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REVIEW

Medication-related problems and adverse drug reactions in Ethiopia: A systematic review

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Abstract

Medication-related problems (MRPs) are an important healthcare problem. This study aimed at reviewing the published literature in Ethiopia to estimate the prevalence of MRPs and to summarize associated factors. A comprehensive systematic search was conducted in PubMed, EMBASE, CINAHL, Scopus, Google Scholar, and Google databases from inception to April 2020. Articles that addressed MRPs were eligible for inclusion. Article screening, data extraction, and study quality analysis were performed independently by two reviewers. Studies targeting specific disease condition were considered as specific, while the remaining were nonspecific. The prevalence of MRPs was then computed in medians and interquartile ranges (IQR), while associated factors were summarized in a table. Of the thirty-two studies included in this review, the majority of them (n = 24) targeted MRPs, while the remaining studies (n = 8) investigated adverse drug reactions (ADRs). Studies varied in the study design, study population, and definition of MRPs and ADRs used. The overall median prevalence was 70.8% (IQR = 61.0-80.2) with a range of 16.0% to 88.7%. The median prevalence of MRPs in specific and nonspecific patients was 71.2% (IQR = 60.7-71.2) and 69.3% (IQR = 60.7-82.0), respectively. In addition, a median of 36.6% (IQR = 10.0-85.7) of patients experienced ADRs. Indication-related and effectiveness-related MRPs were commonly reported in both specific and nonspecific patients, while noncompliance MRPs were more prevalent among specific patients than nonspecific patients. Increasing age, presence of co-morbidity, and an increasing number of drugs were the commonly identified contributing factors of MRPs. The review showed that more than two-thirds of the study participants developed MRPs. Hence, an integrated approach should be designed to improve the optimal use of pharmacotherapy to reduce the burden of MRPs. Further, future research should be undertaken to prepare cost-effective and efficient prevention mechanisms to reduce or halt the development of MRPs.

KEYWORDS

adverse drug reaction, Ethiopia., factors, Medication-related problem

Abbreviations: ADRs, adverse drug reactions; MRPs, Medication-related problems; NHA, National Health Accounts; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols .

1 | INTRODUCTION

Medicines contribute to the improvement of quality of life and life expectancy by relieving symptoms, delaying disease progression, and curing diseases. However, no drug is entirely harmless and can be associated with emergency department visits,[1] hospitalizations,[2] in-patient,[3] and outpatient[4] care complications. MRPs are unwanted effects that actually or potentially interfere with health outcomes.[5]They are significant causes of patient morbidity, mortality, economic loss, and contribute to overall pressure on the healthcare system.[6-8] MRPs include medication errors, adverse drug events, and adverse drug reactions.

For the last three decades, medication safety has been the primary research focus in Africa. The recent review of African studies showed that the median (interquartile range) percentage of patients experiencing adverse drug events during hospital admission and as a cause of hospital admission was 8.4% (4.5-20.1%) and 2.8% (0.7-6.4%), respectively. Interestingly, a median of 43.5% of these events was deemed to be preventable.[9] Patients living in low-income countries experience twice as many disability-adjusted life years lost due to medication-related harm than those in high-income countries.[10]

Ethiopia's healthcare system has also faced these challenges in similar way with other low-income countries. In the past two decades, the Government of Ethiopia has invested heavily in the healthcare system and prepared the Health Sector Transformation Plan (HSTP) to improve the health status of Ethiopians. The fifth round of the National Health Accounts (NHA) showed that the overall nominal health expenditure in 2010/11 raised by 138% compared to the 2007/08 total budget. As a result, Ethiopia achieved 67% and 69% reduction in the under-five mortality and maternal mortality, respectively, that raised the average life expectancy from 45 years in 1990 to 64 years in 2014.[11] Despite these achievements, MRPs remain a major challenge in the healthcare system. A recent systematic review of Ethiopian studies indicated that 36.8% of patients practiced self-medication.[12] This further increases the occurrence of the problem. There are several MRP studies conducted in Ethiopia; however, the scope of these problems has not been summarized, and their magnitude remains unclear.

