ASSESSMENT OF PHYSICIANS' AWARENESS ON DRUG-DRUG INTERACTIONS AND COMMON SOURCES OF INFORMATION IN GENERAL HOSPITALS OF ADDIS ABABA

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This is to certify that the thesis prepared by Getachew Moges, entitled: "*Assessment of Physicians' Awareness on Drug-drug Interactions and Common Sources of Information in General Hospitals of Addis Ababa, Ethiopia*" and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmacoepidemiology and Social Pharmacy, compiles with the regulations of the University and meets the accepted standards originality and quality.

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Abstract

BACKGROUND: Drug-drug interactions are an ever-evolving and still critical safety issue in disease management and treatment. Health care professionals' ability to recognize DDIs is important in reducing the risk of their adverse consequences.

OBJECTIVES: To assess physicians' awareness on DDIs and common sources of information in general hospitals of Addis Ababa.

METHODS: Cross sectional survey using simple random sampling and convenience sampling methods was conducted among physicians in general hospitals of Addis Ababa, Ethiopia between January and March 201. Data was collected using self administered questionnaire. To test physicians' knowledge of drug-drug interactions, 15 drug pairs were used.

RESULTS: A total 140 questionnaires were found valid. The percentage of physicians who correctly classified the drug pairs ranged from 12.9% to 65.7%. The average number of correctly categorized drug pairs was 5 (33.3%). Physicians who specialized in internal medicine or pediatrics had better DDI knowledge than those who specialized in other areas. Physicians who perceived the risks of DDIs are high and those who used other information sources had better DDI knowledge. The mean DDI information source usefulness score was found to be 3.59. Physicians who worked for more than 20 years, physicians who agreed up on the importance of learning about DDIs and those who agreed to consider DDIs as part of prescribing decisions had a higher mean DDI information source usefulness score.

CONCLUSIONS and RECOMMENDATIONS: Physicians in this study had poor DDI knowledge. Area of specialization, perceptions on risks of DDIs and DDI information sources were factors associated with physicians' DDI knowledge. Physicians in Addis Ababa had poor perceptions towards the importance of DDI information sources. Years

of professional experience, the extent to which the risk for a DDI affects drug selection, perceptions towards the importance of learning about DDIs and perceptions towards considering DDIs as part prescribing decisions were predictors of DDI information sources perceived usefulness. On job trainings such as workshops and seminars and continuing education programs especially for specialists other than internists and pediatricians should be provided for physicians so as to increase their awareness of the importance of DDIs information sources and encourage them to pay close attention to DDIs. Physicians should update their DDI knowledge through continuing education and should improve their familiarity with information sources such as smart phone applications, Compendia of drug products.

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DEDICATED TO THE MEMORY OF

MY GRAND MOTHER

MEKOYA HAILU

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Acronyms

ACE	Angio-tensin converting enzyme
ADE	Adverse drug event
ADR	Adverse drug reaction
AHFS	American Hospital Formulary Service
ANOVA	Analysis of variance
AOR	Adjusted Odds Ratio
COR	Crude Odds Ratio
CYP450	Cytochrome P450 isoenzyme
DACA	Drug Administration and Control Authority
DDI	Drug-drug interaction
FDA	Food and Drug Administration of America
FMHACA	Food, Medicines and Healthcare Administration and Control Authority
FMoH	Federal Ministry of Health
GP	General practitioner
NSAID	None steroidal anti inflammatory drug
PDA	Personal digital assistant
STG	Standard Treatment Guideline
WHO	World Health Organization

1. Introduction

1.1 Background

A drug- drug interaction (DDI) is defined as the alteration of the effect of one drug by the presence of another (Merlo, *et al*., 2001). The prescribing of a drug is the most common outcome of a patient visit to a physician; 60% of physician visits result in a prescription for patients (Chisholm-Burns *et a.l*, 2008) and drug interactions are an ever-evolving, challenging, and still critical safety issue in disease management and treatment (Bai, 2010). DDIs are an important cause of drug related problems including significant morbidity and mortality. They are a common event in current pharmacotherapy (Becker *et al*., 2006). There are several reasons for this. Among these are health care providers may not be aware of interactions with drugs they prescribe, several health care professionals may prescribe medications for one patient, aging patients have multiple health issues and take many medications, drug interactions may not be identified as the cause of unexpected treatment results or side effects and health care providers may not know about all medications and supplements their patients are taking (AIDS InfoNet, 2011).

DDIs can be the consequence of various situations that reflect the growing number of drugs available on the market. The increasing complexity of poly-therapy is a major source of DDIs. The very widespread practice of self-medication makes the situation more severe and difficult (Magro *et al.*, 2007).

Health care professionals' ability to recognize potential DDIs is important in reducing the risk of potential DDIs and their adverse consequences (Ko *et al*., 2008). But physicians and other prescribers fail to recognize between 37% and 47% of clinically meaningful DDIs (Glassman *et al*., 2006).

Exposure to DDIs can be associated with a wide range of outcomes, including lack of medication efficacy, poor tolerability, and serious adverse events. Negative clinical outcomes are associated with harmful DDIs (Grizzle et *al.*, 2007).

1.2 Rationale of the Study

DDIs comprise a significant cause of morbidity and mortality worldwide as they may lead to adverse clinical events, result in decrease or inactivation of the therapeutic effect of a drug, enhance drug toxicity and indirectly compromise treatment outcomes and adherence (Riechelmann *et al.*, 2009). DDIs are an important and widely under-recognised source of medication errors, which represent significant risk of harm to patients and opportunity cost for healthcare systems (Khoo, *et al.*, 2009). They also lead to increased utilization of healthcare services such as higher rates of emergency department visits and hospitalizations (Bjerrum et *al.*, 2003).

A study conducted in Brazilian teaching hospital revealed that the overall prevalence of potential DDI was 49.7%. In this study about 73.6% prescriptions presented more than one DDI with different adverse drug reactions, while 26.4% presented one DDI (Mara *et al.*, 2006).

In a study of Potential DDIs on in-patient medication prescriptions at Mbarara Regional Referral Hospital in western Uganda, the overall prevalence of potential DDIs was approximately 23% (Lubinga and Uwiduhaye, 2011).

Despite the evidence of deleterious outcomes associated with many DDIs, still very little is known about the potential determinants of knowledge of the most commonly occurring potential DDIs (Cruciol-Souza *et al.* 2006, Ko *et al*., 2008). Physicians often lack the ability to identify and recall potential DDIs (Glassman *et al*., 2002). In a study conducted in the Veneto region, northern Italy, it was found that physicians are less aware of the risk from the combination of potentially interacting drugs (Magro *et al*., 2007).

DDIs are preventable medication errors associated with potentially serious adverse events and death (Indermitte *et al*, 2007). Therefore, hospital managers should investigate ways to prevent the prescription of drugs with potentially dangerous DDIs. One way of realizing this goal is to identify factors that encourage or discourage prescribers' DDI knowledge. In Ethiopia to the investigator's search no studies were attempted so far to assess physicians' awareness on DDIs and common sources of information. Therefore, this study will help to reveal physicians' DDI knowledge and factors associated with their ability to recognize important potential DDIs and also their perceptions on the importance of information sources for DDIs in Addis Ababa, Ethiopia. The results of the study could help to identify the prescribers with insufficient potential DDI knowledge and those physicians with poor perceptions on the importance of information sources for DDIs who could be the targets for educational intervention by hospital managers and Addis Ababa regional health bureau. The data from this study could also be useful to fill the existing information gap regarding this issue in Addis Ababa and could serve as base line data for other researchers.

The major reason for selecting the capital city is that as to the knowledge of the researcher there was no previous study in this area concerning this issue and also it is major urban center of the country where many high level governmental and non-governmental hospitals, which are better equipped with personnel and high tech-equipment, are found. Two developments cause an increase of poly-pharmaceutical combination therapies in highly developed health care systems: An increased life expectancy which leads to an increase of chronic diseases and therefore leads to an enhanced demand for drugs, which is associated with the necessity of one individual patient to be treated by multiple practitioners or specialists and due to chronic diseases long-term therapies and preventive actions become more important (Juurlink and Hansten, 2005). And also Addis Ababa has the highest number of hospitals than other cities in the country. The number of hospitals is even more than that of hospitals at each regional state. Moreover, more than 43% of physicians of the country are found in Addis Ababa (934 Vs 2,152) (FMoH, 2010/11).

Only physicians are included in this study assuming that in Ethiopia complex drug regimens which are prone for interaction are usually held by physicians than other prescribers such as health officers and nurses.

The DDI knowledge test instrument was designed by the researcher so as to reflect local availability of the drugs included. Therefore, instrument validity was assessed to check whether it functioned well in evaluating physicians or not.

2 Literature Review

2.1 Drug- Drug Interactions

2.1.1 Definitions and mechanisms of Drug- Drug Interactions

DDIs are defined as ‘‘two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered’’ (Hartshorn, 2006). They are preventable medication errors associated with potentially serious adverse events and death (Indermitte *et al*, 2007).

DDIs mechanisms can be pharmacodynamic, pharmacokinetic, combination of these two or pharmaceutical. Pharmacodynamic interactions are due to competition at receptor sites or activity of the interacting drugs on the same physiological system (Woods, 2010). Pharmacodynamic interactions occur when two or more drugs have either additive (agonistic) or opposing (antagonistic) pharmacological effects (Katzung, 2003). Pharmacokinetic interactions are when one drug affects the absorption, distribution, metabolism or excretion of another drug. A change in blood concentration causes a change in the drug’s effect (Woods, 2010). Many drugs are metabolized in the liver mainly by the Cytochrome (CY) P450 enzyme system. Some drugs activate this enzyme system (induction) thus increasing the metabolism of other drugs. This may result in a reduced effect. The converse may occur with drugs which are enzyme inhibitors. If two drugs metabolised by the same isoenzyme are co-administered then the concentration of one or both drugs may be increased (Katzung, 2003). Pharmaceutical interactions are interactions that occur prior to systemic administration. For example incompatibility between two drugs mixed in an intravenous fluid. These interactions can be physical (e.g. with a visible precipitate) or chemical with no visible sign of a problem (Woods, 2010).

2.1.2 Rates of Drug- Drug Interactions

A Pharmacoepidemiologic study of potential DDIs in outpatients of a university hospital in Thailand revealed that the overall rate of potential DDIs was 27.9% with a maximal value of 57.8% at the department of Psychiatry. The rate of the most potentially significant interactions was 2.6%, being the highest in the department of Medicine (6.0%), with isoniazid vs. rifampin as the most common interacting combination. The rate increased with the patient's age and prescription size. The odd's ratio of having at least one potential DDI was 1.8 (64.2%) when age increased by 20 years and 2.8 (165.7%) when another drug was added. In this study the rate of potential drug interactions was the same for both genders. The rate of potential drug interactions detected across prescriptions was higher than within prescriptions and was dependent on the time interval between prescriptions (Janchawee, *et al.*, 2005)

Bertolia *et al* found high prevalence (62.5% of patients) of potential harmful drug-combinations prescribed at hospital discharge; each patient having on average 1.9 DDI (all types of severity included). They identified a total of 373 potential DDI among prescribed drugs in 200 patients at hospital discharge. From these, 60% (n = 223) were of minor severity, 38% (n = 143) of moderate severity and 2% (n = 7) of major severity. Seventy three percent (n = 272) of the overall detected interactions were considered clinically relevant and resulted in a written warning for the treating physician. Compared to the younger patients (≤65 years), older patients (>65 years) had an increased number of minor DDI (0.48 vs. 1.4 DDI/patient) and moderate DDI (0.38 Vs 0.87 DDI/patient) (Bertolia et *al.*, 2010).

In a retrospective study of all patients who visited the primary care setting of the Universiti Sains Malaysia, 386 DDI events were observed in a cohort of 208 patients exposed to more than one drug from a total of 23 733 patients, representing a 2-year period prevalence of 876.4 per 100 000 patients. Of the 208 exposed patients, 138 (66.3%) were exposed to one DDI event, 29 (13.9%) to two DDI events, 15 (7.2%) to three DDI events, 6 (2.9%) to four DDI events and 20 (9.6%) to more than five DDI events. Overall, an increasing mean number of episodes of DDIs was noted among exposed patients within the age category ≥70 years (Dhabali *et al*., 2011)

A one year retrospective follow-up study of outpatient prescription data in Italy in 2004 revealed 8894 potential DDIs were observed among a cohort of 7902 individuals exposed to more than one drug. The most commonly identified potentially interacting medication pairs were warfarin and non-steroidal anti-inflammatory drugs (6824 cases), theophylline⁄aminophylline and ciprofloxacin⁄ fluvoxamine (930), and warfarin and barbiturates (567) (Indermitte *et al*., 2007).

Mara *et al* found that the overall prevalence of potential DDI in 2004 in Brazilian teaching hospital prescriptions was 49.7%; prevalence of major DDI was 3.4% (Mara *et al*., 2006). Another retrospective cross-sectional analysis of prescription data and medical records from a public hospital in Brazil involving 589 patients and 3,585 prescriptions revealed that 37% of the patients were exposed to at least one potential interaction during their stay in the hospital. The most frequent interacting pair was Digoxin and Furosemide (11%) (Moura *et al*., 2009).

