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FOURTH YEAR PHARMACY STUDENTS AND PHARMACY GRADUATES' ABILITY TO IDENTIFIY POTENTIAL DRUG-DRUG INTERACTION IN BENGHAZI LIBYA

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ABSTRACT:

OBJECTIVE: This study aims to evaluate and compare the ability of fourth-year pharmacy students and graduated pharmacists to identify clinically significant drug-drug interactions (DDIs).

METHODS: A questionnaire designed to measure DDI knowledge was distributed to both fourth-year pharmacy students (n = 89) in a school of pharmacy and graduated pharmacists(n=65) in community pharmacies and hospitals.

RESULTS: The question that examine the ability of respondents to recognize the DDI mechanisms, showed that (38.2%) of 4th- year students selected the right responses, while (48.5%) of pharmacy graduates selected the correct one. However, the knowledge of respondents regarding drug pairs interactions showed that 4th- year pharmacy students and graduates correctly categorized an average of 32.99% and 25.125% of DDI pairs respectively. In a question that examined the knowledge of 4th-year pharmacy students and graduates concerning drugs with low therapeutic index interactions with two groups of drugs, the correct answers regarding increasing digoxin serum level were (62.9% and 87.9%) respectively, while the correct answers regarding increasing warfarin serum level were (66.3% and 86%) respectively.

CONCLUSION: Pharmacy students' ability to identify important DDIs is generally poor except that for interactions of drugs with low therapeutic index. However, of the 4 interactions categorized as contraindicated, the students showed better significant responses in compare to graduates. However, this finding does not showed any significant difference between 4th-year pharmacy students and pharmacy graduate regarding identifying drugs pairs that may be used together with monitoring or categorized as safe.

KEY WORDS: Pharmacy students, pharmacy graduates, drug-drug interaction, knowledge.

INTRODUCTION:

Drug-drug interactions (DDIs) are very common adverse events in health care delivery settings. A drug-drug interaction (DDI) is one type of medication error and is a physiological response to a combination of drugs that results in an outcome**(Kannan *et al*., 2016).**

The concept of drug interaction is also extended to include; drug-drug interaction, drug-food interaction, drug-herbal interaction, drug-laboratory test interaction and drug-condition interaction **(Sharma *et al*., 2007)**. In the broadest sense, a drug-drug interaction (DDI) may be defined as the pharmacological or clinical response to the administration of a drug combination that is different from that anticipated from the known effects of the two agents when given alone and that can result in reduced effectiveness or increased toxicity **(Margo, 2007).**

DDIs may result in either increase or decrease in efficacy, in treatment failure, or in an increased toxicity of medications. However, more often, DDIs are an undesirable consequence of pharmacotherapy. DDIs account for nearly 19% of drug-related adverse effects **(Tesfaye & Nedi, 2017).**

The prevalence of drug interactions worldwide is 50% to 60%. Pharmacodynamics or pharmacokinetics interactions have a prevalence of approximately 5% to 9% respectively **(McFarland, 2019).** A meta-analysis of 23 clinical studies from around the world revealed that drug–drug interactions (DDIs) cause approximately 0.054% of emergency room visits, 0.57% of hospital admissions **(Kothari & Ganguly,2014)**. Adverse drug reactions (ADRs) are one of the main reasons of hospitalization, thus increasing in economical and medical issues. Drug drug interactions related in adverse drug reactions, particularly in patients under polymedication and in elderly patients **(Köhler *et al.*, 2000).**

Understanding the systemic effect of drug on many levels, specially absorption, elimination, transport and drug metabolism can prevent adverse effect. Predict interactions on pharmacodynamic level require better understanding to mechanism of effect **(Cascorbi, 2012).**

There are different mechanisms by which drugs interact with each other, and most of them can be divided into three general categories: pharmaceutical, pharmacokinetic and pharmacodynamic interactions. Pharmaceutical drug–drug interactions occur when the formulation of one drug is altered by another before it is administered. For example, precipitation of sodium thiopentone and vecuronium within an intravenous administration. Pharmacokinetic drug-drug interactions can occur at the level of absorption, distribution, or clearance of the affected agent which will ultimately alter the concentration and duration of the drug available at the receptor sites **(Huang & Temple, 2008)**. The most important pharmacokinetic interactions are those involving cytochrome P450 isoenzymes in hepatic metabolism (**Wilkinson, 2005; Slaughter *et al*., 1995).**

