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Research Article

Profile of adverse drug reactions in patients on anti-tubercular drugs in a sub Himalayan rural tertiary care teaching hospital

Atal Sood[1]*, Rekha Bansal[2], Aradhna Sharma[1], Himani[1], Suruchi Bhagra[3], Dinesh Kansal[1]

[1]Department of Pharmacology, [2]Department of Pulmonary Medicine, Dr R.P Govt. Medical College, Tanda, Kangra, Himachal Pradesh, India
[3]Department of Microbiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

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***Correspondence:**
Dr. Atal Sood,
E-mail: atalsood7@gmail.com

ABSTRACT

Background: Tuberculosis is a major public health problem, with one out of three people in the world are infected with *Mycobacterium tuberculosis*. The prevalence of MDR TB in India is 2-3% among new cases and 12-17% in reinfection cases. One of the reasons for MDR may be noncompliance to treatment due to adverse drug reactions. The present study was conducted to find out ADRs in patients on antitubercular treatment (ATT) under pharmacovigilance programme of India (PvPI).
Methods: This was a retrospective observational study. Data was collected through voluntary reporting by health-care professionals (HCP) in standard IPC-PvPI prescribed suspected ADR reporting form and analyzed for 100 patients on ATT. Causality assessment was done using WHO causality assessment scale.
Results: The maximum ADRs were reported in adults with a mean age of 40.79±16.79 years. Males (n=66) outnumbered females (n=34). There were 62% MDR-TB on DOTS-plus regimen, followed by 35% on Cat1 ATT for pulmonary and extrapulmonary tuberculosis cases and XDR-TB accounted for 3% of the total cases. The commonest ADRs in patients on MDR treatment were related to CNS 44 (27.5%), followed by Gastrointestinal system 31 (19%), psychiatric 20 (12.5%) otovestibular 13 (8%) and ophthalmic ADRs being the least in frequency 1 (0.6%). In contrast patients on Cat 1 ATT the ADRs involving Gastrointestinal system 44 (44%) followed by CNS 12 (12%), psychiatric 0% and ADRs related to otovestibular manifestations being the least 1 (1%) frequency.
Conclusions: ADRs involving different organ systems were seen in both categories with varied frequency. Adverse drug reactions add to hospitalization expenses, insurance costs and increase in work loss days besides addition to patient suffering and loss of compliance. Prior knowledge can help in better prescriptions and prevent valuable resource loss.

Keywords: Adverse drug reactions, MDR-TB, Cat1 ATT, Pharmacovigilance

INTRODUCTION

Tuberculosis (TB) has been a public health problem affecting our nation for long, inviting attention of physicians, public health specialists, researchers and policy makers in new, efficient, cost effective, pragmatic and different ways to tackle with this burden. One out of every three persons in the world are infected with *Mycobacterium tuberculosis*.[1] Latent infection with tuberculosis becomes active in people owing to factors like patient's immunity, diseases like HIV and diabetes, advancing age and other co-morbidities.

TB is generally treated with a short course of standard or first-line, anti-TB drugs (Cat 1 ATT). Mismanagement of therapy or resistance to drugs often leads to multidrug resistant TB (MDR-TB). MDR-TB is defined as resistance to both isoniazid and rifampin and may be any

number of other anti-TB drugs. MDR-TB takes longer to treat with second-line drugs, is more expensive, has more side-effects and is associated with higher mortality. Treatment of MDR-TB often entails higher cost to the patient and community, higher pill burden, low compliance rates and patient inconvenience.

