Prevalence of potential drug- drug interactions and associated factors among outpatients and inpatients in Ethiopian Hospitals: a systematic review and Meta-analysis of observational studies

Wondim Ayenew (yimesgen20@gmail.com)
University of Gondar College of Medicine and Health Sciences https://orcid.org/0000-0001-8504-8430
Getahun Asmamaw
Arba Minch University
Arebu Issa
Addis Ababa University College of Health Sciences

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Abstract

Background: Drug-drug interaction is an emerging threat to the public health. In Ethiopia, there is high possibility of occurrence of drug-drug interactions in the hospitals. This is because of increased comorbid disease, increased polypharmacy, and increased hospitalization. Therefore, this study aims to summarize the prevalence of potential drug-drug interactions and associated factors in Ethiopian hospitals.

Methods: Literature search was performed through accessing legitimate databases in PubMed/MEDLINE, Google Scholar and Research Gate for English-language publications. Advanced search strategies were applied in Science Direct and HINARI to identify any additional papers and published reviews and to retrieve relevant findings closely related to prevalence of potential drug- drug interactions and associated factors with it. The search was conducted from August 3-25, 2019 and all published articles available online until the day of data collection were considered. The pooled estimate of the outcome measure were analyzed by Open Meta Analyst advanced software. By considering clinical heterogeneity among original studies, Der Simonian and Laird's random effect model were used. I^2 statistics were used to assess heterogeneity among each studies. The publication bias was assessed by CMA version-3 software and presented with funnel plot of standard error and precision with Logit event rate.

Results: A total of 14 studies were included for systematic review and meta-analysis. From 14 studies, 5761 patients were included and a total of 8717 potential drug- drug interactions were found in 3259 of patients. The prevalence patients with potential drug- drug interactions in Ethiopian Hospitals were found to be 72.2% (95% confidence interval: 59.1%, 85.3%). Based on severity, the prevalence of potential drug- drug interactions were 25.1%, 52.8%, 16.9% and 1.27% for major, moderate, minor potential drug- drug interactions and contraindications respectively. The factors associated with potential drug- drug interactions were related to patient characteristics such as polypharmacy, age, comorbid disease and hospital stay.

Conclusions: There is a high prevalence of potential drug- drug interactions in Ethiopian Hospitals. Polypharmacy, age, comorbid disease and hospital stay were the risk factors associated with potential drug- drug interactions.

Background

Drug-drug interactions (DDIs) are types of adverse drug events (ADEs) which can occur when the effect of a drug is altered by another drug that is taken concurrently and results in a qualitative and/or quantitative change in drug action(Stockley's, 2010).

DDIs can be categorized by severity. Major DDIs may be life threating or may cause prolonged or permanent damage. Moderate DDIs may require medical intervention or change in therapy, whereas minor DDIs do not usually require a change in therapy. Regardless of the DDI severity, patient's should be monitored for possible manifestations of the interaction (Varma MV, Pang KS, Isoherranen N, 2015). DDIs can also classified as pharmaceutical, pharmacokinetic and pharmacodynamics based on the mechanisms by which drugs interact with each other (Bolhuis MS, Panday PN, PrangerAD, 2011).

DDIs may have desirable, reduced, undesirable or harmful effects(Varma MV, Pang KS, Isoherranen N, 2015). They may change the diagnostic, preventive and therapeutic activity of any drug and results in treatment failure, toxicity of medications and alternation of drug efficacy(Bjornsson T, Callaghan J, Einolf H, 2003; Bolhuis MS, Panday PN, PrangerAD, 2011).

They are common in clinical practice and in cardiovascular patients, Human Immunodeficiency Virus infected patients and psychiatric patients. This is because of patient characteristics such as age, common disease state and polypharmacy; pharmacokinetic and pharmacodynamic nature of drugs; influence of a disease on drug metabolism; prescriber issues such as multiple drug prescription by multiple prescribers, inadequate knowledge of prescribers' on DDIs or poor recognition of the relevance of DDIs by prescribers (Diksis et al, 2019; Behailu Terefe Tesfaye et al, 2017; Haftay Berhane Mezgebe et al, 2017; Wang JK, Herzog NS, Kaushal R, Park C, Mochizuki C, 2007; Heininger-Rothbucher D, Bischinger S, Ulmer H, Pechlaner C, Speer G, 2001; Ko Y, Malone DC, Skrepnek GH, Armstrong EP, Murphy JE, Abarca J, Rehfeld RA, Reel SJ, 2008).

DDIs are also common in renal and hepatic insufficiency (CKD, cirrhosis) patients. This type of patients require multiple types of drugs, their kidney and liver may decrease the excretion and metabolize ability of medications. Therefore, the occurrence of DDIs in this type of patients may be significant (Alessandra B, 2014; Palatini P, 2016).

They are also more frequent in hospitalized patients, patients who stay in hospital for a longer period of time, and/or receive more drugs per day(Galleli et al, 2017; Janković SM, Pejčić AV, Milosavljevic MN, 2018; Obreli-Neto PR, Nobili A, de Oliveira Baldoni A, 2012; Romagnoli KM, Nelson SD, Hines L, 2017). Hospitalized patients are more likely to be affected by DDIs because of severe and multiple illnesses, comorbid conditions, chronic therapeutic regimens, poly-pharmacy and frequent modification in therapy(Zwart-van-Rijkom JEF, Uijtendaal EV, Ten Berg MJ, Van Solinge WW, 2009). Among hospitalized patients, elderly patients are at higher risk of potential DDIs and occurrence of potential DDIs ranges from 3 to 69%, depending on the specific area and population. This increased prevalence was found to be related to presence of multiple chronic illnesses, use of multiple medications and altered pharmacokinetics in the elderly patients(Wang JK, Herzog NS, Kaushal R, Park C, Mochizuki C, 2007).