Generally, drug metabolism undergoes to two distinct pathways, Phase I and Phase II. Phase I include oxidation, hydrolysis, or reduction reactions and carried out by CytochromeP450 enzyme family. Phase II include biotransformation by certain reactions as methylation, acetylation, glucuronidation, glycineconjugation and sulfation. Change in CYP- metabolism step is considered the major mechanism by which drug interaction take place **(Lewis, 2004).** There are more than 50 CYP450 enzymes, but the CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes metabolize 90 percent of drugs. Inhibition of enzyme activity may result in higher concentrations and/or prolonged half-life of the substrate drug, which enhances the potential for toxic side effects. Enzyme inhibition is considered one of the main reasons of metabolic drug interaction. inhibition of enzyme result in increasing the extent of drug in the body, thus lead to side effect and possible toxicity **(Thummel *et al*., 2000).** Enzyme induction is associated with an increase in enzyme induction. In return, this induction may rising both

hepatic and intestinal clearancs of drugs, then decrease in its concentration and loss the efficacy. The clinical significance of a specific drug-drug interaction depends on the degree of accumulation of the substrate and the therapeutic window of the substrate **(Bachmann *et al*., 2005; Kliewer *et al*., 1998; Lieber, 1997).**

Pharmacodynamic interaction is due to interaction between agonist and antagonist at drug receptors. It is seen when two drugs have additive, synergistic or antagonist pharmacological effects. Either type of drug interaction can result in desired or undesired effects in some individual. an example of synergism when two or more drugs are given as anti-infective in case of a resistant pathogen. for example, coadministration of zidovudine and ganciclovir results in rising neutopenia. famouse example of additive result from taking two hypnotics or sedatives that lead to more increase in central nervous system depression **(Hochster *et al*., 1990).**

However, potentially interacting drugs combinations should not necessary result in adverse clinical manifestations, if they are knowingly prescribed and correctly managed. Pharmacokinetic drug interactions in particular are often manageable, and their risk may be avoided by dose adjustment. Otherwise, drug-drug interaction may be reduced by preventing concomitant use of potentially interacting drugs and, whenever possible, by replacing drugs at interaction risk with effective but safer alternative medications belonging to the same drug class.

Patients should be encouraged to alert physicians, pharmacists and other healthcare professionals to symptoms that occur when new drugs are introduced**(Seymour & Routledge, 1998).** According to **McFarland, (2019**), Pharmacists must take responsibility for monitoring for drug interactions and notifying the physician and patient about potential problems. According to the American Pharmacists Association, pharmacists in all settings have several essential medication-related responsibilities linked

to improving patient safety including comprehensive review of patient's full medication regimen to ensure no interaction of the medications. The pharmacists in Libya play a crucial role in dispensing drugs and patient's drug safety but the pharmacists knowledge and attitude regarding drug interaction were not actually obvious and no previous research have been done before in regard.

Therefore, assessing pharmacists' knowledge and information's regarding DDIs is necessary to evaluate patients' safety and to alert the pharmacists' syndicate about the need for training courses regarding DDI in line with pharmacy requirements.

METHODS:

This study describes the assessment of pharmacy students' and pharmacy graduates knowledge of DDIs using a designed Questionnaires. The population for the study consisted of 4th -year Pharmacy students (n = 89) at a college of pharmacy in university of Benghazi, and graduated pharmacists who working in community pharmacies around the city (n=66). Two-page questionnaires were distributed to pharmacy students during the end of the year prior to final exams as well as to the graduates who worked in community pharmacies.

Demographic information on age and sex, was obtained for both groups. In addition, the graduated pharmacists was asked to provide their profession and years of experience.

The assessment of knowledge part of the questionnaire consisted of 6 questions which include; The source of DDI knowledge, mechanisms by which DDIs occur, the tools and sources used to check the DDIs.

Questions 11 was designed to examine the knowledge of respondents regarding the interactions of low therapeutic index drugs. The items of question 11 consisted of two parts, the first part assesses the 4th-year students' and graduates' ability to identify group of drugs that elevate or lower digoxin serum level.

