
THE IMPACT OF ANTI-TUBERCULOSIS DRUG ADVERSE EFFECTS ON MEDICATION COMPLIANCE IN PATIENTS WITH TUBERCULOSIS IN INDONESIA: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Tuberculosis (TB) remains a major public health problem in Indonesia, with treatment success highly dependent on patients' adherence to anti-tuberculosis drug regimens. However, adherence is often hindered by adverse drug reactions (ADR), including nausea, vomiting, gastrointestinal disturbances, loss of appetite, and other symptoms that discourage patients from completing therapy. This systematic literature review aimed to analyze the impact of ADR on medication adherence among TB patients in Indonesia. Literature searches were conducted in Google Scholar, PubMed, and ScienceDirect databases using predefined keywords, with inclusion criteria covering articles published between 2020 and 2025, written in English or Indonesian, full-text available, and focusing on the relationship between ADR and treatment adherence. From the 22 eligible studies reviewed, the majority reported a significant relationship between ADR and adherence, while several studies indicated no significant effect. The most frequently reported ADR were gastrointestinal disorders, headaches, joint pain, and skin reactions. In addition, psychosocial factors such as family support, knowledge, and patient attitudes were also identified as influencing adherence, with family support emerging as the most dominant factor. Overall, ADR were found to negatively affect adherence in many cases, potentially increasing the risk of multidrug-resistant TB. Strengthened patient education, proactive counseling, and closer monitoring from healthcare providers are recommended to improve adherence and treatment outcomes.

Keywords: Adherence; Adverse Drug Reaction; Anti-tuberculosis Drug; Compliance; Tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a contagious infectious disease that primarily targets the respiratory system, especially the lungs. It is caused by the bacterium *Mycobacterium tuberculosis* and is transmitted through inhalation of airborne droplets released by individuals with active TB (Ministry of Health of the Republic of Indonesia, 2023). In Indonesia, TB cases have also shown a sharp increase. The Ministry of Health estimated that new TB cases would reach 1,060,000 in 2023, with an annual death toll of 134,000.

However, the number of diagnosed TB patients actually reached 820,789, surpassing earlier projections (Ministry of Health of the Republic of Indonesia, 2023).

One of the key aspects of tuberculosis (TB) control is treatment success, which largely depends on patients' adherence to completing therapy regularly and consistently. However, treatment adherence remains a major challenge. Many patients discontinue their medication prematurely because they feel cured, experience drug side effects, lack understanding of the disease, or

receive insufficient support from family members and healthcare providers (Ministry of Health of the Republic of Indonesia, 2022). In fact, TB treatment requires a prolonged duration of at least six months and must be followed consistently to prevent drug resistance and relapse. Non-adherence to the treatment regimen may lead to an increase in multidrug-resistant TB (MDR-TB) cases, which are far more difficult and costly to manage (Mulyadi & Astuti, 2021). Adherence to TB treatment is often hindered by the requirement for strict medication regularity, leading some patients to discontinue therapy prematurely. In addition, the complexity of the regimen, involving multiple drugs, coupled with adverse effects such as nausea, vomiting, gastrointestinal disturbances, and loss of appetite, further contributes to poor adherence (Syafiq *et al.*, 2024).

