

CLINICAL PROFILE, DRUG UTILIZATION PATTERN AND ADVERSE DRUG REACTIONS OF ANTI-TUBERCULAR DRUGS AT DOTS CENTER IN A TERTIARY HOSPITAL

Chaudhary A,¹ Sarraf DP,² Bhattarai NR,³ Chaudhary A,⁴ Rauniar GP²

¹Department of Drug Administration, Kathmandu, ²Department of Clinical Pharmacology and Therapeutics,

³Department of Microbiology, ⁴Department of Orthodontics, College of Dental Surgery, BPKIHS, Dharan, Nepal.

ABSTRACT

Most of anti-tubercular drugs (ATD) cause various adverse drug reactions (ADRs) leading to significant morbidity which may have negative consequences on drug adherence and treatment outcome. The objectives of the study were to know the clinical profile of patients receiving ATD, to identify the pattern of ADRs caused by ATD and to know the drug utilization pattern (DUP) in different types of tuberculosis (TB). A prospective observational study was conducted among patients diagnosed with TB at DOTS center in BPKIHS from June 2017 to May 2018 and occurrence of any ADRs were detected during their monthly visit. Descriptive statistics were used to analyze the data. A total of 126 tuberculosis patients were on ATD therapy during the study period. Seventy five patients (59.5%) were male. Most of the patients (44.4%) belonged to age group 21-40 year. Pulmonary TB (66.7%) was more common than extra-pulmonary TB. Multi-drug resistant TB was detected in 4 patients (3.2%). Seventy one patients (56.3%) were found to be smear positive for acid fast bacilli. First line ATD was given to 122 patients (96.8%). Out of 126 patients, 116 (92.1%) reported occurrence of at least one ADR. A higher number of ADRs were observed in male (68.3%). Change in urine color was the most common ADR (92.9%) followed by nausea and vomiting (39.7%). Further studies covering different regions of Nepal are needed to generalize the findings.

KEYWORDS

Adverse drug reactions, clinical profile; drug utilization pattern; tuberculosis

CORRESPONDING AUTHOR

Dr. Aswani Chaudhary,
Clinical Pharmacologist,
Department of Drug Administration, Kathmandu, Nepal.
Email: chaudharyaswani@gmail.com
Orcid ID: <https://orcid.org/0000-0002-9484-5527>
DOI: <https://doi.org/10.3126/nmcj.v22i3.32650>

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*. It particularly affects the lung which is called as pulmonary TB (PTB); but it can affect other sites as well which is called as extra pulmonary TB (EPTB).¹ TB occurs in every part of the world. In 2016, the largest number of new TB cases occurred in Asia with 45% of new cases followed by Africa with 25% of the new cases. TB is one of the top 10 causes of death worldwide. In 2016, 10.4 million people fell ill with TB and 1.7 million died from it. Over 95% of the TB cases and the related deaths are in developing countries.² TB remains one of the major public health problem in Nepal. It is ranked sixth among the leading causes of death in Nepal. In 2016/17, total of 31,764 cases of TB were notified and registered at National Tuberculosis Program of Nepal. Most cases reported were among the middle aged with the highest of 47 % among 15 to 44 year olds.³ Combinations of isoniazid, rifampicin, pyrazinamide, ethambutol and/or streptomycin are the commonly used anti-tubercular drugs (ATD) for the treatment of TB through Directly Observed Treatment Short-course (DOTS).⁴

Drug Utilization Pattern (DUP) is defined as "The marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences." It provides insights into the drug use and drug prescribing and the efficiency of drug use and facilitates the rational use of drugs in populations.⁵ Common adverse drug reactions (ADR) due to the ATD are visual disturbances, peripheral neuropathy, jaundice, skin rashes, pancreatitis, hyperuricemia, ototoxicity and hypersensitivity reactions.⁶ Worldwide, many countries have started ADR monitoring programs with varying degrees of success. The frequency and nature of ATD induced ADR have been matter of concern in many countries. However, ADR monitoring is still in preliminary phase in Nepal; ADR of ATD has not been evaluated prospectively. DUP in different types of TB are also lacking. Therefore, this study was conducted to study the clinical profile of patients receiving ATD, to identify the pattern of ADRs caused by ATD and to assess the drug utilization pattern (DUP) in different type of TB at DOTS center in B.P. Koirala Institute of Health Sciences (BPKIHS).

MATERIALS AND METHODS

It was a prospective observational study carried among patients with TB registered at DOTS center in BPKIHS from June 2017 to May 2018. New and old cases of TB patients taking ATD, visiting DOTS centre at BPKIHS and patients who gave consent to participate were enrolled in the study. Patients co-infected with HIV/AIDS, diabetes mellitus and heart diseases, psychiatric diseases and patient having surgical cases of TB were excluded. Considering prevalence of ADR in a study by Chhetri *et al* as 54.7% at 95% confidence interval, 20% permissible error and 80% power and adding 5% for removing various bias, the sample size calculated was 126 using formula $z^2 * P * Q / L$.^{2,7} Purposive sampling method was used. A semi-structured proforma was used to collect the relevant data like age, sex, address, ethnicity, occupation, educational status, signs and symptoms, investigations performed, types of TB, DUP and ADR of ATD. Ethical clearance was taken from the Institutional Review Committee, BPKIHS.

