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.
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, hospitalizations, in-patient, and outpatient care complications. MRPs are unwanted effects that actually or potentially interfere with health outcomes. They are significant causes of patient morbidity, mortality, economic loss, and contribute to overall pressure on the healthcare system. 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. 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.

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. 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. 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.

Aims of the review

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

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 (Online Appendix one).

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.

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.

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;
- The reference list of included articles was manually screened for relevant articles.

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 toxicity,” “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.\(^{34}\) 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
TABLE 1 | General characteristics of the included studies focused on MRPs in nonspecific patients

| Study setting | Study design | Sample size | Category of MRPs | Prevalence of MRPs (%) | Sample population |
|---------------|--------------|-------------|------------------|------------------------|------------------|
| TASH          | Prospective cross-sectional study | 225          | Medical inpatients | 52.0                   | 22               |
| Cipolle et al. | 16.1          | 6.4         | 24.3              | 16.1                   | 24               |
| Medical inpatients | 52.0         | 6.4         | 24.3              | 16.1                   | 24               |
| DRH           | Prospective cross-sectional study | 147          | Medical inpatients | 75.5                   | 14               |
| Cipolle et al. | 16.1          | 6.4         | 24.3              | 16.1                   | 24               |
| GUCSH         | Prospective cross-sectional study | 256          | Medical inpatients | 66.0                   | 25               |
| PCNE          | 23.1          | 4.7         | 24.2              | 23.1                   | 4.7              |
| Cipolle et al. | 16.1          | 6.4         | 24.3              | 16.1                   | 24               |
| AKEH          | Prospective cross-sectional study | 230          | Medical inpatients | 60.0                   | 23               |
| Alemayehu et al. | 16.1       | 6.4         | 24.3              | 16.1                   | 24               |
| JUSH          | Prospective cross-sectional study | 200          | Medical and surgical inpatients | 82.0                   | 20               |
| Cipolle et al. | 16.1          | 6.4         | 24.3              | 16.1                   | 24               |
| KEFALE E et al. | Prospective cross-sectional study | 260          | Medical inpatients | 62.0                   | 26               |
| Alemayehu et al. | 16.1        | 6.4         | 24.3              | 16.1                   | 24               |
| JUSH          | Prospective cross-sectional study | 256          | Medical inpatients | 75.5                   | 25               |
| Alemayehu et al. | 16.1        | 6.4         | 24.3              | 16.1                   | 24               |
| JUSH          | Prospective cross-sectional study | 152          | Medical inpatients | 75.7                   | 15               |
| Tadele et al. | Prospective cross-sectional study | 237          | Medical inpatients | 88.7                   | 23               |
| JUSH          | Prospective cross-sectional study | 180          | Medical inpatients | 88.7                   | 18               |