1.1 | Aim of the review

The aim of this systematic review was to summarize the prevalence of MRPs and associated factors in the Ethiopian healthcare system.

2 | MATERIALS AND METHODS

The systematic review protocol was developed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidance [13] (Online Appendix one).

A systematic search of the literature was conducted to identify relevant published studies from journal inception to 01 April 2020. Studies that reported the prevalence and risk factors of MRPs were reviewed based on the following eligibility criteria.

2.1 | Inclusion criteria

Studies on MRPs targeting adult (age ≥ 15 years) in-patient and outpatient departments were eligible for inclusion in this systematic review. Additionally, studies focused on ADRs and adverse drug events (ADEs) were also included. Further, studies examined events associated with the specific drug(s), class of drug(s), organ(s), or system(s) were included.

2.2 | Exclusion criteria

The studies were excluded if they:

- Were conference papers, abstracts, editorial reports, or letters to the editors with limited information;
- Were case studies, case series, and qualitative studies; or
- Focused only in the pediatric population; or
- Studies published in other languages than English.

2.3 | Information sources

The following databases were used as sources of information:

- Electronic databases: Medline via PubMed, EMBASE via Ovid, Scopus, and Cumulative Index to the Nursing and Allied Health Literature (CINAHL);
- Grey literature was sourced through Google and Google Scholar; and
- The reference list of included articles was manually screened for relevant articles.

2.4 | Search strategy

The following search terms were used: "medication-related problem," "drug therapy problem," "Drug-related side effects and adverse reactions," "medication error," "medication related problem," "adverse drug reaction," "adverse drug event," "drug toxicit*," "drug induced problem," "factor," "predictor," and "Ethiopia." The search results were combined using Boolean operators ("OR" and "AND"). All search results from each database were saved in the individual electronic databases and exported into Endnote referencing software. Studies that were identified using manual searches were exported directly into the Endnote library.

2.5 | Study selection and data extraction

Once all search results were transferred into the Endnote library, duplicates were removed. The remaining studies were exported into Covidence software for the title and abstract screening. The inclusion and exclusion criteria were set in the Covidence software to aid the initial screening. This screening was performed by the two researchers (GTT and AD). Three categories (yes, no, maybe) were used during the selection process. The full text of studies considered "yes" or "maybe" during the screening was then assessed based on the eligibility criteria by two researchers (GTT and BK). The disagreement was resolved by consensus. The quality of included studies was assessed using the Newcastle-Ottawa quality assessment scale by two researchers (GTT and BK).[14] Quality assessment was undertaken independently by two reviewers (GTT and BK), with any disagreements resolved by discussion (online Appendix two). The overall review process is shown in Figure 1. A data extraction tool was developed by adapting and customizing the "Data collection form for intervention review—RCTs and non-RCTs" from the Cochrane Collaboration.[14] Data extraction was performed by two independent reviewers (GTT and BK). The following data were extracted from the included articles: study characteristics (author name and year of publication, hospital setting, study design, sample size, and the target population), attributes of MRPs, ADRs or ADEs (components of MRPs, definition, causality, severity, and preventability), and major findings (frequency, risk factors, and clinical outcomes).

2.6 | Data analysis

The prevalence of MRPs and ADRs was summarized with medians and interquartile ranges, and their attributes were described accordingly. Studies were divided as those targeted specific patients (eg, diabetes, cardiovascular, hypertensive) and nonspecific or general patients (eg, medical ward admitted patients). Components of MRPs were summarized using Cipolle et al [5] classification system, as it is frequently used by Ethiopian researchers. Further, associated risk factors of MRPs (for both specific and nonspecific patients) and ADRs were reported as socio-demographic, disease, medication, and healthcare-related using a table.

3 | RESULTS

3.1 | General description of the included studies

A total of 319 articles were eligible for the article screening process. After the removal of duplicates, 228 articles remained for abstract and title screening. Based on the initial title and abstract screening, 65 articles were eligible for full-text assessment. Finally, 32 studies were included for the final review based on the eligibility criteria mentioned above. The remaining 33 articles were excluded for various reasons (Figure 1).