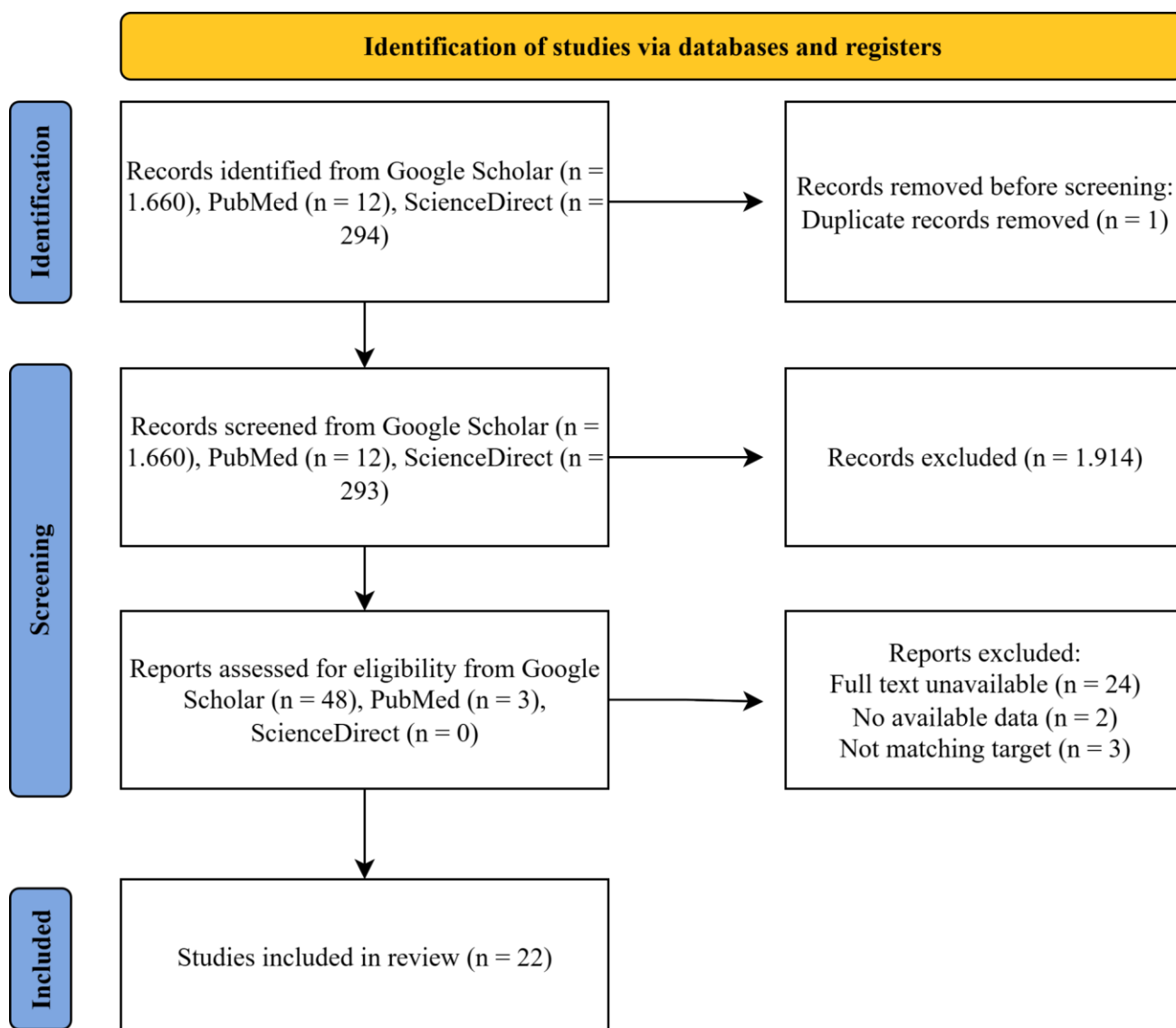
Given the high burden of TB and the critical importance of adherence to therapy, it is essential to understand the extent to which adverse drug effects impact medication compliance in Indonesian TB patients. A systematic literature review provides an evidence-based approach to synthesize existing findings, identify gaps, and inform strategies to improve adherence and treatment outcomes.

METHODS

The research method used in this study was a systematic literature review. The first step was to determine the research objective, which was to analyze the effect of anti-tuberculosis drug side effects on the level of treatment adherence among tuberculosis patients. The next step was to establish inclusion and exclusion criteria. The inclusion criteria for this study were: 1) Articles published in Indonesian or English, 2) Articles available in full-text and open access, 3) Articles with consistency between the article title and abstract, and 4) Articles published between 2020-2025. Meanwhile,

the exclusion criteria in this study are as follows: 1) Articles with research populations outside Indonesia and/or patient populations with MDR-TB or drug-resistant tuberculosis, 2) Articles that did not discuss the relationship between the side effects of anti-tuberculosis drugs and medication adherence, and 3) Articles that had been published several times or duplicate articles in several different databases. Literature searches were conducted through online databases such as Google Scholar, PubMed, and ScienceDirect using keywords relevant to the specified topic.

The keywords used were ("tuberkulosis" OR "TB" OR "tuberkulosis paru") AND ("efek samping obat" OR "reaksi obat yang merugikan" OR "toksisitas obat" OR "adverse drug reaction") AND ("kepatuhan pengobatan" OR "kepatuhan minum obat" OR "kepatuhan terapi" OR "medication adherence" OR "treatment compliance") for searches through the Google Scholar database, and ("tuberculosis" OR "TB" OR "pulmonary tuberculosis") AND ("adverse drug reaction" OR "side effect" OR "drug toxicity" OR "adverse effect") AND ("medication adherence" OR "treatment adherence" OR "drug compliance" OR "patient compliance" OR "medication persistence") for searches through the PubMed and ScienceDirect databases. After obtaining relevant literature, the next step was the screening process by conducting an in-depth reading of articles that met the inclusion and exclusion criteria. All articles were carefully reviewed, and those considered relevant to the research topic were downloaded and reviewed. All data was then collected and processed through data extraction to summarize important information such as the objectives, methodology, results, and conclusions of each article. Next, the results and discussions from these articles were analyzed.

**Figure 1.** PRISMA Diagram**RESULT****Table 1.** Summary of The Literature Review

No	Author(s) and Year	Title	Test Statistics Used	Result and Conclusion
1	Permata & Ramadhan (2025)	Tingkat Kepatuhan Pasien Tuberkulosis terhadap Pengobatan dan Faktor yang Mempengaruhinya	Chi-square test	Based on the research findings, it can be concluded that the level of treatment adherence among tuberculosis patients at Community Health Center X is still predominantly in the moderate and low categories. Bivariate analysis using the Chi-Square test showed a significant relationship between patients' level of

