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Evaluation of Pharmacy Professionals' Knowledge, Attitude and Practice towards Potential Drug-Drug Interactions: A Cross-Sectional Study

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ABSTRACT

Background: The use of multiple medications the increased risk of Potential Drug-Drug Interactions (PDDIs) and the prevalence of PDDIs in the world is high, and this is a consequence of the complex Adverse Drug Effects (ADEs). This work assessed pharmacy professionals' ability to recognize clinically significant Potential Drug-Drug interactions (PDDIs) as well as the information sources they use.

Methods: A cross-sectional study was conducted among pharmacy professionals in Ethiopia. A self-administered survey was created to assess pharmacists' familiarity with PDDIs and their preferred sources of PDDI information. We employed 16 drug pairs to assess pharmacists' awareness of drug-drug interactions. The regression model was run to look at potential PDDI knowledge predictors.

Results: From 183 pharmacy professionals, practical questionnaires were collected. Allopurinol and pyrazinamide received a correctly classified range of 19.7%, whereas acetaminophen/codeine and amoxicillin received a correctly classified range of 66.01% from pharmacy professionals. Only four of the 16 medication pairings evaluated were accurately categorized by more than 50% of the pharmacy professionals. Internet or applications for mobile devices were the most frequently utilized sources by respondents (n=66, 36.1%) to check PDDI data. Years of work experience and education level regarding PDDIs were found to be the most significant indicators of a higher number of recognized drug pairs in the multiple regression analysis.

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Conclusion: The results of our research showed that pharmacists are lacking in knowledge and practice towards PDDIs and years of experience and working institutions of participants had strongly associated with pharmacist professionals' knowledge of PDDIs.

Keywords: Drug-drug interactions; Knowledge; Medication; Pharmacy professionals

INTRODUCTION

The use of multiple medications in recent years is extensive throughout the world [1]. However, multiple medications are commonly associated with the increased risk of Potential Drug-Drug Interactions (PDDIs) [2,3]. The prevalence of PDDIs in the world is high, and this is a consequence of the complex Adverse Drug Effects (ADEs) [4-9]. The therapeutic effects of a drug that is influenced by Adverse Drug Reactions (ADEs) may be reduced or increased, drug toxicity may be increased, and treatment outcomes and adherence may be indirectly harmed [10,11]. ADEs also the cause of the increment of patient hospitalization and therapeutic cost, and reduction in the efficacy of concomitant drugs which in turn compromise the quality of life of the patients and even death [12,13]. A prevalence of 74.41% was found for clinically significant PDDIs and up to 2.8% of hospital admissions are caused by ADEs related to PDDIs, this may result in negative consequences such as diminished effectiveness, an increase in adverse responses, and even death [14].

PDDIs are often avoidable if adequate emphasis is given and early noticed by the Health Care Professionals (HCPs) [15-17]. Healthcare professionals must identify potentially interfering drug pairs in order to lower the risk of PDDIs and the accompanying drug-related morbidity and mortality [18]. Numerous studies assessed the expertise of healthcare professionals as a deficiency in their capacity to recognize suspected PDDIs [7,19]. In order to prevent dispensing combination medications that could cause major PDDIs, pharmacy staffs are responsible for restricting the use of dangerous prescription regimens [20].

Pharmacy experts play a significant role in the safe and effective use of medications, and patients frequently turn to them as the first healthcare provider when they need help. They are responsible for patient counseling in addition to distributing medications and reviewing prescriptions. Therefore, understanding PDDIs is crucial for pharmacy staff in order to provide correct patient education, prevent serious side effects, and increase treatment effectiveness [7].

Pharmacy professionals regularly need to consult information sources introducing new medications to the market and existing drugs when dispensing. One study conducted in Sudan found that 72.8% of pharmacy professionals use a handbook or software program as an information source to check drug interaction. Another study at Addis Ababa University found that pharmaceutical package inserts and drug reference books were the most popular sources of information for physicians [11].