A total of 32 studies encompassing 12 792 study participants from most parts of Ethiopia were included. The number of study participants varied from a smaller prospective study of 97 patients[15] to a larger retrospective study involving 3921 study participants.[16] The oldest study was published in 2012,[17] while the most recent was in 2020.[18] Twenty-four studies were conducted on MRPs, of which 15 studies were conducted in a specific patient population, and the remaining were conducted among general/nonspecific patient populations.[19-26] In addition, eight studies targeted ADRs.

More than two-thirds of the included studies used prospective study design, while the remaining seven studies[20,27-33] employed retrospective design. However, Esayas et al [16] employed both retrospective and prospective study designs. Furthermore, more than half of the

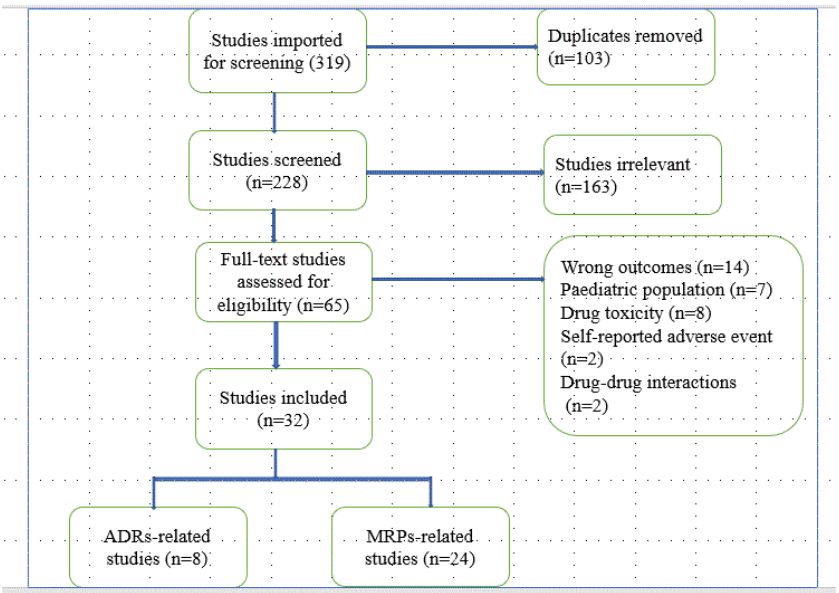

FIGURE 1 Flow chart showing article screening process.

TABLE 1 General characteristics of the included studies focused on MRPs in nonspecific patients

Author	Study setting	Study design	Study population	Sample size	Prevalence of MRPs (%)	Categorization of MRPs	Indication-related problem (%)	Efficacy-related problem (%)	Safety-related problem (%)	Noncompliance (%)
Mohammed et al.[22]	TASH	Prospective cross-sectional study	Medical inpatients	225	52.0	Cipolle et al.	16.1	6.4	24.3	23
Yaschilal et al.[23]	DRH	Prospective observational	Medical inpatients	147	75.5	Cipolle et al.	66.09	15.1	13.2	9.43
Gashaw et al.[37]	GUCSH	Prospective cross-sectional	Medical inpatients	256	66.0	PCNE	28.5	39.1	23.1	4.7
Berhane et al.[24a]	JUSH	Prospective cross-sectional	Medical and surgical inpatients	200	82.0	Cipolle et al.	46.6	21.0	40.1	24.2
Kebede et al.[25]	AKEH	Prospective observational	Medical inpatients	260	62.0	®	54.0	25.6	12.0	NR
Alemayehu et al.[26]	JUSH	Prospective observational	Medical inpatients	300	16.0	Cipolle et al.	47.0	14.8	18.7	10.7
Gosaye et al.[21]	JUSH	Prospective observational	Surgery inpatients	300	69.3	Cipolle et al.	21.9	37.5	23.0	5.5
Bereket et al.[20]	JUSH	Cross sectional	Medical inpatients	257	73.5	Cipolle et al.	47.5	27.2	15.5	NR
Tadele et al.[19]	JUSH	Prospective observational	Medical inpatients	152	75.7	Cipolle et al.	58.5	38.1	23.7	17

AKEH Alem Ketema Enat Hospital, *DRH* Dessie Referral Hospital,
[a]Elderly inpatients, *GUCSH*, Gondar University Comprehensive Specialized Hospital, *JUSH*, Jimma University Specialized Hospital, ® medication error, *NR*, not reported, *PCNE*, Pharmaceutical Care Network of Europe, *TASH*, Tikur Anbessa Specialized Hospital.

included studies (n = 18) were conducted in ambulatory patients, of which one study [34] focused on ADR-related hospital admissions. Two studies[35,36] focused on both in and outpatients (Table 1-3).