A cross-sectional study involving 400 randomly-selected patients who had been admitted to pulmonology ward of Ayub Teaching Hospital, Pakistan revealed that 45% patients had at least one DDI; 24.25% were having at least one major DDI, and 36% patients had at least one moderate DDI. Among 558 identified DDIs, most were of moderate (53.6%) or major severity (34%); good (74.2%) or fair (16.3%) and delayed onset (70%). Top 15 common DDIs included 6 major, 7 moderate and 2 minor interactions (Ismail *et al.*, 2011).

A four year retrospective cohort study of hospitalized patients treated for systemic fungal infections with an oral or intravenous azole medication between July 1997 and June 2001 in a tertiary care hospital in Boston revealed that among the 4185 admissions, potential azole-related DDIs occurred in 2941 admissions (70.3%). Among 3953 admissions, in which patients were on oral or intravenous fluconazole therapy, potential fluconazole associated DDIs occurred in 2716 (68.7%). One thousand four hundred forty (36.4%) patients had two or more potential DDIs. The most frequently prescribed fluconazole interacting medications with major or moderate severity were prednisone (18.8%), midazolam (13%), warfarin (10.9%), methylprednisolone (10.5%), cyclosporine (8%), nifedipine (7.5%), phenytoin (5.5%), clonazepam (5.2%) and simvastatin (5.1%), while potential DDIs with minor severity were more frequent with amphotericin (11.1%) and zolpidem (6.2%). Among 212 admissions, in which patients were on itraconaozle, in 203 (95.8%) admissions, patients had at least one potential itraconazole-associated DDI; in 183 (86.3%), patients had two or more potential DDIs. The medications most frequently concomitantly prescribed with itraconazole were antacids (54.2%), prednisone (50%), omeprazole (42.5%), ranitidine (25.5%), amphotericin (22.6%), methylprednisolone (19.8%), cyclosporine (19.3%), tacrolimus (19.3%) and nizatidine (15.6%). Of 68 admissions in which patients were on ketoconazole, 60 (88.2%) had at least one potential

DDI; 40 (58.8%) had multiple potential DDIs; potential DDIs were more frequent in patients on antacids (55.9%), ranitidine (22.1%), prednisone (19.1%) and nizatidine (19.1%). Of each azole agent treatment group, potential DDIs with moderate to major severity occurred in 61.3% of admissions in which patients were on fluconazole, in 94.9% of those patients were on itraconazole and 88.2% on ketoconazole (Yu *et al*., 2005).

A study by Kotirum *et al* in North Thailand revealed that among 1093 patients receiving warfarin therapy, 914 (84%) patients received at least one potentially interacting drug and half of them (457 patients) received at least one drug with high potential for interaction. (Kotirum *et al.,* 2007).

In India a total of 269 potential DDI in 134 (19%) patients were detected during the review of 565 prescriptions. Of these interactions, 188 were of mild in nature, while two were severe in nature (Hotaa *et al.*, 2011).

Solberg *et al.* found that 2.3% of all adults in one United States health maintenance organization were exposed to a potential DDI in 2001 (Solberg, *et al*. 2004) and Malone *et al.* found that clinically important potential DDIs occurred in 374 000 of 46 million (813 per 100 000) persons covered by a national United States pharmacy benefits manager over a 2-year period (Malone *et al*., 2005).

A retrospective study using administrative data from the Ottawa Hospital showed 19.3% cumulative incidence of DDIs (Reimche *et al*., 2011).

In a study by Cristiano Moura *et al* a total of 1,282 potential DDI in 816 (23%) prescriptions were found and 220 (37%) patients were exposed to at least one potential interaction during their stay in the hospital. Among the 816, 504 had one potential drug interaction (62%), while 312 (38%) had more than one. Those of major severity level accounted for 22%. The most frequent interacting drug pairs were Digoxin+Furosemide, Amitriptilin+Phenytoin, Amikacin+ Ketoprofen, Captopril + Spironolactone, Phenytoin+ Dexamethason (Moura *et al*., 2009).

Laura Galatti *et al* in their study involving 4843 itraconazole and 1446 fluconazole users found that potentially interacting drugs were prescribed in 8.7% of itraconazole and 6.1% of fluconazole users. For itraconazole, calcium channel blockers were the most common interacting drugs (3.3%), followed by statins (1.7%) and clarithromycin (1.3%), whereas gestodenþethynylestradiol (2.5%) and benzodiazepines (1.8%) resulted as the most common interacting drugs among (Galatti *et al*., 2007).

Among outpatient population assessed by Catherine *et al*, the incidence of clinically relevant potential DDIs was most likely between 6 and 32 cases per 1,000 patients (Peng *et al*., 2003).

Magro *et al* in their one year study found 119 different severe potential DDIs (out of 895), which occurred 1,037 times in 758 patients (4.7% of the total number of patients). The majority of patients (559, 74%) had only one potential DDI, 144 patients with 2 different DDIs, 36 patients with 3 different DDIs, 13 patients with 4 different DDIs, 6 patients with 5 different DDIs (Magro *et al.*, 2007).

A survey in elderly outpatients of visits with a prescription of warfarin, 6.60% were prescribed a drug with potentially harmful interaction (Zhan *et al*., 2005).

Peng et al in their retrospective study found that the one year prevalence of potential DDIs in a large ambulatory population to be 19% (Peng *et al*., 2003)

A one year retrospective analysis of prescriptions written by 16 general practitioners in North Italy showed that 4.7% of the patients concomitantly used drugs that could cause a severe potential DDI (Magro *et al.*, 2007).

Martinebiancho et al in their study on drug interactions in hospitalized children found among 11,181 prescriptions 6857 drug interactions were present, being 1.9 interactions per prescription and approximately 7 interactions/patient (Martinbiancho *et al*., 2007). A study conducted in Thailand reported a 16% rate of potential interactions (Janchawee *et al*., 2005).

Analysis of the medication histories in community pharmacies in Switzerland yielded a total of 961 potential drug interactions affecting 375 (62.5%) patients. Of those, 413 (43.0%) were classified as minor, 538 (56.0%) as moderate, and 10 (1.0%) as severe. Most prevalent drug classes involved were drugs affecting the cardiovascular system (30.8%), the nervous system (17.6%), the alimentary tract and metabolism (15.4%), and the musculoskeletal system (15.0%) (Indermitte *et al*., 2007).

In a study of Potential DDIs on in-patient medication prescriptions at Mbarara Regional Referral Hospital in western Uganda, a total of 75 potential DDIs were identified. Interactions were most prevalent in the medical department (*n*=32; 33%) followed by the emergency/surgery (*n*=13; 28.3%), paediatrics (*n*=5; 11.4%) and obstetrics/gynaecology (*n*=4; 8.3%) departments. With regard to clinical importance, most (*n*=32, prevalence=11.9%) interactions required "*use with caution*" as a management strategy. Twenty-nine (prevalence=10.6%) were "modify treatment/monitor",11 (prevalence=3.4%) were "avoid combination/use alternative", while 3 (prevalence=1.3%) were "*contraindicated*" combinations. The two contraindicated combinations were diclofenac and aspirin and rifampicin and fluconazole. Three potential DDIs accounted for over 60% of the interactions identified: corticosteroids and NSAIDS (30.6%), diuretics and ACE inhibitors (22.7%) and NSAIDS and antihypertensives (14.7%) (Lubinga and Uwiduhaye, 2011).

2.1.3 Clinical and Economic Impact of Drug- Drug Interactions

DDIs are an important cause of adverse drug reactions and may lead to an increased risk of hospitalization and higher health care costs (Janchawee *et al*., 2005). In the United States the cost of drug-related morbidity and mortality exceeded $177.4 billion in 2000. Hospital admissions accounted for nearly 70% ($121.5 billion) of total costs, followed by long-term-care admissions, which accounted for 18% ($32.8 billion). Since 1995, the costs associated with drug related problems have more than doubled (Ernst *et al*., 2011)
The adverse clinical outcomes of drug related morbidity are potentially substantial, while the economic impact in ambulatory care patients in the US has been estimated to cost $177 billion each year (Morris *et al*., 2006). Howarda *et al* in their study in a teaching hospital in Nottingham, UK found that drug related morbidity to be the cause of 6.5% of the admissions, and 67% of these were found to be potentially preventable. In this study the majority of preventable drug related admissions were found to be caused by problems with prescribing (35%) (Howard *et al*., 2003)

A review by Reimche *et al* revealed that of 437 consecutive adverse drug reactions causing hospitalization to a university hospital 26% were due to DDIs. They also found that 25% of adverse drug reactions due to DDIs led to serious or life-threatening events (Reimche *et al*., 2011).

A meta analysis of articles describing adverse patient outcomes due to DDIs revealed that of the 19 patients who had visited the emergency department, 7 patients were hospitalized due to drug-drug interactions. Fifteen percent of an adverse patient outcome attributed to DDIs (Becker *et al.*, 2006).

Medication errors may have significant clinical and economic impact (Peng *et al*., 2003). Up to 8% of hospital admissions are due to adverse drug reactions and over 20% of these are due to drug interactions (Reis *et al*., 2011). Drug interactions can cause undesirable patient responses, with effects ranging from treatment inefficacy to serious adverse events. Juurlink *et al* in their study in Ontario Canada found that many hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions. Many of these interactions could have been avoided (Juurlink et *al*., 2003).

A retrospective database analysis of 3,309,630 patients with osteoarthritis revealed that patients with drug-drug exposures had longer average number of hospital days than similar patients without drug-drug exposures. In the younger population, patients with drug-drug exposures had $1,087 more 6-month total payments (medical care plus prescriptions) than similar patients with no drug-drug exposures ($9,469 vs. $8,382, respectively. In the older patient population, patients with DDIs incurred $1,207 more 6-month total payments (medical care plus prescriptions) than similar patients with no drug-drug exposures ($9,829 vs. $8,622, respectively. Among older patients, prescription payments for non opioid drugs were $184 higher in the drug-drug exposure group compared with the no-drug-drug exposure group ($2,197 vs. $2,013, respectively (Jr *et al.*, 2011).

Adverse drug events have been associated with significantly longer length of hospital stay and increased associated payments of $5.6 million in additional costs annually (Jr, *et al.,* 2011). A study of hospitalized patients who experienced in-hospital adverse drug events was associated with an increased length of hospital stay and an increased payment of $2,262, compared to patients without adverse drug events. Furthermore, the risk of death among hospitalized patients who experienced adverse drug events was 88% higher in patients without adverse drug events (Classen *et al.,* 1997). Adverse drug events can substantially increase hospital payments. A study of patients with psoriasis concurrently taking methotrexate and cyclosporine found that patients with a drug-drug exposure were significantly more likely to experience certain clinical conditions (renal, gastrointestinal, or pulmonary events) and have significantly higher healthcare resource utilization and associated higher healthcare payments than patients without a drug-drug exposure (Saurat *et al*., 2010). Drug-related morbidity and mortality in nursing facilities represent a serious economic problem. For every dollar spent on drugs in nursing facilities, $1.33 in health care resources are consumed in the treatment of drug-related problems (Bootman *et al.,* 1997).

2.2 Healthcare professionals' knowledge of Drug –Drug Interactions

Physicians and pharmacists often lack the ability to identify and recall potential DDIs (Glassman *et al*., 2002). Physicians and other prescribers fail to recognize between 37% and 47% of clinically meaningful DDIs (Glassman *et al.*, 2007). In a study conducted in the Veneto region, northern Italy, it was found that physicians are less aware of the risk from the combination of potentially interacting drugs (Magro *et al*., 2007).

A study conducted by Ko *et al* to evaluate potential determinants of prescribers' DDI knowledge revealed that specialists had lower potential DDI knowledge test scores than generalists. This study found that prescribers who had seen a patient harmed by a potential DDI had a higher potential DDI knowledge score than those who had not. In addition the prescribers whose drug selections were affected by the risk of potential DDIs "very much" scored higher than those who reported that their prescribing was affected by the risk "a little" or "not at all". This study also revealed that specialists had a lower potential DDI knowledge score than generalists, whereas prescribers in internal medicine other than cardiology and those in emergency medicine had a score comparable with generalists (Ko *et al*., 2008). Glassman *et al* found that clinicians correctly categorized 44% of the 14 drug pairs. They showed that younger clinicians recognized more potential DDIs than older clinicians. In addition, the number of days spent in clinic was found to have a positive relationship with clinicians' ability to recognize contraindicated drug pairs (Glassman *et al*., 2002).

A retrospective prescription analysis in Brazilian teaching hospital revealed that medical specialty and prescription week day presented significant differences in DDI prevalence. In this study cardiology and ophthalmology, as medical specialties showed the greatest potential DDI prevalence (87.2%, 123/141 for prescriptions from Cardiology; 85.0%, 17/20 for Ophthalmology) (Mara *et al*., 2006).