Patients who meet the inclusion criteria were approached at the end of the consultation at DOTS center and the informed consent was taken. A self-designed proforma was used to collect sociodemographic data, signs and symptoms and investigations performed at first visit. Data on DUP and ADR were collected after one month of starting ATD and/or whenever patient visited to DOTS center for complaining of any ADR. The patients' health cards were reviewed for laboratory investigations and face-to-face interview was also conducted to collect the relevant data. PTB was defined as cases involving lung parenchyma with radiographic abnormalities. EPTB cases were defined as tuberculosis of organs other than the lungs, such as lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc. Smear positive cases were defined as having sputum smear examinations positive for acid fast bacilli (AFB). Cases with three sputum smears negative for AFB but clinical and radiological features compatible with active tuberculosis and showing improvement after empirical ATD were considered to be smear-negative cases. New cases were defined as patients never treated for TB or those who have received treatment for <1 month and previously treated were defined as patients who have received treatment for TB for >1 month from any source.

The data were entered into Microsoft Excel 2010. Descriptive statistics mean, mode, median, SD, frequency and percentage were calculated. The data were presented as tables

and graphs. The data were analyzed using SPSS version 11.

RESULTS

A total of 126 tuberculosis patients were enrolled for the study during the study period of one year. Most of the patients were male (57.9%), married (87.3%), aged 21-40 years and businessmen (33.3%). One hundred and twenty one patients (96%) were from Sunsari district. The mean age was 37 ± 17.3 year, median age was 22 years and the age ranged from 6 to 84 years. Most of the patients (42, 33.3%) had completed secondary level of education; higher secondary level education was completed by 21.4% (Table 1).

Fever (78.6%) was the most common sign at the time of diagnosis followed by cough (73.8%), weight loss (69.8%), night sweats (52.4%), malaise (50.8%) and blood in sputum (20.6%) (Fig. 1).

Liver function test (LFT), chest X-ray and sputum for AFB (Acid fast bacilli) were the most common investigations performed in the patients for confirming the diagnosis followed by urea and creatinine (31.7%), Genexpert (20.6%), sodium and potassium (17.4%) and adenosine deaminase (7.9%) (Fig. 2). Multidrug resistant TB were detected in 4 (3.17%) patients.

Eighty four patients (66.7%) had PTB and 42 patients (33.3%) had EPTB. Sixty patients (47.6%) were found to be smear positive for

Table 1: Sociodemographic characteristics of patients (n=126)

Variables		Frequency	Percentage
Gender	Male	73	57.9
	Female	53	42.1
Marital status	Married	110	87.3
	Single	26	12.7
Age group (years)	18-20	20	15.9
	21-40	57	45.2
	41-60	34	27.0
	>60	15	11.9
Residence (District)	Sunsari	121	96.0
	Terathum	2	1.6
	Jhapa	1	0.8
	Janakpur	1	0.8
Educational level	Dhankutta	1	0.8
	Illiterate	23	18.3
	Primary	9	7.1
	Secondary	42	33.3
Occupation	Higher secondary	27	21.4
	Bachelor and above	25	19.8
	Business	42	33.3
	Housemaker	32	25.4
	Student	26	20.6
	Job holder	15	11.9
	Unemployed	11	8.7