3.2 | Studies conducted on MRPs among nonspecific/general patient population

Concerning studies (n = 9) conducted in nonspecific patients, a total of 2,097 (147-300) patients were involved. All studies used Cipolle et al[5] MRPs categorization system, except Alemayehu et al[37] that used the Pharmaceutical Care Network of Europe.[38] All of them were prospective cross-sectional studies. Except Berhane et al,[24] which targeted elderly patients (>=60 years), other studies investigated the adult population. Seven out of nine studies[20,22,23,25,26,37] targeted patients admitted to medical wards. In addition, Berhane et al [24] and Gosaye et al[21] studied surgical and medical inpatients, and surgical inpatients, respectively. Further, Gosaye et al[21] and Tadele et al[19] focused on antibiotic-related MRPs (Table 1).

The median prevalence of MRPs in studies involving patients from general wards was 69.3% (IQR 60.7-82.0). MRPs' prevalence ranged from 16.0%[26] to 82.0%.[24] Frequently identified MRP types were unnecessary drug therapy (23.4%), need additional drug therapy (23.2%), and dose too high (15.1%). In addition, a median of 29.0% MRPs was dose-related. All of the studies reported the rate of non-compliance except two studies[22,25]. However, none of them used a standardized tool to measure noncompliance (Table 4). Further, only one study[23] reported clinical outcomes of MRPs, and Bereket et al[20] was also the only study that did not report causative agents (drugs) of MRPs.

3.3 | Studies conducted on MRPs among the specific patient population

Among 15 studies conducted in specific patient cohorts, a total of 3,420 (97-418) patients were involved. None of these studies focused on elderly patients. Most studies categorized MRPs using Cipolle et al classification system[5] except two studies,[28,35]. In addition, two-thirds of the studies used prospective designs except for Haymen et al,[27] Yohanes et al,[28] Abadir et al,[39] and Hailu et al[29] studies. More than half (n = 10) of the included studies investigated one or more cardiovascular disease conditions,[15,28,32,35,36,39-42] while Gebre et al,[43] Aster et al[44] and Beshir et al[18] studied ambulatory diabetic patients, hospitalized chronic kidney disease patients, and ambulatory epileptic patients, respectively. Moreover, Haymen et al[27] and Hailu et al[29] targeted ambulatory type II diabetes mellitus patients. Only two studies, Mohammednur et al[41] and Beshir et al,[18] reported clinical outcomes of MRPs (Table 2). Further, seven studies[27-29,42-45] reported the specific causative agents (drugs) responsible for MRPs.

The median prevalence of MRPs in specific patients was 71.2% (IQR 60.7-71.2). The prevalence ranged from 42.3%[43] to 88.7%.[15]

TABLE 2 General characteristics of the included studies focused on MRPs in specific patients