The long treatment duration of 24 months and other factors deter the patient to take medicines as soon as they feel better. India accounted for 24 percent of the 5.7 million new and relapse TB cases notified globally in 2010.[2]India had the second highest total number of estimated MDR-TB cases (99,000) in 2008 after China (100,000 cases). Drug resistance surveys in several states have indicated that the prevalence of MDR-TB in India is 2–3 percent among new cases and 12-17 percent among reinfection cases.[3]

Primary MDR-TB in treatment naïve patients is also a challenge as it threatens to jeopardize and wipe out the gains made in the preceding years by successful RNTCP-DOTS implementation and by reducing TB deaths among people living with HIV/AIDS. Non treated MDR-TB patients often land up in extensively drug-resistant tuberculosis (XDR-TB) which is a form of tuberculosis caused by bacteria resistant to most effective anti-TB drugs often caused by misuse of second-line drugs.

XDR-TB strains have emerged from mismanagement of MDR-TB and once created can spread rapidly in the community due to restricted treatment options. XDR-TB is defined as TB that has developed resistance to at least rifampin and isoniazid, as well as any member of fluroquinolone family, and at least one of the following second line anti- tubercular injectable drugs among kanamycin, capreomycin or amikacin.[4] This definition of XDR-TB was agreed by the WHO Global Task Force on XDR-TB in October 2006.

Adverse drug reaction (ADR) reporting in our hospital started in 2015 under the Pharmacovigilance Program of India (PvPI). ADRs themselves are defined by WHO as an unintended and noxious response to a drug that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function.[5] ADRs themselves add to work loss, hospitalization costs, morbidity and mortality.

Aims and objectives

The purpose of this study was to find out the commonly encountered ADRs among patients on anti-tubercular therapy (ATT) in the hospital and assessment of their severity and causality.

METHODS

The study was conducted at ADR monitoring center (AMC) of Dr RPGMC Kangra at Tanda; Himachal Pradesh, India, a 585-bedded rural tertiary care teaching hospital after approval of institutional ethics committee. This was a retrospective observational study. Data was collected through voluntary reporting by health-care professionals (HCP) in standard IPC-PvPI prescribed suspected ADR reporting form and analyzed for 100 patients on ATT from 1st April, 2015 to 31th May 2016.

Causality assessment of ADEs was done by causality assessment committee using WHO causality assessment scale.

RESULTS

The data was analyzed for age and gender distribution, TB categorization, commonly reported ADRs among MDR-TB and TB including pulmonary and extra-pulmonary, time latency and seriousness of ADRs, followed by their causality assessment.

Age and gender distribution

Maximum cases were reported in adults. Mean age of patients was 40.79±16.79 years. Out of the total patients (n=100), twice the number of ADRs were reported in males (n = 66) than females (n = 34).

TB categorization

It was done on basis of therapy undertaken. 62 patients were suffering from MDR-TB, 31 patients on pulmonary TB (PTB), 4 patients on extra-pulmonary TB (EXTRA-PTB) and 3 patients on XDR-TB (Figure 1).

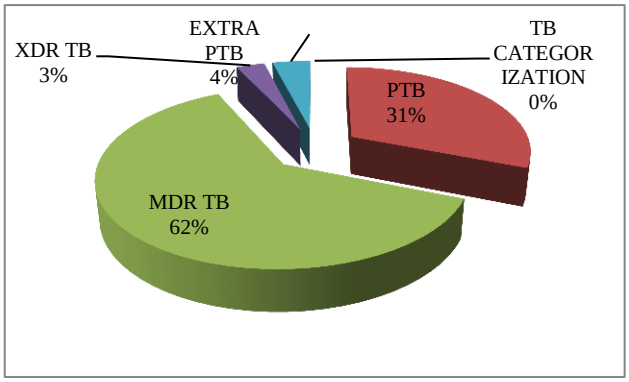

Figure 1: Disease distribution of patients among various categories of TB.

Common reported ADRs among various ATT regimes

A total of 160 ADRs were reported in 62 patients of MDR-TB and 100 ADRs were reported in 35 patients of PTB and Extra-PTB. Grouping of PTB with Extra-PTB was done since both patients received same treatment (Cat1 ATT). In 3 patients of XDR-TB 10 ADRs were reported. Commonest drugs causing ADRs observed in this study were DOTS-Plus anti-tubercular drugs for MDR-TB. As high as 62 patients out of total 186 (33.3%)

on MDR therapy in Chest and TB clinic reported with ADRs. Drugs include levofloxacin or ofloxacin, cycloserine or Para amino salicylic acid (PAS), ethionamide, pyrazinamide, ethambutol and kanamycin. Standard Cat1 ATT includes rifampin, isoniazid, ethambutol and pyrazinamide.