2.3 Healthcare professionals' Sources of Information on Drug-drug Interactions

No one can possibly memorize all the potential DDIs that have been identified to date, and new interacting drug pairs are identified every month. To cope with this task drug interaction compendia in the form of books, journals, colleagues, pharmacists, computer or personal digital assistant software or online databases such as the US-database by Thompson Micormedex™ or the British Greenwood Village or Stockley's Drug Interactions, Pharmavista®, ABDA-Database etc are offered to health care providers (Wirz 2006; Ko, *et al.* 2007). Selected sources of information on drug interactions include clinical pharmacology (CD-ROM, Internet) which is complete database for drug interactions as well as clinically useful drug information and updated quarterly, Hansten and Horn's Drug interactions analysis and management (manual) which is an easy-to-use index that categorizes a drug interaction by clinical significance, along with a concise reference monograph discussing the interaction; updated quarterly ; Handbook of adverse drug interactions (manual); Adverse drug interactions program (software, Internet) and Drug interactions analysis and management (loose-leaf or bound manual); Drug interaction facts (loose-leaf or bound manual with software) which provides information about drug-drug and drug-food interactions in a quick reference format, along with descriptive monographs of drug interactions selected on the basis of their potential to alter patient outcomes; updated quarterly (Ament *et al.*, 200).

In a study by Ko *et al* a quarter of the prescribers reported using personal digital assistants and another quarter used printed material. The majority of the prescribers (68.4%) reported that they were usually informed by pharmacists about their patients' potential exposure to DDIs (Ko, *at al.* 2008).

A study conducted in US revealed that 40.3% (n = 253) of prescribing nurses consulted computerized alert systems, 31.6% (n = 253) consulted pharmacists and 22.1% (n = 253) consulted their personal digital assistant as their information sources of DDIs where as almost 6% (n = 253) use other references which included drug reference books and on-line sources (Carithers, 2011).

3 Study Objectives

3.1 General Objective

To assess physicians' awareness on DDIs and common sources of information in general hospitals of Addis Ababa

3.2 Specific Objectives

- To examine physicians' DDI knowledge
- To identify factors associated with physicians' DDI knowledge
- To assess physicians perceptions on the usefulness of usual DDI information sources
- To assess factors associated with physicians perceptions on the usefulness of DDI information sources

4 Methods

4.1 Study Area

The study was conducted in Addis Ababa, capital city of Ethiopia. According to the 2010 Central Statistical Agency of Ethiopia (CSA) population census, the population of Addis Ababa was 2.917 million (CSA, 2010). Addis Ababa covers 540 square kilometer land area.

During the survey time Addis Ababa had 42 hospitals. Out of these 12 were government owned hospitals and the remaining 30 were private hospitals. Four are under the Federal Ministry of Health including St. Paul’s General Specialized Hospital which is a teaching hospital and one is a university hospital under the Addis Ababa University (Tikur Anbesa general specialized hospital). Five were general hospitals and under the Addis Ababa regional health bureau (Yekatit 12 Hospital, Ras Desta Damtew Memorial Hospital, Zewditu Memorial Hospital, Minelik II Hospital and Ghandi Memorial Hospital). The remaining two were Army and Police Hospitals (FMoH, 2011). Seven of the 12 governmental hospitals and 12 of the 30 private hospitals provide general services.

According to the 2010 health and health related indicators there are 934 physicians (396 GPs and 538 specialists) working both in governmental and private health care settings in Addis Ababa (FMoH, 2010). Out of these, 345 were working in general hospitals.

4.2 Study Design

Cross sectional survey was conducted among prescribing physicians in general service hospitals in Addis Ababa between January and March 2013. Self-administered questionnaire has been employed for data collection.

4.3 Source population

The source population for this study was all physicians working as prescribers in general service hospitals in Addis Ababa.

4.4 Study Population

Participants are prescribing physicians drawn from general service hospitals in Addis Ababa who fulfilled the inclusive criteria.

4.5 Inclusion and Exclusion Criteria

Inclusion Criteria:

- General practitioners and specialists who prescribe medicines were candidates for this study
- General practitioners and specialists who have been selected by the sampling method and who were willing to participate in the study.

Exclusion Criteria:

- Physicians who do not prescribe or prescribe little number of medicines (such as radiologists, anesthesiologists and pathologists).
- Physicians who were not present during time of data collection.
- Prescribers who were not voluntary to participate in the study.

4.6 Sample size determination and Sampling Procedure

4.6. 1 Sample Size Determination

There were no previous studies conducted regarding the same issue in Ethiopia. Therefore, the following assumptions were made to obtain the largest possible sample size (Belle *et al.*, 2004). p=0.5 and d (tolerable sampling error) = 5% and using 95% confidence level:

$$ni = \frac{z^2 p(1-p)}{d^2}$$

Where, ni = initial sample size, z = z statistic for 95% level of confidence; d = precision / margin of error/ and p = proportion of physicians who have good DDI knowledge level.

$$\Rightarrow ni = \frac{(1.96)^2 * (0.5) * (1-0.5)}{(0.05)^2} = \underline{\underline{384}}$$

Based on estimation of proportion from a finite population of size N, the final sample size was calculated as follows (Belle *et al.*, 2004);

$$nf = \frac{ni}{1+(\frac{ni}{N})}$$

Where nf = final sample size and N = total number prescribing physicians in the general service hospitals

$$\Longrightarrow nf = \frac{384}{1+\left(\frac{384}{345}\right)} = \mathbf{\underline{\underline{182}}}$$

Adding 10% none and inappropriate responses, the total sample size required for this study was 200.

Then the number of physicians to participate in the study from each hospital was decided based on proportionate to size.

4.6.2 Sampling Procedure

The list of all physicians was retrieved from the human resource department of each hospital and this was used as the sampling frame. The total sample size was proportionally allocated to each hospital based on the number of physicians in each hospital. Then the respondents were selected from each hospital using simple random sampling by lottery method (in private hospitals) and convenience sampling method in governmental hospitals. In government hospitals there was high patient flow and since physicians were too busy, it was hard to reach them through neither simple random sampling nor systematic random sampling procedures. Therefore, convenient sampling was used to recruit participants from government hospitals (Annexes I and II).

4.7. Study Variables

Dependent variables:

- Physicians' DDI knowledge
- Physicians' perceived usefulness of common DDI information sources

Independent variables:

- Socio demographic characteristics: age, gender, education level, area of specialization and number of years practicing as a licensed prescriber
- Trainings on DDIs
- Workload: average number of patients seen per day, average hours per week seeing patients and weekly prescription volume
- Familiarity with the Ethiopian STGs for hospitals

- Factors influencing physicians decisions of new drug prescription: Safety and efficacy/effectiveness of the drug
- History of encountering DDIs
- The extent to which the risk of DDIs affects drug selection for prescription
- Perceptions on drug safety and DDIs

4.8 Operational Definitions

Construct	The dimension that the measure is intended to assess (attribute or trait)
Good DDI knowledge level	DDI knowledge test score with the mean (i.e., 5) and above out of 15
General practitioner	A medical doctor who has been registered and licensed by FMHACA and whose practice consists of providing ongoing care covering a variety of medical problems in patients of all age
General hospital	A hospital providing ongoing care covering a variety of medical problems, such as internal medicine, gynecology and obstetrics, cardiology, etc. (includes general or specialized general hospitals)
None pharmacist clinicians	Health professionals other than pharmacists (includes health officers, nurses etc)

Outfit	An outlier-sensitive fit statistic that picks up rare events that have occurred in an unexpected way. >>1.0 unexpected outliers.

4.9 Data Collection and Management

4.9.1 Data Collection Instrument

Self administered questionnaire (Annex IV) which was developed after reviewing relevant literatures, such as Stockley's Drug Interactions, Handbook of Drug Interactions: A Clinical and Forensic Guide, standard treatment guidelines for hospitals of Ethiopia and essential drug lists for Ethiopia (Davis *et al*., 2009; DACA, 2010; FMHACA, 2010, Mozayani *et al*., 2004) and online articles (Carithers, 2011; Ko *et al*., 2008; Malone *et al*., 2004, Warolak *et al*., 2011), has been employed in this study. It consisted of five sections. The first section contained questions concerning physicians' demographics characteristics that might account for differences in prescribers' ability of identifying common DDIs and perceived usefulness of usual DDIs information sources. Section two consisted of questions regarding physicians' opinion on drug safety and drug interactions. In this part there are four questions to identify prescribers' perception of DDIs. Question set three targets on physicians' knowledge regarding potential DDIs of selected drug pairs. This segment contained fifteen drug-drug pairs which are locally available and routinely prescribed. Only fifteen drug pairs were selected for inclusion to this instrument assuming that more than this might decrease response rates. Local availability of the drugs and whether they are routinely prescribed or not were checked by disseminating the drug lists to hospital and community pharmacies. Then Potential DDIs were identified using the DRUG-REAX® System from the US database by Thomson Micromedex, an interactive drug interactions program developed by Thomson Micromedex and stockly's drug interactions. (Davis *et al*., 2009; Thomson Micromedex, 2012). To evaluate the validity of the DDI knowledge test instrument, construct variance and construct representation were assessed.

Among the fifteen drug pairs, six are contraindicated; five could be used under monitoring and four had no known interaction. Without the aid of any reference, respondents were asked to classify each drug pair in one of four categories: a) contraindicated; b) may be used together but with monitoring; c) no interaction and d) not sure. The "not sure" option was added to prevent guessing.

The last section contained questions regarding the source that usually inform prescribers about their patients' exposure to potential DDIs along with five questions to explore their opinion on the usefulness of these information sources. Five closed ended questions were used to assess the usefulness of DDI information sources, and the response option was Likert scales ranging from never(1) to always(5).

4.9.2 Recruitment and Training of Data Collectors

Four pharmacy graduate students were recruited for data collection and a one day training was given by the principal investigator a day prior to the start of the actual data collection. The training focused on the aim of the study, the content of the instrument and how to deliver it to the participants including how to assure confidentiality.

4.9.3 Data Collection

Data were collected by trained data collectors using self administered questionnaire between January and March 2013.

4.9.4 Data Quality Assurance

To assure the quality of the data, the survey questionnaire was properly designed. Then it was pre tested on 10 physicians in Gandhi memorial hospital who were not included in the study. This was in order to check whether the questions are understandable and answerable. The pre test showed that the instrument was understandable and answerable and therefore, no modification was made.

All completed questionnaire were examined for completeness and consistency during data management, storage and analysis.

4.9.5 Data Entry and Processing

Responses to each question were coded individually and entered in to a computer using Epi-info version 3.5.1 and then exported to SPSS version 17.0 for Windows. Then data analyses were performed using SPSS 17.0. Univariate analyses were used to describe the categorical variables (percentage and frequency distribution of different characteristics of the questionnaire). Rasch analysis was employed to assess the instrument validity. This was conducted with MINISTEP version 3.75.0.

Bivariate logistic regression analysis was done to assess the presence and degree of association between physicians' DDI knowledge and each independent variable. Then multivariate logistic regression model was used to control for possible confounding effects. A One-way analysis of variance (ANOVA) with scheffe test was performed to compare the mean perceived DDI information sources usefulness scores among physicians. For all of statistical test used in this study, the significant levels were set at p-value < 0.05. For the Rasch analysis, items with outfit mean square between 0.5 and 1.5 were considered for inclusion.

Ethical considerations

Ethical clearance was obtained from Addis Ababa University School of Pharmacy ethical review Board (Annex V). Full explanation about the purpose of the study was made to authorities of the respective hospital and to the participants. Data collection was conducted after approval of the study by the medical directors of each hospital. The respondents were informed of their right to refuse or agree to participate in the study. All participants gave a written informed consent before the start of the study (Annex III). To assure confidentiality, participants were not asked to identify themselves by name.

6 Results

6.1 Socio-demographics of the Respondents

A total of 140 questionnaires with an adjusted response rate of 70 % were complete and included in the analysis. The majority of the respondents, 111 (79.3%) were males and 29(20.7%) were females. Ages of respondents ranged from 24 to 75 years with, 34(24.3%) reporting less than 30 years old , 71(50.7%) between 30 and 40 years and 35(25%) above 40 years with an average of 36.57± 8.78(mean ± SD). Seventy five (53.6%) of the respondents were general practitioners where as 65(46.4%) were specialists. Seventy seven (55%) of the respondents were practicing in general area of practice while 63(45%) were practicing in specialty area. Among those working in a specialty area, 13(16.9%) were practicing in obstetrics and gynecology, 32(41.6%) were practicing in internal medicine other than cardiology, 16(20.8%) were pediatricians, only 2(2.6%) and 3 (3.9%) were practice in Emergency medicine and cardiology respectively. Eleven (14.3%) were practicing in other departments which included dermatology/venereology, neurology, dentistry and general surgery (Table 1).