				knowledge and treatment adherence ($p = 0.001$), as well as family support ($p = 0.005$). In addition, there was a significant association between medication side effects ($p = 0.022$) and access to healthcare services ($p = 0.010$) with patients' adherence levels.
2	Safitri & Setiyadi (2025)	The Relationship Between Family Support, Drug Side Effects, Patient Attitudes and Tuberculosis Treatment Compliance at Dr. R. Soeprapto Cepu Hospital	Chi-square test	A p value of less than 0.05 indicated that the Chi-Square test results were significant or that a relationship existed, namely the variables of Family Support (p value $0.003 < 0.05$), Side Effects of Anti-Tuberculosis Drugs (p value $0.015 < 0.05$), and the variable of Patient Attitude (p value $0.001 < 0.05$). and in the knowledge variable, the results were not significant with (p value $0.433 > 0.05$) It indicates that knowledge and adherence were unrelated to pulmonary tuberculosis treatment at dr. R. Soeprapto Cepu Hospital.
3	Yulita <i>et al.</i> (2025)	Analisis Kepatuhan Minum Obat Anti Tuberkulosis Paru pada Penderita Tuberkulosis di Kabupaten Empat Lawang Tahun 2024	Chi-square test	There is a significant relationship between age, education, occupation, knowledge, family support, attitude, adverse drug reactions, and motivation with tuberculosis medication adherence, while gender has no effect. Knowledge was the most dominant factor ($OR = 58.503$), indicating that higher patient knowledge strongly increases treatment adherence.
4	Andira <i>et al.</i> (2024)	Hubungan Efek Samping Obat Anti Tuberkulosis (OAT) dengan Kepatuhan Berobat Pada Pasien Tuberkulosis di Puskesmas Jongaya Makassar	Chi-square test	There is a significant relationship between ATD side effects and treatment adherence, where the lower the side effects, the higher the patient's level of adherence.
5	Fakhrul <i>et al.</i> (2024)	Hubungan Efek Samping Obat dan Pengetahuan	Chi-square test	There is no relationship between drug side effects and adherence

		dengan Kepatuhan Minum Obat Anti Tuberkulosis Pasien Tuberkulosis Paru		to antituberculosis medication in pulmonary tuberculosis patients $P = 0,636$, ($> \alpha 0,05$) and there is no relationship between knowledge and adherence to antituberculosis medication in pulmonary tuberculosis patients.
6	Qhumairah <i>et al.</i> (2024)	Faktor yang Berhubungan dengan Kepatuhan Minum Obat Penderita TB Paru RSUD dr. La Palaloi Maros	Chi-square test	The results of this study indicate a relationship between knowledge (p value 0.0000), drug side effects (p value 0.002), family support (p value 0.000) and medication supervisors (p value 0.001) with medication adherence of pulmonary TB patients at Dr. La Palaloi Regional Hospital. There is no relationship between attitudes (p value 0.593) with medication adherence of pulmonary TB patients at Dr. La Palaloi Regional Hospital, Maros Regency.
7	Syafiq <i>et al.</i> (2024)	Hubungan Efek Samping Obat Anti Tuberkulosis (OAT) dengan Kepatuhan Berobat Pasien Tuberkulosis Paru di Wilayah Kerja Puskesmas Tambang	Chi-square test	The results of the study showed a relationship between the side effects of anti-tuberculosis drugs (OAT) and the level of treatment compliance of pulmonary tuberculosis patients in the Tambang Community Health Center Work Area with a p-value of 0.003 ($p \leq 0.05$). Based on these results, it was concluded that there was a relationship between the side effects of anti-tuberculosis drugs and compliance with treatment of tuberculosis patients in the Puskesmas Tambang work area.
8	Tobing <i>et al.</i> (2024)	Faktor Yang Mempengaruhi Kepatuhan Penderita TB Paru Dalam Mengonsumsi Obat Di UPT Puskesmas Batang Beruh Kecamatan Sidikalang Kabupaten Dairi	Chi-square test	There is a significant influence of knowledge, attitude, family support, and drug side effects on the medication adherence of pulmonary TB patients, with family support being the dominant factor (OR = 37.543). Gender showed no significant effect on adherence.
9	Nabilah <i>et al.</i> (2023)	Hubungan Kejadian Efek Samping Penggunaan	Chi-square test	The research results obtained through a chi-square test with a

		Obat Anti Tuberkulosis dengan Kepatuhan Minum Obat Pada Pasien Tuberkulosis di Puskesmas Kuwarasan Kabupaten Kebumen Tahun 2023		p-value of 0.715, indicating a p-value > 0.05. Based on these results, it was concluded that there was no significant relationship between medication adherence and the side effects of tuberculosis drugs experienced by patients.
10	Ruben <i>et al.</i> (2023)	Korelasi Efek Samping Obat Anti Tuberkulosis dengan Kepatuhan Pengobatan Pasien TB Paru	Chi-square test and fisher's exact test	The p-value obtained was 0.008. This indicates a significant correlation between drug side effects and medication adherence in pulmonary TB patients. The milder the side effects of OAT, the more compliant the patient will be in taking the medication. The more severe the side effects, the less compliant the patient will be.
11	Ryansyah <i>et al.</i> (2023)	Faktor-Faktor Yang Mempengaruhi Kepatuhan Pengobatan Pada Pasien TB	Fisher's exact test	The results of the fisher test analysis in this study showed a p value = 0.0042 in the relationship between knowledge and adherence to medication, p = 0.001 in the relationship between side effects of treatment and adherence to medication, p = 0.002 which means there is a relationship between the variable of family role and adherence to medication, p = 0.004 in the relationship between distance and adherence to medication, p = 1.000 in the relationship between availability of transportation and adherence to medication, p = 0.145 in the relationship between the role of officers and adherence to medication and p = 0.000 in the relationship between perception of self-medication and adherence to medication. Based on these results, it is known that there is a relationship between the factors of knowledge, side effects, family role, distance and perception of self-medication on adherence to medication, while there is no relationship between the role of TB officers and availability of