Assessing the need for and potential impact of dispensing assistance systems in lowering PDDIs could be done by testing the capacity of pharmacy workers to identify PDDIs without the aid of pharmacological references. As a result, this study sought to evaluate the extent to which pharmacy professionals can recognize PDDIs and the information sources they used to raise their level of understanding of PDDIs.

MATERIALS AND METHODS

Study Area, Design and Period

A cross-sectional study design was conducted among pharmacy professionals in public hospitals, private pharmacies, and drug stores in Gondar city. Gondar city is 727 km away from Addis Ababa, capital city of Ethiopia. The fourth-largest city in Ethiopia is known as Gondar. Based on forecasts, the city had 358,257 residents overall in 2017. There is just a single government referral hospital within the city (48 male and 36 female pharmacy professionals were working in 2022) affiliated to one of the main health science colleges in the country, 2 private hospitals, 8 governmental health centers (have 8-degree pharmacy professionals and 12 diploma pharmacy professionals), 54 pharmacies, and 42 drug stores. According to data from the Gondar city health office, 296 pharmacy professionals will be employed in the city's public and private healthcare facilities in 2022. Out of these, 192 of them was employed by private healthcare facilities. The majority of pharmacies and drug stores employ two pharmacy professionals full-time. The study had been carried out between July and September in 2022.

Sampling and Sampling Technique

The study participants for this study were all pharmacy professionals working in government health institutions and private pharmacies in Gondar city who were at least diploma holders in pharmacy education, present during the time of the data collection period and willing to participate in the study were included as study respondents. Pharmacy professionals who were not present during the time of data collection and did not voluntarily participate in the study were excluded from the study.

Study Tools and Data Managements

The questionnaire was created after evaluating prior literature, standard treatment guidelines for Ethiopian hospitals, essential prescription lists for Ethiopia and articles. The questionnaire was divided into five sections: Section 1 dealt with soco-demographic information of the pharmacy

professional, such as age, gender, and level of education, working institution, and the number of years in service. Section 2 consisted of questions regarding pharmacy professionals' history of encountering drug interactions and workload. In this section, there are six questions regarding pharmacy professionals' history of encountering drug interactions and workload. The assessment of the knowledge of life-threatening PDDIs of particular medication pairings among pharmacy professionals was done in section 3. There were sixteen locally accessible and frequently prescribed drug-drug pairings in this segment. By sending the medicine lists to hospitals and neighborhood pharmacies, it was possible to determine whether the medications were readily available locally and whether they were regularly prescribed or not. The Drug-Reax® System, interactive drug interaction software created by Thomson Micromedex drug interactions (Thomson Reuters Healthcare Inc., Greenwood Village, CO, USA), was then used to identify PDDIs from the US database. Sixteen drug combinations were tested, and seven of them are contraindicated; five could be administered with supervision; and four had no known interactions. Respondents were tasked with categorizing each drug combination into one of four categories without the use of any references: a) Contraindicated; b) May be used together with monitoring; c) No interaction; and d) Not sure. In order to avoid speculation, the "not sure" option was included. Using the top bloom's cut-off points, knowledge levels were classified. Section 4 consisted of questions regarding attitude of pharmacy professionals towards life-threatening DDIs and the final section included practice related questions of towards life-threatening DDIs. The questionnaire was shown as supplemental material.

To assure the questionnaire quality, was pretested, and self-administered on pharmacy staff members who weren't included in the study. This was done to see if the questions could be understood and answered. Since the instrument could be understood and answered using the pretest, no modifications were made. Throughout the data management, storage, and analysis processes, the consistency and completeness of each filled questionnaire was checked.

Data Collection

The surveys were collected by four pharmacy graduate students. A returned questionnaire was considered valid if all drug-related questions were addressed, at least 8 of the 16 questions on the common PDDI knowledge test were addressed, the question asking about the pharmacist professionals' typical source of PDDI information was addressed, and four out of the five questions evaluating the usefulness of the information source were addressed. Only the usable questionnaires were used in the analyses. The questionnaire was excluded from the analysis if the respondents submitted the same answers for all the PDDIs questions.

