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A Critical Analysis of Literature Associated with Adverse Drug Reactions Experienced by Tuberculosis Patients

Don Rameez[1] & Saurabh Kumar Banerjee*[2]
[1] Ph.D. Research Scholar, School of Pharmaceutical Management, IIHMR University, Jaipur, Rajasthan, India | Email: rameez.j17@iihmr.in
[2] *Dean & Associate Professor, School of Pharmaceutical Management, IIHMR University, Jaipur, Rajasthan, India | Email: saurabhk77@gmail.com, Mobile: +91-8890398067

ABSTRACT
Tuberculosis (TB) has been one of the most fatal diseases in the world, especially in the recent decades, with majority of its presence in India and other developing countries. The treatment of TB includes directly observed treatment (DOTS) therapy which comes with its efficacy and drug resistance issues, including high incidence of adverse drug reactions (ADRs), since a greater quantity of drugs given to the patients causes a higher rate of adverse effects.

This paper is a critique (critical analysis) that focuses on reviewing various research papers exploring ADRs associated with the management of TB across urban hospitals in India. Five research papers were analyzed, that aimed to identify the types and incidence of ADRs occurring during the treatment of TB and to evaluate the effectiveness of the pharmacovigilance system in reporting and managing ADRs in these settings. The studies were conducted for an average of nine months and consisted of about 100-200 HIV negative TB patients in the age group of 16 - 60 years with similar demographics. These patients were not MDR-TB positive and received both Category 1 & Category 2 DOTS therapy for controlling TB.

The factors contributing to ADRs were examined and ways to minimize their occurrence were explored.
Aim: The aim of this critical analysis is to help improve the safety and efficacy of TB treatment in urban hospitals in India and contribute to the development of better pharmacovigilance strategies, by performing a critical analysis of five research papers detailing studies conducted in TB patients of similar demographics in urban healthcare settings.

Keywords: Pharmacovigilance, Tuberculosis, Adverse Drug Reactions (ADRs), India, Critical Analysis

INTRODUCTION

Tuberculosis (TB) being one of most deadly diseases, has almost a fourth of us infected, and it has been a key public health issue in India since more than three decades. India reports one-fifth of global TB cases each year and tops the curve among the highest afflicted countries. The estimation is that yearly about 330,000 Indians have died due to TB.

Treatment of TB comprises of drug combinations to increase the efficacy and reduce the development of drug resistance. But the more the quantity of drugs given to the patients, the higher is the rate of adverse effects of drugs that get added further. The incidence of adverse drug reactions (ADRs) being excessive and severe with these drugs results in further dropouts, modification of regime and inadequate treatment. This contributes to the occurrence of multi-drug resistant (MDR) and extensive drug-resistant (XDR) strains that increase the morbidity and mortality rates. These resilient strains necessitate second-line drugs for cure, which have greater cost and added seriousness of ADRs. The overall incidence of ADRs with first-line anti-TB drugs is also high, and it varies from 8.4% to 83.5%, prominently of higher incidence rates in males than in females.

ADRs account for 5% of infirmary admissions, appear in 10-20% of hospitalized patients and are the fourth leading cause of mortality globally. The need to identify and address ADRs can never be overemphasized as ADRs adversely affect the quality of life of patients, instigate them to lose confidence in their physicians, raise the expenses of healthcare, preclude the use of medicines in most patients, causing futile investigations and interruption in the management of TB. India launched its National Program of Pharmacovigilance in 2005 which was renamed as Pharmacovigilance Program of India (PvPI) in 2010. World Health Organization (WHO) based Vigi-Base is the largest individual case safety reports (ICSR)

database for ADRs. Active drug safety monitoring (aDSM) in India since 2015 is used to identify, manage and report alleged or established drug toxicities of TB patients on treatment with novel medicines for MDR and XDR TB.

The objective of this critical analysis is to evaluate five (5) research white papers published in 2020s, presenting studies performed to understand and collect information regarding ADR management and reporting limitations in patients of TB who undergo directly observed treatment (DOTS) therapy in urban hospitals across India. These papers also assess the corresponding limitations that are faced from a pharmacovigilance perspective and provide further guidance for future researchers.

SUMMARY

5 research papers were reviewed which consisted of studies performed for an average duration of 9 months with about 150 HIV negative TB patients in the age group of 16-60 across both genders with similar demographics, having TB but not MDR-TB, on DOTS therapy and gave their consent for being a part of the research. The patients enrolled in the studies were across both Category 1 & 2 DOTS therapy which is an accepted TB treatment strategy for over two decades to control the increasing deaths due to TB and for controlling its spread across India.