				transportation on adherence to medication.
12	Abidin <i>et al.</i> (2022)	Hubungan Efek Samping Obat dengan Kepatuhan Minum Obat pada Pasien Tuberkulosis di Wilayah Kerja Puskesmas Kunir	Spearman rank test	The results of the study obtained through the Spearman Rank test showed a Sig. (2-tailed) value of 0.028. The Sig. value <0.05 so that H_0 is rejected and H_1 is accepted. Based on these results, it can be concluded that there is a relationship between drug side effects (AEs) and medication adherence in tuberculosis patients.
13	Christy <i>et al.</i> (2022)	Hubungan Tingkat Kepatuhan Minum Obat Pasien Tuberkulosis Terhadap Efek Samping Obat Anti Tuberkulosis (OAT)	Chi-square test	There is a significant relationship between the side effects of OAT and medication adherence (p value = 0,024)
14	Depo Pademme & (2022)	Faktor Yang Berhubungan Dengan Kepatuhan Berobat Penderita Tuberkulosis Paru di Kota Sorong	Chi-square test	There is a significant relationship between drug side effects and medication compliance (p-value 0.013 < 0.05), which means that respondents who experienced the effects of anti-tuberculosis drug use became less compliant with treatment.
15	Lucya & Arief (2022)	Factor Affecting Treatment Compliance in TB Patients	Simple linear regression test and pearson product moment	There is a significant relationship between drug side effects and medication compliance (p-value 0.007 < 0.05) and the correlation coefficient is moderate (r - 0.460). This study shows that the lower perceived side effects, the higher the level of medication compliance.
16	Asriwati <i>et al.</i> (2021)	Risk factors analysis of non-compliance of Tuberculosis (TB) patients taking medicine in Puskesmas Polonia, Medan, 2021	Logistic regression test	Respondents who experience drug side effects and have a 6.873 times greater risk of non-adherence to taking medication than those who do not experience drug side effects.
17	Bakri <i>et al.</i>	The Impact Of Adverse	Chi-square test	There is a significant correlation

	(2021)	Drug Reaction Occurrence To Drug Adherence Level: A Cross-Sectional Study In Patients With Tuberculosis		between adverse drug reactions and adherence to anti-tuberculosis treatment during the intensive phase ($p\text{-value} = 0.02288 < 0.05$). Patients who experienced ADR were less likely to adhere to their treatment regimen.
18	Retnowati <i>et al.</i> (2021)	Hubungan Efek Samping Obat Anti Tuberkulosis Kombinasi Paket 4 Terhadap Tingkat Kepatuhan Pasien Tuberkulosis Di Instalasi Rawat Jalan Puskesmas Jiken Kabupaten Blora	Chi-square test	There is a significant relationship between adverse drug reactions from category 4 anti-tuberculosis drugs and patients' medication adherence ($p\text{-value} = 0.000 < 0.05$). Patients who experienced adverse reactions were more likely to show non-adherence to treatment.
19	Safitri <i>et al.</i> (2021)	Pengaruh Reaksi Obat Yang Tidak Dikehendaki (ROTD) Terhadap Kepatuhan Pasien Tuberculosis Paru di Puskesmas Bumiayu Tahun 2021	Simple linear regression test	There is no significant effect of unintended drug reactions on treatment adherence in pulmonary tuberculosis patients ($p\text{-value} 0.053 > 0.05$). This study shows that although all respondents experienced various adverse reactions, the majority (95.7%) remained adherent to their medication regimen, suggesting that ROTD did not reduce patient compliance.
20	Wiratmo <i>et al.</i> (2021)	Riwayat Pengobatan, Efek Samping Obat dan Penyakit Penyerta Pasien Tuberculosis Paru terhadap Tingkat Kepatuhan Berobat	Chi-square test	The results of the study showed no association between treatment history and TB treatment adherence, with a $p\text{-value}$ of 0.722. Meanwhile, there is a relationship between drug side effects and comorbidities with the level of TB treatment compliance with $p = 0.002$ and $p = 0.001$.
21	Aini & Astuti (2020)	Hubungan antara Efek Samping Obat Anti Tuberkulosis (OAT) dan Peran Pengawas Obat (PMO) dengan Kepatuhan Berobat Pada Pasien Tuberculosis (TB) Paru	Ch-square test	There was a relationship between the side effects of anti-tuberculosis drugs (ATD) and treatment adherence in pulmonary tuberculosis patients at the Palembang Special Pulmonary Hospital in 2019 ($p\text{-value} = 0.011$).