Statistical Analysis

The collected data were analyzed by using the Statistical Package for Social Sciences (SPSS), version 27.0 (SPSS, Chicago, IL, USA), following the respondents' responses. Means, frequency distributions, and descriptive statistics were used, respectively, to describe categorical and continuous variables. The presence and degree of an association between pharmacy professionals' PDDI knowledge and each independent variable were evaluated using bivariate logistic regression analysis. Following that, a multivariate logistic regression model was employed to account for any potential confounding factors. First, we performed bi-variable binary logistic regression to identify candidate variables for the final analysis using p-value<0.2 as a cut-off point. Then, multivariable logistic regression was carried out to decide statistically significant variables of pharmacy professionals' PDDI knowledge at p-value<0.05.

Selection of Studies

This review considered all the peer-reviewed articles that described and discussed the addictive abuse of tropicamide drug and other anticholinergic medications, and the titles, abstracts and full-text of all such papers were scrutinized for possible inclusion. The articles that discussed the impact of tropicamide misuse on public health and within the ophthalmology community were also explored. The articles not satisfying the present study inclusion criteria like conference abstracts, dissertations, or other non-peer-reviewed sources were ignored for inclusion in present study.

Measuring Technique

Knowledge: Each knowledge related question were categorized into one of four categories without the use of any references: Coded as “contraindicated” 1, “may be used together with monitoring” was assigned 2, “no interaction” was assigned 3 and “not sure” was assigned 4 and then recoded as” correct answer “1 the rest “in correct “ 2. Then level of knowledge categorized as poor and good based on Blooms cut point after sum up each respondents response. Those who scored between 80 and 100% (12 to 14 points) were considered to have "good knowledge", while those who scored between 60 and 79% (9 to 11 points) fell into the category of “moderate knowledge". On the other hand, pharmacists who scored below 60% (0 to 8 points) were labelled as having "poor knowledge" but moderate knowledge merge in to good knowledge level for sake of regression.

Attitude-related questions, the responses were grouped into five categories. The answer of “strongly agree" was assigned 1 “agree” was assigned a score of 2, while the answer of “neutral” was assigned a score of 3, and the answers of “disagree” was assigned a score of 4 and “strongly disagree” was assigned a score of 5. Compute the mean of each attitude related questions and grand mean. Then, categorization was performed based on grand mean score.

Those who scored above the grand mean were considered to have "positive attitude", while those who scored below the grand mean level were considers as having "negative attitude".

Practice-related questions, the responses were grouped into two categories. The answer of frequency “yes” was assigned a score of 1, while the answer of frequency “no” was assigned a score of 0. Then, categorization based on Bloom’s cut off point was performed. Those who scored between 80 and 100% (6 to 7 points) were considered to have "good practice", while those who scored between 60 and 79% (5 to 6 points) fell into the category of "moderate practice", while scoring below 60% (0 to 4 points) were labelled as having "poor practice".

RESULTS

Socio-demographic Characteristics of Respondents

106 questionnaires out of a total of 289 were eliminated as ineligible due to predetermined criteria, whereas 183 questionnaires with a response rate of 63.3% were finished and included in the study. 98 (53.6%) of the responders were men, while 85 (46.4%) of the responders were female. The respondents' ages ranged from 22 to 61 years, with an average age of 31.96 ± 7.22 (mean ± SD). Of those, 85 (46.4%) reported being under 30, 74 (40.4%) between 30 and 40, and 24 (13.1%) above 40. The majority of respondents, 98 (53.6%) worked in the public sector, and 103 (56.3%) had Bachelor's degrees (B. Pharm) and above as their most recent professional degrees. Less than a quarter of pharmacy professionals 40 (21.9%) had over 10 years of work experience, and the majority of respondents 96 (52.5%) had less than five years (**Table 1**).