Table 1: Common ADRs experienced in different ATT regimens.

Organ system involved	Symptoms	MDR therapy ADRs N (%): n = 160	CAT 1 ATT ADRs N (%) : n = 100
CNS	Insomnia, dizziness, headache, amnesia, tremor, confusion, peripheral neuropathy	44 (27.5%)	12 (12%)
Gastrointestinal	Anorexia, nausea, vomiting, gastritis, hepatic dysfunction	31 (19%)	44 (44%)
Psychiatric	Depression, psychosis	20 (12.5%)	0 (0%)
Otovestibular	Hearing loss, tinnitus,vertigo	13 (8%)	1 (1%)
Musculoskeletal	Joint pains, hyperuricaemia	8 (5%)	6 (6%)
Dermatological	Rashes, pruritus	3 (2%)	10 (10%)
Endocrinal	Gynaecomastia	3 (2%)	0 (0%)
Ophthalamic	Blurred vision	1 (0.6%)	0 (0%)
Others	Irritability, slurred speech, suicidal thoughts, fatigue, alopecia, dysguesia, haemoptysisetc	37 (23.4%)	27 (27%)

System wise distribution of ADRs was done for ease of analyzing data and it was observed that CNS and psychiatric ADRs predominated among MDR patients with less frequent gastrointestinal complaints. On the other hand gastrointestinal ADRs were the chief complaints in patients on Cat1ATT, followed by CNS ADRs. Contrast could also be observed in the near absence of psychiatric ADRs in patients on Cat1 ATT with respect to patients receiving DOTS-plus regimen (Table 1).

Sub-analysis of data revealed that amongst these MDR patients, CNS ADRs like insomnia (21%) dizziness (19.3%) depression (17.7%) psychosis (14.5%) and hearing loss (13%) were found followed by gastrointestinal ADRs anorexia (16%) nausea (14.5%) vomiting (9.7%), gastritis and liver dysfunction (4.5%). Other ADRs with declining frequency were tinnitus (8%) joint pains and hyperuricaemia (6.5%) and still less were gynaecomastia, rashes, rarer CNS ADRs like amnesia, tremors and confusion all observed in 4.5%.

This was contrary to the observations in patients on Cat1 ATT, for PTB and Extra-PTB. The commonest ADRs were gastrointestinal including anorexia (40%) liver dysfunction (37%) vomiting (25.7%) gastritis (14.3%) and nausea (8.5%). Commonest CNS ADRs observed in patients on Cat1 ATT were dizziness (20%) and insomnia (8.5%).

Dermatological ADRs like rashes and pruritus were observed in 14.3% of the patients on Cat1 ATT. Hyperuricaemia was seen in 11.4% of these patients while rare ADRs included joint pains, fever, fatigue and urine discoloration each with a frequency of 5.7% (Figure 2).

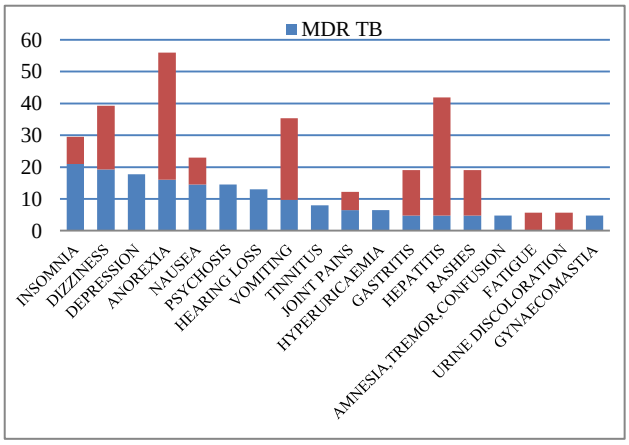

Figure 2: Category wise ADRs amongst patients on ATT.