The second part assesses the ability of students and graduates to identify the group of drugs that elevate of lower warfarin serum level. The selection of these drugs that affect LTD drugs' serum levels were based on official references e.g. Katzung, stockly references and Medscape DDI checker website **(Table1)**.

The items of question 13 consisted of 12 drug pairs, those drug pairs were the most common DDIs found in published literature(**Weideman *et al,* 1999; saverno *et al* ,2009**; **Gilligan *et al*,20011**) which included 5 pairs that should not be used together(contraindicated), 3 pairs that may be used together with monitoring, 4 pairs that could be safe /no interaction. The following numbers were assigned for the severity rating categories for each drug pairs: (1) should not be used together (contraindicated), (2) may be used safely together with monitoring, (3) safe or no interaction, and (4) not sure. The respondents were allowed to select the correct category for each drug pairs.

The classification of drug interactions across many scientific sources was not fully consistence. Therefore three online drug interactions checker were used to act as the basis for the correct severity rating assigned to each drug pairs in the questionnaire: Drug Interactions Checker(**WebMD, 2018**), drug interactions checker (**drug.com, 2018**) and Drug Interactions Checker(**Medscape, 2018).** In addition, a drug interactions chapter in clinical pharmacology book (**Katzung, 2007**) as well as Stockley's drug interactions book**(Bakster, 2008)** were also used as a references. All drug interactions checkers categorize DDIs by severity. For example, drug.com checker severity rating assigned; contraindicated, major, moderate, and minor. In both Medscape and WebMD drug checkers severity rating assigned as: Don't use together/contraindicated or Serious, Monitor closely, Minor or no interaction**(Table2).**

The questionnaire was distributed to 4th- year students of 2018 and to graduates pharmacists who worked in community pharmacies. They were asked to complete the questionnaire without any assistance and they were given approximately 15 minutes to complete the questionnaire.

Using Statistical Package for the Social Sciences(SPSS) software to do descriptive statistics analysis for both pharmacy graduates and 4th -year students. Also to find a correlation(using Pearson chi –square for qualitative data) between answers of graduates and 4th year students.

Table 1 : Shows groups of drugs that increase or decrease LTD drugs' serum levels according to Katzung, stockly books and Medscape DDI checker website (Medscape, 2018; Bakster, 2008)

LTI drugs	**Drugs groups**		**Katzung,2007**	**Stockley,2008**	**Medscape website DDI checker**
Digoxin	Group1	Amiodarone Benzodiazepines Macrolides Omeprazole Quinidine	**Increase** Benzodiazepines and Omeprazole not mentioned	**Increase** All	**Increase** All
Digoxin	Group2	Aminoglycosides Aluminum/magnesium antacids Activated charcoal Cholestyramine Rifampin	**Decrease** Activated charcoal Cholestyramine not mentioned	**Decrease** All	**Decrease** All
Warfarin	Group1	Amiodarone Cimetidine Lovastatin Macrolides Metronidazole NSAIDs Quinolones Tricyclic antidepressants	**Increase** Tricyclic antidepressants, not mentioned	**Increase** All	**Increase** All
Warfarin	Group2	Barbiturates Carbamazepine Cholestyramine Phenytoin Rifampin Vitamin K	**Decrease** Vitamin K not mentioned	**Decrease** All	**Decrease** All

Table 2: Shows the categorizations of drug combinations according to three drug-drug interaction checkers and Stockley's drug interaction book (Drug.com; Medscape.com; WebMed.com; Bakster, 2008)