The most common ADRs observed in TB patients were majorly Hepatitis and issues relating to gastrointestinal tract, thereafter fatigue, nausea and vomiting, and issues with liver, skin, urinary system, nervous system, otovestibular apparatus and vision. In most cases, severe ADRs were not a majority of the ADRs observed

MATERIALS AND METHODS

The methodology used for this paper included a search across various virtual databases (PubMed, ScienceDirect, Shodhganga and Google Scholar) using multiple search strings including terms like ‘Pharmacovigilance’ ‘Tuberculosis’ ‘India’ etc. to arrive at a few articles matching required criteria. Several papers were reviewed to shortlist five research papers with similar conditions of tuberculosis being studied having comparative demographical backgrounds. These were analysed individually and simultaneously for lacunae and shortcomings which were recorded along with the factual correctness of the papers studied.

RESULTS

All papers clearly mention the appropriate titles/ topic which was followed by the names of the authors and their affiliations. The 5 papers reviewed are well-structured and material is organised under appropriate headings. The sections match up and are divided logically into subsections and paragraphs and there is adequate clarity across the paper.

CRITIQUE OF THE INDIVIDUAL PAPERS:

Paper 1[1]:

This was an overall clearly written paper and adequately described study. Barring a few grammatical errors, the quality of this paper is quite commendable.

This study involved 222 patients observed/enrolled for 6 months (Jul 2017 – Dec 2017). For the critique related to each section, refer to **Table 1** below.

Table 1

Have we missed reporting adverse drug reactions under Revised National TB Control Programme (Krishnappa L, Gadicherla, S, Jan 2020)

Section	What was observed
Abstract	The abstract concisely mentions the overall summary of the paper and clearly mentions the main aim and findings. It has been neatly divided into sections such as Objective,

	Methods, Result & Conclusion. It represents the overall concept of the paper and gives a brief overview of what has been mentioned ahead in the various sections of the paper. It does not mention any data that is not represented in the paper or material that cannot be substantiated. The statement of purpose matches between the abstract and introduction. **Is the overview of research conducted mentioned concisely?** Yes, and it covers the required points adequately. **Has the research problem been identified?** It explains the challenges relating to ADR reporting researched during the study in the 'Objective' section. **Have the methods used have been outlined, and the main findings and recommendations detailed?** The methods used and the main findings are outlined but the recommendation mentioned in the conclusion section of the abstract is not entirely satisfactory as it simply brushes upon the results, not further discussing the key results. A recommendation (section) could mention a summary of further details as discussed in the paper.
Introduction	The introduction provides a capsule summary of the disease and its treatment in India, it gives a brief history of the issues with anti-TB treatment (ATT) and its associated ADRs, hence providing a rationale for the study. It also refers to a few related studies conducted and provides a context for the aim of the study. **Is the problem clearly identified?** Yes, it is clearly identified and described with an applicable background. **Is the aim and rationale given for the research?** Yes, it is to identify the prevalence of ADRs during the ATT initial phase amongst TB patients in RNTCP and to determine the challenges faced and any gaps in the reporting of ADRs. **Is the need for the research proposed identified in the literature?** Yes, (since ADR reporting studies conducted with ATT receiving TB patients under RTNCP were limited). **Do the literature review topics have any gaps?** There is always a question of whether all research articles or studies which have been published relevant to the topic were covered or not, for providing an introductory background to the research paper. Although there is no separate 'Literature Review' section in the paper, there is a study background in the reviewed literature for the paper. It is provided a by the examination and evaluation of other area research, which led to a need for the new research that was proposed in the initiation phase of ATT for TB patients in India.