22	Dewi <i>et al.</i> (2019)	Gambaran Reaksi Obat Yang Tidak Dikehendaki pada Pengobatan Tuberkulosis di Puskesmas Kabupaten “X” Yogyakarta dan Hubungannya dengan Kepatuhan Minum Obat	Chi-square test	There is no significant relationship between unintended drug reactions and medication adherence ($p = 0.602 > 0.05$). Although 66.6% of patients experienced various ROTD, these adverse reactions did not affect adherence to tuberculosis treatment.
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DISCUSSION

Based on the results of a systematic review, most of the 22 articles reviewed showed a relationship between the side effects of antituberculosis drugs and the level of treatment adherence among tuberculosis patients in Indonesia, as described in Table 1. The study conducted by Permata and Ramadhan (2025) involved 60 respondents with tuberculosis at Puskesmas X East Java. Data collection was carried out using a structured questionnaire that had been tested for validity and reliability. A total of 60 tuberculosis patients undergoing treatment, both in the intensive and continuation phases, participated in the study. Univariate analysis revealed that the majority of respondents were between 26–45 years old (53.3%), male (65%), and had a secondary education level (high school or equivalent) of 61.7%. In terms of treatment adherence, 58.3% of respondents fell into the moderate adherence category, 26.7% into the low adherence category, and only 15% demonstrated high adherence. Bivariate analysis using the Chi-Square test showed a significant relationship between patients' knowledge levels and treatment adherence ($p = 0.001$), as well as family support ($p = 0.005$). In addition, significant associations were also found between drug side effects ($p = 0.022$) and access to health services ($p = 0.010$) with patients adherence levels.

The study conducted by Safitri and Setiyadi (2025) at the Pulmonary outpatient clinic of Dr. R. Soeprapto Hospital provides treatment for tuberculosis (TB) patients who have been undergoing treatment for less than six months. The study population consisted of 317 TB patients receiving treatment at the

hospital. A purposive sampling method was employed, and the sample size was determined using the Lemeshow formula, resulting in 165 respondents. the majority of respondents 56 (33.9%) were in the pre-elderly age category, and 93 (56.4%) of the respondents were female. The majority of responders have a high school diploma/vocational school as much as 59 (35.8%). Based on occupation, the most dominating are housewives with 63 people (38.2%). The duration of symptoms was the most in 3-6 months as many as 72 respondents (43.6%), and the most number of families in one household was around 4-5 people with 68 respondents (41.2%). A p value of less than 0.05 indicated that the Chi-Square test results were significant or that a relationship existed, namely the variables of Family Support (p value $0.003 < 0.05$), Side Effects of Anti-Tuberculosis Drugs (p value $0.015 < 0.05$), and the variable of Patient Attitude (p value $0.001 < 0.05$). and in the knowledge variable, the results were not significant with (p value $0.433 > 0.05$) It indicates that knowledge and adherence were unrelated to pulmonary tuberculosis treatment at dr. R. Soeprapto Cepu Hospital.

The study conducted by Yulita *et al* (2025). Involved 85 tuberculosis patients in Kabupaten Empat Lawang in 2024, with 49 respondents (57.6%) categorized as non-adherent to tuberculosis treatment and 36 respondents (42.4%) categorized as adherent. Based on demographic characteristics, the majority of respondents were young adults (69.4%), female (61.2%), and had completed senior high school (42.4%). In terms of occupation, most were farmers (27.1%). Regarding psychosocial factors, 54.1% had

low knowledge, 50.6% had low family support, 55.3% demonstrated a positive attitude, 67.1% reported no adverse drug reactions, and 58.8% had high motivation. Statistical analysis using the Chi-square test showed that age ($p = 0.004$), education ($p = 0.019$), occupation ($p = 0.000$), knowledge ($p = 0.000$), family support ($p = 0.000$), attitude ($p = 0.002$), adverse drug reactions ($p = 0.023$), and motivation ($p = 0.031$) had significant relationships with treatment adherence ($p < 0.05$). Gender ($p = 0.660$), however, showed no significant association. Multivariate analysis identified knowledge as the most dominant factor influencing adherence ($p = 0.001$; OR = 58.503).

The study conducted by Andira *et al* (2024), The respondents were 30 (61.2%) male and 19 (38.8%) female. Based on age, the majority of respondents were aged 16-25 years (10 respondents (20.4%). Based on observations, 40 patients (81.6%) experienced mild side effects, 7 patients (14.3%) experienced moderate side effects, and 2 patients (4.1%) experienced severe side effects. The level of medication adherence was as follows: 5 respondents (10.2%) had low adherence, 5 respondents (10.2%) had moderate adherence, and 39 respondents (79.6%) had high adherence. The majority of tuberculosis patients at Jongaya Community Health Center demonstrated good awareness of medication adherence, with only a few patients being irregular in taking their medication. The Chi-square test showed a p-value of 0.000, which indicates a significant relationship between the side effects of anti-tuberculosis drugs (OTD) and treatment adherence in tuberculosis patients.