Author	Study setting	Study design	Study population	Sample size	Prevalence of MRPs	Categorization of MRPs	Indication-related problem (%)	Efficacy-related problem (%)	Safety-related problem (%)	Noncompliance (%)
Ousman et al.[35]	GUCSH	Cross sectional	CVD in & out patients	227	63.4	PCNE	24.9	19.7	3.0	17.4
Haymen et al.[27]	HFSUH	Retrospective cross sectional	Ambulatory DM II Patients	148	64.2	Cipolle et al.	33.1	55.9	11.0	NR
Yohanes et al. [28]	HFSUH	Retrospective cross sectional	Ambulatory DM II & HTN patients	203	49.2	PCNE	31.8	NR	19.0	NR
Abadir et al.[39]	DCRH	Cross sectional	Ambulatory HTN patients	271	71.2	Cipolle et al.	63.7	2.7	0.8	32.8
Gebre et al.[43]	TASH	Cross sectional	Ambulatory DM patients	418	42.3	Cipolle et al.	34.8	54.1	11.1	24.0
Aster et al.[44]	JUSH	Prospective observational	CKD inpatients	103	78.6	Cipolle et al.	35.5	28.0	16.5	20.0
Mohammednur et al.[41]	AHMC	Cross sectional	Ambulatory HTN patients	192	80.7	Cipolle et al.	2.2	0.9	18.6	19.5
Tamene et al.[36]	HFSUH	Cross sectional	CVD in & outpatient	216	60.7	Cipolle et al.	70.2	6.9	NR	12.2
Kaleab[45]	GSGH	Prospective cross sectional	Ambulatory CVD patients	130	72.0	Cipolle et al.	39.2	12.9	19.7	28.2
Hailu et al.[29]	WSUTRH	Cross sectional	Ambulatory DM II patients	243	83.1	Cipolle et al.	63.0	30.1	10.7	51.9
Beshir et al.[18]	TASH	Prospective cross sectional	Ambulatory epileptic patients	291	70.4	Cipolle et al.	6.0	34.6	46.6	44.3
Yirga et al.[42]	JUSH	Prospective observational	Ambulatory HF patients	340	83.5	Cipolle et al.	31.1	55.4	4.6	9.0
Gobezie et al.[15]	Two hospitals[a]	Cross sectional	CVD inpatients	97	88.7	Cipolle et al.	58.4	11.5	22.2	46.4
Asgedom et al.[32]	ACSH	Cross sectional	Ambulatory HTN patients	241	55.6	Cipolle et al.	28.3	29.1	2.5	40.1
Mohammed et al.[40]	JUSH	Prospective cross sectional	Ambulatory DM II and HTN patients	300	82.0	Cipolle et al.	39.7	43.2	4.4	12.2

ACSH, Ayder Comprehensive Specialized Hospital; *AHMC*, Adama Hospital Medical College; *CKD*, chronic kidney disease, *CVD*, cardiovascular disease, *DCRH*, Dil Chora Referral Hospital, *DM II*, diabetes mellitus type II, *FHRH*, Felege hiwot referral hospital, *GSGH*, Gebretsadik Shawo General Hospital; *GUCSH*, Gondar University Comprehensive Specialized Hospital; *HF*, heart failure, *HFSUH*, Hiwot Fana Specialized University Hospital; *HTN*, hypertension; *JUSH*, Jimma University Specialized Hospital.

[aa]JUSH & FHRH; *NR*, not reported, *PCNE*, Pharmaceutical Care Network of Europe; *TASH*, Tikur Anbessa Specialized Hospital; *WSUTRH*, Wolaita Sodo University Teaching Referral Hospital.

Need additional drug therapy (28.5%), noncompliance (22%), and dose too low (13.2%) were the frequently identified MRPs. Among studies targeted ADRs, three studies[27,28,35] did not report the rate of noncompliance. Among the studies that report noncompliance, all except Tegegne et al.[15] did not use a standardized tool (Table 4).

3.4 | Studies conducted on ADRS

Among eight studies conducted on ADRs, 7275 (211-3,921) patients were included. Of these, three studies used retrospective study design,[30,31,33] while Esayas et al[16] used both prospective and retrospective study designs. The remaining studies used a prospective study design. Except for Sewunet et al that studied ADRs on Cancer patients,[46] other studies focused on ambulatory patients; of these studies, Mehari et al[31] investigated ADRs on drug-resistant tuberculosis patients and others focused on ambulatory HIV/AIDS patients.[16,17,30,46,47] Further, Mulugeta et al[34] investigated ADR-related hospital admission.

Most studies[16,30,33,34,46,47] used WHO ADRs definition, while Abdissa et al[17] did not report the definitions they used. In addition, Mehari et al[31] investigated ADEs despite the definitions they used was not reported. All except Etsegenet et al,[30] reported the clinical outcome of ADRs. Further, two studies[34,46] reported the causative agents of ADRs.