Physicians and pharmacists alert fatigue is a common reason for the occurrence drug-drug interactions for patients receiving interacting drugs. Even though computerized DDI alert systems may decrease the occurrence of DDIs, numerous alerts produced by such system leads physician and pharmacist alert fatigue. This alert fatigue results in considerable override of DDI alerts. A study done in Japan showed, physicians overrode DDI alerts at high rate in computerized drug interaction alert system (Nasuhara Y. et al, 2015).

Clinically significant DDIs may cause a potential harm to patients, harmful outcomes and resulting in an estimated cost of more than $1 billion per year to governmental health care system expenditure(Qorraj-Bytyqi H, Hoxha R, Krasniqi S, Bahtiri E, 2012).

DDI is an emerging threat to public health(Kothari N, 2014). In Ethiopia, now a days, polypharmacy is increased due to comorbid conditions in the hospital health care system(Berha AB, 2018; Sisay M. , Mengistu G., Molla B., 2017), a large number of patients are hospitalized and there is a high possibility for DDIs. Furthermore, due to economic problems, the probability of monitoring patients with comorbid diseases using sophisticated instruments is not feasible causing the patient to DDIs.

As a result, potential DDIs causing serious risk to patient health. Therefore, this study attempted to review and quantitatively estimate the prevalence of potential DDIs and associated risk factors in hospitals, both among inpatients and outpatients in Ethiopia.

Methods

Study protocol

The identification of records, screening of titles and abstracts as well as evaluation of eligibility of full texts for final inclusion was reported in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) flow diagram. PRISMA checklist was also strictly followed while reporting this systematic review and meta-analysis (additional file 1: table 1)(Liberati, 2009).

The study protocol is registered on PROSPERO with reference ID number: CDR42020149416 and the published methodology is available at https://www.crd.york.ac.uk/prospero/display_recored.php?ID=CDR42020149416.

Screening and eligibility of studies

WA designed the study. Two authors WA and GA screened title and abstracts of the studies based on the inclusion and exclusion criteria. They also collected the full texts, evaluated the eligibility of the studies for final inclusion, assessed the quality of the study and analyzed the data. AI commented the review and meta-analysis.

Inclusion and exclusion criteria

Inclusion criteria

- Observational studies addressing prevalence of potential DDIs and conducted in Ethiopia were included(prospective, retrospective and descriptive crossectional studies)
- All male and female patients in any age(pediatrics, adults, and geriatric) and admitted to hospital wards or visited outpatients were included
- All published articles without time limit were included
- Patients who had any disease and admitted to hospital wards or visited outpatients
- Studies which were published in English language and provided sufficient data for the review were included

Exclusion criteria

- Articles with missing or insufficient outcomes were also excluded.
- Drug interactions with herbs, diseases, and nutrients were excluded
- Studies that were conducted in primary health care settings

Search strategy and data sources

Literature search was performed through accessing legitimate databases in PubMed/MEDLINE, Google Scholar and Research Gate for English-language publications. Advanced search strategies were applied in Science Direct and HINARI to identify any additional papers and published reviews and to retrieve relevant findings closely related to prevalence of potential DDIs and associated factors **with DDIs among outpatients and inpatients in Ethiopian Hospitals.**

The search was conducted with the aid of carefully selected search-words without specification in time. “Prevalence”, “occurrence”, “potential DDIs”, “associated factors” and “Ethiopia” were the search words used in this review and meta-analysis. AND/OR words were used for the identification of the articles. The search was conducted from August 3-25, 2019 and all published articles available online until the day of data collection were considered.

Data Extraction

A standardized data extraction form was prepared in Microsoft Excel by the investigators and important information which were related to study characteristics (Region, Study area, Author, Year of publication, study design, Pathology, Target population, Study setting, Interaction data base, Number of patients, Number of patients with DDIs, and lists of medications that caused the interactions) and outcome of interest (Prevalence of DDIs (%), Potential DDIs (major, moderate and minor) and associated factors of DDIs) were extracted.

Fourteen studies were selected based on their abstract, inclusion and exclusion criteria. Studies were searched, identified and screened from different search engines which are published in English language.

Quality assessment

The quality of selected studies were performed. All selected studies was reviewed according to 12 criteria adapted from a previous study(Nabovati E., Vakili-Arki H., Taherzadeh Z., Reza Hasibian M. & Eslami A., 2014). The 12 criteria's were: objectives of the study, definition of what constitutes a DDI, DDI categories, DDI categories defined, mention of DDI reference, data collection method described clearly, setting in which study was conducted described, study subjects described, sampling and calculation of sample size described, potential or actual DDIs assessed, measures in place to ensure that results are valid and limitations of study listed. Each criteria is related to a quality assessment criterion with score 0 or 1 and the total quality scores ranged from 0 to 12 (scores 0 to 6 = poor quality, 7 to 9 scores = moderate quality, 10 to 12 points = high quality) (Table 1).