Table 1 Socio -demographic characteristics of respondents in general hospitals of Addis Ababa, 2013. (N=140)

Variables		Frequency	Percentage
Gender	Male	111	79.3
	Female	29	20.7
Age group	< 30 yrs	34	24.3
	30-40 yrs	71	50.7
	> 40 yrs	35	25
Education level	General practitioner	75	53.6
	Specialist	65	46.4
Area of Specialization	Obstetrics and gynecology	13	9.3
	Internal medicine other than cardiology	32	22.9
	Cardiology	3	2.1
	Pediatrics	16	11.4
	Emergency medicine	2	1.4
	Other*	11	7.9
Area of practice	Specialty area	63	45
	General area of practice	77	55
Practice setting	Governmental hospital	63	45
	Private hospital	61	43.6
	At both	16	11.4
Years of professional experience	<10 yrs	65	46.4
	10-20 yrs	57	40.7
	>20yrs	18	12.9

***** *dermatology/venereology, neurology, general surgery and dentistry*

6.2 Physicians' Trainings on Drug-Drug Interactions

The majority of the respondents 130 (92.9%) didn't take any training regarding DDIs. Among those respondents who took trainings on DDIs, 4 (40%) participated in workshops and seminars, 3 (30%) took DDI trainings via continuing education and the remaining 3 (30%) took DDI trainings via other means which they didn't mention.

6.3 Work load

This finding revealed that over one-third (38.6%) of the respondents were examining 15 to 20 patients per day on average. Sixty three (45%) of the respondents worked 41 to 50 hrs per week. Fifty five (39.3%) of the respondents reported they were writing 10 to 20 prescriptions daily on average (Table 2).

Table 2 Work load of physicians in general hospitals of Addis Ababa, 2013 (N=140)

Variable	Frequencies	Percentages
Average number of patients examined per day		
< 15	29	20.7
15-20	54	38.6
21-30	50	35.7
>30	7	5
Average number of hours spent in work per week		
< 20	3	2.1
20-30	21	15
31 -40	35	25
41-50	63	45
> 50	18	12.9
Average number of prescriptions written daily		
< 10	36	25.7
10-20	55	39.3
21-30	44	31.4
>30	5	3.6

6.4 Level of Familiarity of Physicians with STGs for Hospitals

Over one third of the respondents (37.9%) reported that they were little familiar with STGs for hospitals, 34 (24.3%) were somewhat familiar, 13 (9.3%) were very familiar (Fig. 1).

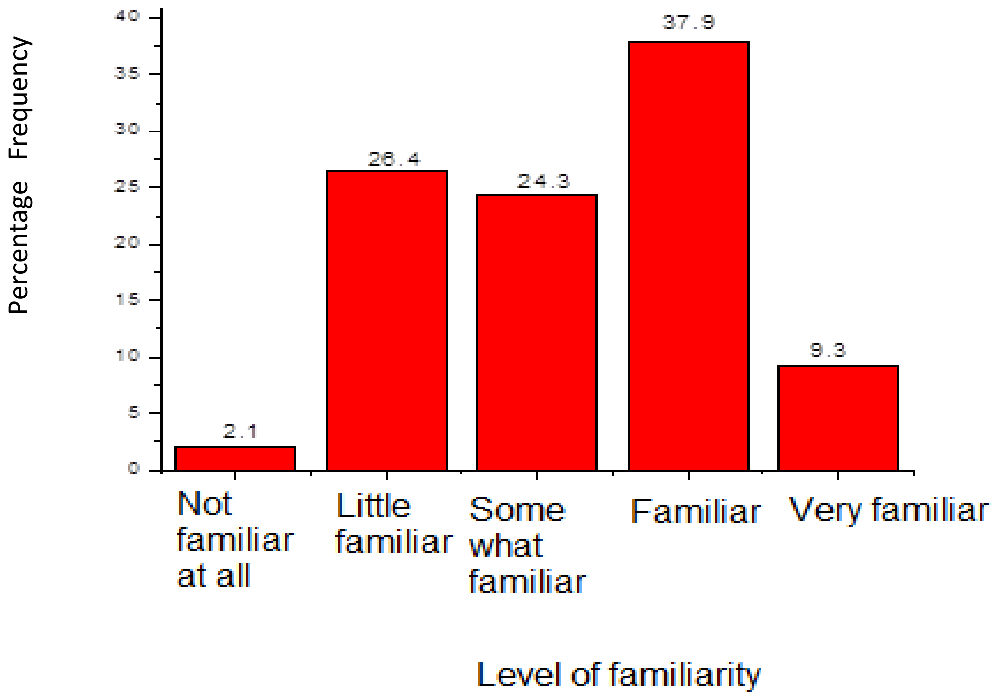


Figure 1 Level of physicians' familiarity with STGs for hospitals in general hospitals of Addis Ababa, 2013. (N=140)

6.5 Factors Influencing Physicians Choice of New Drugs for Prescription

When asked what factor(s) was/were highly influencing their decisions when prescribing new drugs, 41(29.3%) reported that only safety /including DDIs influence their drug selection the most. The majority of the physicians, 83 (59.3%) reported that a combination of these factors influence their drug selection the most. None of the respondents reported that patient requests for the drug influence their drug selection for prescription (Table 3).

Table 3 Factors influencing physicians choice of new drugs for prescription in general hospitals of Addis Ababa, 2013, (N=140)

Factor	Frequency	Percentage
Safety /including drug-drug interactions	41	29.3
Efficacy/effectiveness of the drug	14	10
A combination of the above factors	83	59.3
Others*	2	1.4

* *Cost of the drug, colleagues and/or specialists through referral and recommendations*

6.6 Physicians' History of Encountering Drug-Drug Interactions

The majority of the respondents, 99(70.7%) indicated that they had ever come across a patient who experienced a DDI that caused harm. Sixty nine (49.3%) of the respondents encountered DDIs several times that caused harm to the patient and only 5 (3.6%) of the respondents come across DDIs that caused harm to the patients once in their practice (Table 4).

Table 4 Physicians' history of encountering DDIs in general hospitals of Addis Ababa, 2013. (N=140)

Item	Frequency	Percentages
Had ever come across a drug-drug interaction that resulted in adverse outcomes		
Yes	99	70.7
No	41	29
Commonly observed adverse outcomes caused by drug-drug interactions		
Intoxication/ overdosage	20	20.2
Bleeding	24	24.2
Hypotension	18	18.2
Therapeutic failure	37	37.4
Frequency of encountering a drug-drug interaction that caused harm		
Once	5	3.6
Twice	13	9.3
Three times	11	7.9
Several times	69	49.3

6.7 The Extent to Which the Risk of DDIs Affects Physicians' Drug Selection

The risk of DDIs very much affected over one-third (34.3%) of respondents' drug selection for prescription. Fifty six (40%) of the respondents reported that their drug selection was somewhat affected by the risk for DDI and one-fourth of them (25.7%) reported that the risk for DDI affected their drug selection a little.

6.8 Physicians' Perceptions of Drug Safety and DDIs

Over one-third of the study participants, 50 (35.7%) somewhat agreed that the risk for DDIs is high. Forty seven (33.6%) of the respondents agreed that the risk for DDIs is high and 31(22.1%) of the respondents somewhat disagreed towards the presence of higher risk of DDIs. The majority of respondents 87(62.1%) agreed that it is important for prescribers to learn about DDIs. Forty one (29.3%) somewhat agreed whereas 12(8.6%) somewhat disagreed about the importance of learning about DDIs (Fig. 2).

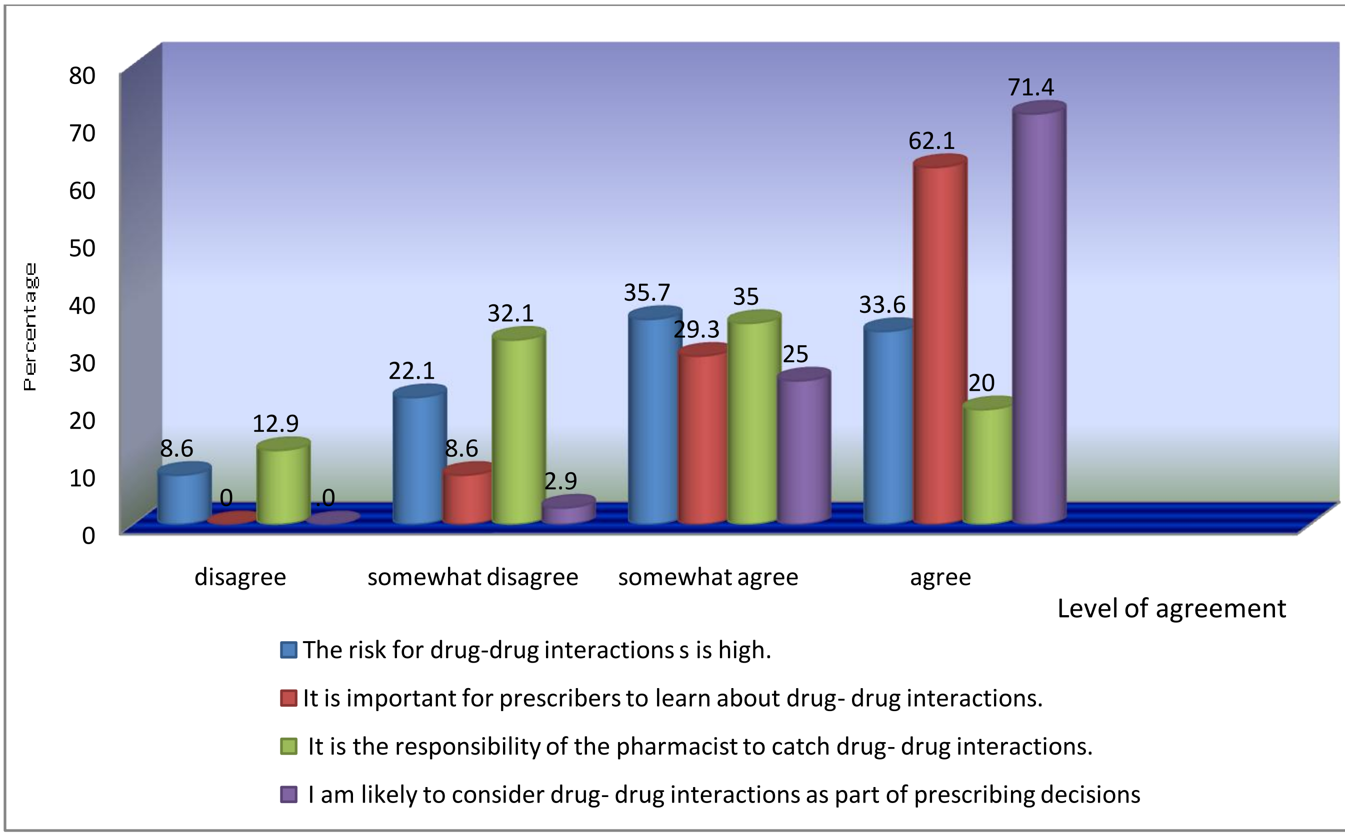
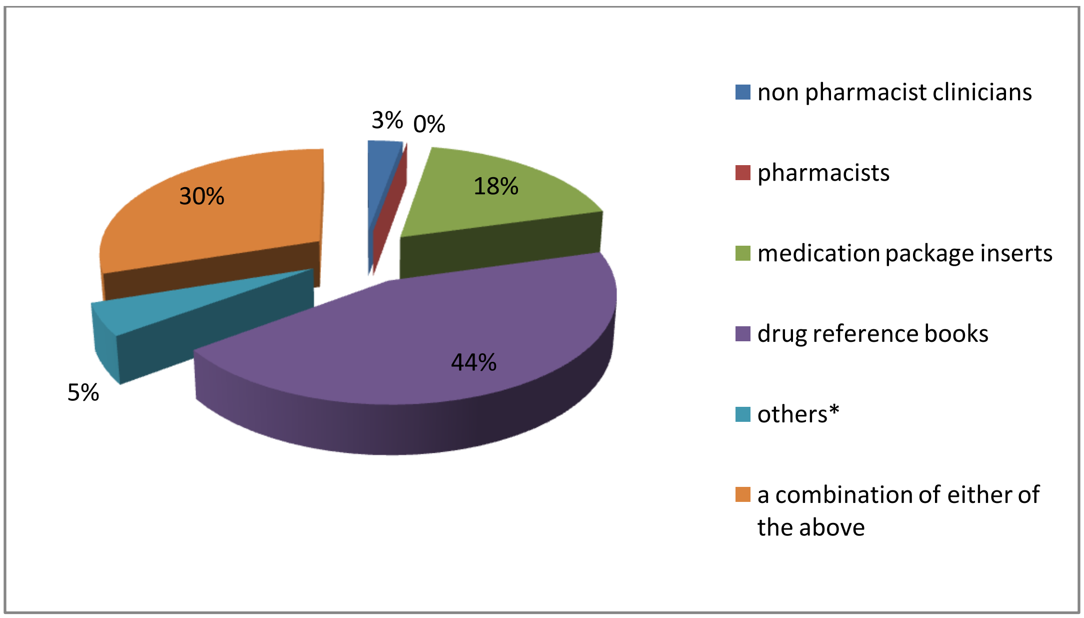


Figure 2 Physicians' perceptions of drug safety and DDIs, 2013. (N=140)

6.9 Physicians' Usual Information Sources on Drug-Drug Interactions

Drug reference books was the most cited information source used by 62 (44.3%) of the study physicians followed by medication package inserts which were used by 25 (17.9%) of the respondents. None of the respondents reported pharmacists as source of DDI information. Non pharmacist clinicians were used by 4 (2.9%) of the respondents as DDI information source. Seven (5%) of the respondents were using other references which included smart phone applications, up to date and themselves (their clinical background) and 42 (30%) of the respondents reported that they are using a combination of either of the above DDI information sources to identify DDIs (Fig. 3).