Ethics	The ethics section adequately mentions the name of the board granting the ethics approval and specifies that the study was initiated after receiving the approval and written consent from participants.
Methods	The methods section of the paper adequately covers the mixed method research (quantitative and qualitative) that was performed, along with the study setting. The various sections describe the study execution, geography, its inclusion and exclusion criteria, and other study related details. **Have the methods been coherent with the quantitative and qualitative research?** Yes, the research methods have been followed. **Is the approach clearly stated?** Yes, the sequence of the study conduct seems to be satisfactory. **Have the methods been justified and explained clearly?** Yes, the quantitative method clearly mentions recruitment, questionnaire-based interviews, follow up, causality assessment and validation of the ADRs observed. **Have any vital details been provided, in order that anyone can replicate the research?** Yes, the details of a questionnaire that is previously tested and is semi-structured that is being utilised to assess the understanding, approach and training of RTNCP staff, is mentioned in a table further; however, all the providers of health-care were self-administering them during monthly meetings of the study and hence there is a possibility of bias being created during self-filling of the form by the HCPs, and not only misunderstandings. **Have the data collection details been clearly justified and described?** Yes, they are undoubtedly described. The methods of data collection could have been more robust by exploring the following: • Qualitative research could have been carried out by an independent investigator and not a part of the 12 researchers executing the study. • Furthermore, the documentation of the group discussions (GD) was also done by 2 investigators from the team of researchers. • Even though this was conducted in local language, a third party fluent in local language should have moderated the GD & documented the results. • It wasn't clear how qualified was the treatment supporter who was monitoring the treatment of the patient, adherence counselling and ensuring adequate documentation was maintained, throughout the study phase which was quantitative. **Any ethics considerations that are defined and clarified?** Yes, it has been adequately documented.
Analysis	The analysis sections describe the research method which was mixed (quantitative and qualitative) and conducted to analyse the results of the study using various techniques.

	It is noted that the standards used for the qualitative research can be more clearly referenced in terms of the actual parameters used for the study. For example, the further details regarding: "The decision regarding theme generation was done using standard procedures and based on consensus. Concurrence for codes was checked and disagreement in codes were settled by discussion among investigators and final set of codes were prepared"
Results	The results are elaborately discussed in the paper touching upon each objective of the study and describing how it was fulfilled clearly with relevant data representation. The summary is presented in the form of well-defined tables and the qualitative aspect was covered well with quoted examples. **Are the results presented clearly and consistently?** Yes. In fact for the qualitative aspect of the study, sufficient detail is provided on how response was elicited and the relevant details are mentioned in this section. **Any tables or graphs adequately presented and consistent?** Yes there are tables and graphs for pictorial representation of data. A slight discrepancy is noted in the rounding off of 32.4% to 33% instead of 32% across text and table. Hence it cannot be ascertained for the remaining tables with no text to cross-check. **Has sufficient level of detail been provided?** Yes, details are sufficiently provided. **Any gaps in the gathering of data have been accounted?** Yes, the results section starts with enlisting all the gaps and issues noted during the study data collection phase.
Discussion	The discussion of the results obtained accurately catches the lacunae in the PV system and addresses the issues to be explored further and compares certain existing studies in the area. **Is the analysis and discussion balanced?** Yes, it is. **Is there acknowledgement of the strengths/weaknesses of the study?** Yes, the gaps are noted in the last para after discussion. **Is the discussion referring back to the points being raised in the review of literature?** Since there isn't a separate section of review of literature, it was still done to a certain extent.
Conclusion	The conclusion seems to serve the purpose of concluding all the findings of the study inadequately and seems too short not covering all the aspects that a conclusion should ideally cover like the gaps and weaknesses, and maybe recommendation, etc. **Have the conclusions been supported by the results?**

	Yes. **Have any study implications been identified?** Not in detail as it is a very short conclusion.
Recommendations for future research	Although this wasn't a separate section in the paper, the discussions section highlighted the gaps which can be worked upon in future studies. **Have any recommendations outlined any possible areas of research in the future?** Not very exclusively. **Have any ways to improve current research been recommended?** Yes. Since training was provided in English instead of the local language, the qualitative part of the study had gaps although a majority of them had been trained (88%).
Acknowledgement	This study was a government (of Karnataka) sponsored study and all stakeholders are acknowledged sufficiently for their contributions.
Financial Support	Although it was a government sponsored study, it is explicitly mentioned that the relative officers did not have a role in or influence in any way, the conduct, design or analysis of the results.
Conflicts of Interest	It is clearly mentioned in the section that there were no conflicts of interest.
References	The section adequately mentions references to 14 publications in all and also mentions the hyperlinks to access each one of them.
Other Miscellaneous Observations	Since training was provided in English and not the local language, the qualitative part of the study has gaps noted although a majority of them had been trained (88%). Although the causality could not be associated as probable/possible/likely, the ADR should have still been documented but there were training gaps which could probably be the reason.

Paper 2[2]:

This study led to the writing of a good paper and the overall comparison between active and passive ADR collection methods in the various sections throughout the paper.
This study involved 303 patients observed/enrolled for 12 months (Jan 2019 – Dec 2019). For the critique related to each section, refer to **Table 2** below.