Table 1: Quality assessment of included studies in the review

Studies	Total scores	Quality
Gunasekaran et al, 2016	9	Moderate
Behailu Terefe Tesfaye et al, 2017	12	High
Diksis et al, 2019	12	High
Chelkeba L et al, 2013	12	High
B.Akshaya Srikanth et al., 2014	12	High
Admassie, et al, 2013	10	High
Henok Getachew et al, 2016	12	High
Teka et al, 2016	12	High
Zeru Gebretsadik et al, 2017	11	High
Haftay Berhane Mezgebe, 2015	11	High
Teklay et al, 2014	11	High
Yesuf TA, et al, 2017	10	High
Tesfaye and Nedi, 2017	11	High
Kibrom et al, 2018	11	High

Outcome measurements

The outcome measure in this review and meta-analysis is the prevalence of potential DDIs. It is primarily aimed to assess the pooled estimates of potential DDIs in the Hospitals of Ethiopia. This study has also two secondary outcome measures: Associated risk factors for potential DDIs and number of potential DDIs (major, moderate and minor) in Ethiopian Hospitals.

Data processing and statistical analysis

Analyses of pooled estimate of outcome measures i.e. Prevalence of potential DDIs, as well as for subgroup analysis were done by Open Meta Analyst advanced software. CMA version-3 software was used for publication bias assessment. The presence of publication bias was evaluated by using Egger's regression tests and presented with funnel plots of standard error and precision with Logit event rate. A statistical test with a P value less than 0.05 (one tailed) was considered significant(Begg CB, 1994; Egger M, Davey Smith G, Schneider M, 1997).

Heterogeneity assessment

Heterogeneity may be defined as any type of variability among studies in a systematic review and eta analysis. When there is variability in participants, interventions and outcomes studied, we call it clinical heterogeneity. In this review and meta-analysis, Der Simonian and Laird's random effects model were used by considering clinical heterogeneity among studies. Variability in study design and risk of bias may be described as methodological heterogeneity (Laird N. and DerSimonian R., 1986).

Variation in intervention effects being evaluated in different studies is defined as statistical heterogeneity. This type of heterogeneity is usually a result of clinical or methodological heterogeneity or both among studies. Statistical heterogeneity is assessed by using Cochran's Q- statistics, chi-squared and I^2 test. In this review and meta-analysis, clinical heterogeneity of studies was assessed using I^2 statistics. Based on the result of the statistical test, I^2 statistics value of less than 25% were considered as low heterogeneity and I^2 statistics value from 50% to 75% and I^2 statistics value greater than 75% were considered as medium and high heterogeneity respectively(Julian PT Higgins et al, 2002).

Results

Article search results

A total of 69 articles were identified through the search strategy. After duplication was removed, 49 articles were remained for screening. From these, 30 articles were excluded by their titles and abstracts. The remaining 19 articles were then evaluated as per predetermined eligibility criteria for inclusion. Five articles were also excluded with justification (additional file 2: table 2). Finally, a total of 14 full-text articles which passed the eligibility criteria and quality assessment were included for final review and analysis (Fig. 1).

General characteristics of the included studies

A total of 14 studies were included for systematic review and meta-analysis and important information which were related to study characteristics were presented in Table 2. All studies employed were observational cross-sectional study designs i.e. six retrospective crossectional study (CS); three prospective CS and five CS design. The year of publication of included studies ranges from 2013 to 2019. The study included a wide range of population characteristics (pediatric, adult and geriatric patients). Regarding geographic distribution, 14 studies were obtained from three regions and one city administration (Addis Ababa). The studies included all types of disease which had been treated in medical ward and outpatient setting.

Nine articles analyzed patients with all type of pathologies without focusing on any specific disease, 2 articles analyzed patients with cardiac disorder, 1article studied HIV patients and1 article analyzed patients with psychiatric disorders.

Nine articles studied DDIs in inpatient ward (7 articles in medical ward; 1 article in pediatric ward; 1 article in all wards); four articles studied DDIs in outpatient setting (ART Clinic, Cardiac clinic, Psychiatric unit, and Outpatient pharmacy) and one articles studied in Inpatients and Outpatient setting.

Among fourteen studies analyzed, six different databases were used to detect potential interactions. About half of the studies used Micromedex® 2.0 data base system (7 articles; 50.0 %), 2 articles (14.2%) used Medscape online, 2 articles (14.2%) used Micromedex® 3.0 data base system. The other three articles used Medscape online and drug.com, Drug.com and Micromedex online (Table 2)

Table 2: General characteristics of studies included for systematic review and Meta-analysis