* *Smart phone applications, up to date and themselves (their clinical background)*

Figure 3 Physicians' common information sources on DDIs in general hospitals of Addis Ababa, 2013. (N=140)

6.10 Drug-Drug Interactions knowledge Test Instrument Validation

To evaluate the validity of the DDI knowledge test instrument, construct variance and construct representation were assessed using Rasch model. The Rasch analysis revealed that item reliability was 0.90 and person reliability (analogous to Cronbach's Alpha coefficient) was 0.57.

6.10.1 Construct variance evaluation

All of the 15 DDI knowledge items indicated acceptable fit statistics (outfit mean square values are between 0.5 and 1.5) (Linacre, 2012). This supported the unidimensionality requirements of the Rasch model. Therefore, the item was measuring what it was intended for (the instrument is productive). Item difficulty estimates ranged from _1.93 logits to 1.98 logits, with a mean of 0.00 and a SD of 0.98 (Table 5).

Table 5 DDI knowledge item statistics derived from Rasch analysis

Drug pairs	Item difficulty	Outfit MNSQ*
Praziquantel + Rifampicin	1.98	1.40
Allopurinol + Pyrazinamide	1.47	0.81
Warfarin + co trimoxazole	0.76	1.18
Digoxin + sildenafil	0.48	1.19
Simvastatin + itraconazole	0.23	0.89
Carbamazepine + cimetidine	0.07	0.88
Warfarin + fluconazole	0.07	1.12
Digoxin + clarithromycin	-0.01	0.78
Digoxin + verapamil	-0.08	1.06
Metformin + erythromycin	-0.08	1.28
Carbamazepine + clarithromycin	-0.36	1.09
Warfarin + cimetidine	-0.36	0.81
Atenolol + ranitidine	-0.43	0.88
Nitroglycerin + sildenafil	-1.78	0.72
Acetaminophen/codein+amoxacillin	-1.93	1.12

*Mean square value

6.10.2 Construct representation evaluation

The item/person map in Fig. 4 provides a visual representation of the distribution and hierarchical order of physicians' potential DDI knowledge and item difficulty estimates. This logit scale is an interval scale so equal distances anywhere up and down the vertical line have an equal value. Each physician's ability to correctly classify the drug pairs is depicted on the left side of the item map (represented by the pound and period symbols). The least able persons are located toward the bottom of the map, and the most able persons are located toward the top of the map. Each item's difficulty is depicted on the right side of the map. Items at the bottom are the easiest for physicians to answer correctly and the items at the top are the most difficult for physicians. Item 1 and 7 (acetaminophen with codeine + amoxicillin and Nitroglycerine + sidenafil) were the easiest for physicians to correctly classify, whereas item 14 (Praziquantel + Rifampicin) was the most difficult. The figure also shows that there were many physicians around the mean and there were many drug pairs close to them. This implies that there was satisfactory precision of measurement. Physicians at -3 and -4 have no items targeted at their ability level. At +2 there is one difficult item without a physician aliening to it.

```
better DDI knowledge| more dificult
   2               +T Praziquantel+Rifampicin
                .#  |
                 .  |  Allopurinol+Pyrazinamide
   1               T+S
                 .  |  warfarin+cotrimoxazol
                ##  |  digoxin+Sildenafil  simvastatin+Itraconazol
   0         ##### S+M Carbamaze+Cimetid  digox+Clarith  digox+Verap  metform+Eryth  warf+Fluc
               .##  |  atenolol+Ranitidine   carbamazepin+Clarithromycin  warfarin+cimetidine
         .########  |
  -1               M+S
            ######  |
             #####  |  nitroglycerin+Sildenafil
  -2               S+T actaminophene with codeine+Amoxicillin
              ####  |
                   T|
  -3             #  +
                    |
                    |
  -4             #  +
  poor DDI knowledge|less dificult
```

Each "#" represents two physicians and each "." (Period) represents one physician. M, mean; S, 1 Standard deviation; T, 2 Standard deviations.

Figure 4 Person-item map derived from Rasch analysis

6.11 Physicians' knowledge of Potential Drug-Drug Interactions

The percentage of physicians who correctly classified the drug pairs ranged from 12.9%, for the drug pair "praziquantel + rifampicin" (contraindicated drug combination) to 65.7%, for the drug pair "acetaminophen with codeine + amoxicillin" (non interacting drug combination). Of the 15 drug pairs tested, only 2 were classified correctly by more than 50% of the physicians. The number of drug pairs correctly classified ranged from 1 to 11. Six (4.3%) the respondents correctly classified only 1 drug pair while 3 (2.1 %) of the respondents correctly classified 11 of the drug pairs. The average number of accurately categorized drug pairs was 5 (33.3%) with a standard deviation of 2.29.

Nitroglycerin + sildenafil was correctly classified by over half of the respondents, 78 (55.7%) as contraindicated and warfarin + fluconazole was correctly classified by over one third, 54 (38.6%) of the respondents as contraindicated while three of the six drug pairs that were considered as contraindicated were correctly classified by less than one-fourth of the respondents; Allopurinol + Pyrazinamide by 31 (22.1%), Praziquantel + Rifampicin by 18 (12.9%), and warfarin + co trimoxazole by 25 (17.9%) respondents as a combination considered as contraindicated. Smvastatin+ itraconazole (a combination considered as contraindicated) was correctly identified by 39 (27.9%) of respondents.

All of the five drug combinations to be prescribed with monitoring were correctly identified by over one-third of the physicians; carbamazepine + clarithromycin by 57 (40.7%), digoxin + verapamil by 52 (37.1%), digoxin + clarithromycin by 46 (32.9%), atenolol + ranitidine by 52 (37.1%), and Carbamazepine + cimetidine by 48 (34.3%) of the physicians.

Twelve (8.6%) of the respondents chose the response category “not sure” for the drug pair “acetaminophen with codein + amoxicillin” and 56 (40 %) chose the response category “not sure” for the drug pair “praziquantel + rifampicin”. Over one third of the respondents answered”not sure” for three of the drug pairs which were contraindicated (Allopurinol + Pyrazinamide, Praziquantel + Rifampicin, and warfarin +co trimoxazole); for two of the drug pairs which had no any interaction (digoxin + sildenafil and metformin + erythromycin) and for one of the drug pairs which was to be used with monitoring (carbamazepine + digoxin and clarithromycin) (Table 6).

Table 6 Physicians' knowledge of potential Drug-drug interactions in general hospitals of Addis Ababa, 2013. (N=140)

Drug Pair	Contraindicated n[%]	Can be used under monitoring n[%]	No interaction n[%]	Not Sure n[%]
Acetaminophen with codeine + amoxicillin	1[.7]	35[25.0]	**92[65.7] ***	12[8.6]
Carbamazepine + clarithromycin	20[14.3]	**57[40.7] ***	30[21.4]	33[23.6]
Digoxin + verapamil	33[23.6]	**52[37.1]***	29[20.7]	26[18.6]
Digoxin + clarithromycin	18[12.9]	**46[32.9]***	38[27.1]	38[27.1]
Digoxin + sildenafil	31[22.1]	44[31.4]	**27[19.3]***	38[27.1]
Metformin + erythromycin	7[5]	47[33.6]	**43[30.7]***	43[30.7]
Nitroglycerin + sildenafil	**78[55.7]***	37[26.4]	8[5.7]	17[12.1]
Simvastatin + itraconazole	**39[27.9]***	66[47.1]	12[8.6]	23[16.4]
Warfarin + cimetidine	54[38.6]	**56[40]***	17[12.1]	13[9.3]
Atenolol + ranitidine	9[6.4]	55[39.3]	**52[37.1]***	24[17.1]
Carbamazepine + cimetidine	48[34.3]	**48[34.3]***	17[12.1]	27[19.3]
Warfarin + fluconazole	**54[38.6]***	49[35]	9[6.4]	28[20]
Allopurinol + Pyrazinamide	**31[22.1]***	49[35]	12[8.6]	48[34.3]
Praziquantel + Rifampicin	**18[12.9]***	52[37.1]	14[10]	56[40]
Warfarin + co trimoxazole	**25[17.9*]**	48[34.3]	17[12.1]	50[35.7]

* *correct responses*

6.12 Factors Associated with Physicians' Drug-Drug Interactions knowledge

Crude analysis of potential determinants of physicians' DDI knowledge level revealed that some variables such as gender, education level, years of professional experience, trainings on DDIs, work load, familiarity with STGs, factors influencing physicians decisions of new drug prescription, experience of a DDI that caused harm to a patient, frequency of encountering a patient who had a DDI that caused harm, the extent to which the risk for a DDI affect drug selection for prescription, perception on the importance of learning about DDIs did not show statistically significant association with DDI knowledge level (Table 7). On the other hand, age, area of specialization, perceptions on the prevalence of DDIs, level of agreement to the statement " I am likely to consider DDIs as part of prescribing decisions" and information sources on DDIs were significantly associated with DDI knowledge of physicians ($p<0.05$) (Table 9).

A multivariate analysis was also performed to identify independent predictors of DDI knowledge of physicians. The model explained 88.3% of the variance in DDI knowledge level which is satisfactory. Area of specialization, perceptions of prescribers on the risk for DDIs and usual method of DDI information sources were found to be independent predictors of DDI knowledge. The results from the multivariate analysis indicated that a higher potential DDI knowledge level was associated with specialization in internal medicine other than cardiology and pediatrics, seeking DDI information from other sources and level of agreement on the presence higher risk of DDIs. Physicians who pursued specialization in internal medicine other than cardiology scored higher on the DDI knowledge test than those who reported having specialization in ''others'' with AOR (95% CI): 255[4.57-14323]; those who have specialized in pediatrics were forty nine times more likely to have good DDI knowledge than those who reported having specialization in ‘‘others’’ with AOR (95% CI): 49 [1.17-2121]. The odds of better DDI knowledge was fifty times more likely in Physicians who were being informed by other sources of information about the exposure of a patient to a potential DDI than those who used drug reference books as their DDI information source (Table 7).

The inflated odds of ratios might be due to the smaller sample size.

Table 7 Association between physicians' attributes and DDI knowledge level in general hospitals of Addis Ababa, 2013 (N=140)

Variables		DDI knowledge level		Odds Ratio	
		Good n[%]	Poor n[%]	COR [95%CI]	AOR [95%CI]
Gender	Male	61[54.9]	50[45.1]	0.99[0.44-2.26]	
	Female	16[55]	13[45]	1	
Age group					
	< 30 yrs	8[23.5]	26[76.5]	**0.26[0.09-0.73]***	9.10 [0.20-422.47]
	30-40 yrs	50[70.4]	21[29.6]	2.0[0.87-4.63]	1.50 [0.20-11.17]
	> 40 yrs	19[54.3]	16[45.7]	1	1
Educational level	General practitioners	38[50.7]	37[49.3]	0.68 [0.35-1.34]	
	Specialist	39[60]	26[40]	1	
Area of Specialization					
	Obstetrics & gynecology	6[46.2]	7[53.8]	2.23[0.41-12.7]	5.20[0.20-137.76]
	Internal medicine other than cardiology	27[84.4]	5[15.6]	**14.4[2.8-73.82]****	**255.72[4.57-14323]****
	Cardiology	2[66.7]	1[33.3]	5.33[0.34-82.83]	11.89[0.06-2477.31]
	Pediatrics	9[56.25]	7[43.75]	3.4[0.66-17.93]	**49.00[1.17-2121.52]***
	Emergency medicine	2[100]	0[0]	4.30[0.00]	6.76 [0.00]
	Other [a]	3[27.3]	8[72.7]	1	
Area of practice	at specialty area	49[63.6]	28[36.4]	2.12[1.11-4.32]	
	at general area of practice	28[44.4]	35[55.6]	1	
Years of professional experience					
	<10 yrs	32[49.2]	33[50.8]	1.21 [0.43-3.46]	
	10-20 yrs	37[64.9]	20[35.1]	2.31 [0.79-6.79]	
	> 20 yrs	8[44.4]	10[44.6]	1	