The research of Fakhrol *et al* (2024), The respondents ($n=31$) were mostly male, with 18 respondents (58.1%), and most of the pulmonary tuberculosis patients were aged 56-65 years, with 9 respondents (29%). The majority of pulmonary tuberculosis patients experienced moderate/severe side effects, with 26 respondents (83.9%), and 5 respondents (16.1%) experienced mild side effects. Respondents' compliance with anti-tuberculosis medication was illustrated by the

17 (54.8%) respondents who were compliant with their anti-tuberculosis medication and the 14 (45.2%) respondents who were non-compliant. The results of the Chi-square statistical test using the Fisher's Exact test yielded a P value of 0.636 ($>\alpha$ 0.05), indicating there is no relationship between drug side effects and medication adherence in patients with pulmonary tuberculosis.

Qhumairah and colleagues (2024) explored factors influencing treatment adherence in 89 pulmonary tuberculosis patients at RSUD dr. La Palaloi, Maros, using a cross-sectional design with random sampling from a population of 216 cases. Their analysis found that 79.8% of respondents were adherent, and side effects from anti-tuberculosis drugs were common, reported by 83.1% of participants. Chi-square testing showed a significant association between drug side effects and adherence ($p = 0.002$), alongside significant relationships for knowledge ($p = 0.000$), family support ($p = 0.000$), and treatment supervisor involvement ($p = 0.001$), while patient attitude showed no significant effect ($p = 0.593$). The authors noted that common adverse reactions included nausea, vomiting, and skin irritation, which can discourage patients from completing therapy, but the presence of family support and an appointed medication supervisor (PMO) mitigated this risk. These findings highlight that in Indonesian TB programs, comprehensive counseling, active monitoring, and strong social support can counterbalance the negative impact of drug side effects on adherence and are critical to sustaining treatment success.

The study by Syafiq *et al.* (2024) reinforces the strong link between adverse effects of anti-tuberculosis drugs (OAT) and medication adherence among Indonesian patients. Conducted as a cross-sectional survey of 36 pulmonary TB patients receiving OAT in three villages within the Puskesmas Tambang working area, the research found that 47.2 % experienced severe adverse effects and 47.2 % were non-adherent. Chi-square testing yielded a p-value of 0.003 and an odds ratio of 12.18, indicating that patients

with severe adverse effects were over twelve times more likely to be non-adherent than those with mild effects. These findings echo earlier Indonesian studies reporting that nausea, gastrointestinal discomfort, and hepatotoxicity are major drivers of treatment interruption, a key contributor to multidrug-resistant TB. The authors also highlight demographic factors like older age, male sex, and low education as amplifiers of risk, suggesting that targeted counseling, proactive pharmacovigilance, and strong family support are essential to sustain adherence and prevent resistance within high-burden settings.

The study conducted by Tobing *et al* (2024) involved 56 pulmonary tuberculosis patients at UPT Puskesmas Batang Beruh, Sidikalang District, Dairi Regency. Respondents were dominated by males (76.8%) and the largest age group was 41–50 years (39.3%). In terms of education, most had completed senior high school (57.1%), while the majority of occupations were farmers (51.8%). The bivariate analysis showed that knowledge ($p = 0.010$), attitude ($p = 0.006$), family support ($p = 0.000$), and drug side effects ($p = 0.000$) significantly influenced medication adherence, while gender had no significant effect ($p = 0.057$). Multivariate analysis identified family support as the most dominant factor influencing adherence, with an OR = 37.543 (95% CI: 2.715–519.110). These findings indicate that despite demographic variations, psychosocial and treatment-related factors play a more critical role in determining patient adherence than biological characteristics such as gender.

The research conducted by Nabilah *et al*. (2023) shows that adverse reactions to anti-tuberculosis drugs do not necessarily reduce patient adherence when strong support systems are in place. Using a prospective cross-sectional design with total sampling of 60 patients at Puskesmas Kuwarasan, the investigators found that almost all participants (98.3 %) remained compliant even though every patient experienced at least one mild effect, most often reddish urine from rifampicin and a small proportion (11.7 %)

reported more serious reactions such as skin redness or burning sensations. Statistical testing ($p = 0.715$) confirmed the absence of a significant association between side effects and medication compliance. The authors attribute the high adherence rate to consistent counseling from health workers, the presence of treatment supervisors (PMO), and strong family motivation, factors that appear to outweigh discomfort from drug reactions. This suggests that effective education and social support can maintain excellent adherence in Indonesian TB programs despite frequent but generally mild adverse effects.

In the study conducted by Ruben *et al* (2023), the total sample size of 30 respondents was obtained, with 16 males (53.3%), 14 females (46.7%). The largest number of respondents were in the 15-24 age group (12 respondents (40.0%)), and 11 respondents (36.7%) in the 24-49 age group. The study obtained data from 20 respondents (66.7%) with mild side effects and 10 respondents (33.3%) with severe side effects. The side effects experienced by respondents included orange urine, nausea, heartburn, dizziness, itching, redness, joint pain, and tingling. The study obtained data showing that 26 respondents (86.7%) were compliant with their medication and 4 respondents (13.3%) were non-compliant. The Chi-Square test, with a significance level of $\alpha = 0.05$, using Fisher's Exact Test, yielded a p -value of 0.008. This indicates a significant correlation between drug side effects and medication adherence in pulmonary TB patients.