Drug combinations	Category	Stockly reference	Drug.com DDI checker	Medscape DDI checker	WebMed DDI checker
1.Amiodarone & Azithromycin	Contraindicated	should be avoided	Major, Avoid combination increase the risk of an irregular heart rhythm that is potentially life-threatening	Serious, contraindicated both increase QTc interval. Avoid or Use Alternate Drug.	Serious, use alternative both increase causing a dangerous abnormal heart rhythm
2.Captopril & Simvastatin	Safe		NO interaction	NO interaction	NO interaction
3.ACE inhibitors & Spironolactone	Monitor Closely		Major, need a dose adjustment may increase the levels of potassium in your blood (hyperkalemia)	Monitor Closely Risk of hyperkalemia. Monitor blood pressure and potassium.	Monitor Closely Combination increases blood potassium levels (hyperkalemia)
4.Theophylline & Ciprofloxacin	Contraindicated	Serious toxicity has been seen in patients	Major, GENERALLY AVOID, Ciprofloxacin may significantly increase the blood levels of theophylline, which may lead to potentially serious and life-threatening side effects	Serious - Use Alternative ciprofloxacin will increase the level or effect of theophylline by affecting hepatic metabolism Serious and fatal reactions.	Serious alternate medication may be needed ciprofloxacin will increase the level or effect of theophylline by altering drug metabolism
5. Sildenafil & Isosorbide Mononitrate	Contraindicated		Contraindicated Severe hypotension, syncope, or myocardial ischemia may result from use of the combination.	Contraindicated additive vasodilation causing Potentially fatal hypotension.	Don't use together Combination increases risk for potentially fatal hypotension
6.Clopidogrel & Ca++ Channel Blockers	Monitor Closely	No significant pharmacodynamic interactions were seen when clopidogrel was given with **Nifedipine**	No interaction found	Monitor Closely nifedipine will decrease the level or effect of clopidogrel by affecting hepatic metabolism	Monitor closely nifedipine will decrease the level or effect of clopidogrel by altering drug metabolism
7.Theophylline & Omeprazole	Safe		NO interaction	NO interaction	NO interaction
8.SSRIs(Fluoxetine) & MAOIs(Phenelzine)	Contraindicated	Fatal report in patients given fluoxetine with phenelzine.	Major, contraindicated Combining these medications can increase the risk of a serious condition called the serotonin syndrome	Contraindicated phenelzine and fluoxetine both increase serotonin levels..	Don't use together Too much serotonin is a potentially life-threatening situation. Severe signs and symptoms include high blood pressure and increased heart rate that lead to shock.
9.Oral contraceptive & rifampicin	Contraindicated	Increase oral contraceptive metabolism and reduce its efficacy.	Major, use alternative increased risk of breakthrough bleeding and unintended pregnancy.	Serious - Use Alternative rifampin will decrease the level or effect of ethinylestradiol by affecting hepatic metabolism.	Serious - This combination reduces the effect of the hormonal contraceptive and may increase incidence of menstruation associated adverse effects.
10.Atenolol & ranitidine	Safe		NO interaction	NO interaction	NO interaction
11.Bromocriptine & Pseudoephedrine	Monitor Closely	.	Moderate, Monitor closely Increase BP & tachycardia The combination has led to postpartum psychosis	Monitor closely increases effects of each other by pharmacodynamic synergism. Monitor. Hypertension, V tach.	Monitor closely May cause heart rhythm problems and increased blood pressure.
12. Acetaminophen & Clopidogril	Safe		NO interaction	NO interaction	NO interaction

RESULTS:

A total of 155 respondents have answered the questionnaires; (89) 4th -year students, and (66) graduated pharmacists, **Table 1** provides demographic information on those respondents, for the 4th -year students class of 2018, 68.5% of respondents were between 20-25years, and 67.4% of the them were female, while among graduated respondents 72.7% were between 26-35years, and 65.2% of them were female. There were no significant differences between students and pharmacy graduates in any of the demographic variables

Table 3: demographic information for 4th year pharmacy students and pharmacy graduates.

Variables	**Fourth-year pharmacy students class 2018**	**Pharmacy graduated respondents**
Age range in years, No.(%)	20-25(68.5%)	26-35(72.7%)
Gender, No. (%) female	60(67.4%)	32(65.2%)
Pharmacy-Related Work:		
Community pharmacy, No. (%) Years of experience(%)	-	45(68.2%) 1-4 years(71.1%)
Hospital pharmacy, No. (%) Years of experience(%)	-	10(10.6%) 1-4 years(62.5%)
Clinical pharmacy, No. (%) Years of experience(%)	-	11(12.1%) >4years(71.4%)

As shown in **Table 3**, 68.2% of graduated pharmacists have worked in community pharmacy with (71.1%) of them had work experience ranging from 1 to 4 years, 10.6% were worked in hospital pharmacy with (62.5%) of them had work experience ranging from 1 to 4 years, and 12.1% were worked as a clinical pharmacists and(71.4%) of them had work experience over than 4 years.