Trained on drug –drug interactions			
Yes	6[60]	4[40]	1.25[0.34-4.63]
No	71[54.6]	59[45.4]	1
Average number of patients examined/day			
< 15	16[55.2]	13[44.8]	0.00
15-20	30[55.5]	24[44.5]	0.00
21-30	24[48]	26[52]	0.00
>30	7[100]	0[0]	1
Average number of hours spent in work/week			
< 20	1[33.3]	2[66.7]	0.32[0.02-4.20]
20-30	6[28.6]	15[71.4]	0.26[0.07-0.97]
31 -40	21[60]	14[40]	0.95 [0.3-3.06]
41-50	38[60.3]	25[39.7]	0.97[0.33-2.83]
> 50	11[61.1]	7[38.9]	1
Average number of prescriptions written/day			
< 10	20[55.5]	16[44.5]	0.31 [0.03-3.08]
10-20	31[56.4]	24[43.6]	0.32 [0.03-3.08]
21-30	22[50]	22[50]	0.25 [0.03-2.42]
> 30	4[80]	1[20]	1
Have come across a patient who had a DDI that caused adverse outcomes			
Yes	57[58.2]	41[41.8]	1.46 [0.70-3.04]
No	20[48.8]	21[52.2]	1
Frequency of encountering a DDI that caused adverse outcomes			
Once	2[40]	3[40]	0.27[0.04-1.75]
Twice	4[30.8]	9[69.2]	**0.18[0.05-0.66] ****
Three times	2[18.2]	9[81.8]	**0.09[0.02-0.46] ****
Several times	49[71]	20[29]	1

The extent to which the risk of DDIs affect drug selection				
a little	16[44.4]	20[55.6]	0.36[0.15-0.89]	
somewhat	28[50]	28[50]	0.45[0.20-1.02]	
very Much	33[68.75]	15[32.3]	1	
The risk of drug-drug interactions is high				
Disagree	2[16.7]	10[83.3]	1	1
Somewhat disagree	15[48.4]	16[51.6]	4.69[0.88-24.99]	**105.7[1.90-5937.40]***
Somewhat agree	24[48]	26[52]	**4.61[0.92-23.24]***	**157.36[3.20-7739.76]***
Agree	36[76.6]	11[23.4]	**16.40[3.11-86.20] ****	**1066[17- 7406.45] ****
It is the responsibility of the Pharmacist to catch DDIs				
Disagree	8[44.4]	10[55.6]	0.38[0.11-1.29]	
Somewhat disagree	22[48.9]	23[51.1]	0.45[0.17-1.21]	
Somewhat agree	28[57.1]	21[42.9]	0.63 [0.24-1.67]	
Agree	19[67.9]	9[32.1]	1	
I am likely to consider DDIs as part of prescribing decisions				
Somewhat disagree	1[25]	3[75]	0.20[0.02-2.00]	0[0.00]
Somewhat agree	13[37.1]	22[62.9]	**0.36[0.16-0.79**]*	0.89[0.10-7.59]
Agree	63[62.4]	38[37.6]	1	1
Usual information sources on DDIs				
Non pharmacist clinicians	0[0]	4[100]	0.99[0.00]	0.00[0.00]
Medication package inserts	17[68]	8[32]	0.66[0.22-1.99]	0.92 0[.07-11.61]
Drug reference books	22[35.5]	40[64.5]	**0.17[0.07-0.41] ****	**0.02[0.00-0.32] ****
Other [b]	6[85.7]	1[14.3]	1	1

** p- value < 0.05* ** *Significant association at p-value <0.01*

[a] *dermatology/venereology, neurology, dentistry and general surgery*

[b] *up to date, smart phone applications, themselves (their clinical back ground)*

6.13 Physicians' Perceived Usefulness of DDIs Information Sources

The overall mean perceived usefulness score of DDI information sources was found to be 3.59±0.64[SD], with a range from 2 to 5.

For the statement regarding how often the DDI information changes their initial prescribing decisions, 50(35.7%) respondents reported the information sometimes changed their initial prescribing decisions and only 1 (0.7%) respondent chosen the response category 'never' for this statement. The DDI information provided by their DDI information sources was always new to 53 (37%) of the physicians. Fifty (35.7%) of the respondents reported that the information was sometimes relevant to the patient.The DDI information was frequently sufficient to manage the interaction for 58(41.4%) of the respondents. Concerning the future usefulness of the information, half (50.7%) of the study participants reported that the information is always useful in the future (Table 8).

Table 8 Physicians' Perceived Usefulness of DDIs Information Sources in general hospitals of Addis Ababa, 2013. (N=140)

Questions	Never n[%]	Infrequently n[%]	Sometimes n[%]	Frequently n[%]	Always n[%]
1. **How often does the drug-drug interaction information change your initial prescribing decisions**?	1[0.7]	35[25]	50[35.7]	38[27.1]	16[11.4]
2. **How often is the drug-drug interaction information new to you?**	3[2.1]	35[25]	53[37]	39[27.9]	10[7.1]
3. **How often is the drug interaction information relevant to the patient?**	0[0]	15[10.7]	50[35.7]	30[21.4]	45[32.1]
4. **Is the drug interaction information sufficient for you to manage the interaction?**	6[4.3]	21[15]	37[26.4]	58[41.4]	18[12.9]
5. **How often is the drug interaction information useful to you in future prescribing?**	2[1.4]	3[2.1]	21[15]	43[30.7]	71[50.7]

6.14 Differences in DDI Information Sources Usefulness Score by Socio Demographic characteristics of Physicians

Results of the one-way ANOVA revealed there were significant difference in mean DDI information usefulness scores among physicians by years of professional experience, $p = 0.024$, F (3.824). Post hoc procedures with scheffe test showed physicians who had more than 20 years of professional years experience had better perceptions on the usefulness of DDI interaction information sources than those who worked for 10-20 years. Other socio demographic characteristics did not show significant effect on physicians' perceptions of DDI information sources usefulness (Table 9).

Table 9 Differences in DDI Information Sources Usefulness Score by Socio demographic characteristics of physicians in general hospitals of Addis Ababa, 2013. (N=140)

Variable		**Frequency(n)**	**usefulness score mean**	**[SD]**	***F***	***P***
Gender	Male	111	3.59	0 .66	0.86	0.355
	Female	29	3.46	0.71		
Age group	< 30 yrs	34	3.40	0.62	1.376	0.256
	30-40 yrs	71	3.62	0.61		
	> 40 yrs	35	3.61	0.79		
Education level	Generalist	75	3.58	0.61	0.05	0.824
	Specialist	65	3.55	0.73		
Area of Specialization	Obstetrics and gynecology	13	3.62	0.63	0.753	0.586
	Internal medicine other than cardiology	32	3.74	0.65		
	Cardiology	3	3.80	0.92		
	Pediatrics	16	3.35	0.64		
	Emergency medicine	2	3.80	0.00		
	Other*	11	3.65	0.92		
Years of professional experience	<10 yrs	65	3.59	0.63	3.824	0.024**
	10-20 yrs	57	3.43	0.64		
	>20 yrs	18	3.91	0.76		

dermatology/venereology, neurology, and dentistry, ****significant association at p-value < 0.05***

6.15 Differences in DDI Information Sources Usefulness Score by Workload of Physicians

The findings of this study showed that there were no statically significant differences in the mean DDI information source usefulness score by physicians' workload: average number of patients seen per day, average number of hours worked per week and average number of prescriptions written per day (Table 10).

Table 10 Differences in DDI Information Sources Usefulness Score by work load of physicians in general hospitals of Addis Ababa, 2013. (N=140)

Variable		**Frequency (n)**	**usefulness score**		***F***	***P***
			mean	**[SD]**		
Average number of patients seen per day	<15	29	3.68	0.56	0.141	1.848
	15-20	54	3.47	0.71		
	21-30	50	3.54	0.65		
	>30	7	4.03	0.63		
Average number of hours spent in hospital/week	< 20	3	3.67	0.31	0.324	1.176
	21-30	21	3.45	0.67		
	31 -40	35	3.53	0.75		
	41-50	63	3.53	0.63		
	> 50	18	3.87	0.62		
Average number of prescriptions written daily	<10	36	3.62	0.70	0.863	0.247
	11-20	55	3.51	0.65		
	21-30	44	3.59	0.67		
	>30	5	3.48	0.67		

6.16 Differences in DDI Information Sources Usefulness Score by History of Encountering DDIs

As shown in Table 11 physicians' history of encountering DDIs had no significant effects on DDI information usefulness scores.

Table 11 Differences in DDI Information Sources Usefulness Score by history of encountering DDIs in general hospitals of Addis Ababa, 2013 (N=140)

Variable	**Frequency (n)**	**usefulness score mean**	**[SD]**	***F***	***P***
Have ever come across a drug-drug interaction that caused adverse outcomes					
Yes	98	3.59	0.67	0.417	0.519
No	41	3.51	0.67		
Frequency of encountering a drug-drug interaction that caused adverse					
Once	5	3.56	0.43	1.358	0.261
Twice	13	3.43	0.64		
Three time	11	3.27	0.66		
Several times	69	3.66	0.68		

6.17 Differences in DDI Information Sources Usefulness Score by the Extent to Which the Risk of DDIs Affects Their Drug Selection

There was significant difference in mean DDI information source usefulness score by the extent to which the risk for a DDI affected physicians' selection of a drug product for prescription, $p < 0.05$.

Compared with the physicians whose drug selection was a little affected by a risk for a DDI, those whose selection was somewhat affected scored lower to the five items that assessed the usefulness of the information source. Those whose drug selection was affected very much had higher score than those who were a little affected, $p = 0.00$, F (10.592).

6.18 Differences in Physicians' DDI Information Sources Perceived Usefulness Score by Their Perceptions on Drug safety and DDIs

There was significant difference in mean DDI information source usefulness score by physicians' perceptions on the importance of leaning about DDIs and physicians' perceptions on considering DDI as part of prescribing decisions, $p < 0.05$. Those physicians who completely agreed up on the importance of learning about DDIs had a higher score to the five items that assessed the usefulness of the information than those who somewhat disagreed. Those who somewhat disagreed and somewhat agreed to this item gave lower scores to the usefulness statements than those who completely agreed respectively, $p < 0.01$, F (12.16). Those physicians who somewhat disagreed and somewhat agreed to the statement "prescribers are likely to consider DDIs as part of prescribing decisions" gave lower score than those who completely agreed respectively, $P < 0.05$, F (9.028) (Table 12)

Table 12 Differences in Physicians' DDI Information Sources Perceived Usefulness Score by Their Perceptions on Drug safety and DDIs in general hospitals of Addis Ababa, 2013 (N=140)

Variable	Frequency (n)	usefulness score mean	[SD]	*F*	*P*
The risk of drug-drug interactions is high					
Disagree	12	3.67	0.66	2.481	0.064
Somewhat disagree	31	3.43	0.66		
Somewhat agree	50	3.44	0.64		
Agree	47	3.76	0.67		
It is important for prescribers to learn about drug-drug interactions					
Somewhat disagree	12	3.35	0.77	12.16	0.000*
Somewhat agree	41	3.20	0.62		
Agree	87	3.76	0.59		
It is the responsibility of the pharmacist to catch drug-drug interactions					
Disagree	18	3.82	0.65	2.465	0.065
Somewhat disagree	45	3.37	0.69		
Somewhat agree	49	3.58	0.58		
Agree	28	3.67	0.72		
I am likely to consider DDIs as part of prescribing decisions					
Somewhat disagree	42	0.85	0.76	9.028	0.000*
Somewhat agree	35	3.26	0.64		
Agree	101	3.70	0.62		

***significant association** *at p-value < 0.05*

6.18 Differences in DDI Information Sources Usefulness Score by DDI Information Source Category

As shown in Table 13 DDI information source categories had no significant effects on DDI information usefulness scores.

Table 13 Differences in DDI Information Sources Usefulness Score by DDI information source category of physicians in general hospitals of Addis Ababa, 2013.

DDI information source category	Frequency(n)	usefulness score mean	[SD]	*F*	*p*
1. Non pharmacist clinicians	4	3.65	0.10	2.095	0.085
2. Medication package inserts	25	3.60	0.74		
3. Drug reference books	62	3.40	0.62		
4. Others*	7	3.86	0.81		
5. A combination of either of these sources	42	3.73	0.59		

* *Smart phone applications, up to date and themselves (their clinical background)*

7 Discussion

This study assessed physicians' awareness on DDIs and common sources of information in general hospitals of Addis Ababa. To attain this, the study identified physicians' socio demographic characteristics, workload, familiarity with the Ethiopian STGs for hospitals, perception of drug safety and common method of DDI information sources and tested physicians knowledge of DDIs.

The Rash analysis conducted to evaluate instrument validity and reliability revealed that the DDI knowledge assessment questionnaire had good validity and reliability (item reliability of 0.9 and person reliability of 0.57) which is comparable to the finding by Ko *et al*., (2008). Great attention was paid during selecting the drug pairs for the DDI knowledge test. Therefore, it is justifiable to have such a high item reliability of 0.9 from this instrument. This item also showed satisfactory model-data-fit (outfit mean square values are between 0.5 and 1.5) which implies the instrument met Rasch model unidimensionality requirements (Linacre, 2012). Therefore, the DDI knowledge questionnaire measured what it was intended to measure. Items (the drug pairs) and the physicians spread close each other along the scale in the person-item map. This implies that the instrument had well targeted the physicians' DDI knowledge levels. Therefore, the DDI knowledge questionnaire can be used as a reliable instrument. This instrument could also be used by modifying based on patient populations, practice settings, provider type (such as health officers and nurse practitioners).