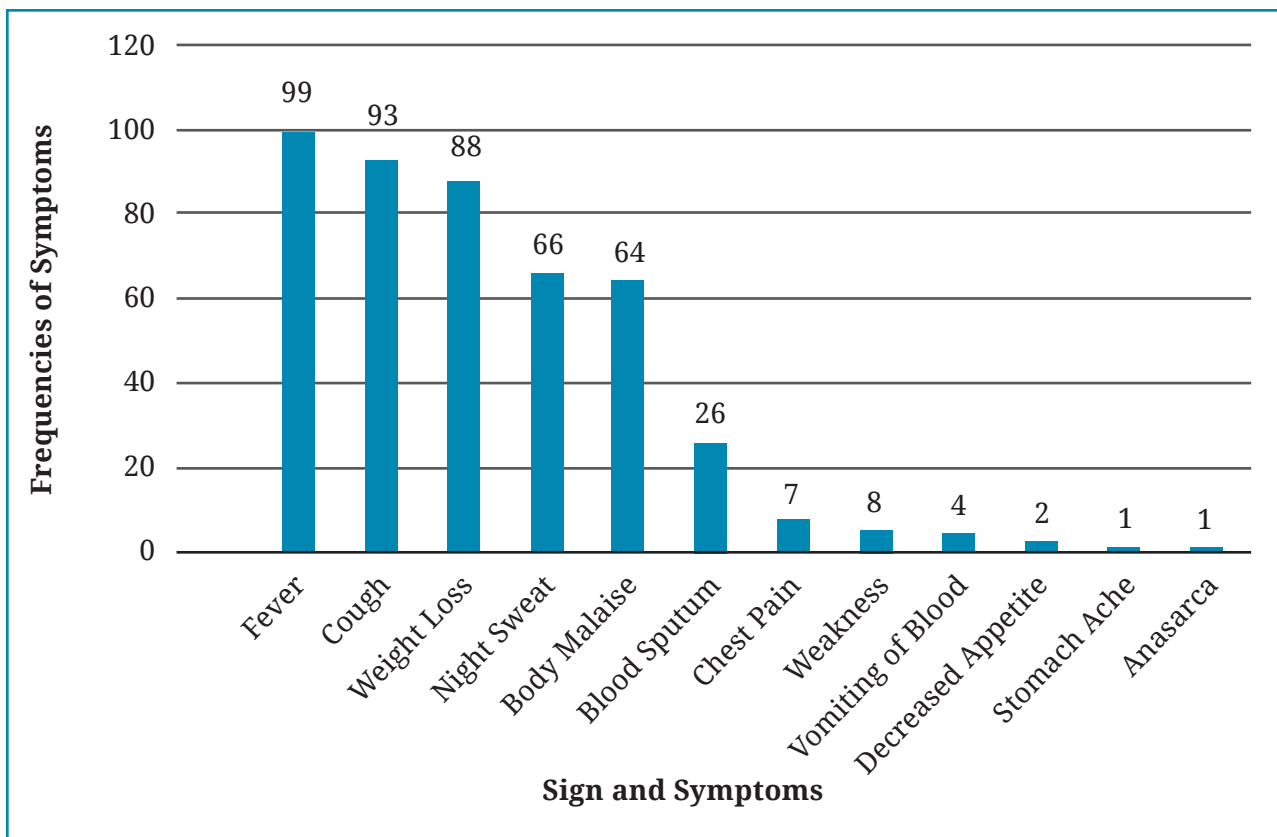


Fig. 1: Signs and symptoms at the time of diagnosis of TB (n=126)

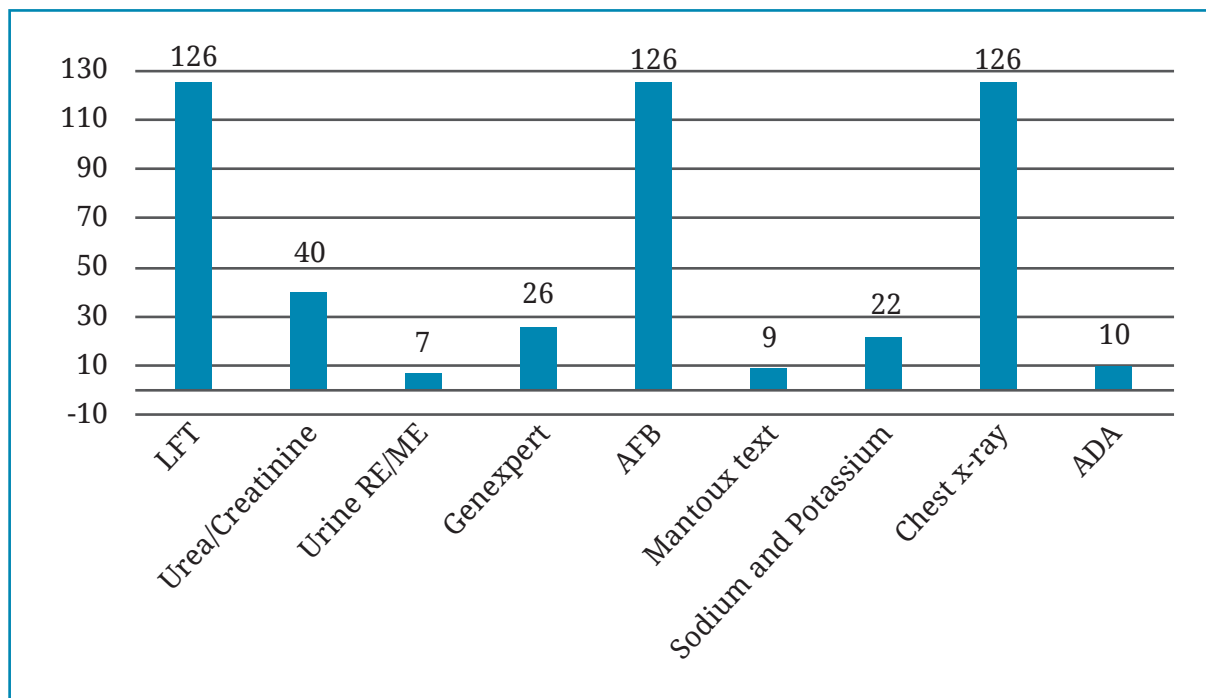


Fig. 2: Investigations done before starting ATD (n=126)

AFB. Out of 84 patients with PTB, 58 cases (69.0%) were found to be smear positive for AFB. Two cases (4.8%) of all EPTB patients were found to be smear positive for AFB (Table 2).