Region	Study area	Author and publication year	Study design	Pathology	Target population	Study setting	Interaction data base
Oromia	Middle East Ethiopia, Adama	Gunasekaran et al, 2016	Retrospective CS	All	All hospitalized patients	All wards	Medscape online
	South East of AA, Bishoftu	Behailu Terefe Tesfaye et al, 2017	CS	HIV/AIDS	All HIV infected patients	ART Clinic	Meds cape online & Drug.com
	South West Ethiopia, Jimma	Diksis et al, 2019	Prospective CS	Cardiac disorder	Cardiac adult patients	Medical ward	Micromedex 3.0 DRUG-REAX®
		Chelkeba L et al, 2013	CS	Cardiac disorder	Patients on CV medication in OPD	Cardiac clinic	Micromedex 2 ®
Amhara	North West Ethiopia, Gondar	B.Akshaya Srikanth et al., 2014	Prospective CS	All	All hospitalized patients	Medical ward	www.drugs.com
		Admassie, et al, 2013	Retrospective CS	All	All hospitalized patients	Inpatients and Out patients	Micromedex2®
		Henok Getachew et al, 2016	Retrospective CS	All	All hospitalized pediatric patients	Pediatric ward	Micromedex 2
Tigray	Northern Ethiopia	Teka et al, 2016	CS	All	All hospitalized elder patients	Medical ward	Micromedex® 2.0
		Zeru Gebretsadik et al, 2017	Retrospective CS	All	All patients who come for medical service	Outpatient pharmacy	Micromedex® 2.0
		Haftay Berhane Mezgebe, 2015	Retrospective CS	Psychiatric illness	Patients with psychiatric illness	Psychiatric unit	Micromedex 2.0 Drug-Reax®
		Teklay et al, 2014	Prospective CS	DVT	Patients on warfarin therapy	Medical ward	Micromedex® online
		Yesuf TA, et al, 2017	CS	All	All hospitalized patients	Medical ward	Micromedex 2 ®
AA	TASH	Tesfaye and Nedi, 2017	CS	All	All hospitalized patients	Medical ward	Medscape online
	SPHMMC	Kibrom et al, 2018	Retrospective CS	All	Adult patients	Medical ward	Micromedex 3.0 DRUG-REAX®

Abbreviations: HIV: Human Immune Deficiency Virus; AIDS: Acquire Immune Deficiency Syndrome; ART: Antiretroviral Therapy; CV: Cardio Vascular; OPD: Outpatient Department; CS: Crossectional Study; TASH: Tikur Anbessa Specialized Hospital; SPHMMC: Saint Paulos Millennium Medical

Quality of included studies

The quality of included studies ranges from moderate to high quality (additional file 3: table 3).

Study outcome measures

Prevalence of potential DDIs

Prevalence and number of potential DDIs for each studies is presented in Table 3.

Table 3: Studies of prevalence of potential DDIs in included articles

Region	Author	Pathology	Target population	Study setting	No. of patients	No. of patients with DDIs	Prevalence patients with DDIs (%)	No. of potential DDIs			
								Major	Moderate	Minor	Unknown& Contrair
Oromia	Gunasekaran et al, 2016	All	All hospitalized patients	All wards	300	267	89.00	62(23.2%)	95(35.58%)	110(41.2%)	
	Behailu Terefe Tesfaye et al, 2017	HIV/AIDS	All HIV infected patients	ART Clinic	350	350	100.00	2(0.08%)	1767(72.69%)	662(27.2%)	
	Diksis et al, 2019	Cardiac disorder	Cardiac adult patients	Medical ward	200	195	97.50	316(32.7%)	441(45.6%)	210(21.7%)	
	Chelkeba L et al, 2013	Cardiac disorder	Patients on CV medication in OPD	Cardiac clinic	322	297	92.24	88(29.6%)	200(67.34%)	9(3.03%)	
Amhara	B.Akshaya Srikanth et al., 2014	All	All hospitalized patients	Medical ward	100	78	78.00	53(12.8%)	253(61.26%)	107(25.9%)	
-	Admassie, et al, 2013	All	All hospitalized patients	Inpatients and Out patient	2180	711	32.61	127(9.59%)	1020(77.04%)	177(13.4%)	Contraindication=11
	Henok Getachew et al, 2016	All	All hospitalized pediatric patients	Pediatric ward	384	176	45.83	40(10.2%)	201(51.15%)	152(38.7%)	
Tigray	Teka et al, 2016	All	All hospitalized elder patients	Medical ward	140	87	62.14	46(51.6%)	36(43.9%)	0(0.0%)	Contraindication=5(
	Zeru Gebretsadik et al, 2017	All	All patients who come for medical service	Outpatient pharmacy	596	275	46.14	34(110.3%)	210(63.444%)	87 (26.3%)	unknown=22(6.65%
	Haftay Berhane Mezgebe	Psychiatric illness	Patients with psychiatric illness	Psychiatric unit	216	176	81.48	198(43.8%)	232(51.33%)	22 (4.87%)	Contraindication=13
	Teklay et al	DVT	Patients on warfarin therapy	Medical ward	133	132	99.25	11827.6(%)	310(72.43%)	0(0.00%)	
	Yesuf TA, et al	All	All hospitalized patients	Medical ward	204	135	53.43	150(80.6%)	36(19.35%)	0(0.00%)	Contraindication=80
Addis Ababa	Tesfaye and Nedi	All	All hospitalized patients	Medical ward	252	197	78.17	94(13.1%)	385(53.55%)	240(33.4%)	
	Kibrom et al	All	Adult patients	Medical ward	384	209	54.43	105(35.7%)	157(53.4%)	32(10.9%)	Contraindication=2(

Abbreviations: HIV: Human Immune Deficiency Virus; AIDS: Acquire Immune Deficiency Syndrome; ART: Antiretroviral Therapy; CV: Cardio Vascular; OPD: Outpatient Department

From 14 studies, the pooled prevalence of patients with potential DDIs in Ethiopian Hospitals were found to be 72.2% with 95% CI between 59.1 and 85.3). Fig 2 showed heterogeneity across 14 studies were high (I^2 = 99.78%, p < 0.001).

Based on the severity of DDIs, the pooled prevalence of potential DDIs were 25.1%, 52.8%, 16.9% and 1.27% for major, moderate, minor potential DDIs and contraindications respectively. Fig 3, 4 and 5 showed heterogeneity across 14 studies were high.