Table 1: Participant’s demographic characteristics (n=183).

Variables	Categories	Frequency	Percent
Sex	Male	98	53.6
	Female	85	46.4
Age	<30 years	85	46.4
	30-40 years	74	40.4
	>40 years	24	13.1
Education level	Diploma	80	43.7
	Degree and above	103	56.3
Work experience	<5 years	96	52.5
	6-10 years	47	25.7
	>10 years	40	21.9
Working institution	Public	98	53.6
	Private	56	30.6
	Mixed	29	15.8

Knowledge of Pharmacy Professionals towards PDDIs

The average percentages of respondents who correctly identified the 16 drug pairs ranged from 19.7% for the drug combination allopurinol and pyrazinamide (no interaction) to 66.01% for the drug combination acetaminophen/codeine and amoxicillin (no interaction). Only four of the 16 medication pairs studied had classifications that were accurate by more than 50% of pharmacy professionals.

In the knowledge test, four of the seven drug combinations that were deemed contraindicated were properly identified by less than half of the participants. According to the responses of the participants, many pharmacists may fail to recognize some potentially dangerous drug interactions. Nearly 65.6% of the respondents were incorrectly classified for the seven drug combinations that are regarded as being in contradiction. Less than one-third of respondents correctly identified the four drug combinations that interact and require careful monitoring: Warfarin and cotrimoxazole 76 (26.3%), theophylline and ciprofloxacin 60 (20.8%), carbamazepine and cimetidine 70 (24.2%), and warfarin and itraconazole 64 (22.1%). The highest unsure answer was for PDDIs between Simvastatin and itraconazole (22.8), followed by Simvastatin and Clarithromycin (22.5%), and Warfarin and itraconazole (22.1%). In summarized pharmacy professionals had low level of knowledge (11.5%) towards PDDIs as shown **Table 2** and **Figure 1**.

Table 2: Knowledge of PDDIs of responses classification (in percentages) (n=183).

Drug pairs	Should not be used together (contraindicated)	May be used together with monitoring	No interaction	Not sure
Acetaminophen/codeine and amoxicillin	24 (13.1%)	30 (16.4 %)	**121 (66.1%)**	8 (4.4%)
Warfarin and cotrimoxazole	71 (38.8%)	**50 (27.3%)**	47 (25.7%)	15 (8.2%)
Warfarin and digoxin	63 (34.4%)	41 (22.4%)	**58 (31.7%)**	21 (11.5%)
Methotrexate and cotrimoxazole	**83 (45.4%)**	46 (25.1%)	29 (15.8%)	25 (13.7%)
Digoxin and sildenafil	86 (47%)	33 (18.0%)	**41 (22.4%)**	23 (12.6%)
Simvastatin and itraconazole	**98 (53.6%)**	30 (16.4%)	13 (7.1%)	42 (23.0%)
Nitroglycerin and sildenafil	**99 (54.1%)**	32 (17.2%)	23 (12.6%)	29 (15.8%)
Theophylline and ciprofloxacin	77 (42.1%)	**36 (19.7%)**	38 (20.8%)	32 (17.5%)
Carbamazepine and cimetidine	81 (44.3%)	**48 (26.2%)**	35 (19.1%)	19 (10.4%)
Clopidogrel and Erythromycin	**63 (34.4%)**	45 (24.6%)	43 (23.5%)	32 (17.5%)
Simvastatin and Clarithromycin	**78 (42.8%)**	23 (13.7%)	38 (20.8%)	38 (20.8%)
Allopurinol and Pyrazinamide	80 (43.7%)	28 (15.3%)	**36 (19.7%)**	39 (21.3%)
Praziquantel and Rifampicin	**85 (46.4%)**	39 (21.3%)	35 (19.1%)	24 (13.1%)
Warfarin and cimetidine	**98 (53.6%)**	41(22.4%)	14 (7.7%)	30 (16.4%)
Warfarin and itraconazole	79 (43.2%)	**42 (23.0%)**	21 (11.5%)	41 (22.4%)
Metformin and erythromycin	46 (25.1%)	41 (22.4%)	**65 (35.5%)**	31 (16.9%)

Note: Percentages in bold type represent correct answers.