Out of 126, 114 (90.5%) TB patients were new cases. Tubercular lymphadenitis was observed in 18 cases (42.8%) followed by pleural effusion (10, 23.8%) and bone and joint TB (6, 14.2%) (Fig. 3).

First line ATD were given to 122 patients (96.8%) and second line ATD to 4 patients (3.2%). Out of 126 patients, 116 (92.1%) reported at least one ADR. The higher numbers of ADR were observed in males (58.6%). Change in urine color was the most common ADR (92.06%) followed by nausea and

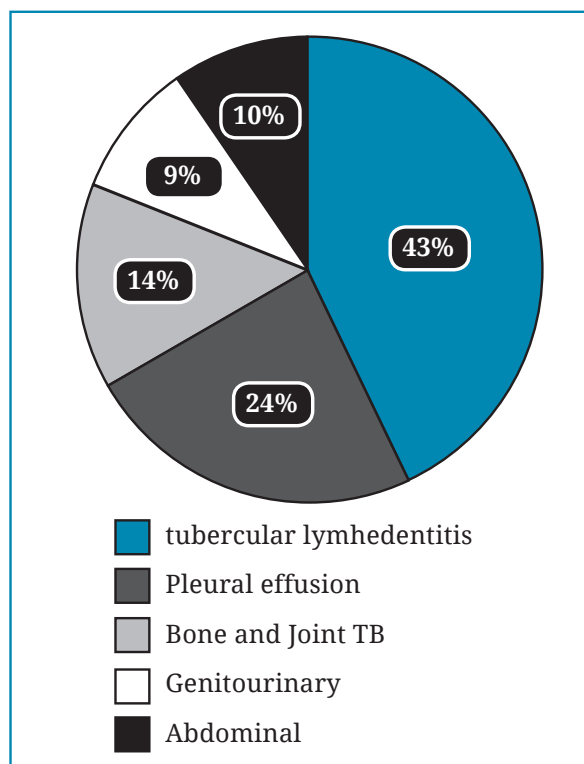


Fig. 3: Types of Extra pulmonary TB (n=42)

Table 2: Bacteriological status of TB patients (n=126)

Variables	Male	Female	Total (%)
Pulmonary TB (n=84)			
Smear positive	39	19	58 (69.0)
Smear negative	15	11	26 (31.0)
Total	54	30	84 (100.0)
Extra pulmonary TB (n=42)			
Smear positive	1	1	2 (4.8)
Smear negative	18	22	40 (95.2)
Total	19	23	42 (100.0)

Table 3: Drug utilization pattern of ATD (n=126)

Variables	Frequency	Percent
1st line ATD		
Isoniazid	122	96.8
Rifampicin	122	96.8
Pyrazinamide	122	96.8
Ethambutol	122	96.8
Streptomycin	2	1.6
2nd line ATD		
Kanamycin	4	3.2
Cycloserine	3	2.4
Levofloxacin	3	2.4
Other drugs		
Pyridoxine	126	100.0
Ranitidine	3	2.4