DDIs are an important cause of adverse drug reactions and may lead to an increased risk of hospitalization and higher health care costs (Janchawee *et al*., 2005). Therefore, better

DDI knowledge is crucial to reduce the adverse clinical outcomes of DDI related morbidity and health care costs. However, physicians in the present study had low score on the DDI knowledge questions with an average of 33.3 % correct responses. This is lower than the studies conducted in USA by Glassman *et al*., (2002) and Ko (2007), which reported correct responses of 44% and 42.7% respectively. The reason behind the low score for the DDI knowledge assessment might be due to the fact that physicians in Ethiopia were reluctant to seek and utilize different DDI information sources. For example, none of the physicians in the present study reported that they were consulting pharmacists about DDIs. While, a study in USA by Malone *et al*., (2008) revealed that the majority of the physicians 650(68.4%) reported that they consulted pharmacists about DDIs.

DDIs are preventable medication errors associated with potentially serious adverse events and death (Indermitte *et al*, 2007). Therefore, hospital managers should investigate ways to prevent the prescription of drugs with potentially dangerous DDIs. One way of realizing this goal is to identify factors that encourage or discourage prescribers' DDI knowledge. This study found that area of specialization, perceptions of prescribers on the risks of DDIs and usual method of DDI information sources were factors associated with physicians' DDI knowledge.

The present study disclosed that physicians specialized in internal medicine other than cardiology had better DDI knowledge than those who reported having specialization in other areas such as dermatology/venereology, neurology, dentistry and general surgery.

This is in line with the finding by Ko *et al* (2008). The findings from the present study also showed that pediatricians had better DDI knowledge than physicians who specialized in other areas. Physicians in internal medicine and pediatrics are more likely to see patients with a variety of diseases. Therefore, they have more opportunities to come across medications from a variety of drug classes whereas physicians who specialized in other areas usually prescribe medications of limited categories. Hence they may not be familiar to DDIs as those internists and pediatricians.

The other predictor of DDI knowledge identified in this study was physicians' perceptions on the risks of DDIs. Compared to those physicians who somewhat disagreed, somewhat agreed or completely agreed on the statement "the risk of DDIs is high", those who completely disagreed had lower DDI knowledge scores. But a study conducted in USA by Carithers (2011) revealed that there was no significant association between physicians' perceptions on the prevalence of DDIs and their DDI knowledge. Physicians who assumed that there are many DDIs to keep up with may pay more attention to DDIs and be more likely to stick to DDI information sources and thereby acquired more knowledge than those who are indifferent.

This study found that there was significant association between DDI information sources and prescribers' DDI knowledge level. This is in contrast with the study by Carithers (2011). The current study revealed that compared with those prescribers who used other sources, prescribers who used drug reference books as their usual DDI information source had a lower mean DDI information source usefulness score. Other information sources such as up to date and smart phone applications provide DDI information that is up to date and also these information sources are easy to use and portable than drug reference books. Therefore, those physicians who relied on these information sources can seek DDI information at any time. Thus, they can update themselves with relevant and up to date information. This implies that they are closer for information than those who were using drug reference books.

This study documented that there was no statically significant association between physicians' DDI knowledge and experiencing DDIs that caused adverse outcomes and the extent to which the risk of potential DDI affected physicians' selection of a drug product for prescription. This is in contrast with the study by Ko *et al., (2008)*. They found that physicians who felt that the risk of potential DDI affected their selection of a drug product ''very much'' had better DDI knowledge than those who reported that the risk affected the selection ''a little'' or ''not at all''. These discrepancies might be due to differences in sample size and study area.

A one way ANOVA performed to see the effect of socio demographic profiles on DDI information source usefulness score revealed that only years of professional experience had effect on DDI information usefulness score. Post hoc procedures with Scheffe test showed physicians who had more than 20 years of professional experience had better perceptions on the usefulness of DDI information sources than those who worked for 10 to 20 years. Physicians who prescribed for many years might come across many adverse drug events that are caused by DDIs and therefore they became aware of such risks and pay attention for the importance of such aids used to identify potential DDIs.

The extent to which the risk of a DDI affects drug selection for prescription had significant effect on DDI information source usefulness score. Compared with the physicians whose drug selection was “a little” or “somewhat” affected by a risk of a drug interaction, those whose selection was “very much” affected scored higher to the five statements that assessed the usefulness of the information. Physicians who paid attention for the risk of DDIs might have relied up on information sources during their day to day activities. Therefore, they had better understanding towards the importance of DDI information sources.

8 Limitations

Since physicians in government hospitals were too busy, it was hard to reach them through neither simple random sampling nor systematic random sampling procedures. Therefore, convenient sampling was used to recruit participants from government hospitals. This might affect the representativeness of the sample drawn from governmental hospitals.

Because of time constraints in some hospitals with high patient flow, respondents were allowed to complete the questionnaire and return it later. In such cases questionnaire completion was not in front of the data collector, therefore the respondents may have used references which might increased the DDI knowledge scores.

Because the questionnaire was focusing on knowledge, consequently, most recipients chose not to participate in this study. Therefore, the low response rate might affect generalizability of the result.

As is obvious most of the hospitals in Ethiopia have high patient flow and respondents were requested to complete the questionnaire during work or times of distractions. Therefore, they may be reluctant to attentively complete the questionnaire.

This study is the first of its kind in Ethiopia. Therefore, unavailability of similar published studies in Ethiopia made the discussion less comprehensive.

9 Conclusions

The DDI knowledge assessment questionnaire used in this study demonstrated good reliability and validity. Though this study revealed that physicians had generally poor DDI knowledge, better DDI knowledge level was associated with having specialization in internal medicine and pediatrics. Physicians who perceived the risk of DDIs is high had better DDI knowledge. Better DDI knowledge was also associated with using other DDI information sources. Physicians who relied on other DDI information sources had better DDI knowledge than those who were using drug reference books.

Over all, physicians in general hospitals of Addis Ababa had unsatisfactory perceptions towards the importance of DDI information sources. Physicians who worked for less than 20 years, physicians whose drug selection was a little affected by the risk of DDIs, physicians who believe that learning about DDIs is not important and those physicians who refused to consider DDIs as part of prescribing decisions had poor DDI information source usefulness score.

10 Recommendations

Based on the findings of this study the following recommendations are forwarded:

For physicians

- Physicians should update their DDI knowledge through continuing education and should improve their familiarity with information sources such as smart phone applications, Compendia of drug products (such as AHFS Drug Information, Martindale, and Physician's Desk Reference) that assist in identifying potential DDIs.

For Addis Ababa regional health bureau

- The health bureau should prepare on job trainings such as workshops and seminars and continuing education programs especially for specialists other than internists and pediatricians so as to increase their awareness of the importance of DDIs information sources and encourage them to pay close attention to potential interactions when prescribing and to promote safe prescribing habits.
- All of the respondents in this study reported that they were not being informed about their patients' exposure to potential DDIs by pharmacists. Therefore, efforts have to be made to promote team work to prevent the prescription drugs that can cause harm full DDIs.
- The health bureau also should provide resources to governmental hospitals such as ICT infrastructure like online internet resources to encourage physicians' information seeking habit.

For Researchers

- Further research on Physicians with large sample size should be conducted.
- Further study on other prescribers such as health officers and nurses and comparative study: physicians Vs other provider types are recommended.

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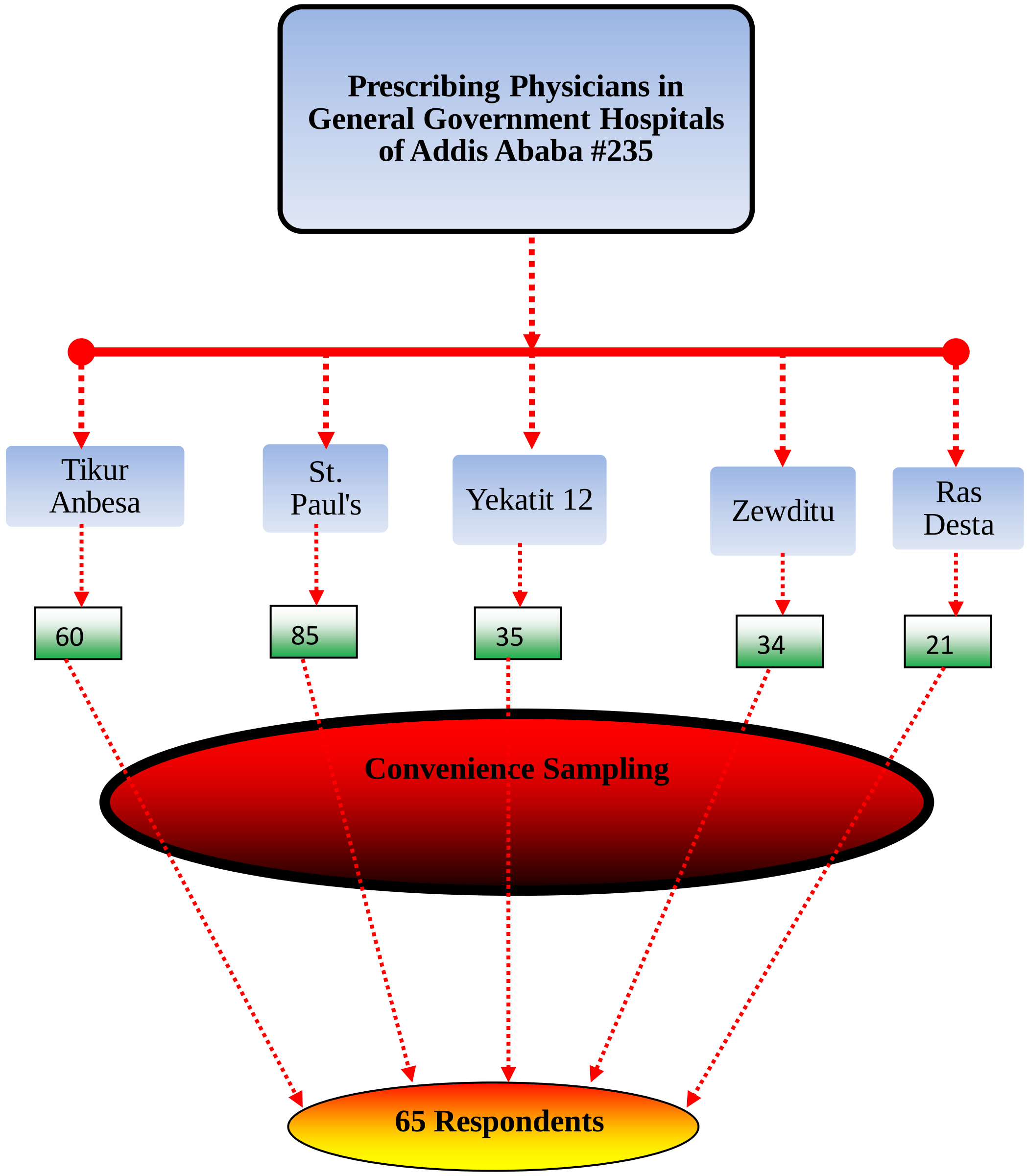
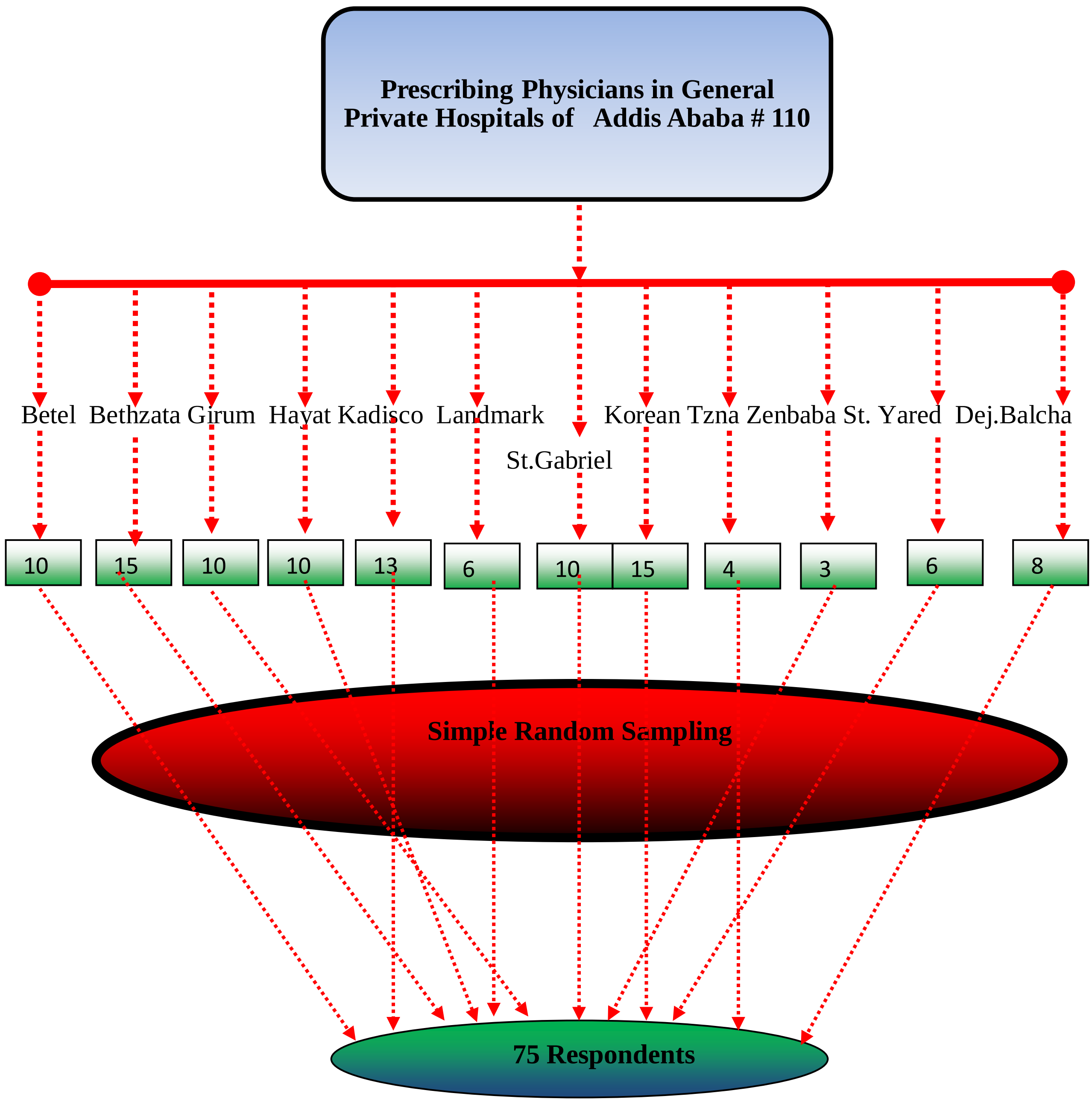
Annex I Schematic representation of sampling procedure in governmental hospitals, 2013. (N=235)