A question 7, asked both groups of respondents to pick up the main source of their DDIs knowledge and as shown in the **Figure 1,** the primary source for 4th- years students was their undergraduate study (69.7%), while the primary source for graduated pharmacists was the pharmacy practice(48.5%).

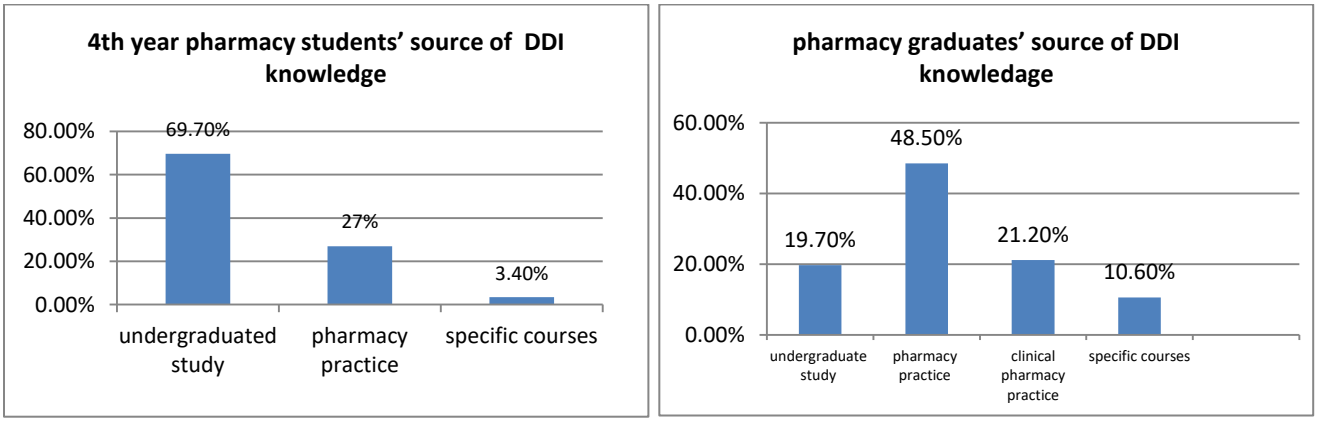


Fig. 1: Shows the main sources of DDIs knowledge for 4th -years students(Left) as well as pharmacy graduates(Right)**.**

The question 8 asked the respondents to choose the main tools used to learn about DDIs, the majority of 4th-year pharmacy students as well as pharmacy graduates picked the internet (80.9% and 74.2% respectively), however the difference between groups was not statistically significant (p=0.765). Both groups were asked about their opinions in question 9 about whether the pharmacist has a duty to report DDIs, the majority of students said Yes (56.5%), while the majority of pharmacy graduate said No (39.4%)(**Figure2**).

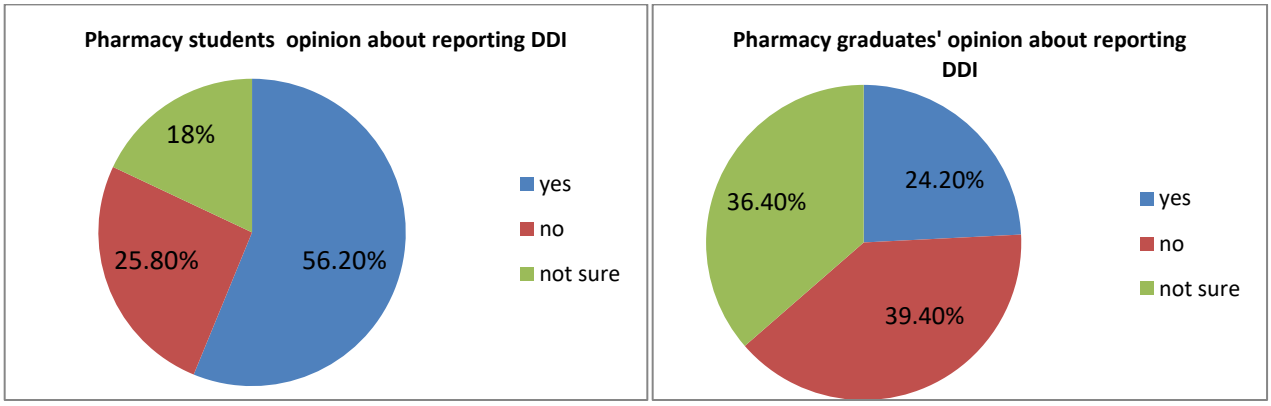


Fig 2: 4th year pharmacy students and pharmacy graduates opinions about pharmacist duty to report DDI**.**

