

INCIDENCE AND RISK FACTORS FOR ADVERSE DRUG EVENTS AMONG PATIENTS ON ANTI-TUBERCULAR MEDICATIONS IN PUBLIC HOSPITALS, ILORIN, NIGERIA.

BELLO Shakirat I.^{1*}, YUSUF Hadiza², ALIYU Fullaila O.¹ and FALOKUN Emmanuel P¹

¹Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin, Nigeria. ²Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, University of Maiduguri, Maiduguri, Nigeria.

***Corresponding Author's E-Mail:**

sibello10@yahoo.com

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Abstract

Background: Tuberculosis (TB) is a major global health burden, threatening patients' physical and mental health. **Objective:** The study's objective was to evaluate the incidence and determinants of Adverse Drug Events (ADEs) among patients on anti-TB medications attending primary and secondary healthcare facilities in Ilorin, Kwara State.

Methods: From November 2021 to January 2022, a cross-sectional, retrospective, and prospective survey using questionnaires and oral interviews was conducted among 178 TB patients attending General Hospital (GHI), and Olufadi Health Centre (OHCI) in Ilorin metropolitan were enrolled. Out of the 178 patients enrolled, 91 patients with ADEs were interviewed. Convenience sampling was used to enrol patients. Participation in the study was voluntary. Descriptive and multivariate logistic regression analyses were employed for the data collected.

Results: Two hundred and seventeen of ADEs to anti-tubercular medications were encountered among 70 patients in GHI, giving an incidence rate of 53.4%. In OHCI, ninety-six (44.7%) ADEs were recorded. In GHI, the most frequently involved organs/systems were the gastrointestinal/hepatobiliary/renal system and central and peripheral nervous system. In OHCI, mostly affected organ/system is the central and peripheral nervous system. In both facilities, the majority of the patients reported ADEs experienced to the doctors. An appreciable number of the patients attending GHI and OHCI experienced moderate adverse effects. The majority of the patients in GHI had proficient knowledge of ADEs, while most of the patients in OHCI had deprived knowledge of ADEs. The most frequently reported ADEs were nausea, vomiting, skin rash, increased thirst and urination.

Conclusion: In the settings of this study, the incidence rates of ADEs found among the patients undergoing anti-tubercular therapy were high. The major risk factors associated with the ADEs were age and male in both facilities.

Keywords: Adverse drug events; incidence rate; determinants; anti-TB medications; patients' knowledge.

Introduction

Tuberculosis (TB) incidence has increased in recent years, posing a major threat to patients' physical and mental health.^[1] Every year, around 10 million cases of TB are reported worldwide, with 1.5 million deaths.^[2] In 2019, 87% of new TB cases occurred in the 30 high TB-burden countries, with eight countries accounting for two-thirds: India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.^[3] In sub-Saharan Africa, about 2.5 million people were infected, with 665,000 deaths.^[4] Despite the region's appreciable improvement in TB management, it remains one of the top causes of morbidity and mortality^[3]. Multiple medications administered for a long time in treating TB might cause adverse drug events (ADEs)^[4].

The majority of ADEs associated with anti-TB are mild and can be handled with proper supervision and monitoring. Severe ADEs, usually necessitate discontinuation of the offending drugs.^[5] ADE incidence varies, ranging from 8% to 85%. The disparity in ADE incidence could be due to differences in physician definitions of

ADE terminologies and whether ADEs were reported by patients or detected by clinicians, among others.^[6] According to a study in Nigeria, patients getting monitored treatment and short-course treatment-experienced about 14% and 13% ADEs at 6 and 8 months, respectively.^[6] Severe ADEs were also found to be less common (2% to 8%) and resulted in treatment termination or modification.^[7] Further studies reported various incidence rates of ADEs with anti-TB medications; India (2.3% to 17%), Mehrotra (17.39%), and Calcutta (27.9-35%).^[5] The study aimed at evaluating ADEs among patients on anti-TB medications attending primary and secondary health care facilities in Ilorin, Nigeria, with the view to assessing patients' knowledge of ADEs and determining the risks for the adverse events experienced.