The research conducted by Ryansyah *et al* (2023) investigated factors influencing treatment adherence in 44 tuberculosis patients treated at Puskesmas Kecamatan Tebet, Jakarta, using a cross sectional design with consecutive non random sampling and Fisher Exact testing. Among the respondents, 81.8% were adherent to therapy and 90.9% experienced only mild adverse effects, while 9.1% reported severe reactions. Bivariate analysis showed that knowledge ($p = 0.042$), drug side effects ($p = 0.001$), family or treatment supervisor support ($p = 0.002$), distance to the health facility ($p = 0.004$), and

perception of self medication ($p = 0.000$) were all significantly associated with adherence, whereas transportation availability ($p = 1.000$) and the role of TB officers ($p = 0.145$) were not. The authors highlight that well informed patients with strong family or PMO involvement were more likely to maintain adherence even when facing mild drug reactions, while longer travel distances and negative perceptions of self care increased the risk of non adherence. These results underscore the combined importance of patient education, supportive supervision, and accessible services in sustaining TB treatment completion in urban Indonesian settings.

Abidin et al. (2022) examined the relationship between anti-tuberculosis drug side effects and medication adherence among 41 patients receiving OAT at Puskesmas Kunir, Lumajang. Using a cross sectional analytic survey with the Morisky Medication Adherence Scale, they found that nearly all participants (97.8%) were adherent despite most reporting some drug related effects, which were predominantly mild, with 82.6% experiencing only low grade reactions such as transient gastrointestinal discomfort or mild skin symptoms. Spearman rank analysis yielded a p value of 0.028, indicating a statistically significant but modest positive association ($r = 0.325$) between side effect occurrence and adherence. The authors suggest that strong health center support, relatively young participant age, and a high proportion of respondents with at least a senior high school education likely contributed to the excellent adherence rates. These findings imply that when education and counseling are effective, the presence of mild side effects may not hinder and might even encourage patients to maintain treatment, reinforcing the role of patient education and proactive health services in Indonesia's TB control efforts.

In the study conducted by Christy *et al* (2022), data collection was conducted at the Sungai Betung District Community Health Center, Bengkayang Regency. The data used were primary data (questionnaires) and secondary data (patient medical records). Of

the 35 respondents, 82.85% were male and 17.14% were female. The dominant age group suffering from pulmonary tuberculosis is the productive age group (71.42%), while the remaining 28.57% are among the elderly. Medication adherence showed that of the 35 respondents, 65.71% were in the high compliance group and 34.29% were in the low compliance group. Respondents in the "good" response group regarding drug side effects had high compliance of 42.9% and low compliance of 8.5%, while respondents in the "poor" response group regarding drug side effects had high compliance of 22.9% and low compliance of 25.7%. The Chi-square test yielded a p -value < 0.05 (p -value = 0.024). Therefore, it can be concluded that there is a significant relationship between the side effects of OAT and medication adherence in pulmonary tuberculosis patients.

The study by Depo and Pademme (2022) included 72 respondents, with 52.8% male and 47.2% female. Based on age, 55.6% are over 35 years old and the rest are under 35 years old. This study showed that 59.7% of patients did not experience side effects and 40.3% of respondents said they experienced side effects. Statistical test results using the Chi-square test show a significant relationship between the presence of drug side effects and treatment adherence among pulmonary tuberculosis patients in Sorong City. This means that respondents who experienced the effects of anti-tuberculosis drugs became less compliant with treatment. This study also explains that the side effects of anti-tuberculosis drugs caused many respondents to be afraid to continue taking the drugs regularly due to the lack of information available about the side effects of the drugs.

The study conducted by Lucya and Arief (2022) included 33 respondents, with 36.4% male and 63.6% female. Based on the highest level of education attained, 12.1% were at the primary school level, 18.2% at junior high school level, 57.6% at senior high school levels, and 12.1% at college level. The distribution of professions shows that the majority (51.5%) are employed, 36.4% are unemployed, and the rest are students. This

study showed that 84.8% of respondents experienced side effects from anti-tuberculosis drugs and the remaining 15.2% did not experience any side effects. The most commonly experienced side effects were difficulty urinating (57.6%), followed by tremors (39.4%), vomiting and joint pain (36.4%), headaches (33.3%), and muscle pain (30.3%). Based on this study, the results of the simple linear regression test showed a p-value of $0.007 < 0.05$, indicating that there is a significant relationship between drug side effects and treatment adherence in tuberculosis patients. The results of the Pearson Product Moment test showed an r value of -0.460, meaning that the lower the perceived side effects, the higher the level of medication compliance.

In the study conducted by Asriwati *et al* (2021), it is found that in general, respondents aged 15–24 years are 35 people (25.7%), and at least 65–74 years are six people (4.4%), while the male gender is 76 people (9 55.9%) greater than women as many as 60 people (44.1%) and based on the occupation of the respondents generally do not work, namely 51 people (37.5%) and at least as fishermen, namely five people (3.7%). Complaints of side effects that often occur in patients include pain, nausea, abdominal pain, joint pain, tingling, skin redness, itching, and severe side effects such as respiratory syndrome (shortness of breath), shock, kidney failure, and redness of the skin, deafness, jaundice, without other causes, and other disorders. Based on multiple logistic analyses, the Odds Ratio value was 6.873 with a significant level of $p = 0.000 < 0.05$ (95% CI; 2,435–19,398, so the drug side effect variable is a risk factor for non-compliance with taking medication for pulmonary TB patients.