The question 9 examined the knowledge of students and graduates regarding the types of drug-drug interactions, in which the answer to be correct should include all the three types (Pharmaceutical, Pharmacokinetics and Pharmacodynamics interactions). (38.2%) of 4th - year students selected the right responses, while (48.5%)of pharmacy graduates selected the correct one (**Figure 3)**.

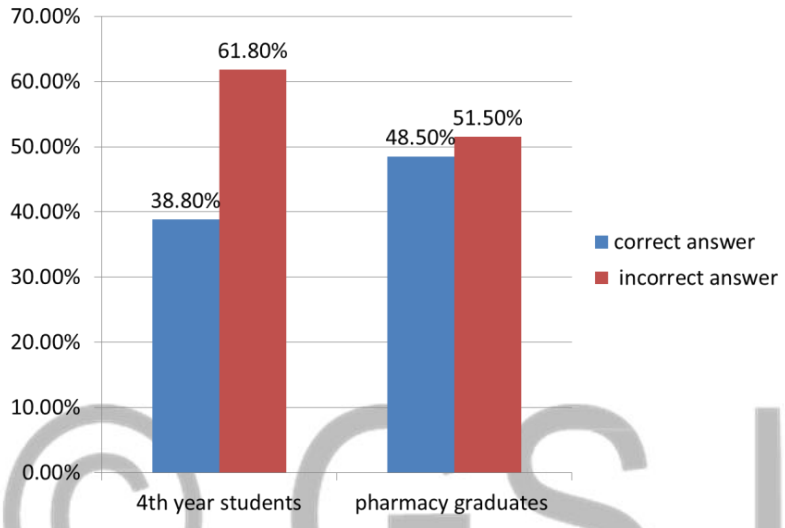


Figure 3: shows the answers of students and graduates regarding the types of DDI mechanism

However, comparing the percentage of correct responses of both groups of respondents founding that it was not statistically significant (p=0.2) using Pearson chi -square correlation test. Furthermore, the correlation test showed that there was no significant correlation between the correct answer of graduates and their gender (p=0.339) and years of experience (p=0.127).

A question 11 that examined the knowledge of 4th-year pharmacy students and graduates concerning low therapeutic index drugs(LTI) interactions with two groups of drugs. In the first part of the question, respondents were asked to determine which group of drugs that elevate or lower digoxin serum level. The correct answer was drugs in group1 increase digoxin serum level. (62.9%) of pharmacy students provided the correct responses, and (87.9%) of graduates gave the correct response (**Figure4**). While

drugs in group 2 decrease digoxin serum level. (68.5%) of pharmacy students provided the correct responses, and (87.9%) of graduates did (**Figure5**).

In the second part of the question, respondents were requested to answer which group of drugs could elevate or lower warfarin serum levels. The drugs in group 1 increase warfarin serum level, and (66.3%) of pharmacy students provided the correct responses, and (86%) of graduates did. While drugs in group 2 decrease warfarin serum level, (67.4 %) of pharmacy students provided the correct responses, and (86.4%) of graduates did, the difference in both parts of this question was statically significant (p=0.000129).