Methods

Study Setting

The study was carried out in the General Hospital, Ilorin (GHI) and Olufadi Health Centre, Ilorin (OHCI), Kwara State. GHI is a well-known secondary healthcare facility in Ilorin West Local Government Area, Kwara State. It came into existence on 2 May 1980. OCHI is a primary healthcare facility located in Ilorin South Local Government Area. It is located in the centre of Ilorin and ran by the Kwara State Ministry of Health. GHI is a 100-bed hospital that provides in-patient and outpatient medical services to people in Kwara State and neighbouring states. The facility has pharmacists, physicians, nurses, and other healthcare providers. OCHI is a primary healthcare centre managed by the Ilorin South Local Government of Kwara State. The facility provides health promotion, disease prevention and appropriate treatments for patients within the area and the suburb. It consists of nurses, community health workers, and health information personnel. The patients' turnaround was about 76 per week^[8]. Kwara State is in the North Central Geopolitical Zone of Nigeria. The indigenous tribes in Ilorin are the Yorubas and the Hausa-Fulanis^[9].

Study Design

In November 2021 and January 2022, a cross-sectional, retrospective and prospective survey using questionnaires and oral interviews was conducted among TB patients attending two public facilities in the Ilorin metropolitan (TB clinics of GHI and OCHI). One hundred and seventy-eight patients on anti-TB medications were enrolled on the study. The Ilorin metropolitan was purposively chosen based on high recorded TB patient numbers.

Study Population and Sample Size

The total population of TB-infected patients on active anti-TB medications in the two studied facilities was 178, with GHI at 131 and OCHI having 47. The entire population for the sample size was used since the population is small^[10]. Thus, this study's entire population of 178 patients was used as a sample size. Those involved in the study were outpatients within the age range of 16 years and over. The patients were able to express themselves verbally. Participation in the study was voluntary and written informed consent was obtained before enrolling participants. A pharmacist directed patients, and a nurse was trained as a recruiter in each facility. The pharmacist conducted face-to-face interviews with the enrolled patients in English language, pidgin English, Hausa, or Yoruba language (the predominant local language). All the patients involved agreed to participate in the study.

Study Tool and Data collection

The administered questionnaire was designed by selecting relevant questions from previously published research. The questionnaire comprised four sections, including (i) socio-demographic information, (ii) information on anti-TB medication taken, (iii) Information on ADEs experienced by the patients and (iv) patients' knowledge about ADEs. Patients' socio-demographic characteristics such as age, gender (male or female), formal education attainment (primary school or lower, secondary school or National Senior Certificate and higher), marital status (married, single, divorced, or widowed) and monthly income earned by the patients. The questionnaire was piloted at one secondary health facility and one primary health facility outside the study setting for validity and reliability. The questionnaire was adjusted before distribution to the targeted patients. Patients were required to indicate their response to each question by choosing either 'yes' or 'no'. Each adverse event was ticked based on subjective information from the patients. A retrospective review of the patient's medical records was also conducted to establish further information on ADEs.

Data Analysis

Data generated were analyzed with Statistical Package for Social Sciences (SPSS) version 23. Descriptive and multivariate logistic regression analyses were performed. Statistical significance was considered at $\alpha < 0.05$ and a 95% confidence interval.

Ethical Consideration

Ethical approval was obtained from the Kwara State Ministry of Health Ethical Review Committee with the assigned number; MOH/KS/EU/777/589 dated 10 November 2021. Cooperation of relevant heads of departments in the study sites was sought and obtained. The confidentiality of data extracted from patients' medical records was ensured.

Results

Demographic Characteristics of the Patients

In GHI and OHCI, most patients were males older than 60 (Table 1). A preponderance of patients attending both hospitals had a primary level of education. Most patients were single in OHCI, while many were married in GHI. Muslims were the majority in OHCI, and about half were Christians in GHI. As many of the patients were high-income earners (above ₦70,000 salary per month) at OHCI, low-income earners (below ₦30,000 salary per month) were the majority in GHI. Among the 131 patients studied in GHI, only seventy had ADEs and 21 patients in OHCI.

Table 1: Socio-Demographic features of Patients on Anti-TB drugs in GHI and OHCI, Nigeria

Variables	GHI (70) n (%)	OHCI (21) n (%)
Gender		
Male	41(58.6)	12(57.1)
Female	29(41.4)	9(42.9)
Age		
16-19	14(20.0)	3(14.3)
20-40	20(28.5)	1(4.7)
41-60	9(12.9)	6(28.6)
> 60	27(38.6)	11(52.4)
Highest Educational Qualification		
Primary	23(32.9)	8(38.1)
SSCE/GCE	21(30.0)	4(19.0)
Diploma	17(24.3)	6(28.6)
B.Sc.	7(10.0)	3(14.3)
Masters	2(2.8)	0(0.0)
Marital Status		
Single	33(47.1)	14(66.7)
Married	34(48.6)	5(23.8)
Divorced	3(4.3)	2(9.5)
Religion		
Islam	30(42.9)	15(71.4)
Christianity	37(52.9)	5(23.8)
Traditional	3(4.2)	1(4.8)
Monthly Income (Naira)		
Low (<30,000)	27(38.6)	4(19.0)
Medium (30,000–70,000)	18(25.7)	4(19.0)
High (>70,000)	25(35.7)	13(62.0)