Table 2 **A Comparative Study of Active and Passive Adverse Drug Reaction Monitoring Methods** **(Bansal A, Advani U, Dec 2020)**	
Section	**What was observed**

Abstract	The abstract concisely mentions the background, aim, methods used, results observed and the conclusion. It gives a holistic overview of what comes up next in the paper. **Is the overview of research conducted mentioned concisely?** Yes, and it covers the required points adequately. **Does it identify the main problem in the research?** No, it doesn't identify the real problem in the research throughout the section of abstract, but consecutively in the section of introduction that follows. **Are the methods, main outcomes and any recommendations outlined?** Yes, the methods and findings along with the conclusions are outlined, but not the recommendations.
Introduction	The introduction provides enough background information on the study with the history of Pharmacovigilance, the types of active & passive ADR monitoring methods including pros and cons with examples for comparison and context. There was no separate 'Literature Review' section in the paper, however, the introduction cited various literature articles reviewed for this study. The literature reviewed provided a background to the study by providing information and examining the lack of other research in the area, which led to a need for the study to be proposed to establish comparison between the active and the passive methods of ADR reporting in the DOTS TB patients in India. **Is the problem clearly identified?** Yes, that there are not enough studies performed in the area of comparing the 2 methods of ADR reporting- active and passive. **Is the aim and rationale given for the study?** Yes. **Is the need for the study proposed identified in the literature?** Since limited studies have been claimed to be conducted in this specific area, the research study has been proposed. **Do the literature review topics have any gaps?** The background to the research paper was sufficiently introduced; however, the question whether all research articles published relevant to the topic are covered or not still remains.
Ethics	There was no separate ethics section in the paper but the section on 'Materials and Methods' began with a note mentioning the study was conducted after Institutional Ethics approval . It was also mentioned that only the subjects ready to consent were included in the study.
Methods	The methods section of the paper outlines the basis of sample size calculations and gives details regarding the study approach and describes the methodology. There was

	a pilot study conducted prior to the study to calculate the sample size and the criteria of inclusion/exclusion for the study, as was mentioned in this section as well. **Have the methods been coherent with the quantitative and qualitative research?** Yes, the methodology used in the study follow the qualitative and quantitative approach. **Is the approach clearly stated?** Yes, it has been clarified exactly what was performed for both comparable groups of the study. **Have the methods been justified and explained clearly?** Yes. The active surveillance group was actively contacted personally or telephonically and the passive ADR monitoring group was permitted to passively report any grievances either by their physicians or themself. **Have any vital details been provided, in order that anyone can replicate the research?** Yes, the particulars of the duration, methodology and basis of the study have been described well. **Have the data collection details been clearly justified and described?** Yes. • The method for active surveillance group was for 6 months through questionnaires • The passive ADR monitoring group would report passively for any complaints through a drop-box having slips for ADR reporting **Any ethics considerations that are defined and clarified?** Yes, only those subjects ready to provide consent were included in the study.
Analysis	The analysis section interprets the results with respect to the lag period and coefficient of variation, analysing the results further.
Results	The results section summarises the findings of the study describing values for both the groups studied in terms of numerical yield, its consistency, comparison of differences and yield durations of ADRs reported. However, it was noted that there are not much details shared on the non-ADR reporting population or the limitations in identification and reporting of ADRs, etc in this section. **Are the results presented clearly and consistently?** Yes, however more detail could have been presented as text despite of the charts and tables containing data. **Any tables or graphs adequately presented and consistent?** Yes, the data is mainly tabulated or displayed in Pareto/Pie Charts or summarised as graphs .

	Has sufficient level of detail been provided? Further detail regarding exact numbers of patients providing ADR reports could not be ascertained as the data provided is only that of the number of ADRs in total and in the 2 groups categorically and the incidence rates. This level of detail seems to be sufficient for the kind of data analysis performed in the results section, but can help further analyse the data in terms of secondary conclusions from the study. **Any gaps in the gathering of data have been accounted?** None of the gaps, if identified, have been accounted for. This should have been included in the paper.
Discussion	The discussion mainly reflected the outcome of the study and comparison between active & passive methods of collecting ADRs. It also compared the types and number of ADRs reported, and also the discussion around yield and lag period observed. **Is the discussion and analysis balanced?** Analysis mainly only mentioned just a couple of statements regarding the stats analysis- lag period & co-efficient of variation. Whereas the discussion cited other studies **Is there acknowledgement of the strengths/weaknesses of the study?** No, the strength/weakness, if any, have not been acknowledged in the study. **Is the discussion referring back to the points being raised in the review of literature?** Yes. Although it is also noted that there weren't too many studies for comparison, due to the lack of enough data to compare, in terms of consistency, the active/passive methods.
Conclusion	The conclusion specifies an integrated approach between active and passive ADR reporting methods would be the best based on analysis of the results. **Have the conclusions been supported by the results?** Yes, based on the results obtained, the conclusions were drawn. **Have any study implications been identified?** The study implications are not identified in sufficient detail.
Recommendations for future research	The section on 'Future scope' recommends similar studies in future for diverse diseases to understand the diverse methods of monitoring of drug safety across varied diseases. **Have any recommendations outlined any possible areas of research in the future?** Yes, as mentioned above. **Have any ways to improve current research been recommended?**