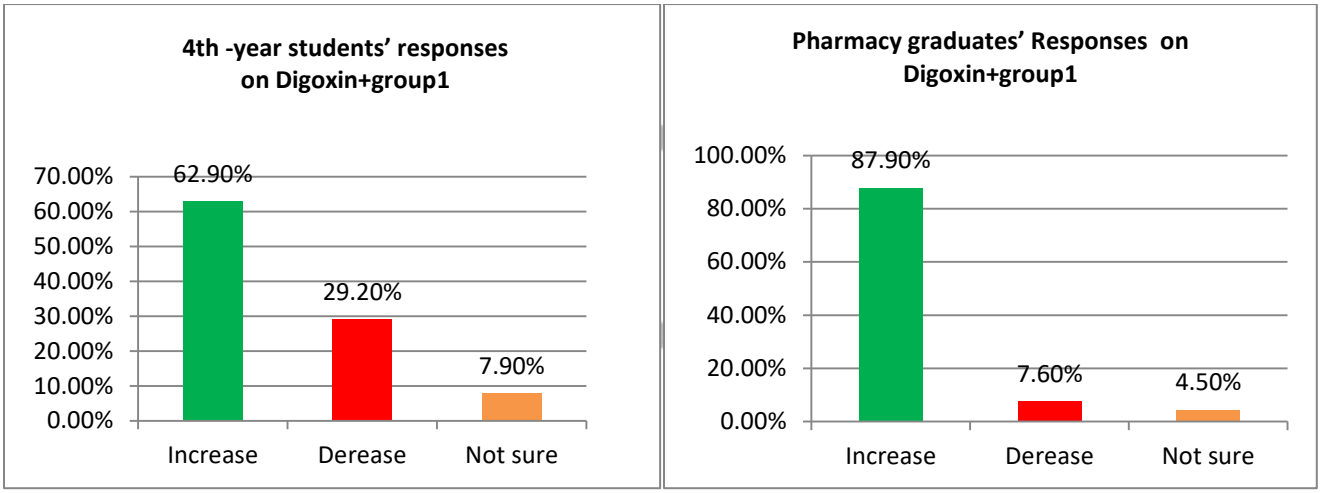
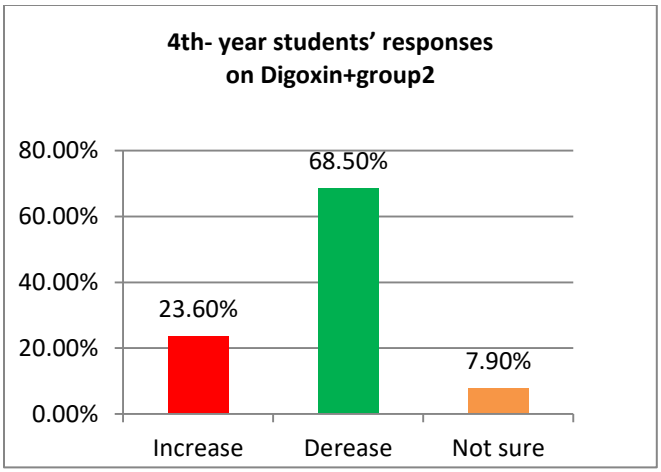


Figure 4: shows respondents answer on digoxin interaction with group1 drugs.



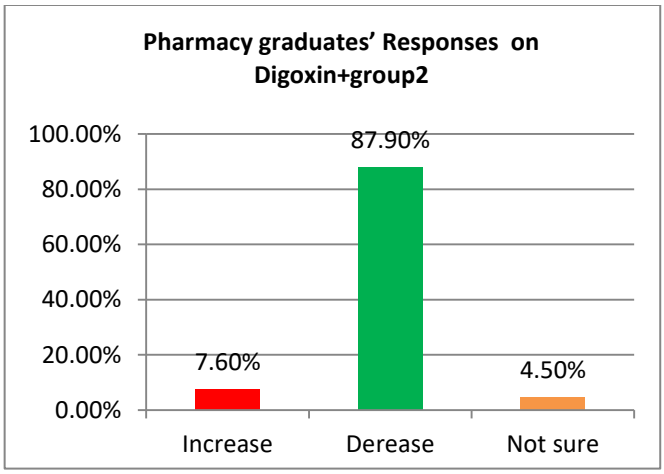
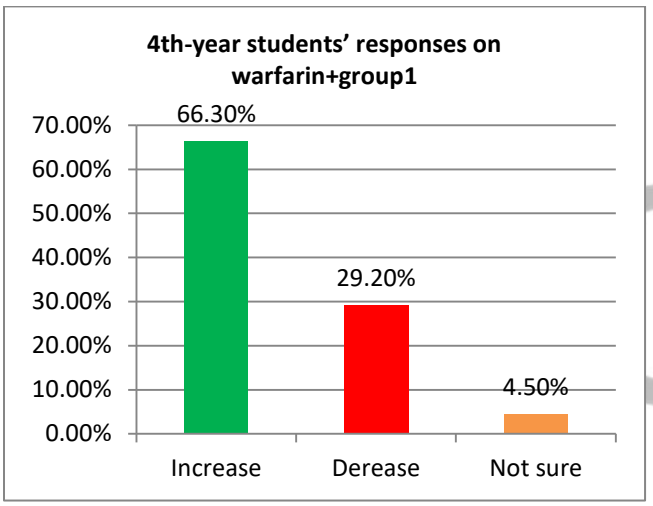


Figure 5: shows respondents answer on digoxin interaction with group2 drugs.