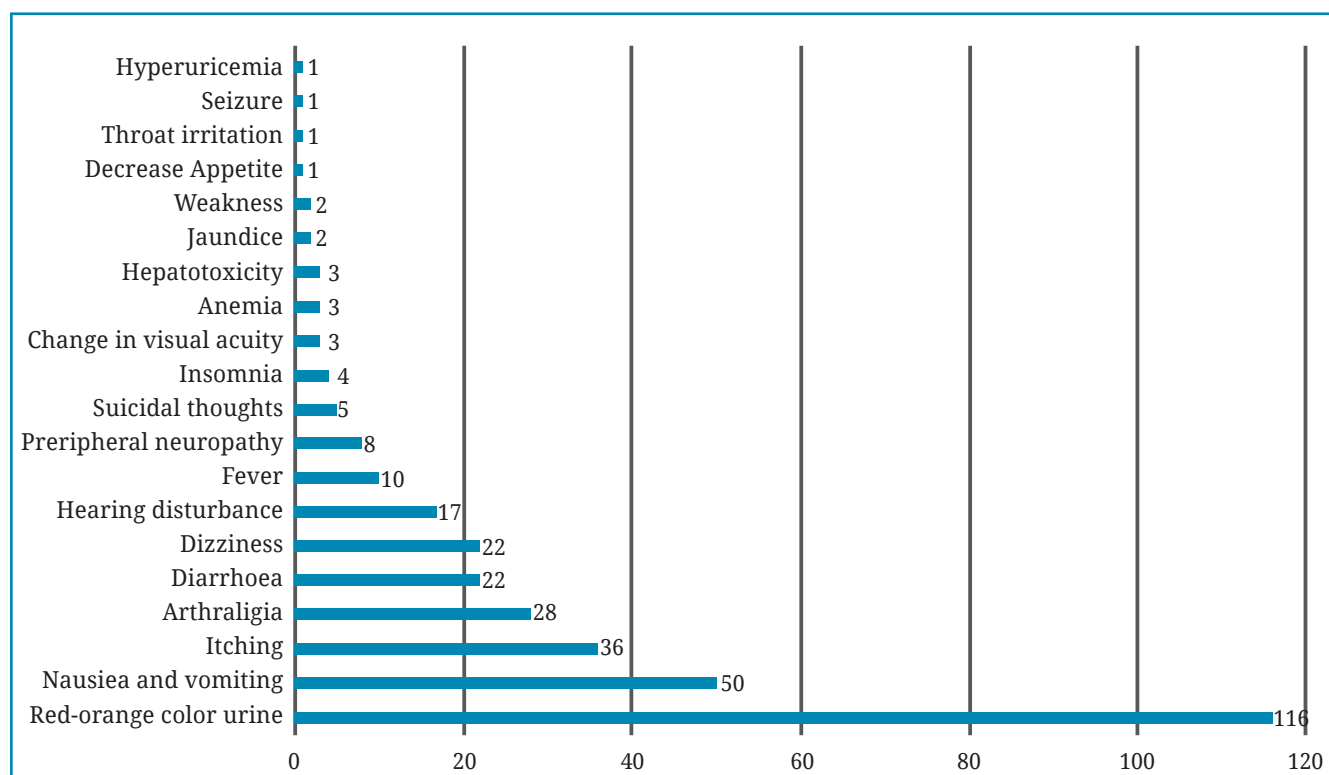


Fig. 4: Pattern of Adverse Drug Reaction in TB patients (n=126)

vomiting (39.7%), itching (28.5%), arthralgia (22.2%), diarrhea (17.5%), dizziness (17.5%) and hearing disturbances (13.5%) (Fig. 4).

DISCUSSION

In spite of being an ancient disease, TB is still a major public health problem globally.⁸ ATD consists of first line drugs used for the treatment of drug-sensitive TB and second-line drugs used for the treatment of MDR TB. Second-line drugs have many adverse effects than the first-line ATD. ATD are not free from ADR and may cause significant reactions both in severity & quantity leading to abstinence from therapy, prolonged hospital stay and even death.⁹

Our study found that more males were affected by TB and similar findings were also reported by Prakasha *et al.*¹⁰ This is probably due to the fact that males, who are usually working are being commonly exposed to the TB bacillus more than females. This may also be due to easy access to the diagnostic and treatment services among male compared to female.

Most of the patient belonged to age group 21-40 year with mean age of 37 years. This was consistent with other studies.¹¹⁻¹³ This is probably because people in this age group are involved in smoking and alcohol intake which results in the weakening of immunity.¹⁴ Most of the TB patients were literate and were businessmen. In contrast to this finding, the majority of the patients were illiterate and farmer in a study by Basnet *et al.*¹⁵

Fever was the most common sign and symptom of the patients at the time of diagnosis. In contrast to our study, cough with expectoration was the most common presenting symptom as reported by Acharya *et al.*¹⁶ Wang *et al* reported that cough was present in all TB patients.¹⁷ Differences in the symptom prevalence noted in the present study might reflect local variations in the disease. All the subjects suffering from signs and symptoms suggestive of TB were subjected to chest X-ray and LFT before starting ATD.

Two third of the cases were PTB. This finding was in accordance with that of Prakasha *et al* in which 58.7% cases were PTB.¹⁰ Similar findings were also reported by Priyadarshini *et al.*¹⁸ However, Thakur *et al* had reported a high prevalence (80.3%) of PTB.¹⁹ Tubercular lymphadenitis was the most common type of EPTB in our study and similar findings were also reported by Thakur *et al* in which lymph node was most commonly involved.¹⁹ Pleural TB was most the common type of EPTB in other

reports.^{10,20} Although PTB is the most common form, EPTB also causes significant morbidity and mortality. Bone TB has been suggested as an important cause of vertebral osteomyelitis and it is a common site of EPTB.²¹ A study conducted in Private Medical College in India revealed that about 83% of all cases diagnosed were EPTB.²¹ This could be due to availability of expertise and facilities for EPTB diagnosis. MDR-TB cases were detected in 3.17% patients in our study. Similar finding was also reported by Swaminathan *et al* and Dean *et al* in which MDR-TB was detected in 4% and 3.9% of the patients respectively.^{22,23} Almost 20% of all TB strains worldwide are resistant to at least one major TB drug, including isoniazid. Drug resistant TB is associated with greater morbidity compared to drug susceptible TB. It accounts for almost 25% of global TB mortality and is extremely costly to treat and it is a major threat to healthcare workers.²⁴

Nearly half of the patients were smear positive for AFB. This was consistent with a study conducted by Priyadarshini *et al.*¹⁸ In contrast to our finding, 37.81% TB patients were found to be smear positive by Prakasha *et al.*¹⁰ First line ATD were given to most of the patients in our study. This shows low prevalence of drug resistance in our study. Second line ATD were given to only four patients in our study. Pyridoxine was also prescribed to all patients as it prevents isoniazid induced peripheral neuropathy.

