data abstraction formats.

Data processing and analysis

Data were entered using Epi data version 4.6 statistical software. Errors related to inconsistency were verified using crisscross-data location techniques. Then managed data was exported to Statistical Package for Social Sciences (SPSS) software version 23. Descriptive analysis was done using frequency and percentages for the variables. Logistic regression was used to analyze the associations between different variables. The model fitness was checked by Hosmer and Lemshow Goodness Fitness Model. Those variables with a P-value of 0.2 during the bivariate analysis were included in the multiple logistic regression analysis to assess the relative effect of confounding variables. Since the outcome variable is categorical, the adjusted odds ratio was calculated through a multiple logistic regression model. After multivariate analysis had been done, the adjusted Odds Ratio (OR) was used to measure the strength of the association between the dependent variable and the independent variable, while the 95% CI and P-value were used to assess whether the association was significant.

Results

Sociodemographic characteristics

The mean age (± SD) of the patients who participated in this survey was 29.58 years (± 11.4) and their ages ranged from 18 to 75 years. Regarding the sex of the participants, 159 (55.6%) were males. More than half, 181 (63.3%) of the patients were from Addis Ababa, followed by the Oromia region 45 (15.7%). Almost equal numbers of the patients are single 136 (47.6%) and married 138 (48.3%). Most of the patients have attended education within grade levels 1 up to 8, 93 (32.5%) and 9 up to 12, 86 (30.1%) (Table 1).

Clinical characteristics

Most of the patients had pulmonary TB, 270 (94.4%). Additionally,

Table 1: Sociodemographic characteristics of MDR-TB patients attending St. Peter Hospital, Addis Ababa, 2009-2016.

Variable	Frequency	Percent
Sex		
Female	127	44.4
Male	159	55.6
Age group (years)		
18-27	166	58.3
28-37	68	23.9
38-47	26	8.8
48-57	11	3.9
>58	15	5.3
Marital status		
Single	136	47.6
Married	138	48.3
Separated	4	1.4
Divorced	8	2.8
Region		
Addis Ababa	181	63.3
Oromia	45	15.7
SNNPR	24	8.4
Others**	36	12.4
Educational status		
Unable to read and write	27	9.4
Read and write	30	10.5
Grade 1-8	99	34.6
Grade 9-12	86	30.1
Certificate/Diploma	18	6.3
Degree and above	26	9.1
Occupational status		
Governmental employee	30	10.5
Non-governmental employee	19	6.6
Daily laborer	17	5.9
Self-employed	75	26.2
Unemployed	18	6.3
Student	75	26.2
Others***	52	18.2

Table 2: Clinical characteristics of MDR-TB patients attending St. Peter Hospital, Addis Ababa, 2009-2016.

Characteristics	Frequency	Percent
Site TB		
PTB	270	94.4
EPTB	16	5.6
Registration group		
New	42	14.7
Relapse	43	15.0
After lost to follow up	6	2.1
After the failure of the first treatment	121	42.3
After the failure of re-treatment	74	25.9
Previous second-line drug use		
Yes	11	3.85
No	275	96.15
Co-morbidities		
Yes	17	5.90
No	269	94.10
Base-line BMI category		
<18.5 Kg/m^2	186	65.03
18.5-24.9 Kg/m^2	97	33.92
≥ 24.9 Kg/m^2	3	1.05

Table 3: Adverse drug reactions which occurred among the patients attending St. Peter Hospital, Addis Ababa, 2009-2016.

ADS	Frequency	Percent
Rash	12	7.1
Nausea and vomiting	97	57.4
Dyspepsia and abdominal pain	74	44
Diarrhea	8	4.7
Hepatitis	3	1.8
Arthralgia	73	43.5
Electrolyte abnormalities	5	3
Nephrotoxicity	9	5.4
Ototoxicity	8	4.8
Peripheral neuropathy	13	7.7
Depression	12	7.1
Headache	38	22.5
Psychosis	12	7.1
Seizures	2	1.2
Hypothyroidism	2	1.2
Anxiety	11	6.5
Insomnia	36	21.3
Visual disturbances	14	8.3
Musculoskeletal pain	10	6
Vestibular toxicity	10	6
Anorexia	32	18.9
Pain at the injection site	5	3
Others***	27	16

***Fever, sweating, body weakness, anemia, weight loss, palpitation, fungal infection, vaginal discharge

the majority of the patients; 244 (85.3%) had a prior history of TB treatment (failure, default, and relapse cases). The majority of the patients 270 (94.4%) had no co-morbidities while the rest had comorbidities such as diabetes and cardiomyopathy. The most frequently used 251 (87.8%) treatment regimen was Capreomycin (Cm), Levofloxacin (Lfx), pyrazinamide (Z), ethionamide (Eto)/ Prothionamide (Pto), and Cyclosporin (Cs) (Table 2).