Still rarer ADRs among MDR patients include peripheral neuropathy, haemoptysis, alopecia, fatigue, hoarseness of voice and irritability each with a frequency of 3.2%. Single case of ethambutol induced ocular toxicity (1.6%) was documented with certainty and subsequent dechallange yielded satisfactory recovery in MDR regime. Similarly rarer ADRs among Cat1 patients included hyponatremia, peeling of skin, peripheral neuropathy, breast nodules, dysguesia, thrombocytopenia, dyspnea and oral ulcers all with a frequency of 2.8% each.

Time latency

Contrast was also observed among patients on DOTS-plus regime and Cat1 ATT with respect to ADRs being reported. Majority of ADRs in MDR-TB were chronic while fewer appeared within 10 days. However, majority of ADRs in patients on Cat1 ATT were acute or sub-acute in onset. Very few of these patients had chronic ADRs (Figure 3).

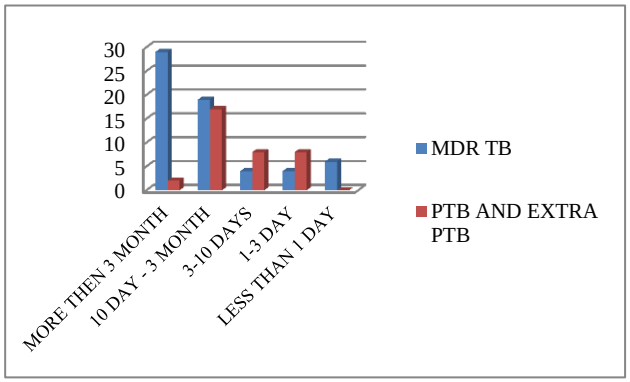

Figure 3: Depicts the time latency for ADRs among various ATT regimes.

Seriousness

Hospitalization was required in 11 patients of MDR-TB and 14 patients on Cat1 ATT. 7 patients developed disability among MDR-TB due to ADRs adding to financial costs, loss of man hours and deterioration of quality of life. Majority of patients (n=64) experienced ADRs which were non-serious. However no death or life threatening ADR was reported in this study (Figure 4).

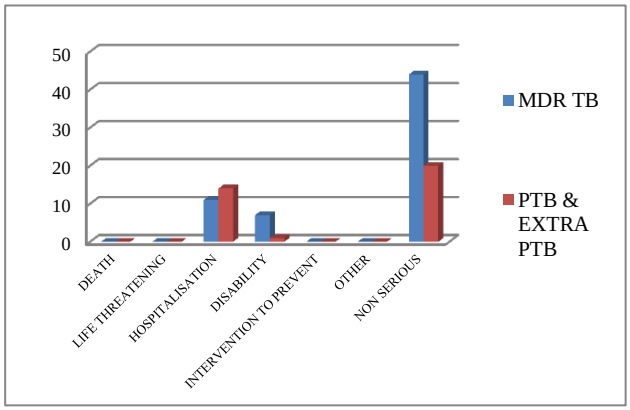

Figure 4: Seriousness of ADRs according to different ATT regimens.

Causality assessment

Causality assessment of the cases was done by the causality assessment committee of hospital and it was observed that among MDR-TB 43 patients (69.3%) had possible ADRs due to the drugs they undertook and 19 patients (30.7%) had probable ADRs. Patients on Cat1 ATT had equal number of possible and probable ADRs (16 each).Certainty to ADRs was ascribed in only 3 patients in the latter group (Figure 5).