Generic names were spelled according to US conventions and US brand names were included on the survey instrument.

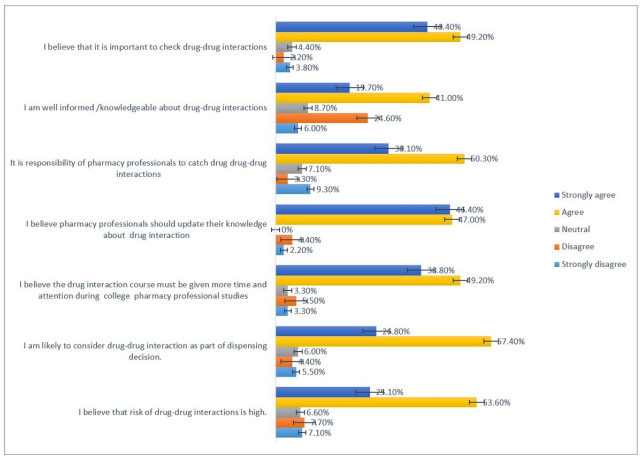

Figure 1: Attitude of pharmacy professionals towards PDDIs (n=183).

Attitude of Pharmacy Professionals towards PDDIs

The attitude towards potential DDIs is summarized in **Figure 1**. Majority of the respondents reported that they were responds as agreed on each attitude questions, I am likely to consider drug-drug interaction as part of dispensing decision (57.4%), I believe that risk of drug-drug interactions is high (53.6%), it is responsibility of pharmacy professionals to catch drug-drug interactions (50.3%), I believe that it is important to check drug-drug interactions (49.2%), and strongly agree were the second majority response reported by respondents' and the lest response were strongly disagreed, disagree and neutral for all questions.

Practice of Pharmacy Professionals towards PDDIs

As shown in **Table 3** is the summarization of the practice of pharmacy professionals related to PDDIs. In term of practice related to questions of PDDIs, majority of the respondents; before dispensing any drug, do not consider its potential interactions 158 (86.3%) and not usually asking patients about the drug, OTC drug, food supplements/herbal medications he/she is using or intended to use 150 (82.0%). Respondents response not counseling patient about the suspected drug interactions is a regular process in my department 124 (67.8 %), not contact doctors when there is a drug-interaction in their prescriptions 119 (65.0%), not documentation of reported drug interactions is a regular procedure in my department 117 (63.9%), and not screening patient's drug interactions are performed regularly in my department 100 (54.6%) and assessment of drug interactions before prescribing or dispensing medications is a regular procedure in my department 84 (45.9%). In general, all of the respondents had low level of practice 120 (65.4%) towards PDDIs as summarized at **Figure 2**.

Table 3: Practice of pharmacy professionals towards PDDIs (n=183).

Variable	Practice items	
	Yes (%)	No (%)
Q1=Before dispensing any drug, do you consider its potential interactions	25 (13.7)	158 (86.3)
Q2=Do you usually ask your patients about the drug, OTC drug, food supplements/ herbal medications he/she is using or intended to use	33 (61.7)	150 (82.0)
Q3=Do you usually contact doctors when there is a drug-interaction in their prescriptions	64 (35.0)	119 (65.0)
Q4=Screening patient's drug interactions are performed regularly in my department	83 (45.4)	100 (54.6)
Q5=Assessment of drug interactions before prescribing or dispensing medications is a regular procedure in my department	84 (45.9)	99 (54.1)
Q6=Ocumentation of reported drug interactions is a regular procedure in my department	66 (36.1)	117 (63.9)
Q7=Patient counseling about the suspected drug interactions is a regular process in my department	59 (32.2)	124 (67.8)