The overall median prevalence of ADRs was 36.6% (10.0-85.7), with a range of 10.0% [30] to 85.7%.[47] Only three studies [34,46,47] used Naranjo et al[48] causality assessment criteria, while others did not report the method of ADRs causality assessment criteria used. All studies[16,34,46,47] did not report the severity and preventability of ADRs except Woldesellassie et al[47] and Mulugeta et al[34] studies. In Woldesellassie et al[47] study, 16.3% of the reactions were preventable, while in Mulugeta et al[34] study, it was reported that 89.1% ADRs (definite 16.0% and probable 73.1%) were preventable. Furthermore, except Abdissa et al study, which reported an 83.2% type A reactions,[17] others did not report ADRs' classification (Table 3).

3.5 | Identified risk factors of ADRs and MRPs among the included studies

Age and gender in both specific[29,40,42,43] and nonspecific patients [20] were the most frequently identified risk factors of MRPs, while age[31,46] was the most frequent risk factors of ADRs.

Considering disease-related variables, the number of diagnoses[24,35] and presence of comorbidity[29,32,39,40,44] in specific patients were the commonly identified risk factors of MRPs. In addition, the number of drugs in both nonspecific[20-22,24,25,35] and specific patients[18,29,36,39,41,42,44] were the frequently reported risk factor of MRPs, while taking zidovudine regimen[16,33,47] was the frequent risk factor of ADRs.

Further, concerning healthcare-related factors, the length of hospital stay[19,21,25,37] in nonspecific patients was the frequent risk factors of MRPs, while there were no statistically significant healthcare-associated risk factors of ADRs (Table 5).

4 | DISCUSSION

This systematic review provides an up-to-date and comprehensive assessment of the prevalence and risk factors MRPs and ADRs in Ethiopia. Thirty-two studies, published from journal inception to April 2020, were identified to look at MRPs in the Ethiopian healthcare system. The findings showed that MRPs and ADRs were critical problems of patient care that posed a significant burden to healthcare professionals and the healthcare system in Ethiopia. Hence, appropriate prevention strategies should be designed to reduce their burden.

The overall median percentage of MRPs among included studies was 70.8% (IQR 61.0-80.2) with the range of 16.0% to 88.7%. In addition, a median prevalence of 71.2% and 69.3% MRPs were identified in the specific and nonspecific patient population, respectively. Higher percentage of MRPs was identified in specific patients than nonspecific patients. Moreover, more than one-third of patients (a median prevalence of 36.6%) experienced ADRs. Further, despite inconsistencies among studies, several sociodemographic, and disease and medication-related characteristics were reported to be independently associated with MRPs and ADRs.

In this review, the median prevalence of MRPs is higher than the review conducted among African studies[9] which reported a median prevalence of 8.4% and 2.8% ADEs that were responsible for inpatient complications and a reason for hospital admission, respectively. ADEs are unwanted MRPs involving side effects, ADRs, and toxicities. In addition, the finding of our review is higher than the recent systematic review performed by Ayalew et al[49] which reported a 15.0% medication-related hospital admissions. This review did not involve MRPs during the hospital stay. Further, our finding is also higher than an international review of studies performed by Wilbur et al.[50] This review reported that 15.4% of hospital visits were drug-related.[50] Higher prevalence in our review maybe due to the minimal effort made to institutionalize clinical pharmacy service.[51] This was seen in Bilal et al study, which reported that 47% of pharmacists rated their service as poor and their overall satisfaction was about 36%.[51] Despite this, majority of healthcare providers (85.71%) had a positive attitude toward clinical pharmacy service.[52]

Despite heterogeneity among the included studies, increasing age, female gender, presence of comorbidity, and increasing number of drugs were consistently reported risk factors of MRPs in both general and specific patients. Higher prevalence of inappropriate medication use and complex prescribing practice makes older patients at a higher risk of MRPs due to age-related physiological changes, the presence of various chronic diseases, and numbers of medications.[53,54] In addition, due to different body compositions, hormonal differences, and blood concentrations of certain metabolic enzymes[55] make females more susceptible to MRPs. Moreover, the existence of comorbidity is often associated with

TABLE 3 General characteristics of the included studies focused on ADRs among patients