Included studies (n = 18) were conducted in ambulatory patients, of which one study focused on ADR-related hospital admissions. Two studies 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's MRP categorization system, except Alemayehu et al that used the Pharmaceutical Care Network of Europe. All of them were prospective cross-sectional studies. Except Berhane et al, which targeted elderly patients (>=60 years), other studies investigated the adult population. Seven out of nine studies targeted patients admitted to medical wards. In addition, Berhane et al and Gosaye et al studied surgical and medical inpatients, and surgical inpatients, respectively. Further, Gosaye et al and Tadele et al 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% to 82.0%. 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. However, none of them used a standardized tool to measure noncompliance (Table 4). Further, only one study reported clinical outcomes of MRPs, and Bereket et al was 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 except two studies. In addition, two-thirds of the studies used prospective designs except for Haymen et al, who used a standardized tool to measure noncompliance. More than half of the included studies investigated one or more cardiovascular disease conditions. While Gebre et al, Aster et al, and Beshir et al studied ambulatory diabetic patients, hospitalized chronic kidney disease patients, and ambulatory epileptic patients, respectively. Moreover, Haymen et al and Hallu et al targeted ambulatory type II diabetes mellitus patients. Only two studies, Mohammednur et al and Beshir et al, reported clinical outcomes of MRPs (Table 2). Further, seven studies 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% to 88.7%.
| 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.           | GUCSH         | Cross sectional                   | CVD in & out patients          | 227         | 63.4               | PCNE                   | 24.9                         | 19.7                        | 3.0                       | 17.4            |
| Haymen et al.           | HFSUH         | Retrospective cross sectional      | Ambulatory DM II Patients      | 148         | 64.2               | Cipolle et al.         | 33.1                         | 55.9                        | 11.0                      | NR              |
| Yohanes et al.          | HFSUH         | Retrospective cross sectional      | Ambulatory DM II & HTN patients| 203         | 49.2               | PCNE                   | 31.8                         | NR                          | 19.0                      | NR              |
| Abadir et al.           | DCRH          | Cross sectional                   | Ambulatory HTN patients        | 271         | 71.2               | Cipolle et al.         | 63.7                         | 2.7                         | 0.8                       | 32.8            |
| Gebre et al.            | TASH          | Cross sectional                   | Ambulatory DM patients         | 418         | 42.3               | Cipolle et al.         | 34.8                         | 54.1                        | 11.1                      | 24.0            |
| Aster et al.            | JUSH          | Prospective observational          | CKD inpatients                 | 103         | 78.6               | Cipolle et al.         | 35.5                         | 28.0                        | 16.5                      | 20.0            |
| Mohammednur et al.      | AHMC           | Cross sectional                   | Ambulatory HTN patients        | 192         | 80.7               | Cipolle et al.         | 2.2                          | 0.9                         | 18.6                      | 19.5            |
| Tamene et al.           | HFSUH         | Cross sectional                   | CVD in & outpatient            | 216         | 60.7               | Cipolle et al.         | 70.2                         | 6.9                         | NR                        | 12.2            |
| Kaleab                  | GSGH          | Prospective cross sectional        | Ambulatory CVD patients        | 130         | 72.0               | Cipolle et al.         | 39.2                         | 12.9                        | 19.7                      | 28.2            |
| Hailu et al.            | WSUTRH        | Cross sectional                   | Ambulatory DM II patients      | 243         | 83.1               | Cipolle et al.         | 63.0                         | 30.1                        | 10.7                      | 51.9            |
| Beshir et al.           | TASH          | Prospective cross sectional        | Ambulatory epileptic patients  | 291         | 70.4               | Cipolle et al.         | 6.0                          | 34.6                        | 46.6                      | 44.3            |
| Yirga et al.            | JUSH          | Prospective observational          | Ambulatory HF patients         | 340         | 83.5               | Cipolle et al.         | 31.1                         | 55.4                        | 4.6                       | 9.0             |
| Gobezie et al.          | Two hospitals  | Cross sectional                   | CVD inpatients                 | 97          | 88.7               | Cipolle et al.         | 58.4                         | 11.5                        | 22.2                      | 46.4            |
| Asgedom et al.          | ACSH          | Cross sectional                   | Ambulatory HTN patients        | 241         | 55.6               | Cipolle et al.         | 28.3                         | 29.1                        | 2.5                       | 40.1            |
| Mohammed et al.         | JUSH          | Prospective cross sectional        | Ambulatory DM II and HTN patients| 300         | 82.0               | Cipolle et al.         | 39.7                         | 43.2                        | 4.4                       | 12.2            |

ACS, 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.

*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\textsuperscript{27,28,35} did not report the rate of noncompliance. Among the studies that report noncompliance, all except Teggene et al.\textsuperscript{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,\textsuperscript{30,31,33} while Esayas et al\textsuperscript{46} 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,\textsuperscript{46} other studies focused on ambulatory patients; of these studies, Mehari et al\textsuperscript{31} investigated ADRs on drug-resistant tuberculosis patients and others focused on ambulatory HIV/AIDS patients.\textsuperscript{16,17,30,46,47} Further, Mulugeta et al\textsuperscript{34} investigated ADR-related hospital admission.