Based on the mechanisms of DDIs involved, seven studies documented well but the remaining seven studies didn't document well the mechanisms of DDIs (Table 4).

Table 4: Studies of prevalence of DDIs according to the mechanisms involved in Ethiopian Hospitals

Authors	Mechanism of DDIs		
	Pharmacokinetic	Pharmacodynamics	Unknown
Gunasekaran et al, 2016	164(61.42%)	101(37.83%)	2(0.75%)
Behailu Terefe Tesfaye et al, 2017	1059(43.56%)	1335(54.92%)	37(1.52%)
Diksis et al, 2019	245(25.34%)	574(59.36%)	148(15.3%)
Henok Getachew et al, 2016	197(50.13%)	181 (46.06%)	15(3.82%)
Yesuf TA, et al, 2017	142(53.38%)	124(46.62%)	0(0.0%)
Tesfaye and Nedi, 2017	358(49.79%)	321(44.65%)	40(5.56%)
Kibrom et al, 2018	142(47.97%)	87(29.39%)	67(22.6%)

Footnote: Seven studies did not report the mechanisms of drug-drug interaction

Factors associated with potential DDIs

The factors associated with potential DDIs were related to patient characteristics (Table 5).

Table 5: Associated factors for potential DDIs

Factors	Description
No of prescribed drugs (Poly pharmacy)	Patients taking three or more than three concomitant drugs are at higher risk of the occurrence potential DDIs(Admassie et al, 2013;B.Akshaya Srikanth et al, 2014) There is association of the occurrence of one or more potential DDIs with the number of medications prescribed per patient who took more than four medications (Kibrom et al, 2018) Polypharmacy(five or more medications) is an important factor which leads to potential DDIs(Diksis et al, 2019;Zeru Gebretsadik et al, 2017;Teka et al, 2016;Henok getachew et al, 2016;Yesuf TA et al, 2017;Tesfaye and Nedi, 2017)
Co-morbid disease	Co-morbid condition independently increased the potential DDIs almost 2-folds(Yesuf TA et al, 2017)
Age	Older age were found to be predisposing factors for the occurrence of DDI(Admassie et al, 2013;Teka et al, 2016;Diksis et al, 2019;Zeru Gebretsadik et al, 2017) Potential DDIs were occurring more frequently in age group of 2–6 years than any other age group of pediatric population (Henok Getachew et al, 2016)
Hospital stay	The chance of taking multiple drugs increases with longer stays(greater than or equal to seven) in the hospital, which in turn increases the risk for potential DDIs(Diksis et al, 2019)
International Normalized ratio(INR value)	Increase in international normalized ratio value was found to be strongly associated with DDI and hence risk of bleeding (Teklay et al, 2014)

Footnote: Ten studies did not report the mechanisms of drug-drug interaction

Common interacting drug-combinations

Most common contraindications, major and moderate DDIs are presented in Table 6.

Table 6: Most common contraindication, major and moderate DDIs identified in the included studies

Test of heterogeneity, subgroup analysis and publication bias

Test of heterogeneity

In this review and meta-analysis, there is clinical and statistical heterogeneity. The tests of heterogeneity showed significant heterogeneity (I^2=99.78%, p < 0.001). In order to differentiate heterogeneity, sensitivity analysis, subgroup analysis and Meta regression was done.

Sensitivity analyses

There was no any significant change on the degree of heterogeneity even if an attempt was done to exclude the expected outliers as well as one or more of the studies from analysis. Therefore, fourteen studies were included for the meta-analysis.

Subgroup analyses

Subgroup analysis also conducted based on Region and Study setting. Subgroup analysis based on region revealed that the highest prevalence of potential DDIs were observed at Oromia Region, 94.9% (95% CI: 90.3 to 99.5) followed by Tigray Region with prevalence of 68.6% (95% CI: 42.6 to 94.5) (Fig 6).

Drug interaction pairs	Number of interactions	Severity	Effect of interaction
Clarithromycin+ simvastatin	6	Contraindication	Increased risk of myopathy or rhabdomyolysis
Chlorpromazine +Thioridazine	4	Contraindication	Risk of an irregular heartbeat which may belief threatening
Clarithromycin ciprofloxacin	1	Contraindication	Increased risk of QT interval prolongation
Aspirin+clopidogrel	160	Major	Bleeding
Aspirin+enalapril	157	Major	Renal dysfunction
Spironolactone + enalapril	101	Major	Hyperkalemia
Omeprazole+clopidogrel	56	Major	Decrease effect of clopidogrel and increased risk for thrombosis
Spironolactone + digoxin	47	Major	Increased the risk of digoxin toxicity
Heparin + aspirin	38	Major	Increased risk of bleeding
Aspirin+furosemide	173	Moderate	Fluid retention
Haloperidol+Trihexphenidyl	74	Moderate	Decrease effect of Trihexphenidyl
Enalapril +Furosemide	59	Moderate	Postural hypotension (first dose)
Simvastatin+azithromycin	39	Moderate	Increased risk of rhabdomyolysis

Subgroup analysis based on study setting revealed that the highest prevalence of potential DDIs were observed at outpatient: 80.0% (95% CI: 58.9 to 101.1 followed by inpatient: 73.2% (95% CI: 60.8 to 85.7 and inpatient and outpatient setting: 32.6% (95% CI: 30.6 to 34.6).