Table 4: Treatment outcomes and the most common anti-TB regimens used among patients in St. Peter Hospital, Addis Ababa, 2009-2016.

Treatment outcomes	Frequency	Percent
Cured	78	27.3
Completed	153	53.5
Lost to follow up	23	8
Died	23	8
Failure	9	2.1
Regimen		
Cm, Lfx, Pto/ Eto, Cs, Z	251	87.8
Cm, Lfx, Pto/ Eto, Cs, PAS, Z	12	4.2
Cm, Lfx, E, Pto/ Eto, Cs, Z	6	2.1

Frequency, management, and treatment outcomes of ADR

Out of 286 patients, 169 (59.1%) were found to be experiencing symptoms associated with ADRs. Most of the patients experienced a combination of ADRs. The most common ADR was nausea and vomiting (57.4%) followed by dyspepsia and abdominal pain (44%) and arthralgia (43.5%). Other ADRs also included headache (22.5%), insomnia (21.3%), anorexia (18.9%), and others (Table 3). From 169 patients, proper management of ADR was given to 119 (70.4%) patients. One hundred fifty-three (53.5%) patients completed their treatments. While 78 (27.3%) of the patients were cured (Table 3).

Treatment regimens used

The highest number 251 (87.8%) of the patients took the standard treatment regimen which is the combination of Cm, Lfx, Pto/ Eto, Cs, Z during the intensive phase and Lfx, Pto/ Eto, Cs, Z during the continuation phase (Table 4).

Multivariate analysis of factors and adverse drug reaction

Variables with P<0.02 during the bivariate analysis were included in the multivariate logistic regression analysis to see the effect of confounding variables. The multivariate analysis indicated that comorbidity and treatment outcomes showed statistically significant associations with an adverse drug reaction. But age and smoking did not show a significant association with adverse drug reactions. The odds of adverse drug reaction in patients who had comorbid diseases were about 6 times higher than those who had no diseases (AOR=5.809, 95% CI (1.106-30.504)). Treatment outcome was significantly associated with adverse drug reactions. Patients who had treatment outcome of cure were more likely to develop adverse drug reactions (AOR=10.012, 95% CI, (2.131-47.036)) than those who had treatment outcome of failure (Table 5).

Discussion

In this study, 59.1% (95% CI; 41.2, 77.0) of the participants developed symptoms associated with ADRs which is higher compared with previous studies that have documented a prevalence rate of 44% in Nigeria [5], 50% in India, and [6], 50.5% in Vietnam [7]. Another study in India has also found a prevalence of 33.96% [8]. This finding is considerably higher than those given in previous reports and the observed variation could be a result of disparity in the definitions of adverse drug reactions used by the researchers, the study design used, the geographic variation, the specific anti-TB drugs used, and the time at which the study was conducted.

The most common ADR experienced by participants were nausea and vomiting (57.4%) followed by dyspepsia and abdominal

Table 5: Multivariate analysis of factors for adverse drug reaction among the patients attending St. Peter Hospital, Addis Ababa, 2009-2016.

Variables	COR (95% CI)	P value	AOR (95% CI)	P value
Age group (years)				
18-27	0.486 (0.165-1.429)	0.19	1.098 (0.306 - 3.938)	0.886
28-37	0.496 (0.159-1.549)	0.227	0.960 (0.251-3.671)	0.952
38-47	0.200 (0.050-0.794)	0.022	3.632 (0.778-16.949)	0.101
48-57	0.250 (0.047-1.344)	0.106	3.311 (0.480-22.849)	0.224
>58	1		1	
History of Cigarette Smoking				
Yes	4.792 (1.061-21.649)	0.042	2.889 (0.510-16.367)	0.231
No	1		1	
Co-morbidities				
Yes	5.601 (1.256-24.976)	0.024	5.809 (1.106-30.504)	0.038
No	1		1	
Treatment outcomes				
Cured	0.104 (0.024-0.462)	0.003	10.012(2.131-47.036)	0.004
Complete	0.730 (0.189-2.823)	0.648	1.367 (0.334-5.601)	0.664
LTFU	1.829 (0.374-8.937)	0.783	0.657 (0.126-3.426)	0.618
Died	1.829 (0.374-8.937)	0.456	0.366 (0.064-2.083)	0.257
Failure	1		1	

pain (44%) and arthralgia (43.5%). Other reported ADRs include headache (22.5%), insomnia (21.3%), and anorexia (18.9%). The result is inconsistent with those reported by [4-8]. This difference may be attributed to the difference in the pharmacokinetic parameter of the patients, and the use of different anti-TB regimens and their doses among countries.