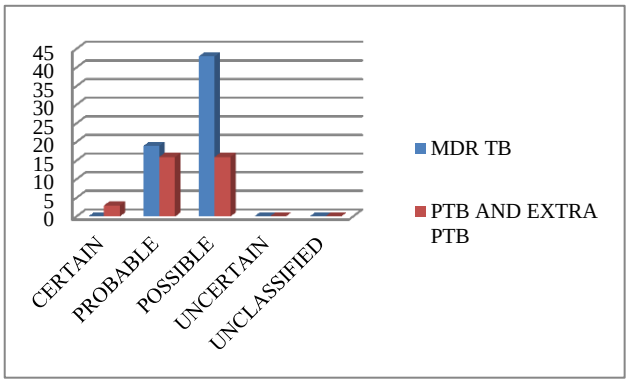

Figure 5: Causality assessment of ADRs among various ATT regimes.

DISCUSSION

Adverse drug reactions are different from the adverse drug events in the fact that adverse drug reactions are well documented and known. Adverse drug events are suspected to be due to drugs and signals picked up in pharmacovigilance help in documenting ADEs as ADRs.

Voluntary spontaneous reporting of adverse reactions has proven to be an effective way in early signal generation. Tremendous efforts have been made by the PvPI to encourage voluntary spontaneous reporting in the form of continuing medical education (CME), media publicity, availability of Smartphone based apps for android and apple platforms (https://medwatcher.org/mobile) and toll free number for voluntary reporting (18001803024 Monday to Friday 9:30-5:30). Adverse drug reactions add to hospitalization expenses, insurance costs and loss of workdays besides adding to patient suffering. At the community level it puts strain to the limited public health resources in the developing world.

The incidence of ADRs among MDR patients was 33.3%. This was much lower than reported by Kapadia VK et al as 57% and Hire R et al as 52%.[6,7] The mean age observed in our study were 40.8±16.8 years with males (66%) outnumbering females(34%). This is in partial agreement with a study from Ahmedabad which reports the mean age as 34±11.5 with male predominance of 63.5%.[7] Sinha K et al reported the mean age as 38.4 with male predominance of 76%.[8] Males are more vulnerable for TB because of higher incidence of smoking, alcoholism, drug addiction, more mobile socially and hence visit public places more often. All these are risk factors for TB. [9]

On comparison of ADRs of DOTS-plus regimen with other studies it was observed that our results were in

concordance with other studies, however other studies report much lower incidence of CNS ADRs (Table 2).

Despite gastrointestinal ADRs with 19% frequency, no patient quit DOTS-Plus therapy. Insistence on treatment continuation by HCPs and family could be an important factor for this. Quinolones and ethionamide were found to be culprit drugs after causality assessment. These ADRs can be mitigated by pretreating the patients one hour prior with domperidone or H2 blockers.

Table 2: Comparison of ADRs according to different studies on MDR patients.

ADR (System involved)	Hire R et al [6]	Kapadia VK et al[7]	Torun T et al[10]	Thomas A et al[11]	Wai Yew W et al[12]	Present study (%)
CNS	4.5	12.7	31.2	8	17.5	27.5
Gastro intestinal	30	22.2	14	67	20	19
Psychiatric	5	-	-	-	-	12.5
Oto-vestibular	-	4.8	41.8	13	14.3	8
Musculoskeletal	5.5	8	11.4	-	7.9	5
Dermatological	3.6	1.6	4.5	13	1.6	2
Endocrine	-	1.6	-	-	-	2
Ophthalmic	0.9	3.2	-	-	3.2	0.6

Hepatic dysfunction is a known ADR and pyrazinamide with ethionamide had a probable causal relationship. Psychiatric ADRs as depression and psychosis constituted 12.5% which were again a bulk of reported ADRs. Cycloserine is known to cause psychosis as a late manifestation as mentioned in previous studies.[13]These patients were started with PAS after omitting cycloserine from DOTS-Plus regimen. Vertigo was having definite causal relationship with kanamycin, as all amino glycosides are known to be otovestibulotoxic due to the production of free radicals.[14]