Univariate meta-regression for prevalence of potential DDIs revealed that sampling distribution is a source of heterogeneity (regression coefficient =7.36; p-value =0.0067) (Fig 7)

Publication bias

Funnel plots of standard error with logit effect size i.e event rate supplemented by statistical tests confirmed that there is no evidence of publication bias on studies reporting prevalence of potential DDIs and associated factors in Ethiopian Hospitals because there is no higher concentration of studies on one side of the mean than the other at the bottom of the plot (Fig 8)

Discussion

This systematic review and meta-analysis aimed to review and summarize the prevalence of potential DDIs and associated factors with it by reviewing and quantitatively summarizing the evidences available in Ethiopia regarding potential DDIs. It was conducted and attempted to analyze 14 original studies addressing prevalence of potential DDIs in Ethiopia. From all included studies, 5761 patients were included for pooled estimation of the primary outcome. A total of 8717 potential DDI was found in 3259 of patients.

The overall prevalence of patients with potential DDIs in Ethiopia was found to be 72.2% (95%CI: 59.1%, 85.3%). Based on the severity of DDIs, the pooled prevalence of potential DDIs were 25.1%, 52.8%, 16.9% and 1.27% for major, moderate, minor potential DDIs and contraindications respectively. These potential DDIs are more likely to produce negative outcomes. The analysis showed high prevalence which indicates the countries drug-drug interactions unstudied problem in the Ethiopians Hospitals.

The review showed that all DDIs studies in Ethiopia assessed potential DDIs, while no study was performed on actual DDIs. This may be due to identifying actual DDIs is much more complicated than potential DDIs.

The analysis showed that the occurrence of potential DDIs in inpatient and outpatient settings reported by studies (inpatient: 73.2% (95% CI: 60.8% to 85.7%; outpatient: 80.0% (95% CI: 58.9% to 101.1%; inpatient and outpatient setting: 32.6% (95% CI: 30.6% to 34.6%). The high incidence of DDIs may be associated with high number of drugs per prescription that was observed in individual studies. The prevalence of potential drug-drug interactions in outpatient setting is higher than the inpatient setting because in this review ART Clinic, Cardiac clinic, Psychiatric unit, and Outpatient pharmacy were considered as an outpatient setting.

Similarly, this review showed all (100%) HIV infected patients treated in outpatient setting (Behailu Terefe Tesfaye et al, 2017), 97.5% of adult patients with heart diseases treated in inpatient ward (Diksis et al, 2019) and 92.23% cardiac disorder patients treated in the outpatient setting (Chelkeba L et al, 2013) were susceptible to DDIs. High number of prescribed drugs and prescribing of drugs with many potential DDIs may cause the high occurrence of potential DDIs in this group of patients. One finding in a developed country showed that 80% of hospitalized patients with heart diseases were susceptible to DDIs(Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, 2000).

In the review studies showed that patient age and polypharmacy were the most reported associated factors with the occurrence of potential DDIs. Similarly, the finding from a review in a developed country highlighted these risk factors. Many studies had emphasized that the high occurrence of potential DDIs in old age is due to physiological changes related to age, comorbid diseases and a high rate of medication use(Espinosa-Bosch M, Santos-Ramos B, Gil-Navarro MV & Marin-Gil R, 2012).

The first limitation of this review and meta-analysis were the drug-drug interactions found were only potential and doesn't address the actual DDIs because of lack of studies. Some of the studies included in the review and meta-analysis had small sample sizes. These might have led to bias. The second limitation of this review were Egger's test funnel plots revealed as there is no publication bias but this estimation may not be accurate as small studies are included for the

review and there are studies which has small size. The third limitation of this review and meta-analysis were clinical heterogeneity among included studies so it should be considered with caution. The classification of severity may defined different between studies so this may be another limitation of this study.

Conclusion

The prevalence patients with potential DDIs in Ethiopian Hospitals were found to be high i.e. 72.2% (95% CI: 59.1%, 85.3%). From this the most prevalent DDIs were moderate severity, 52.8%. In this review polypharmacy, age, comorbid disease and hospital stay were the risk factors associated with potential DDIs. This review and meta-analysis had considerable clinical heterogeneity among included studies so it should be considered with caution.

Abbreviations

ADEs: Adverse Drug Events; ART: Antiretroviral Therapy; CI: Confidence Interval; CMA: Comprehensive Meta-Analysis; CS: Crossectional study; DDIs: Drug- Drug Interactions; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors agreed to publish this research article

Availability of data and materials

All data are available in the manuscript

Competing interests

No conflict of interest

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Authors' contributions

WA designed the study. WA and GA collected scientific studies, assessed the quality of the study, extracted and analyzed the data. AI commented the review. WA also prepared the manuscript for publication. All authors have read and approved the manuscript