ADEs among patients observed in GHI was 217, while 96 were recorded in OHCI (Table 2). In GHI, the gastrointestinal/hepatobiliary/renal system and the central and peripheral nervous systems were prominently affected organs/systems. These were followed by systemic signs and symptoms, metabolic/endocrine, and cardiovascular/respiratory systems. The skin and appendages (6.4%) and musculoskeletal systems (6.4%) were less affected by the ADEs in GHI. In OHCI, 96 ADEs were found among 21 patients, while commonly affected organs/systems were the central and peripheral nervous systems. The least affected organs/systems were skin and appendages and musculoskeletal systems.

Table 2: Adverse Drug Effects among patients on Anti-TB drugs in GHI and OHCI, Nigeria

Organ/System	ADEs	GHI Frequency of ADEs 217 (%)	OHCI Frequency of ADEs 96 (%)
Skin and appendages			
	Pruritus	3(4.3)	1(4.8)
	Skin rash	10(14.3)	6(28.6)
	Steven Johnson syndrome	1(1.4)	0(0.0)
Gastrointestinal/ hepato-biliary/renal system			
	Abdominal pain	6(8.6)	3(14.3)
	Constipation	1(1.4)	2(9.5)
	Diarrhoea	1(1.4)	1(4.7)
	Dyspepsia	0(0.0)	0(0.0)
	Hepatomegaly	0(0.0)	0(0.0)
	Jaundice	1(1.4)	0(0.0)
	Nausea	23(32.9)	8(38.1)
	Vomiting	18(25.7)	5(23.8)
Metabolic/endocrine system			
	Lipodystrophy	0(0.0)	0(0.0)
	Polydipsia (increased thirst)	15(21.4)	6(28.5)
	Polyuria (increased micturition)	15(21.4)	6(28.5)
Systemic signs and symptoms-general			
	Anaemia	0(0.0)	0(0.0)
	Fatigue/Weakness	7(10)	3(14.3)
	Fever	9(12.9)	5(23.8)
	Malaise	4(5.7)	2(9.5)
	Sweating	11(15.7)	7(33.3)
	Rigours/Chills	3(4.3)	2(9.5)
	Others	0(0.0)	0(0.0)
Central and peripheral nervous system			
	Anorexia	6(8.6)	1(4.7)
	Anxiety	3(4.3)	1(4.7)
	Blurred vision	11(15.7)	4(19.0)
	Depression	2(2.9)	2(9.5)
	Dizziness	6(8.6)	3(14.3)
	Headache	11(15.7)	6(28.6)
	Insomnia	2(2.9)	2(9.5)
	Nightmares	0(0.0)	0(0.0)
	Pain/numbness/tingling	9(12.9)	4(19.0)

Table 2: Adverse Drug Effects among patients on Anti-TB drugs in GHI and OHCI, Nigeria (continued)

Cardiovascular system/respiratory system			
	Chest pain/ chest discomfort	13(18.6)	5(23.8)
	Dyspnea/Shortness of breath	5(7.1)	2(9.5)
	Palpitation	0(0.0)	0(0.0)
	Tachycardia	5(7.1)	1(4.8)
	Wheezing	2(2.9)	1(4.8)
	Tachypnea	0(0.0)	0(0.0)
Musculoskeletal system			
	Arthralgia	12(17.1)	6(28.6)
	Myalgia	2(2.9)	1(4.7)
	Myopathy	0(0.0)	0(0.0)

Patients' knowledge of ADEs

In GHI, the majority of patients had ADEs (Table 3). Most of the patients reported to doctors, followed by the nurses, then the pharmacists, and the least to a family member. In OHCI, only one-third of the patients reported ADEs, while most did not. More than one-half of patients reported to doctors and less than half to nurses. The majority of these patients knew ADEs were meant to be reported. Most GHI patients had proficient knowledge of ADEs, whereas, in OHCI, most patients had deprived knowledge of ADEs.