Aminoglycosides induce an increase of free radicals by stimulating the N-methyl-D-aspartate (NMDA) receptor leading to damage to the inner ear hair cells due to this changed milieu. Arthralgia was found in this study could be due to pyrazinamide and quinolones. Pyrazinamide produces arthralgia and arthritis by causing hyperuricaemia while quinolones cause cartilage damage, Achilles tendon rupture and tendinitis.[15] Though tendinitis is rare ADR with quinolones, they exert a number of effects at cellular level, including reduced expression of some extra-cellular matrix proteins, non-cytotoxic inhibition of tendon cell proliferation and inhibition of tendon cell migration.[16]

Dermatological ADRs in the form of localized erythematous rash with hypersensitivity dermatitis and pruritus were observed and pyrazinamide had probable causal relationship. The reported incidence of rash with pyrazinamide ranged from 0.1- 5%.[17,18] Blurred vision was reported in one of the patients and found to have definite causal relationship with ethambutol. Some animal studies show ethambutol to deplete zinc from the optic nerve.[19] Sensory peripheral neuropathy was reported and ethionamide had probable causal relationship. As ethionamide is structurally related to isoniazid, it interferes with the utilization of pyridoxine and its increased urinary excretion leads to this ADR. Hence supplementation with pyridoxine is routinely done in MDR patients.

Comparison of ADRs with Cat1 ATT in various studies revealed that our results are in tandem with earlier studies which report gastrointestinal ADRs as the commonest.[8,20,21] As discussed earlier the commonest GI ADRs include anorexia, liver dysfunction, vomiting, gastritis and nausea in the declining order of frequency. After causality assessment it was found that rifampin and pyrazinamide were responsible for these ADRs. Hepatic dysfunction is more likely in patients with rifampin, pyrazinamide and isoniazid. INH acetylated phenotype also determines its ADR profile, compliance to therapy and its outcome.

Slow acetylators are at an increased risk of developing peripheral neuritis which occurs in nearly 2% of patients who are not administered pyridoxine concurrently, and receive INH at a dose of 5mg/kg/day. Peripheral neuropathy with INH is more common in individuals with diabetes mellitus, poor nutrition or anemia.[22] Other neurological problems include convulsions in patients of seizure disorders, optic neuritis and atrophy, muscle twitching, ataxia, parasthesias and toxic encephalopathy. Rapid acetylators on the other extreme are more likely candidates for treatment failure and relapse if INH is administered on alternate day schedule.[23]

INH is metabolized to acetyl isoniazid, which is further acetylated by NAT2 to diacetyl hydrazine, which is nontoxic. Alternatively, acetyisoniazid can be converted to acetyl hydrazine and then to a hepatotoxic metabolite by CYP2E1. Hence, rapid acetylators will quickly remove acetyl hydrazine while slower acetylators or

inducers of CYP2E1 like rifampin will lead to more toxic metabolites. This is the chief mechanism by which rifampin potentiates INH hepatotoxicity.[24] Deranged serum hepatic transaminases are common occurrence in patients on INH and manifest in a time frame of 4-8weeks after initiation of therapy. Dermatological ADRs as rashes and pruritus were attributed to rifampin, INH and pyrazinamide.

CONCLUSION

Majority of patients on DOTS-plus therapy reported ADRs after chronic administration and this could be due cumulative and toxic effect of drugs whereas the ADRs reported by patients on CAT1 ATT were mostly acute and sub-acute in onset.

Majority of ADRs among both treatment schedules were no serious and few required hospitalizations in both groups. No life threatening ADR or death was reported in either group. As discussed earlier possible ADRs outnumbered probable ADRs by a ratio of 2:1 in DOTS-plus regime, while equal number of possible and probable ADRs was observed in CAT1 ATT.

Limitations

Present study was retrospective and might have missed mild ADRs due to lack of documentation, complacency, ignorance, fear of litigation and compensation claims and lack of time in busy hospital schedules. Voluntary reporting by HCP has its own pitfalls and more such studies are required with more patients to pick up rare ADEs.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee, Approved vide no: HFW-H-DRPGMC/Ethics/2016 protocol no.21/2016.