	No. Though it does mention for the study to explored in different diseases to study their ADR reporting results between active and passive methods for further exploration but not for TB patients and current study scenario.
Acknowledgement	The patients of the study and the staff of the center are thanked for support during the study conduct in this section.
Financial Support	This section mentions that no financial support was received by the authors for their research, authorship, and/or publication of the article.
Conflicts of Interest	The authors have declared zero conflicts of interest in this section.
References	25 references are made throughout the paper, adequately covering the various sections of the paper.

Paper 3[3]:

This study enrolled 241 patients, but 17 were dropouts so effective enrolment was that of 224 subjects observed over a period of 18 months (Jan 2015 – Jun 2016). For the critique related to each section, refer to **Table 3** below.

Table 3
A prospective observational PV study of adverse drug reaction monitoring in patients of TB (Baig M S, Kale M R, Jul 2018)

Section	What was observed
Abstract	The abstract gave a brief overview of the study; however, it could have been framed a bit more appropriately to include the main points regarding the study conduct, maybe including recommendations, etc. The abstract contained sections on Background, Methods, Results and Conclusions. **Is the overview of research conducted mentioned concisely?** Yes. **Has the research problem been identified?** There was no real problem identified to find a solution through the study, since this study evaluated the types of ADRs and their frequency observed in TB patients. **Have the methods used have been outlined, and the main findings and recommendations detailed?** Yes, although the Recommendations could have been covered better in the abstract either within Conclusions section or separately.
Introduction	The introduction provides a background summary to the rationale of the study, referencing some studies from the past. The aims and objectives of the study are delineated clearly. **Is the problem clearly identified?** The problem is identified as ADRs during anti-TB treatment.

	Is the aim and rationale for the study given? Yes, it gives the aim and background rationale for the study. **Is the need for the research proposed identified in the literature?** No, it doesn't, but the study rationale is to study ADRs related to TB medication in further detail with respect to types, frequency, causality, severity and the incidence of treatment discontinuation. **Do the literature review topics have any gaps?** It might be possible that further literature reviewed in similar study settings would have given a better perspective to the research further. Although there was no separate 'Literature Review' section in the paper, the literature reviewed for the paper gave the study background by quoting other studies in the area for TB patients in India.
Ethics	There was no ethics section, but the paper indicated that the study was approved by the Institutional Ethics Committee.
Methods	The methods section of the paper briefly enlists the procedure followed during the study and the parameters researched. The inclusion & exclusion criteria are also outlined clearly. **Have the methods been coherent with the quantitative and qualitative research?** Yes, this study involved a quantitative approach by collecting data and analysing the results statistically. **Is the approach clearly stated?** No, but the parameters have been defined adequately so it could be considered as sufficient. **Have the methods been justified and explained clearly?** Yes, the paper clearly explains and justifies the methods. **Have any vital details been provided, in order that anyone can replicate the research?** Yes, there is sufficient level of detail mentioned. **Have the data collection details been clearly justified and described?** Yes, the details are lucidly described but there was no justification provided for the methods used. **Any ethics considerations that are defined and clarified?** No, except a line at the end of the paper stating the ethics approval was received from the Institutional Ethics Committee.