Author	Study setting	Study design	Study population	Sample Size	ADR Prevalence (%)	ADR definition	Causality of ADR (%)	Severity of ADR (%)
Senbeta et al.[17]	TASH	Prospective observational	HIV Outpatients	228	51.1	NR	NR	NR
Mulugeta et al.[34]	JUSH	Prospective cross sectional	Medical inpatients	1,001	10.3	WHO	Naranjo: definite (26.1%), probable (73.9%)	NR
Woldesellassie et al.[47]	FHRH	Prospective cohort	HIV Outpatients	211	85.7	WHO	Naranjo: definite (1.7%), probable (31.8%), possible (66.5%)	¥52.7 (Grade 1), 25.2 (Grade 3), 22.1 (Grade 4)
Sewunet et al.[46]	*GUCSH*	Cross sectional	Cancer patients	384	52.9	WHO	Naranjo: probable (68.8%), possible (31.4%)	£70.1 (Grade 3-5), 29.9 (Grade 1-4)
Esayas et al.[16]	Multi-hospitals[a]	Prospective cohort	HIV Outpatients	3,921	22.1	WHO	NR	43.3 (life-threatening)
Etsegenet et al.[30]	FHRH	Retrospective	HIV Outpatients	602	10.0 (4.3/100PY)	WHO	NR	NR
Mehari et al.[31]	Multi-hospitals[a]	Retrospective cohort	Drug-resistant Tuberculosis patients	570	51.2 (5.8/100PM)	®	NR	NR
Fitsum et al.[33]	HFSUH	Retrospective	HIV Outpatients	358	17.0	WHO	NR	80.3 (Grade III)

® Adverse Drug Event, ADR adverse drug reaction, *FHRH* Felege Hiwot Referral Hospital,

[a]Four hospitals (University of Gondar comprehensive specialized hospital, Debre Markos Referral Hospital, Borumeda primary hospital, and Woldia primary hospital), *GUCSH* Gondar University Comprehensive Specialized Hospital, *HFSUH* Hiwot Fana Specialized University Hospital, *HIV* human immune virus, *NR* not reported.

[b]Seven hospitals located in Addis Ababa, Hawassa, Jimma, Haramaya, Mekelle and Gondar towns, *TASH*, Tikur Anbessa Specialized Hospital, *WHO*, World Health Organization, £ National Cancer Institute Common Terminology grade 1–5 toxicity, ¥ *DAIDS* adverse events severity grading, 100 PM 100 person month, 100PY, 100 persons year

TABLE 4 Prevalence of each component of MRPs in the included studies

Components of MRPs		Median (range) percentage[b]	Median (range) percentage[a]
Indication-related problems	Unnecessary drug therapy	23.4 (4.3–40.0)	5.4 (0.9–19.7)
	Need additional drug therapy	23.2 (4.9–35.9)	28.5 (5.1–62.4)
	Total	47.0 (16.1–66.1)	33.9 (2.2–70.2)
Ineffective drug-related problems	Ineffective drug therapy	4.6 (1.9–18.4)	10.4 (1.9–27.8)
	Dose too low	13.9 (3.9–32.9)	13.2 (0.8–36.2)
	Total	25.6(6.4–39.1)	23.9 (0.9–55.9)
Safety-related problems	ADEs/ADRs	9.4 (2.3–24.2)	9.4 (1.7–41.5)
	Dose too high	15.1 (1.3–20.7)	2.7 (0.8–14.5)
	Total	23.0(12.0–40.1)	11.5 (2.5–46.6)
Compliance-related problems	Noncompliance	10.7 (4.7–24.2)	22 (9.0–51.9)

[a]For a specific group of patients

[b]For nonspecific patients, *ADE*, adverse drug event; ADRs, adverse drug reactions; *MRPs*, medication-related problem.