Table 3: Knowledge of TB Patients with ADEs in GHI and OHCI, Nigeria

Variables	GHI n (%)	OHCI n (%)
Do you report ADEs		
Yes	53(75.7)	8(38.1)
No	17(24.3)	13(61.9)
Whom reported to		
Doctor	34(64.2)	5(62.5)
Nurses	12(22.6)	3(37.5)
Pharmacist	6(11.3)	0(0.0)
Family	1(1.9)	0(0.0)
Do you know you should report when you have an ADE?		
Yes	45(84.9)	6(75.0)
No	8(15.1)	2(25.0)
Grading of knowledge of ADEs among the patients		
Good	53(75.7%)	8(38.1%)
Poor	17(24.3%)	13(61.9%)

Out of the 217 ADEs experienced by the patients in the GHI, most were moderately followed by mild cases. Only two patients experienced a severe form of ADEs. Also, in OHCI, half of the patients experienced moderate effects, less than half were mild, and few had severe ADEs. In both facilities, none had life-threatening cases (Table 4).

Table 4: Severity of Adverse Effects experienced by the patients on Anti-TB Medications in GHI and OHCI.

Degree of Severity	GHI ADEs experienced n (%)	OHCI ADEs experienced n (%)
Mild	102 (47.0)	42 (43.7)
Moderate	113 (52.1)	48 (50.0)
Severe	2 (0.9)	6 (6.3)
Life-threatening	0 (0.0)	0 (0.0)
Total	217 (100.0)	96 (100.0)

Table 5 shows the list of anti-TB medications in the studied facilities, the strength and the dosages at which they were administered.

Table 5: List of Anti-TB Medications in the Studied Facilities

Name of drugs	Strength	Dosage
Rifampicin	300 mg	600 mg once a day
Isoniazid	100 mg	300 mg once a day
Pyrazinamide	500 mg	1000 mg once a day
Ethambutol Hydrochloride	400 mg	800 mg once a day

Factors Associated with the development of ADEs among TB patients

In OHCI, the risk factors significantly associated with the development of ADEs among TB patients were male, age and income (Table 6). In GHI, those factors were male, age and higher education.

Table 6: Risk factors for ADEs among Patients on Anti-TB Drugs in GHI and OHCI, Nigeria

Factors	Odds Ratio	P-value	95% Confidence Interval
OHCI			
Gender (male)	1.038	0.001	0.769-1.303
Age (older)	2.471	0.001	0.909-2.257
Education (higher)	0.278	0.761	0.587-1.013
Marital Status	3.521	0.681	0.352-2.362
Religion	0.993	0.058	0.338-4.247
Low income	0.447	0.001	0.051-1.424
GHI			
Gender (male)	0.178	0.001	0.065-1.503
Age (older)	3.278	0.001	0.191-1.273
Education (higher)	5.634	0.002	4.957-7.779
Marital Status	4.447	0.981	0.456-3.001
Religion	1.340	0.001	0.869-1.499
Low income	0.387	0.713	0.043-2.356

Discussion

The primary way of preventing ADEs worldwide is through spontaneous reporting, the limiting factor of which is underreporting. Underreporting of ADEs is related to the knowledge and attitude of the patient, as reported by Olsson et al.^[11]. Most of the patients in our study were males in the two facilities studied. This follows the study by Ogbualor and Onwujekwe^[12], Mathew and Chandrasekaran^[13], where TB occurs more in males than in females. The age range of the study population with the highest occurrence of TB was 60 years and above. This was contrary to a study conducted by Michael et al.^[14], where it was found that the most prominent age group for the occurrence of TB was 40 years and over. The variation observed could probably be due to the setting of their study and the population used. Most of the study population had a primary level of education, were single and practised Islam as a religion. This is in agreement with the study carried out by Sadiq et al.^[15]. The study of Sant'Anna et al.^[16] further supported the relationship between religion and the incidence of ADEs.