Analysis	The analysis section was missing; however, a bit of analysis of the results was observed in the discussion & conclusion sections. The data was analysed as follows: • Modified Hartwig-Siegel scale for the Severity of ADRs • Naranjo's scale for Causality of ADRs
Results	The results were documented in tables containing numbers and incidence levels in percentages. **Are the results presented clearly and consistently?** Yes, there was adequate representation of the results. **Any tables or graphs adequately presented and consistent?** Only tables were there depicting the categorisation of numbers and percentages, no graphs. **Has sufficient level of detail been provided?** Yes, the data gathered was provided as text summary and tables. **Any gaps in the gathering of data have been accounted?** No, there was no mention of any difficulties or lacunae observed during the study.
Discussion	The discussion deliberated the results obtained further, and the incidence of ADRs was mainly discussed. **Is the discussion and analysis balanced?** There was no section on analysis to correctly justify this, however, there was a summary of results being discussed in detail in this section. **Is there acknowledgement of the strengths/weaknesses of the study?** No, there's no acknowledgement of any weaknesses or gaps in this paper. **Is the discussion referring back to the points being raised in the review of literature?** Since there was no literature review section, it is difficult to judge as there weren't too many points that were raised in the lit review.
Conclusion	The conclusion summarised key learnings from the study. It lacked any recommendations for future studies or the way forward. The conclusion section was poorly framed, in that it should have not only used better grammar, but also use of better language. Please see corrections advised in the last section of this table. **Have the conclusions been supported by the results?** Yes.

	Have any study implications been identified? Yes.
Recommendations for future research	This was not a separate section in the paper. **Have any recommendations outlined any possible areas of research in the future?** No, none of the recommendations outline any areas of possible future studies. **Have any ways to improve current research been recommended?** No, as it did not explore any gaps noted in the current research.
Acknowledgement	The authors acknowledged 2 departments of GMC, Aurangabad, India for assistance in exploration of ADRs and their substantial support.
Financial Support	It was mentioned that there were no funding sources for this study.
Conflicts of Interest	There were no conflicts of interest declared.
References	There are 13 references enlisted in this paper.
Other Miscellaneous Observations	This paper was poorly written and could use a bit more finesse in terms of language, etc to articulate the points better.

Paper 4[4]:

This was a well-written account of the research conducted to identify the prevalence of ADRs and assess their causality with respect to anti-TB treatment.
There were 164 patients enrolled in the study for 18months (Apr 2016 – Sep 2017). For the critique related to each section, refer to **Table 4** below.

Table 4
Adverse drug reactions associated with first line anti-tubercular drugs, their prevalence and causality assessment in patients (Nazir T, Farhat S, Jan 2019)

Section	What was observed
Abstract	The abstract was well-written and gave a brief background of the study while detailing the methods, results and conclusions. **Is the overview of research conducted mentioned concisely?** Yes, it offers a brief summary of the study. **Has the research problem been identified?** There was no problem identified besides the incidence of ADRs. **Have the methods used have been outlined, and the main findings and recommendations detailed?**

	Yes.
Introduction	The introduction provides context to the study by referencing literature articles. It also mentions the key objective of the study and identifies the means to do so. This research studies the side-effect profile of the first in line anti-TB medications on DOTs course and assesses their severity and causality. **Is the problem clearly identified?** Yes. **Is the aim and rationale given for the research?** Yes. **Is the need for the research proposed identified in the literature?** The literature cites the incidence of ADRs. This has been considered as the background to study the prevalence and causality of ADRs in this study. **Do the literature review topics have any gaps?** It doesn't seem so. However, further reading may have elicited a number of similar studies to learn from in terms of dos and don'ts. There was no separate 'Literature Review' section in the paper, but the literature reviewed for the paper gave context to the research by evaluating & examining other studies in the area, which led to a need for the new research that was proposed for the TB patients in India.
Ethics	A statement in the methods section specified that the study began after getting authorisation from the Institutional Ethics Committee. It was also mentioned that the study participants were given adequate explanation by instituting documented informed consent regarding their inclusion.
Methods	The methods section of the paper clearly describes the study schematics and enlists the inclusion/exclusion criteria, handling of the ADR reports and their causality assessment, and the statistical analysis details. **Have the methods been coherent with the quantitative and qualitative research?** Yes. **Is the approach clearly stated?** Yes. **Have the methods been justified and explained clearly?** Yes, there is adequate clarity on the methods applied. **Have any vital details been provided, in order that anyone can replicate the research?** Yes, quite sufficiently.