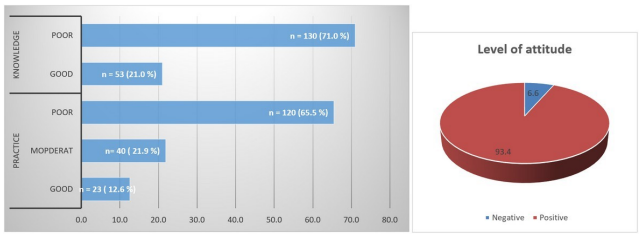

Figure 2: Summarized level of knowledge, practice and attitude of pharmacy professionals towards PDDIs (n=183).

Factors Associated with Pharmacy Professionals' PDDIs Knowledge

Age, educational level, years of experience, working institutions of participants, the average number of hours spent in work/week, and have you ever come across cases of drug-interaction during your practice were candidate variables for multivariable logistic regression (p-value<0.2). A multivariate regression analysis was also performed to identify independent predictors of PDDI knowledge of pharmacy professionals. According to the results of the multivariate analysis, years of experience (AOR=1.937; 95% CI: 0.025–0.562), working institutions of participants (AOR=0.028; 95% CI: 0.001–0.858), the average number of hours spent in work/ week (AOR=0.092; 95% CI: 0.015–0.580), and have you ever come across cases of drug-interaction during your practice (AOR=0.165; 95% CI: 0.049–0.561) were significantly associated with PDDIs (**Table 4**).

Table 4: Predictors of the knowledge level for PDDIs (n=183).

Variables	Categories	Good n (%) (95%CI)	Poor n (%)	COR (95%CI)		AOR
Age group	30 yrs	9 (10.6)	76 (89.4)	1	1	
	30-40 yrs	5 (6.8)	69 (93.2)	3.477 (1.136,10.646)*	2.905 (0.528,15.977)	0.986
	>40 yrs	7 (29.2%)	17 (70.8)	5.682 (1.605,20.121)*	1.242 (0.226,6.812)	0.746
Educational level	Diploma	5 (6.2)	75 (93.8)	1	1	0.012[a]
	Degree and above	16 (15.5)	87 (84.5)	0.269 (0.069,0.0770)*	0.272 (0.071,1.049)	
Work experience in years	<5 yrs	7 (6.7)	98 (93.3)	1	1	
	6-10 yrs	5 (12.2)	36 (87.8)	4.5 (1.538,13.163)*	1.937 (0.025,0.562)*	0.617
	>10 yrs	9 (24.3)	28 (75.7)	2.314 (0.697,7.681)	2.687 (0.056,1.288)	0.569
Working institutions of participants	Public	6(6.1)	92 (93.9)	1	1	
	Private	12 (21.4)	44 (78.6)	0.239 (0.084,0.679)*	0.028 (0.001,0.858)*	0.041[a]
	Mixed	3 (10.3)	26 (89.7)	0.565 (0.132,2.416)	0.144 (0.006,3.262)	0.224
The average number of hours spent in work/ week	<48	8 (12.3)	57 (87.7)	1	1	
	48-64	2 (2.7)	72 (97.3)	5.053 (1.032,24.727)*	0.554 (0.134,2.295)	0.074
	>64	11 (25.0)	33 (75.0)	0.421 (0.154,1.152)	0.092 (0.015,0.580)*	0.017[a]
Have you ever come across cases of drug-	Yes	10 (6.8)	138 (93.2)	1	1	

interaction during your practice?						
	No	11 (31.4)	24 (68.6)	6.325 (2.422,16.516)*	0.165 (0.049, 0.561)*	0.041[a]

Note: P-value <0.02 for COR, P<0.05 for AOR

DISCUSSION

This study aimed to demonstrate pharmacy professionals' knowledge, attitude, and practice on PDDI, and their associated factors about PDDIs in Gondar City. Adverse Drug Responses (ADRs) are brought by PDDIs, which increased the chance of hospitalization and pushed up medical expenses. Thus, pharmacy professionals who have better knowledge, attitude, and practice towards PDDI are crucial to reducing the ADR outcomes of PDDI-related morbidity and healthcare costs. However, pharmacy professionals in the present study had low scores on the knowledge and practice towards PDDI questions with an average of 21.0 % and 12.6 %, respectively as summarized **Figure 1**.