The drugs most likely associated with nausea and/or vomiting were capreomycin, levofloxacin, ethionamide/protionamide, and pyrazinamide. Most of the aforementioned drugs also cause dyspepsia. This finding is also comparable to the other findings reported by Haregewoin and Petros [4,9,10]. The majority of the patients experienced gastrointestinal symptoms during the early weeks of treatment. These symptoms may prevent adequate therapy delivery and lead patients to further problems. Gastrointestinal side effects which were commonest can be largely prevented by proper timing and spacing of drugs with food and if necessary, giving antiemetics, antacids, and Proton Pump Inhibitors (PPIs) or H2 receptor blockers.

Arthralgia was found to be one of the common ADRs encountered by patients in this study. It was likely caused by pyrazinamide and levofloxacin [9]. The present finding is inconsistent with study findings from India [8]. The discrepancy may be due to variations in the inclusion of the causative drugs in the national MDR-TB treatment protocol between the countries.

This study identified determinants of adverse drug reactions among the patients attending St. Peter Hospital in Addis Ababa Ethiopia. Comorbidity and treatment outcome were the independent determinants of adverse drug reactions in the patients. But it found that any of the sociodemographic characteristics were not statistically significant with the development of adverse drug reactions.

Treatment outcome was significantly associated with an adverse drug reaction. The odds of adverse drug reaction in patients whose treatment outcome of cure were about 10 times higher than (AOR=10.012, 95% CI, (2.131-47.036)) those whose treatment outcome of failure. The study finding was also in line with studies conducted in India and Russia [6,10-12]. The possible reason could be those patients who were cured might be closely followed by tuberculosis treatment care providers and as a result, they got better reporting of ADRs and favorable treatment outcomes.

The study revealed that MDR-TB patients who had comorbid diseases were about 6 times more likely (AOR=5.809, 95% CI (1.106-30.504)) to develop adverse drug reactions than those who had not the disease. This finding is consistent with previous reports [13-15]. In the presence of comorbidities, the patients taking several medicines, whether prescription or over-the-counter, contributes to the risk of having an ADR. The number and severity of ADRs increase disproportionately as the number of drugs taken increases. It may also be related to medications that are useful in the treatment of one disease that may precipitate or worsen another condition.

This study showed that a history of smoking, alcohol use, drug abuse, and sociodemographic characteristics such as sex, age, living condition, marital status, educational status, and occupation of MDR-TB patients was not significantly associated with the development of adverse drug reactions. However, a previous study has reported that age, sex, smoking, and alcohol use had a significant association with adverse drug reactions [4,16-20]. The possible explanation for this disparity might be the existence of variations in genetic factors, culture, beliefs, and living conditions. It might also be related to the difference in the number of study participants used among the studies.

Strengths and Limitations of the Study

Clinical records were reviewed using a pre-tested structured data collection format to minimize information bias. Data quality was assured by trained nurse data collectors and close supervision.

The use of complete data from registers and patient cards, and for the reporting of adverse drug reactions and associated factors

is also one of the strengths of this study. Whereas reporting bias might exist, as data were obtained retrospectively through medical card review, especially for adverse events not defined by laboratory tests, such as gastrointestinal disorders, which might overestimate or underestimate the magnitude of adverse events. Some important confounding factors might not have been collected in this study. Electronic medical records are designed for daily use in hospital clinical diagnosis and treatment, not for analysis of adverse reactions/events of drugs used, so the records might lack some information needed to detect adverse events, and these were likely to result in bias in the study.

Conclusion and Recommendation

The prevalence of adverse drug reactions among MDR-TB patients was found to be higher. The majority of the study participants experienced more than one adverse drug reaction. The commonly reported ADRs were nausea, vomiting, dyspepsia, abdominal pain, and arthralgia.

The study showed that comorbidity and treatment outcomes were the independent determinants of adverse drug reactions among MDR-TB patients in the hospital. However, socio-demographic variables and behavioral factors were not significantly associated with the development of ADRs.

Based on the finding of this study, the following important recommendations are forwarded management strategies should be strengthened to minimize ADR occurrence and for better treatment outcomes. MDR-TB Patients having comorbid diseases should be closely monitored and given special counseling to minimize the development of ADRs. Patients should be educated on the possible ADRs of MDR-TB drugs.

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