	Have the data collection details been clearly justified and described? Yes, the statistical handling of data has been clearly described, and data collection described involved follow-up twice weekly throughout the intensive phase and fortnightly follow-up in the continuation phase. **Any ethics considerations that are defined and clarified?** Yes, it mentions that the study was conducted after favourable authorisation from the Institutional Ethics Committee, and the participants were explained clearly, offered the consent form and which was translated in vernacular language in case required.
Analysis	The analysis section was included in the methods describing the statistical analysis methods used for the study. The methods like Microsoft Excel, Chi-square test, pie charts and bar graphs were used. Causality was assessed using Naranjo's scale and WHO-UMC Scale.
Results	The results were clearly presented using tables to outline the incidence of ADRs as per gender, weight, duration and types of ADRs observed along with statistics presented in the form of bar graphs. **Are the results presented clearly and consistently?** Yes. **Any tables or graphs adequately presented and consistent?** Yes. **Has sufficient level of detail been provided?** Yes, the data is presented in necessary detail. **Any gaps in the gathering of data have been accounted?** No there are no gaps, if noted during the study, accounted for.
Discussion	The discussion included background on the disease and associated common ADRs, further discussing the study conducted and its results, especially comparison with other studies in similar settings. **Is the analysis and discussion balanced?** Yes. **Is there acknowledgement of the strengths/weaknesses of the study?** Yes. **Is the discussion referring back to the points being raised in the review of literature?** Yes, and it compares with other literature observations to give a wholistic view of the parameters as well.
Conclusion	The conclusion gave a brief overview of the learnings from the study.

	Have the conclusions been supported by the results? Yes, there are general comments made relevant to what was noticed during the study about the ADRs. **Have any study implications been identified?** It is only briefly touched upon.
Recommendations for future research	Although this wasn't a separate section in the paper, the discussions section highlighted certain gaps which can be worked upon in future studies. The conclusion section also mentions the way ahead. **Have any recommendations outlined any possible areas of research in the future?** No, they are not really stated. **Have any ways to improve current research been recommended?** No, there was no such specific section.
Acknowledgement	There were no acknowledgements in the paper.
Financial Support	There was no financial support sourced mentioned in the paper.
Conflicts of Interest	There were no conflicts of interest declared in the paper.
References	There were 28 references made in the paper and all were adequately presented.
Other Miscellaneous Observations	Not Applicable

Paper 5[5]:

This was a study to identify the issues surrounding anti-TB therapy interruption due to high incidence of ADRs, and aiming for better quality of life for TB patients during their therapy by implementing more accurate PV technique to reporting ADRs. It was however written in poor language and grammar, and also did not cite the reference articles adequately in the references section at the end.
This study enrolled 100 patients for a period of 12 months (Jan2018 – Dec2018). For the critique related to each section, refer to **Table 5** below.

Table 5
Pharmacovigilance study of anti-tubercular drugs in a community healthcare hospital (Sharma B S, Lodhi N S, 2021)

Section	What was observed
Abstract	The abstract provided a succinct summary of the study describing the purpose of the research, the methods used, the results obtained and conclusions drawn. **Is the overview of research conducted mentioned concisely?**

	Yes, it specifies a brief background of the research. **Has the research problem been identified?** There was no problem identified to research upon. **Have the methods used have been outlined, and the main findings and recommendations detailed?** Yes, it outlines the methods and main findings, and the recommendation is briefly stated.
Introduction	The introduction provides a background of the issue regarding anti-TB therapy interruption due to ADRs with reference to literature articles. It also gives information on the anti-TB treatment and how the new patients and drug resistant cases respond differently to different drugs in their regimen. **Is the problem clearly identified?** Yes, the issue is lucidly identified. **Is the aim and rationale given for the research?** Yes, the aim and rationale is given for the study. **Is the need for the research proposed identified in the literature?** Yes, there is sufficient background literature reviewed and described to identify the lacunae surrounding PV for anti-TB therapy. **Do the literature review topics have any gaps?** Many of the cited research articles are not mentioned in the references section. Although there was no separate 'Literature Review' section in the paper, the literature articles reviewed for the paper provided a broad description to the research by assessing other studies in the area in similar situations. This led to a need for the new investigation that was proposed for the TB patients in India.
Ethics	The ethics section was missing in the paper. However, the 'Materials and Methods' section mentioned that the study was carried out after procurement the required permission from the Block Medical Officer. It was also noted that Informed consent was obtained from patients who were conscious or from relatives if the patient was unconscious.
Methods	The methods section of the paper described the conditions of the study and the permissions obtained for the study. There was also information regarding the inclusion and exclusion criteria, the source of data, methods of recording data, the drug dosage regimen, and analysis criteria. **Have the methods been coherent with the quantitative and qualitative research?** Yes. **Is the approach clearly stated?**