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Figures

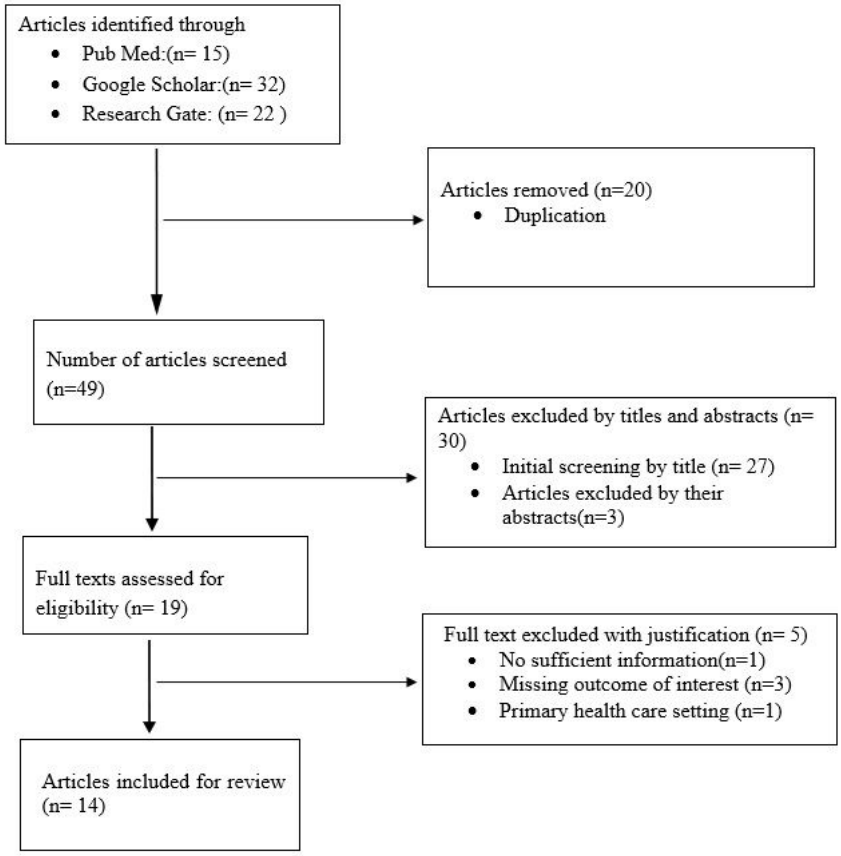

Figure 1

PRISMA flow diagram showing the selection process

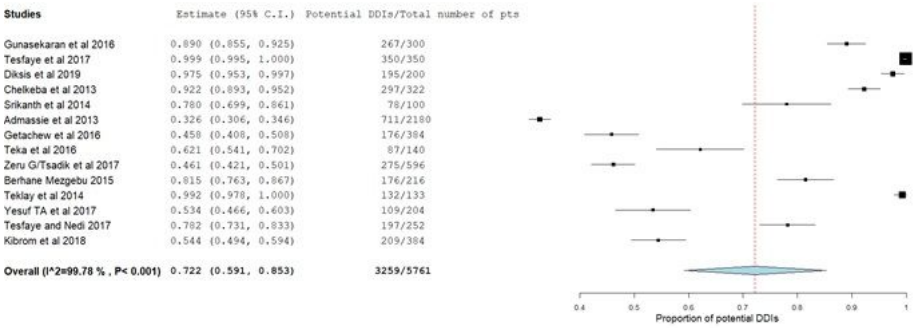

Figure 2

Forest plot depicting the pooled prevalence of patients with potential DDIs of 14 studies in Ethiopian Hospitals

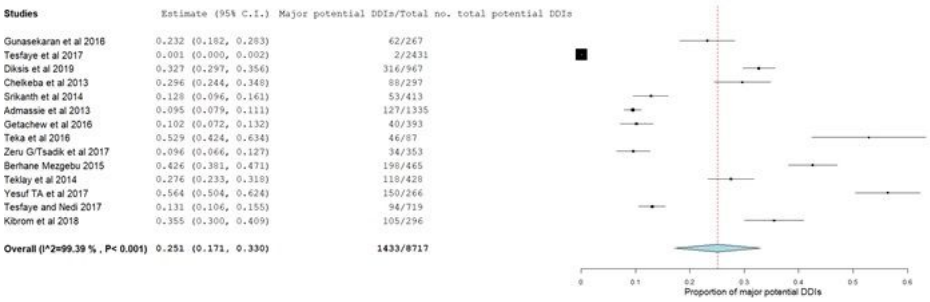

Figure 3

Forest plot depicting the pooled prevalence of major potential DDIs of 14 studies in Ethiopian Hospitals

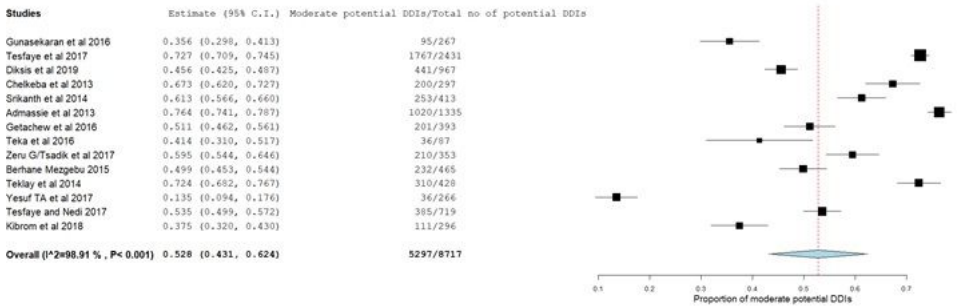

Figure 4

Forest plot depicting the pooled prevalence of moderate potential DDIs of 14 studies in Ethiopian Hospitals