The study conducted by Bakri *et al* (2024). Involved 35 subjects. Drug adherence level was assessed using the Medication Adherence Scale-8 (MMAS-8) questionnaire, while ADR characteristics were collected with a checklist sheet, and their probability was evaluated using the Naranjo Algorithm. The findings showed that the majority of patients were adherent to anti-tuberculosis

drugs (62.8%), while 74.3% experienced at least one type of ADR. Bivariate analysis using the Chi-square test revealed a significant correlation between ADR occurrence and adherence to anti-tuberculosis treatment, with a p-value of 0.02288 (< 0.05).

The study conducted by Retnowati *et al* (2021). Involved a population of 43 tuberculosis patients, with a sample of 38 respondents selected using purposive sampling. Research instruments included questionnaires and checklist sheets, and data were analyzed using bivariate analysis with the Chi-square test. The results showed that among 38 respondents, 19 patients (10.0%) who experienced adverse drug reactions were categorized as non-adherent, while 10 patients (5.3%) experienced adverse reactions by age group, and 10 patients (6.3%) were non-adherent by age group. Statistical analysis using the Chi-square test obtained a p-value of 0.000 (< 0.05), indicating a significant relationship between adverse drug reactions from category 4 anti-tuberculosis drugs and the level of medication adherence.

The study conducted by Safitri *et al* (2021) involved 47 respondents with pulmonary tuberculosis at Puskesmas Bumiayu. All respondents (100%) experienced at least one type of unintended drug reaction (ROTD). The most common adverse reactions were gastrointestinal disorders (27.6%), headaches (23.7%), and reddish urine (14.1%), followed by loss of appetite (12.8%) and weakness (9.0%). Regarding treatment compliance, 95.7% of patients were categorized as adherent and 4.3% as non-adherent. The results of the linear regression analysis showed a significance value of 0.053 (> 0.05), indicating that unintended drug reactions did not significantly affect treatment adherence in tuberculosis patients.

The research conducted by Wiratmo *et al* (2021) analyzed how treatment history, adverse drug reactions, and comorbidities influence tuberculosis treatment adherence at Puskesmas Kecamatan Cengkareng, Jakarta. Using a cross sectional design with 170 respondents and chi square testing, the study

found that 67.8% of patients were adherent while 32.2% were non adherent. Bivariate analysis showed no significant association between prior TB treatment history and adherence ($p = 0.722$), but revealed significant relationships for adverse drug reactions ($p = 0.001$) and the presence of comorbid diseases ($p = 0.002$). Patients without drug side effects or additional illnesses demonstrated much higher adherence rates, indicating that physical discomfort and the burden of multiple diseases can discourage completion of the lengthy TB regimen. The authors conclude that strengthening the role of community health workers in education and monitoring is essential to address side effects early and to support patients with comorbidities, thereby improving the likelihood of treatment completion.

The study conducted by Aini & Astuti (2020), It was found that the number of respondents who adhered to their medication was 37 (72.5%), compared to the number of non-adherent respondents (14) (27.5%). The number of respondents who experienced mild side effects from anti-tuberculosis drugs was 39 (76.5%), compared to the number of respondents who experienced severe side effects from anti-tuberculosis drugs (12) (23.5%). of the 39 respondents, 32 (82.1%) with mild side effects from anti-tuberculosis drugs were compliant with treatment, while 5 (41.7%) of the 12 respondents with severe side effects from anti-tuberculosis drugs were compliant with treatment. The chi-square test yielded a p-value of $0.011 < \alpha = (0.05)$, indicating a relationship between anti-tuberculosis drug side effects and treatment adherence in pulmonary tuberculosis patients at the Palembang Special Lung Hospital in 2019.

The study conducted by Dewi *et al* (2019) included tuberculosis patients who received anti-tuberculosis drugs. The results showed that 66.6% of respondents experienced unintended drug reactions (ROTD), while 33.3% did not. Among those who experienced ROTD, 4.5% reported more than five types of ROTD, 31.8% reported

three types, 27.27% reported two types, and 31.8% reported one type. Of the 12 types of ROTD observed, a total of 51 incidents were recorded, with 11.76% classified as major (such as itchy skin and visual disturbances) and 88.2% classified as minor. The most common reaction was indigestion, reported in 69% of cases, followed by muscle cramps (1.9%) and fever (1.9%). Most ROTD occurred within 1 to 4 weeks after drug initiation. The Chi-square test revealed no significant relationship between the incidence of ROTD and the level of medication adherence, with a significance level of 0.602 (>0.05).

CONCLUSION

This systematic literature review demonstrates a significant relationship between adverse effects of anti-tuberculosis drugs and medication compliance among TB patients in Indonesia. The occurrence of side effects such as nausea, vomiting, gastrointestinal disturbances, and loss of appetite has been shown to negatively impact patients' adherence to therapy. These findings highlight the need for strengthened patient education, close monitoring, and supportive interventions from healthcare providers to improve treatment adherence and reduce the risk of treatment failure and drug-resistant tuberculosis.

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