According to participant responds as shown **Table 2**, many pharmacists may miss some potentially drug–drug interactions. Nearly 81.3% of the respondents were incorrectly categorized for the seven drug combinations that are thought to be contradicted. A significant portion of respondents (43.7%) chose "contradicted" rather than "no contradicted," it might help to explain why no contradicted drug combinations are not fully discovered. The usage of these pharmaceuticals requires continual monitoring. However, up to 21.3% of pharmacists were unaware of these potential PDD. About 29.0% with 95% CI (23.0%, 36.1%) of respondents reported knowledge while 44.3% with 95% CI (37.2%, 51.4%) reported practice and 93.4% with 95% CI (89.6%, 96.7%) reported attitude towards PDDIs. In general, the present study's findings show that pharmacy professionals' had poor knowledge towards PDDIs. This is in line with the finding by Tokka, et al. in Sudan and Albalawi, et al. in Saudi Arabia [11]. For each practice related question respondents' had poor practice towards PDDIs. Pharmacy professionals' had high attitude level 93.4% as shown **Figure 2** towards PDDIs. This finding is in line with the finding reported by Albalawi, et al.

Based on logistic regression analysis (**Table 4**) confirmed that work experience, and have you ever come across cases of drug-interaction during your practice were strongly associated with pharmacist professionals' knowledge of PDDIs. Based on the current study, pharmacy professionals' with 11-15 years of working experiences had the highest level of knowledge, followed by 6-10 years and 0-5 years. This study supported by the finding of Mahmoud Saeed Abdo, et al., in Malaysia. Being working in private institutions and the average number of hours spent in work/week (workload) regarding PDDIs were the common risk factor for PDDIs. The other predictor of PDDI knowledge identified in this study was have you ever come across cases of drug-interaction during your practice had better DDI knowledge than those who did not. This is in line with the finding by Tokka, et al.

For our knowledge, this study was the first finding done in Ethiopia on pharmacist professionals' towards PDDIs. There are several limitations of our study. Some of the limitations of this study include; first, the response rate of respondents was low in our analysis. Thus, the study results are limited to generalizability to all Ethiopian pharmacists. The second limitation of this study is the large number of PDDIs is generalizable by the 16-drug pairs which affect the result. The third, limitation of this study is selection bias because pharmacists who were more knowledgeable about PDDIs were more likely to participate in the study and pharmacists who had lower PDDI knowledge levels than those pharmacists who did not participate in the study.

CONCLUSION

This study indicates that pharmacy professionals had poor knowledge and practice towards clinically significant PDDIs without the aid of reference materials, which indicates the necessity for and potential importance of dispensing support systems in reducing PDDIs and drug-related morbidity and mortality. This study shown those years of experience and working institutions of participants had strongly associated with pharmacist professionals' knowledge of PDDIs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical clearance was obtained from the University of Gondar School of Pharmacy ethical review Board (SOP257/2022). A full explanation of the purpose of the study was made to the authorities of the respective hospital and health centers and the participants. Data collection was conducted after approval of the study by the authorities of each public and private institution as well as obtaining informed consent from each participant. To keep the confidentiality of participants, name and addresses were not recorded in the data collection forms. This study was done with the consideration and compliance with the declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data is available at the correspondence author upon reasonable request.

COMPETING INTERESTS

The authors declare there is no conflict of interest.

FUNDING

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