Out of 126 patients, 92.1% reported at least one ADR. A lower prevalence of ADR due to ATD was reported by Naser *et al* in which incidence rate of ADR was 66.21%.²⁵ Sreekanth had also reported lower incidence (53%) of ADR.²⁶ Only 7.79% TB patients had ATD induced ADR in a study conducted by Dedun *et al* in India.²⁷ In another study conducted in Western Nepal, prevalence of ADR due o ATD was 54.74%.⁷ This relatively high prevalence of ATD induced ADR in our study indicates that there is a need for more evaluation of susceptibility of patients for developing ADR. The difference in prevalence of ADR could have resulted due to various factors like genetic, demographic and nutritional status differences among the populations studied in different studies. These variations in results could be attributed to the varying number of study subjects in these studies. The high incidence of ADR in our study indicates that further studies should be undertaken in this region to corroborate the results and to see whether patients residing in this area are more susceptible for developing ATD induced ADR.

In our study majority of ADR (47.4%) was reported in age group 21-40 years which was similar to a report by Chhetri *et al.*⁷ In contrast to this result, age over 60 years was associated with increased incidence of ADR due to ATD in other reports.²⁸⁻³⁰ In our study ADR were more common in male and similar findings were also reported by Naser *et al.*²⁵ In contrast to this, ADR due to ATD was more common in female in a study by Chhetri *et al.*⁷ Female gender is considered as a risk factor for the occurrence of ADR due to their smaller body size and body weight compared to males.^{28,31,32} In this study, occurrence of ADR was more in the literate population as compared to illiterate. In contrast to our findings, occurrence of ADR was equal among the literate and illiterate population in the study by Chhetri *et al.*⁷ Educational programs can be targeted to the patients to make them more aware of the ADRs which ultimately help to increase the patient compliance.

Our study revealed that change in urine color, nausea and vomiting were the most common ADR due to ATD. Similar findings were also reported by Abideen *et al.*³³ This finding was also comparable to that found in the study conducted by Vieira *et al.*³⁴ Singh *et al* had also reported change in urine color as the most common ADR.³⁵ Multiple drug therapy may be the major predisposing factor for developing gastrointestinal problem. In contrast to our study, skin itching and rashes were most common ADR due to ATD in a study conducted by Fivy *et al.*³⁶ Itching was also observed in majority of patients in our study. pyrazinamide, rifampicin and isoniazid (INH) may be responsible for this ADR. In our study hepatitis was observed in 0.02% cases. Sreekanth had reported a higher prevalence (25.77%) of ATD induced hepatitis in his study.²⁶ It has been estimated that 10-20% of patients receiving INH developed elevated liver enzymes.³⁷ Liver toxicities can be the major side effect of INH, rifampicin and pyrazinamide. ATD induced hepatitis is due to formation of toxic metabolites or reduced clearance within three month. The drug dose may also play a role in ATD induced hepatotoxicity facilitated by pharmacogenetic factors.³⁸ The principal determinants of the ATD induced ADR are the dose and time of day at which the medication is administered as well as patient age and nutritional status together with the presence of preexisting diseases or dysfunctions such as alcoholism, impaired liver function, impaired kidney function and HIV coinfection.³⁹ According to a study done by WHO, ATD are known to be associated with number of adverse effects that can lead to drug discontinuation in up to 23%

of patients.⁴⁰ In general, patients who present with minor side effects should be encouraged to continue the treatment with symptomatic measures. In patients with major adverse reactions the offending drug, if identified, must be stopped or regimen should be modified so that patient could be protected from worsening of the underlined disease. The study had some limitations. It was a single-center study and therefore the findings could not be generalized to whole of the population of Nepal. Laboratory investigations to determine plasma or tissue drug concentrations could not be measured to correlate the ADR. Treatment outcomes could not be studied as it was a cross-sectional study. Sample size was small. Causality assessment of ADR was also not performed.

Present study shows that TB was more prevalent in the age group 21-40 years and among the males. Majority of the patients had PTB. Tubercular lymphadenitis was the commonest EPTB. Prevalence of MDR-TB was 3.17%. First line ATD was used in most of the patients. ATD have caused ADR mostly in male in 21-40 years age group. Most common ADR were change in urine color, nausea and vomiting, itching, arthralgia, dizziness, hearing disturbances and peripheral neuropathy. The results may help identify local variations in disease and improve the effectiveness of TB infection control programs. Identification of the ADR profile of drugs in a hospital setup can be useful for the prevention, early detection and management of ADR. There is a need for a system for proper monitoring for ADR due to ATD. A proper educational system may promote more ADR reporting by patients. These strategies may improve the patient adherence to the treatment plan. To generalize our results, further studies in large population is needed. Counseling of patients for timely prevention, detection and management of ADR should be incorporated in the TB management program.

ACKNOWLEDGEMENT

We would like to thank the patients who participated in the study.