	Yes. **Have the methods been justified and explained clearly?** Yes. **Have any vital details been provided, in order that anyone can replicate the research?** Yes. **Have the data collection details been clearly justified and described?** Yes, there was sufficient information provided. **Any ethics considerations that are defined and clarified?** It was mentioned that the consent was acquired from conscious patients and if they were unconscious, then from relatives. Written informed consent was obtained from the patients in their native language'.
Analysis	The analysis criteria were mentioned in the Methods section as follows: • At 0, 30 and 60 days, the physical characteristics were studied • Using the WHO-UMC causality criteria, the causality assessment was performed • Hartwig 's severity scale was used for severity assessment • Demography of patients, prevalence of ADRs and the impact on sputum conversion rate were assessed and analysed using ANNOVA (F) test Chi-square (x2) test
Results	The sections on Results and Discussions were combined for this paper. The results described the total TB patients identified in the hospital during the treatment duration, and the statistical data obtained from 100 patients recruited for this study with discussion regarding the results. **Are the results presented clearly and consistently?** No, they are not given lucidly and consistently. Please see last section for additional information. **Any tables or graphs adequately presented and consistent?** Yes, but also please see last section for additional information. **Has sufficient level of detail been provided?** Yes, sufficient detail is provided. **Any gaps in the gathering of data have been accounted?** No, there are no comments on any gaps or lacunae observed during the study.
Discussion	The sections on Results and Discussions are combined for this paper, followed by another section on Discussion.

	The discussion begins towards the end of the previous section with referencing similar results obtained in similar studies in the past. The discussions are regarding the current scenario of TB and its drug regimen and the way forward with the learnings especially with the local and global drug safety standards. **Is the analysis and discussion balanced?** The discussion/analysis sections are not well-adjusted since the discussion regarding analysis of results was done in the previous section along with the results. This section was mainly focussed on the PV aspect of TB & the global and local perspectives. **Is there acknowledgement of the strengths/weaknesses of the study?** The text barely acknowledges the strengths/weaknesses of the study. **Is the discussion referring back to the points being raised in the review of literature?** There was no separate section on Literature review, but the points discussed across the paper referred to certain published literature articles.
Conclusion	The conclusion section talks about the importance of PV. **Have the conclusions been supported by the results?** The conclusions are not really supported by the outcomes since the conclusions do not throw any light on the results obtained in the study but on the current and future PV scenario in India. **Have any study implications been identified?** No, the paper does not identify the implications of the research.
Recommendations for future research	This section in the paper discusses the gaps in PV methods today and how it can be reconsidered in the future by all stakeholders. **Have any recommendations outlined any possible areas of research in the future?** The recommendations do not outline the areas of possible future research but suggest actions that can help make PV better in the future. **Have any ways to improve current research been recommended?** No, there are no recommendations how current research could be improved.
Acknowledgement	Acknowledgements were given to colleagues.
Financial Support	There were no funding sources mentioned in the paper.
Conflicts of Interest	There were no conflicts of interest declared in the paper.
References	There were 15 references mentioned at the end of the paper, but not numbered, and not all were referenced adequately across the paper.

Other Miscellaneous Observations	There were several instances across the document where the numbers were randomly mentioned and not in superscript to denote references. There were also several numbers missing in the sequence and these were not mentioned in the refences as numbers or as footnotes. There was data missing or mis-spelt or incorrectly entered in several places across the paper.

DISCUSSION

Across the papers, it was noted that timely association, reporting and managing ADRs during anti-TB treatment could warrant better treatment compliance and results. There could be variations in methods of detection of ADRs based on whether ADRs were gathered from physical patient interviews and review of charts, or in hindsight from medical records; and genetics could also have played a role in the number of ADRs and better outcome of medications.

CONCLUSION

Based on the review of the said five research papers, it can be concluded that they were ethically conducted studies to identify the issues surrounding the lack in prompt ADR reporting and issues surrounding pharmacovigilance management. Based on an average sample of about 150 TB patients enrolled in the studies, it was noticed that if knowledge relating to ADRs is imparted to patients then the ADR reporting can be elicited with more efficiency since most of the ADRs are inclined to appear in the first 2-3 months of anti-TB treatment. The education regarding importance of PV documentation with respect to ADR Reporting and other PV processes needs to be imparted to institutions, HCPs and patients at each of their levels to enhance treatment adherence as well as promptly identify and mitigate the issues surrounding ADRs relating to anti-TB treatment.

Conflict of interest statement: The Authors declare no conflicts of Interest

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