The gastrointestinal tract was the most common system affected by ADEs of anti-TB medications. These ADEs were abdominal pain, constipation, diarrhoea, dyspepsia, hepatomegaly, jaundice, nausea and vomiting. This agrees with the study by Eric and Menzies^[17]. The second most common system is the central and peripheral nervous system, the ADEs of which include anorexia, anxiety, blurred vision, depression, dizziness, headache, insomnia, nightmares, pain, numbness and tingling. This was also observed in Berenguer et al.^[18], which reported a similar observation and was consistent with our study. General symptoms seen in our study included anaemia, fatigue/weakness, fever, malaise, sweating, rigours and chills, as supported by Sharma et al.^[19]. Out of the 91 patients studied, the incidence of ADEs was 44.7% at OCHI and 53.4% at GHI. The result was in line with a study by Shet et al.^[20], which shows a range of incidence rates of ADEs from 19.5% to 86%. Other studies reported incidence rates of 39.7% by Arriaga et al.^[21], 46.19% by Ahmad et al.^[22], 37% by Merid et al.^[23] and 34.5% (Ganiyu et al.^[24]); which are similar to our results. Earlier reports with results higher than the current findings were 71.5% by Caminero et al.,^[25] and 76% by Safurah et al.^[26]. The ADEs incidence rates recorded in both facilities studied were higher than that of Fei et al.^[27] (0.9%), Prasad et al.,^[6] (2%), Ganiyu et al.,^[24] (6.3%) and Han et al.,^[28] (19.5%). Our study showed that most TB patients had poor knowledge about ADEs in OCHI compared to the patients in GHI. This could be due to various factors, including age, which has a critical impact on ADEs. Both very young and very old patients are more vulnerable to these reactions than other age groups. This was supported by the research work of Wang et al. in China. Other factors were gender, race, pregnancy, breastfeeding, kidney problems, liver function, drug dose and frequency. Taking these factors into consideration during medical evaluation enables medical practitioners to choose the best drug regimen, as reported by Kigozi et al.,^[29].

The challenge of ADEs from anti-TB drugs in hospital-treated patients has two significant aspects. One is the patient's immediate risk of developing severe life-threatening complications. Such complications can easily be reduced if patients at risk are monitored appropriately using frequent laboratory testing. The other part of the problem was that ADEs might lead to the withdrawal of one of the essential drugs. Meanwhile, the termination of a single drug can be compensated for by other drugs, such as ethambutol or streptomycin. However, these alternatives do not provide the best treatment for three reasons. Firstly, the total duration of treatment is prolonged because any treatment without isoniazid or pyrazinamide must be continued for at least nine months, and treatment without rifampicin must be for at least 12 months^[30]. Secondly, it is well known that adherence to therapy decreases with increasing duration, making treatment failures more probable. Finally, patients who do not receive an entire course of standard therapy have a slightly higher risk of relapse^[31].

Most of the population in this study experienced moderate ADEs, including nausea, vomiting, diarrhoea and chest pain. This was in line with the findings of Dela et al.,^[32] where moderate ADEs were observed. Few patients had severe ADEs, which is in line with Prasad et al.,^[6] who reported severe ADRs among their patients. Most of our patients reported their ADEs to the physician during consultation, while others expressed them to the nurses during clinic visitation^[33]. Only a few informed the pharmacists in the two studied clinics, and only pharmacists documented the ADEs reported by the patients. This was found during the review of patients' medical folders in the TB clinics. The physicians receive most complaints but are never documented for pharmacovigilance interventions. This was similar to the work reported by Prashar et al.,^[34]. The reasons alluded to the lack of documentation by physicians were, firstly, the unavailability of the National Agency for Food and Drug Administration and Control (NAFDAC) yellow forms in the clinic. Secondly, time constraints to filling out the form and, thirdly, improper monitoring of documentation by the (NAFDAC) staff attached to the clinic, who could have served as a reminder to the busy physicians. Probably, retraining and retraining of physicians could enhance better documentation of ADEs to improve patients' drug adherence and clinical outcomes due to ADEs. The anti-TB medications used in the studied facilities include; rifampicin, pyrazinamide, isoniazid and ethambutol. Rifampicin is generally a well-tolerated drug but is associated with orange discolouration of the body, nausea, anorexia, and diarrhoea^[35]. Mild arthralgia and myalgia have been reported frequently with pyrazinamide therapy^[36]. Hypersensitivity reactions, including rash, urticaria and pruritus, also have been reported with pyrazinamide.^[37] Gastrointestinal disturbances, including nausea, vomiting, and anorexia, also have occurred in patients receiving the drug.^[38] Muscle weakness, dizziness, nausea, dry mouth and vomiting are common with

isoniazid. Ethambutol's adverse effects include colour blindness, loss of vision, chills and swelling joints, as reported by Denholm et al.^[39]. In this study, the significant determinants of ADEs in the patients in both facilities were age, corroborated by Ganiyu et al.,^[16] low income, in consonance with the study of Vo^[40] and higher educational qualification, similar to Imam et al.,^[41]

Conclusion

In the present study, the incidence of ADEs among patients on anti-tubercular therapy was high with the concurrent use of multiple anti-tubercular agents. However, the overall ADEs to anti-tubercular drugs observed in both hospitals were moderate. The significant risk factors of ADEs among patients in both hospitals were age and male.

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