TABLE 5 Summary of the risk factors associated with MRPs and ADRs in Ethiopia

Category of associated risk factors	Risk factors of MRPs (nonspecific patients)	Risk factors of MRPs (specific patients)	Risk factors of ADRs
Patient-related	Age [20], Gender [20]	Age[29,40,42], Gender[43], Place of residence[43], Marital status[41,43,44], Nonadherence[43]	Age[31,46], Unemployment[47], BMI[34], Marital status[16], Occupation[30], Educational status[30]
Disease-related	Number of diagnoses[24,35], Presence of comorbidity[25], Overall clinical outcome[21], CDC wound class[21], Indication for antibiotic use[21]	Uncontrolled BP[39], Presence of comorbidity[29,32,39,40,44], Number of diagnoses[41–43], Presence of DM II[43], Stage of CKD[44], Complication[41], Heart failure[15]	Previous AKI[34], Liver disease[34], Number of diagnoses[34], History of ADRs[34], HIV clinical stage[30], Comorbidity[31], Anaemia[31]
Medication-related	Number of drug[20–22,24,25,35], Significant DDI[20], Drug availability[25], Antibiotic exposure[21]	Number of drugs[18,29,36,39,41,42,44], Substance use[32]	Number of drugs[34,46], Taking ZDV regimen[16,33,47], Taking anti-TB drugs[16], OI prophylaxis[30]
Healthcare-related	Length of hospital stay[19,21,25,37], Type of surgery[21]	History of hospitalization[29], Negative belief on medication use[42], Poor involvement of patients on therapeutic decision[42]	

AKI acute kidney disease, *BMI* body mass index, BP blood pressure, *CDC* communicable disease control, *CKD* chronic kidney disease, DDI drug-drug interaction, *DM* diabetes mellitus, *OI* opportunistic infection, *TB* tuberculosis, *ZDV* zidovudine

the use of more than one medication. Studies revealed that multiple medication use and drug–drug interactions predispose patients to MRPs.[56,57] Moreover, increasing age, number of drugs, and drug regimen containing Zidovudine were the frequently reported predictors of ADRs. This is in line with a review by Mulugeta et al.[58]

Based on our findings, the following recommendations are forwarded for future studies. Future studies should use standardized definitions for MRPs and ADRs, and standardized tool for ADRs causality, classification, severity, preventability, and noncompliance assessment. Noncompliance assessment tool indicated by Cipolle et al[5] and Pharmaceutical care network of Europe[38] are not standardized; hence, other tools like the Morisky adherence scale may be used. In addition, researchers ought to focus on a specific disease condition to investigate MRPs and ADRs.

4.1 | Strength and limitations

The strengths of our systematic review include complete literature search in more than one relevant database (PubMed, EMBASE, CINAHL, Scopus, Google, and Google scholar) and proper screening of eligible studies by two independent reviewers. In addition, our review has the following limitations; due to the heterogeneity of

studies, it was not possible to undertake a meta-analysis. As lists of medications responsible for MRPs and ADRs were too many, and the way studies reported these medications were inconsistent, it was challenging to summarize causative agents of MRPs/ADRs. Finally, we acknowledge that we may not have been able to retrieve unpublished data and grey literature.

5 | CONCLUSION

Although the prevalence of MRPs and ADRs varied among studies due to the definition, study population and method used more than two-third and one-third of patients experienced MRPs and ADRs, respectively. Higher prevalence of MRPs was found in studies targeting specific patients than nonspecific patients. In addition, the review showed that almost half of the study participants had an indication-related MRPs, while effectiveness and safety-related MRPs occurred among one in four patients. Further, different socioeconomic, disease-related, medication-related, and healthcare-related variables contribute to the development of MRPs and ADRs. This review found that MRPs and ADRs constitute significant problems in the Ethiopian healthcare system. Hence, healthcare professionals' coordinated effort is necessary and efficient prevention strategies that target the identified risk factors should be designed to lessen the burden of the problem. Furthermore, an efficient healthcare system that involves pharmacists in patient care should be strengthened. Last but not the least, a qualified and sufficient number of pharmacists should be allocated to the different hospital wards and follow-up clinics.

ETHICS APPROVAL

Not applicable.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

The authors consented to publish this review.

CODE AVAILABILITY

Not applicable.

DISCLOSURE

The authors declared that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

GTT and BK were participated in the review process starting from conceptualization, methodology, data curation, formal analysis, and writing. In addition, AD was highly involved in methodology, formal analysis, and writing–review & editing.

DATA AVAILABILITY STATEMENT

The extracted data are available if required.

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