REFERENCES

1. WHO, Fact sheet, Tuberculosis. Geneva, 2017. Available at <http://www.who.int/mediacentre/factsheets/fs104/en/> (Accessed on 22nd March, 2017).
2. Fact sheet: tuberculosis. WHO, 2018. [Available at <http://www.who.int/news-room/fact-sheets/>

- detail/tuberculosis (Accessed on 18th August, 2018.)
3. Annual Report 2073/74, National Tuberculosis Program. Ministry of Health & Population. National Tuberculosis Center, Bhaktapur, Nepal, 2017. Available at <https://nepalntp.gov.np/wp-content/uploads/2018/03/Final-Annual-Report-NTPN-2018.pdf> (Accessed on 18th August, 2018)]
 4. Hamlet N, Baral SC. Case Study of National Tuberculosis Programme Implementation in Nepal, 2002. Available at: http://siteresources.worldbank.org/NEPAL/EXTN/Resources/publications/tuberculosis_study.pdf. (Accessed on March 2, 2017).
 5. Introduction to Drug Utilization Research. WHO, Geneva, 2003. Available at <http://archives.who.int/tbs/rational/s4876e.pdf> (Accessed on March 2, 2017)
 6. Safety of Medicines: A guide to detecting and reporting adverse drug reactions. World Health Organization, 2002, Geneva. Available at http://archives.who.int/tbs/safety/esd_safety.pdf (Accessed on March 2, 2017)
 7. Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. A study of adverse drug reactions caused by first line anti tubercular drugs used in DOTS therapy in Western Nepal, Pokhara. *J Pak Med Assoc* 2008; 58: 531-6. [PMID: 18998303]
 8. Chen YH, Lin CB, Harnod T, et al. Treatment modalities for tuberculosis of the spine: 22 years' experience in east Taiwan. *Formosan J Surg* 2013; 46: 189-94. [DOI: 10.1016/j.fjs.2013.06.005]
 9. Tawanda Gumbo. Chemotherapy of Tuberculosis. In: Laurence Brunton (ed.) (2011). Goodman and Gillman's The Pharmacological Basis of Therapeutics. 12th edition. New York: Mc Graw Hill; pp.1549-1571.
 10. Prakasha SR, Suresh G, D'sa IP, Kumar SG, Rao R, Shetty M. A study of clinical characteristics and trend of different types of tuberculosis in coastal South India. *Ann Trop Med Public Health* [serial online] 2012; 5: 489-94. [DOI: 10.4103/1755-6783.105141]
 11. Edoh D, Adjei R. Rapid assessment of a National tuberculosis (TB) control Programme in Eastern Ghana. *Afr J Health Scin* 2002; 9: 159-64. [PMID: 17298160]
 12. Devesh KJ, R Yogananda, Anand BG, Sreeharsha. A study on anti-tubercular drug-induced adverse reactions in South Indian district tuberculosis center. *Int'l J Basic Clin Pharmacol* 2015; 4: 1267-70. [DOI: 10.18203/2319-2003.ijbcp20151370]
 13. Sinha K, Marak IR, Singh WA. Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy: Experience at an outpatient clinic of a teaching hospital in the city of Imphal, Manipur, India. *J Assoc Chest Physicians* 2013; 1: 50-3. [DOI: 10.4103/2320-8775.123213]
 14. Horne N. Tuberculosis and other mycobacterial disease. In: Cook G, editor. Manson's Tropical Diseases. Volume. 971. London: W.B. Saunders; 1996: 1015.
 15. Basnet R, Hinderaker SG, Enarson D, Malla P, Mørkve O. Delay in the diagnosis of tuberculosis in Nepal. *BMC Public Health* 2009; 4; 9: 236. [DOI: 10.1186/1471-2458-9-236.]
 16. D Acharya, JP Majra. A clinical-epidemiological study of tuberculosis among hospitalized cases in Dakshina Kannada district of Karataka. *NTI Bulletin* 2007; 43: 43-6. Available at <http://medind.nic.in/nac/t07/i3/nact07i3p43.pdf> (Accessed on 18th August 2018)
 17. CS Wang, HC Chen, CJ Yang, et al. Clinical characteristics of pulmonary tuberculosis patients from a southern Taiwan hospital-based survey. *Kaohsiung J Med Sci* 2008; 24:17-24. [DOI: 10.1016/S1607-551X(08)70068-8.]
 18. Priyadarshini BG, Ravikumar P, Umme S. A study of adverse drug reactions among pulmonary tuberculosis patients treated under DOTS in a tertiary care hospital. *Int'l J Basic Clin Pharmacol* 2017; 6: 779-83. [DOI: 10.18203/2319-2003.ijbcp20170941.]
 19. Ravikumar P, Priyadarshini BG. A study of extra-pulmonary tuberculosis and its outcome. *Int'l J Adv Med* 2017; 4: 209-13. [DOI: 10.18203/2349-3933.ijam20170113].
 20. Thakur CK, Khanal LK, Jain SK, Lamichhane B, Poudel A. Extrapulmonary Tuberculosis: A retrospective Study at a tertiary care hospital in Palpa, Nepal. *L M Coll J* 2013; 1: 56-8. Available at <https://jlmc.edu.np/index.php/JLMC/article/view/19/19> (Accessed on 18th August , 2018)
 21. VK Chadha, P Praseeja, J Gupta, et al. A descriptive study of tuberculosis case finding in private health care facilities in a South Indian district. *Int'l J Tuberc Lung Dis* 2014;18(12):1455-8. [DOI: 10.5588/ijtld.14.0228.]
 22. Swaminathan S, Datta M, Radhamani MP, et al. A profile of bacteriologically confirmed pulmonary tuberculosis in children. *Indian Pediatr* 2008; 45: 743-7. [PMID: 18820380]
 23. Dean AS, Cox H, Zignol M. Epidemiology of Drug-Resistant Tuberculosis. *Adv Exp Med Biol* 2017; 1019:209-20. [DOI: 10.1007/978-3-319-64371-7_11]
 24. Dheda K, Chang KC, Guglielmetti L, et al. Clinical management of adults and children with multi-drug resistant and extensively drug-resistant tuberculosis. *Clin Microbiol Infect* 2017; 23: 131-40. [10.1016/j.cmi.2016.10.008]
 25. Naser SM, Nandy M, Banu P, et al. Adverse drug reaction monitoring through active surveillance of antitubercular therapy in an urban tertiary care center. *Community Acquir Infect* 2016; 3: 51-4. [DOI: 10.4103/2225-6482.184913.]
 26. AS Sreekanth. Pharmacovigilance Study on Antitubercular Therapy in the Department of Pulmonary Medicine at a Tertiary Care Hospital. *IOSR JDMS* 2015; 14: 68-70. [DOI: 10.9790/0853-14876870]
 27. A Dedun, D Patel. A Profile of Adverse Effects of Anti-Tubercular Drugs. *GCSMC J Med Sci* 2016; 5: 37-41. Available at <http://www.gcsmc.org/xadmin/myaccount/upload/resource/a-profile-of-adverse-effects-of-anti-tubercular-drugs201810051243293676790.pdf> (Accessed on 18th August, 2018)

28. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003; 167: 1472-7. [DOI: 10.1164/rccm.200206-626OC.]
29. Gholami K, Kamali E, Hajiabdolbaghi M, Shalviri G. Evaluation of antituberculosis induced adverse reactions in hospitalized patients. *Pharm Pract (Granada)* 2006; 4: 134-8. [PMID: 25214900]
30. Koju D, Rao BS, Shrestha B, Shakya R, Makaju R. Occurrence of side effects from anti-tuberculosis drugs in urban Nepalese population under DOTS treatment. *Kathmandu Univ J Sci Engineering Technol* 2005; 1. [Available at <http://old.ku.edu.np/kuset/aej/dinesh.pdf> (Accessed on 18th August, 2018)]
31. Shakya R, Rao BS, Shrestha B. Management of antitubercular drugs-induced hepatotoxicity and therapy reintroduction strategy in a TB clinic of Nepal. *Kathmandu Univ Med J* 2005; 3: 45-9. [PMID: 16401944]
32. Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK *et al.* Adverse drug reactions associated with firstline antituberculosis drug regimens. *Int'l J Tuberc Lung Dis* 2007; 11: 868-75. [PMID: 17705952]
33. Abideen SP, Chandrasekaran K, Maheswaran U, Vijayakumar A, Kalaiselvan V, Mishra A *et al.* Implementation of Self Reporting Pharmacovigilance in Anti Tubercular Therapy Using Knowledge Based Approach. *J Pharmacovigilance* 2013; 1: 101. [DOI: 10.4172/jp.1000101.]
34. Vieira DE, Gomes M. Adverse effects of tuberculosis treatment: Experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. *J Bras Pneumol* 2008; 34: 1049-55. [DOI:10.1590/s1806-37132008001200010]
35. AK Singh, N Pant. Adverse effects of first line antitubercular medicines on patients taking directly observed treatment short course: A hospital based..... *IJMEDPH* 2014; 4: 354-8. [DOI: 10.4103/2230-8598.144063]
36. Fivy K, Azhar SSS, Syed WG. Adverse Drug Reactions of Primary Anti-tuberculosis Drugs Among Tuberculosis Patients Treated in Chest Clinic. *Int'l J of Pharm Life Sci* 2012; 3: 1331-8. Available at http://www.ijplsjournal.com/issues%20PDF%20files/january_2012/1.pdf (Accessed on 18th August 2019)
37. Kays MB, Koda-Kimble MA, Young LY, *et al.* Tuberculosis in applied therapeutics, clinical use of drugs, 8th edition, 2005. Lippincott Williams and Wilkins, USA. pp. 71-83.
38. Mohammad S, Ebrahim A, Hosein K, Mahboobeh H, Kheirollah G, Reza M. Antituberculosis Drug-Induced Hepatotoxicity in Iranian Tuberculosis Patients: Role of Isoniazid Metabolic Polymorphism. *Iran J Pharm Res* 2011; 10: 633-9. [PMID: 24250397]
39. Schaberg T, Rebham K, Lode H. Risk factors for side-effects of isoniazid, rifampicin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J* 1996; 9: 2026-30. [DOI: 10.1183/09031936.96.09102026]
40. N Awofeso. Anti-tuberculosis medication side effects constitute major factor for poor adherence to tuberculosis treatment. *Bull World Health Organ* 2008; 86: B-D. [DOI: 10.2471/BLT.07.043802]