Most studies\textsuperscript{16,30,31,34,46,47} used WHO ADRs definition, while Abdissa et al\textsuperscript{24} did not report the definitions they used. In addition, Mehari et al\textsuperscript{31} investigated ADEs despite the definitions they used was not reported. All except Etsegenet et al,\textsuperscript{30} reported the clinical outcome of ADRs. Further, two studies\textsuperscript{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% to 85.7%.\textsuperscript{47} Only three studies\textsuperscript{34,46,47} used Naranjo et al\textsuperscript{48} causality assessment criteria, while others did not report the method of ADRs causality assessment criteria used. All studies\textsuperscript{16,34,46,47} did not report the severity and preventability of ADRs except Woldesellassie et al\textsuperscript{47} and Mulugeta et al\textsuperscript{34} studies. In Woldeselassie et al\textsuperscript{47} study, 16.3% of the reactions were preventable, while in Mulugeta et al\textsuperscript{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,\textsuperscript{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\textsuperscript{29,40,42,43} and nonspecific patients\textsuperscript{20} were the most frequently identified risk factors of MRPs, while age\textsuperscript{31,46} was the most frequent risk factors of ADRs.

Considering disease-related variables, the number of diagnoses\textsuperscript{24,35} and presence of comorbidity\textsuperscript{19,32,39,40,44} in specific patients were the commonly identified risk factors of MRPs. In addition, the number of drugs in both nonspecific\textsuperscript{20-22,24,25,35} and specific patients\textsuperscript{18,29,36,39,41,42,44} were the frequently reported risk factor of MRPs, while taking zidovudine regimen\textsuperscript{16,33,47} was the frequent risk factor of ADRs.

Further, concerning healthcare-related factors, the length of hospital stay\textsuperscript{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\textsuperscript{4} 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\textsuperscript{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.\textsuperscript{50} This review reported that 15.4% of hospital visits were drug-related.\textsuperscript{50} Higher prevalence in our review maybe due to the minimal effort made to institutionalize clinical pharmacy service.\textsuperscript{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%.\textsuperscript{51} Despite this, majority of healthcare providers (85.71%) had a positive attitude toward clinical pharmacy service.\textsuperscript{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.\textsuperscript{53,54} In addition, due to different body compositions, hormonal differences, and blood concentrations of certain metabolic enzymes\textsuperscript{55} make females more susceptible to MRPs. Moreover, the existence of comorbidity is often associated with
| 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                  |
| Woldeselassie 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) |
| Etsagenet 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)   | WHO             | NR                   | NR                  |
| Fitsum et al. \(^{33}\) | HFSUH         | Retrospective         | HIV Outpatients   | 358        | 170                | WHO            | NR                   | 80.3 (Grade III)    |

\(^{a}\) 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

\(^{©}\) Adverse Drug Event, ADR adverse drug reaction, FHRH Felege Hiwot Referral Hospital.
the use of more than one medication. Studies revealed that multiple medication use and drug–drug interactions predispose patients to MRPs. 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. 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 and Pharmaceutical care network of Europe 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

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

| Components of MRPs | Median (range) percentage\(^a\) | Median (range) percentage\(^b\) |
|--------------------|---------------------------------|---------------------------------|
| Indication-related problems | Unnecessary drug therapy | 23.4 (4.3–40.0) |
|                      | Need additional drug therapy | 23.2 (4.9–35.9) |
|                      | Total                          | 47.0 (16.1–66.1) |
| Ineffective drug-related problems | Ineffective drug therapy | 4.6 (1.9–18.4) |
|                      | Dose too low                   | 13.9 (3.9–32.9) |
|                      | Total                          | 25.6 (6.4–39.1) |
| Safety-related problems | ADEs/ADRs                      | 9.4 (2.3–24.2) |
|                      | Dose too high                  | 15.1 (1.3–20.7) |
|                      | Total                          | 23.0 (12.0–40.1) |
| Compliance-related problems | Noncompliance                 | 10.7 (4.7–24.2) |

\(^a\)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 20,40,42, 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 37, Presence of comorbidity 29,32,39,40,44, Number of diagnoses 21, Stage of CKD 21, Complication 21, Heart failure 15 | Previous AKI 24, Liver disease 34, Number of diagnoses 34, History of ADRs 24, HIV clinical stage 20, 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
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
GT 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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How to cite this article: Kefale B, Degu A, Tegegne GT. Medication-related problems and adverse drug reactions in Ethiopia: A systematic review. Pharmacol Res Perspect. 2020;e00641. https://doi.org/10.1002/prp2.641