Annex II Schematic representation of sampling procedure in private hospitals, 2013. (N=110)



Annex III Consent Form

Hello, my name is Getachew Moges. I am a post graduate student at Addis Ababa University School of Pharmacy. Currently I am conducting a research as required for my Masters Degree of Pharmacy. The focus of the research is to investigate determinants of physicians' drug-drug interaction knowledge in general service hospitals in Addis Ababa. To attain this purpose, your knowledge and insights would be very valuable and I will be very grateful if you can assist me by completing this questionnaire.

The information you provide is confidential and at no time will you be required to identify yourself by name. Data will be analyzed in aggregate. If you have any question, don't hesitate to ask the data collector. The information you give is very important and therefore kindly be frank in your responses. You have the right to turn down if you are not voluntary to participate.

Do you agree to participate? ☐ Yes ☐ No

Sig. ____________________

Thank you very much for your time

The principal investigator

Address: mob. + 251 91 24 42 643

E-mail- getachewmoges@yahoo.com

Annex IV Questionnaire

Part I. Socio demographic characteristics of respondents

Direction: Please encircle the appropriate choice of each statement which corresponds most closely to your desired response.

1. Gender 1. M 2. F

2. Age ________years

3. What is the highest education level you completed?

   1. General practitioner 2. Specialization

4. At which setting are you currently practicing as a prescriber?

   1. Governmental hospital 2. Private hospital 3. At both

5. At which of the following area are you currently practicing?

   1. At a specialty area 2. At general practice

6. If you are working at specialty area, at which medical department are you currently working as a prescriber?

   1. Obstetrics and gynecology 2. Internal medicine other than cardiology

   3. Cardiology 4. Pediatrics

   5. Emergency medicine 6. Other [please specify] _________________

7. Have you received training on drug-drug interactions other than your formal medical education?

   1. Yes 2. No

8. If your answer to question **no. 7** is **Yes**, what type of training have you attended?

   1. Workshops, seminars 2. Continuing education

   3. Other [please specify] ____

9. For how many years have you practiced as a licensed prescriber? __________

10. How many patients, on average do you see per day?

    1. Less than 15 2. 15-20 3. 21-30 4. More than30

11. How many hours, on average do you spend in your hospital per week?

    1. Less than 20 2. 20-30 3. 31 -40 4. 41-50 5. More than 50

12. How many prescriptions, on average do you write daily?

    1. Less than 10 2. 10-20 3. 21 -30 4. More than 30

13. Are you familiar with the Ethiopian standard treatment guideline for hospitals?

    1. Yes 2. No

14. If **Yes**, to what extent are you familiar with the Ethiopian standard treatment guideline for hospitals?

    1. Little familiar 2. Somewhat familiar 3. Familiar 4. Very familiar

15. Which of the following factor/s highly influence/s your decisions when prescribing a new drug? (Choose either one or more responses that apply)

    1. Safety /including drug interactions 2. Efficacy/effectiveness of the drug

    3. Cost of the drug 4. Patient requests for the drug

    5. Colleagues and/or specialists through referral and recommendations

16. Does the risk for a drug interaction affect your selection of a drug product?

    1. Yes 2. No

17. If **Yes**, to what extent does the risk for a drug interaction affect your selection of a drug product?

    1. A little 2. Somewhat 3. Very Much

Part II. Assessment of Physicians' History of Encountering Drug-drug Interactions

Directions: Please encircle the appropriate choice of each statement which corresponds most closely to your desired response.

1. Have you ever come across a patient who had a drug-drug interaction that caused adverse outcomes?

   1. Yes 2. No

2. If **Yes**, which of the following adverse outcomes had you observed?

   1. Intoxication/ over dosage
   2. Bleeding
   3. Hypotension
   4. Therapeutic failure

2. If your answer to question **no. 1** is **Yes**, how often did you encounter?

   1. Once 2. Twice 3. Three time 4. Several times

3. Which one occurs more often, interaction caused by drugs prescribed by two different prescribers or same prescriber?

   1. by same prescriber 2. by two different prescribers

Part III. Assessment of Physicians' Perception on Drug Safety and Drug-drug Interactions

Directions: Please indicate level of your agreement to each statement presented below on a four point scale where Disagree =1, Somewhat disagree =2, Somewhat agree =3 and Agree =4. (Mark "√" on the number which shows level of your agreement)

1. The risk of drug-drug interactions is high.	1	2	3	4
2. It is important for prescribers to learn about drug- drug interactions.	1	2	3	4
3. It is the responsibility of the pharmacist to catch drug- drug interactions.	1	2	3	4
4. I am likely to consider drug- drug interactions as part of prescribing decisions.	1	2	3	4

Part IV. Assessment of Physicians' Drug- Drug Interactions Knowledge

Directions: **Following is a list of 15 drug pairs which are commonly encounterd in community and hospital pharmacies. Please mark "√" on the choice that reflects how you feel about the interaction of each pair of drugs where 1= Contra indicated, 2= Could be used under monitoring, 3= No interaction, and 4= Not Sure.**

Drug Pair	**1**	**2**	**3**	**4**
1. Acetaminophen with codeine + amoxicillin				
2. Carbamazepine + clarithromycin				
3. Digoxin + verapamil				
4. Digoxin + clarithromycin				
5. Digoxin + sildenafil				
6. Metformin + erythromycin				
7. Nitroglycerin + sildenafil				
8. Simvastatin + itraconazole				
9. Warfarin + cimetidine				
10. Atenolol + ranitidine				
11. Carbamazepine + cimetidine				
12. Warfarin + fluconazole				
13. Allopurinol + Pyrazinamide				
14. Praziquantel + Rifampicin				
15. warfarin + co trimoxazole				

Part IV. Assessment of Physicians' Information Sources on Drug-Drug Interactions

1. What is your method of being informed that a patient is about to be exposed to a potential drug interaction (choose either one or more responses that apply)

1. Pharmacists 2. Non pharmacist clinicians 3. Medication package inserts

4. Drug reference books 5. Others [please specify] ___________________

Directions: Please rate the usefulness of your usual drug-drug interaction information sources on a five-point scale where Never = 1 , Infrequently =2, Sometimes =3, Frequently =4 and Always =5					
2. How often does the drug interaction information change your initial prescribing decisions?	1	2	3	4	5
3. How often is the drug interaction information new to you?	1	2	3	4	5
4. How often is the drug interaction information relevant to the patient?	1	2	3	4	5
5. Is the drug interaction information sufficient for you to manage the interaction?	1	2	3	4	5
6. How often is the drug interaction information useful to you in your future prescribing?	1	2	3	4	5

Thank you very much!

Annex V Ethical clearance

ADDIS ABABA UNIVERSITY
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School of Pharmacy
Dean's Office

ቀን Date: 11 January 2013
ቁጥር Ref. No.: IRB/SOP/02/05/2013

Msc Student Getachew Moges,
Department of Pharmaceutics and Social Pharmacy,
School of Pharmacy

Re: **Assessment on Determinats of Drug-Drug Interaction knowledge of Physicians in General Service Hospitals in Addis Ababa, Ethiopia**

It is to be recalled that you submitted the aforementioned project for Ethical approval by the School's Ethical Review Board. The Board thoroughly reviewed the project based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines.

It is therefore, to inform you that the project is ethically approved for implementation.

With regards

Fitsum Feleke (PhD)
Chairman, IRB, SOP.

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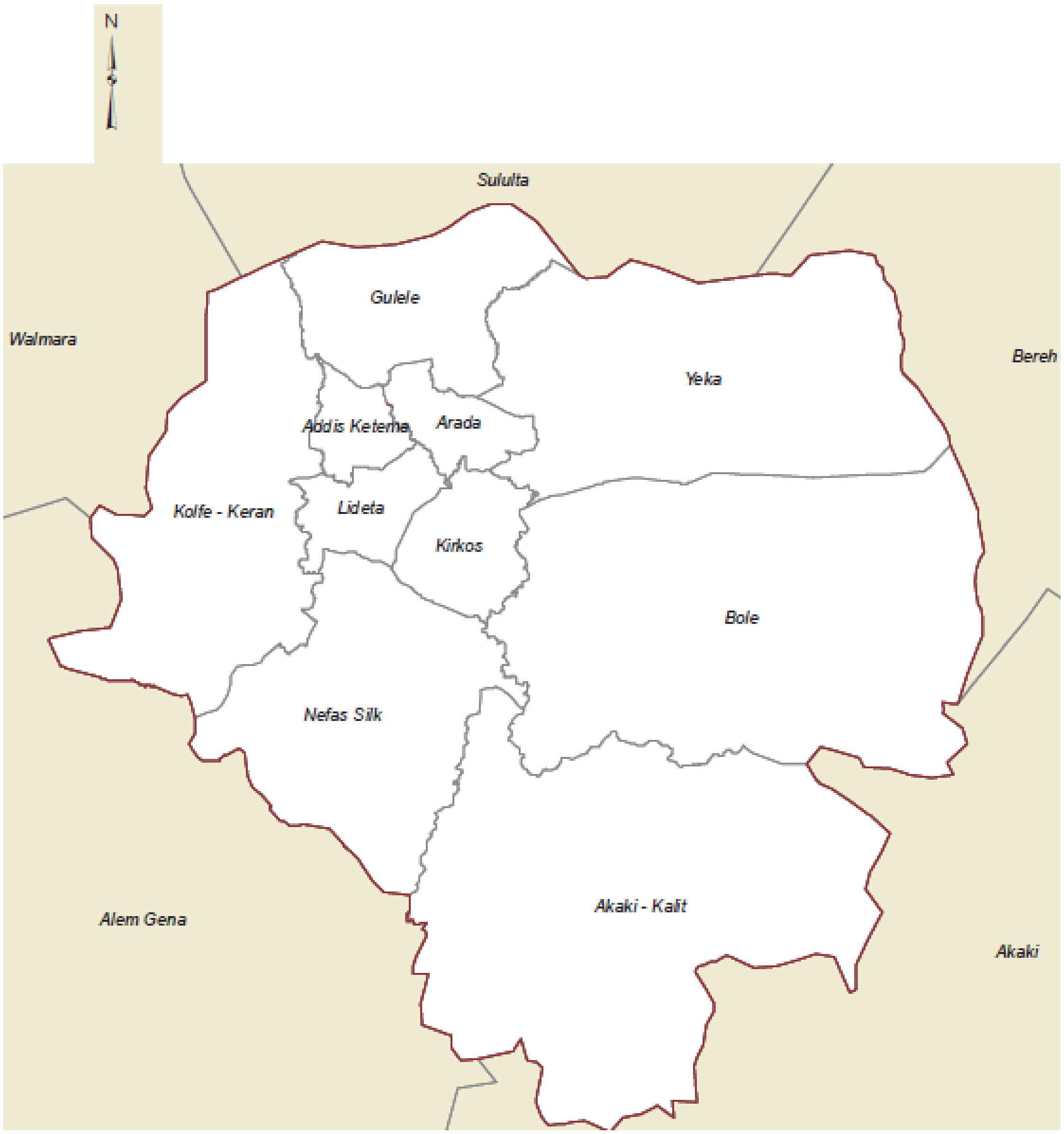
Annex VI Map of Addis Ababa city



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