REFERENCES

1. World Health Organization. Fact Sheet No. 104: Tuberculosis. 2007.
2. WHO. Global Tuberculosis Control: WHO Report 2011. 2011. [November 15, 2011]. http://whqlibdoc.who.int/ publications/ 2011/ 9789241564380_eng.pdf.
3. World Health Organisation (2006). Press release: "WHO Global Task Force outlines measures to combat XDR-TB worldwide.
4. WHO. Global Tuberculosis Control: WHO Report 2010. 2010. [September 18, 2011]. http://www.who.int/ tb/ publications/ global_report/ 2010/en/index.html.
5. World Health Organization. Technical report series no. 425. Geneva, Switzerland: World Health Organization; 1966. International drug monitoring: the role of the hospital. 1-24.
6. Hire R, Kale AS, Dakhale GN, Gaikwad N. A Prospective, Observational Study of Adverse Reactions to Drug Regimen for Multi-Drug Resistant Pulmonary Tuberculosis in Central India. Mediterr J Hematol Infect Dis. 2014;6(1):e2014061.
7. Kapadia VK, Tripathi SB. Analysis of 63 patients of MDR TB on DOTS plus regimen: An LG hospital, TB unit, Ahmedabad experience. Guj Med J. 2013;68(2):52-7.
8. 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.
9. Lonnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008;8:289.
10. Torun T, Gungor G, Ozmen I, Maden E, Bicakci B, Atac G, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005;9(12):1373-7.
11. ThomasA, Ramchandra R, Rehaman F, Jaggarajamma K, Santha T, Selvakumar N, et al. Management of multi-drug resistant tuberculosis in the field- Tuberculosis Research Centre experience. Indian J Tuberc. 2007;54:117-24.
12. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of Patients With Multidrug-Resistant Pulmonary Tuberculosis Treated With Ofloxacin/ Levofloxacin-Containing Regimens. Chest. 2000;117:744-51.
13. Vega P, Sweetland A, Acha J, Castillo H, Guerra D, Smith Fawzi MC, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8:749-58.
14. De Jager P, Van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis. 2002;6:622-7.
15. Arora VK, Tumbanatham A. Severe arthropathy with ofloxacin in two cases of MDR tuberculosis. Int J tuberc lung dis. 1998;2(11):941-6.
16. Wen-Chung Tsai, Yun-Ming Yang. Fluoro-quinolone-associated Tendinopathy. Chang Gung Med J. 2011;34:461-7.
17. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide

in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996;9:2026-30.
18. Reider HL. Interventions for tuberculosis control and elimination. International union against tuberculosis and lung disease, Paris, France. 2002:1-251.
19. Kahana LM. Toxic ocular effects of ethambutol. Can Med Assoc J. 1987;137:213-6.
20. Athira B, Manju CS, Jyothi E. A study on adverse drug reactions to first line antitubercular drugs in DOTS therapy. Int J Pharmacol and ClinSci. 2015;4:7-11.
21. Nanda GS, Singh H, Sharma B, Arora A. Adverse Reactions Due to Directly Observed Treatment Short Course Therapy: An Indian Prospective Study. IAIM. 2016;3(1): 6-12.
22. Gumbo T. Chemotherapy of Tuberculosis, Mycobacterium Avium complex Disease, and Leprosy. In: Brunton LL, Chabner B, Knollman B editors. Goodman & Gilman's. The Pharmacological Basis of Therapeutics.12thed. New York: McGraw Hill; 2011;1549-70.
23. Pande JN, Pande A, Singh SPN. Acetylator status, drug metabolism and disease. Natl Med J India. 2003;16:24-6.
24. Roy PD, Majumder M, Roy B. Pharmacogenomics of anti-TB drug-related hepatotoxicity. Pharmacogenomics. 2008;9:311-21.

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