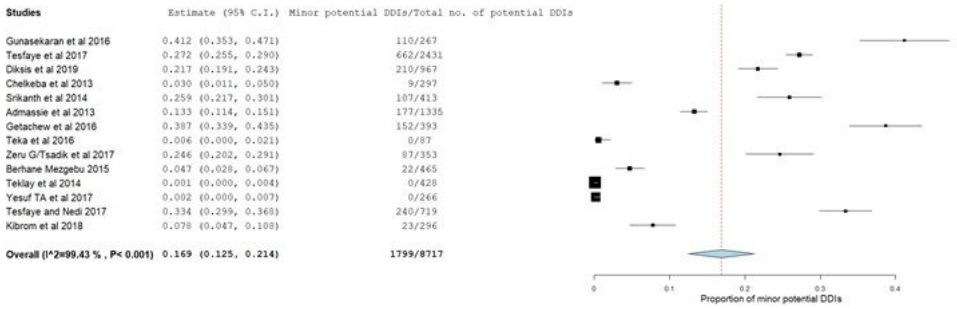

Figure 5

Forest plot depicting the pooled prevalence of minor potential DDIs of 14 studies in Ethiopian Hospitals

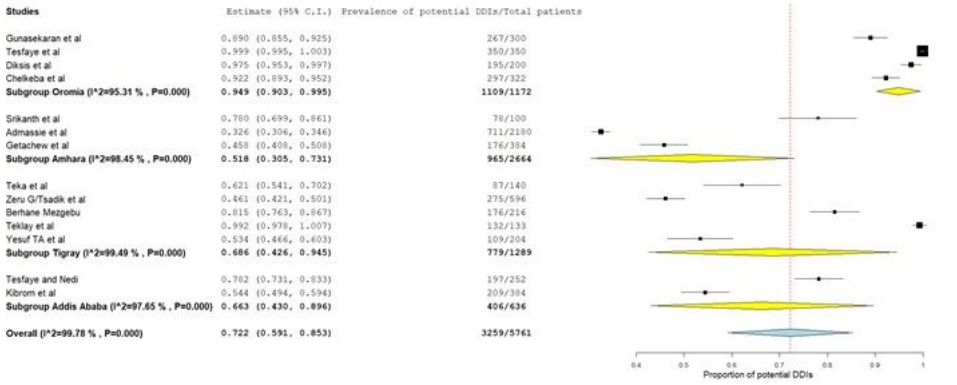

Figure 6

Subgroup analysis of prevalence of potential DDIs based on region

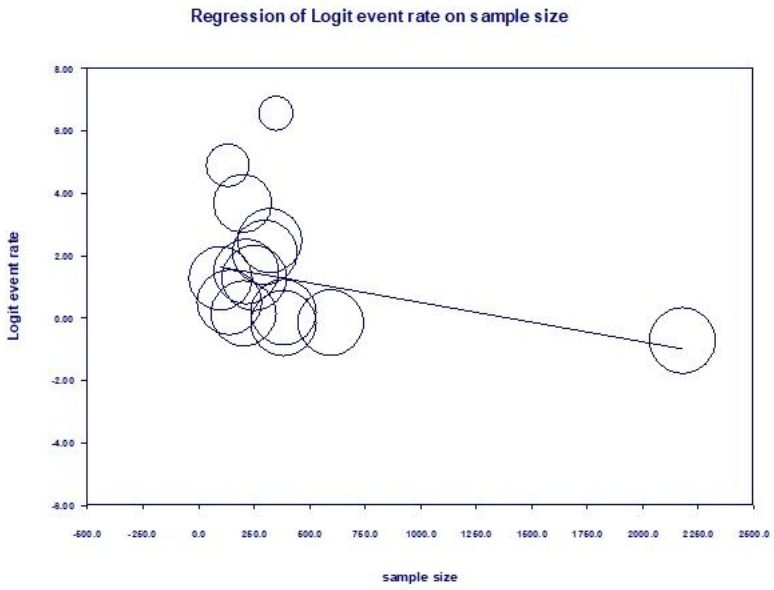

Figure 7

Univariate meta-regression model using sample size for prevalence of potential DDIs

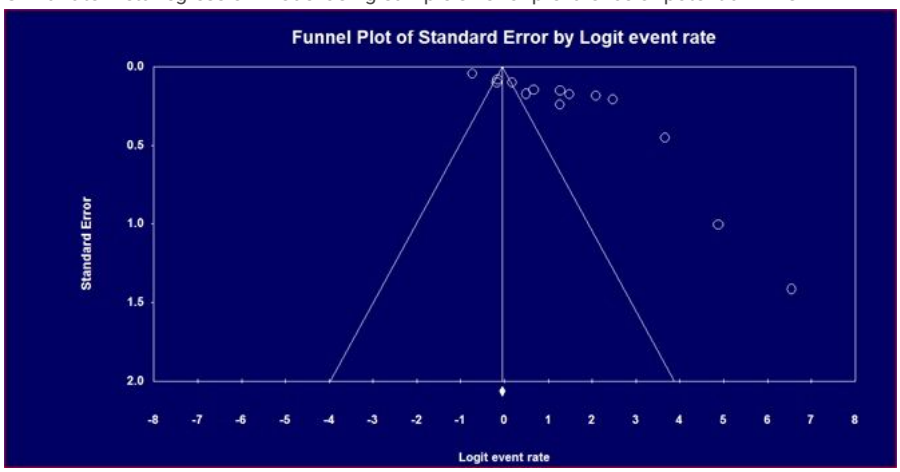

Figure 8

Publication bias using funnel plot of standard error by Logit event rate

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- JustificationAF2T2.pdf
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