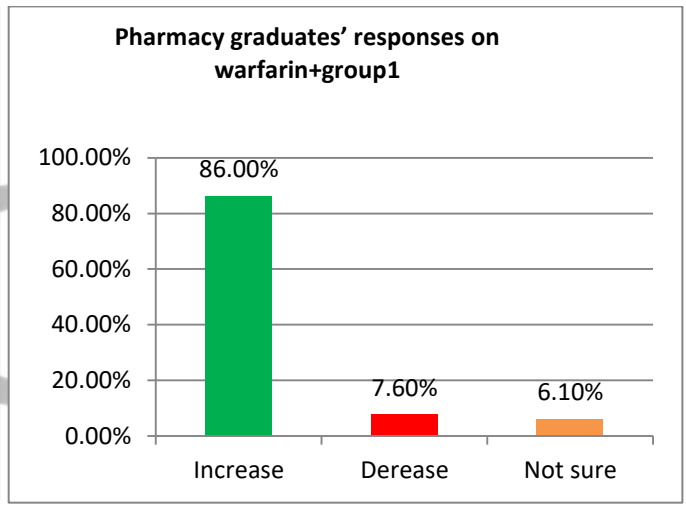
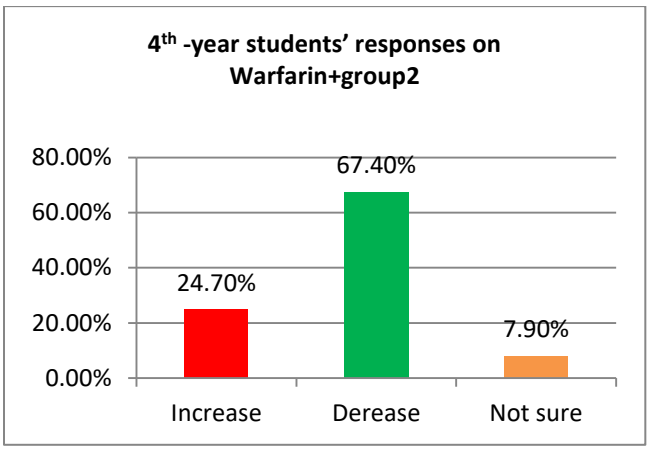


Figure 6: shows respondents answer on Warfarin interaction with group1 drugs.



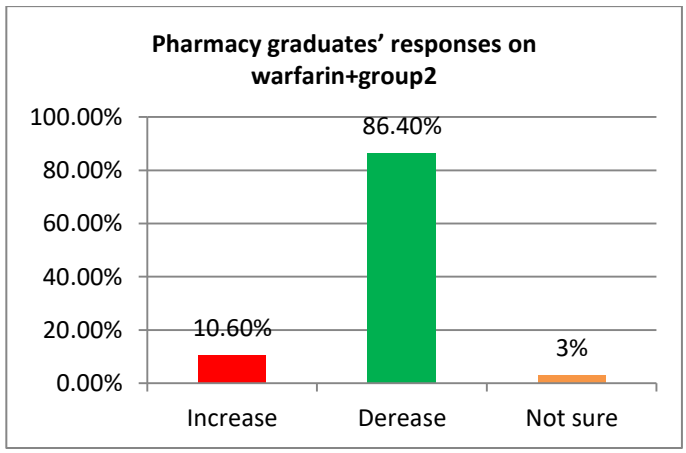


Figure 7: Shows respondents answer on Warfarin interaction with group2 drugs.

In the last and the biggest part of the questionnaire the respondents were asked to categorize 12 pairs of different pairs of drugs, and they had to choose between three answers (1.contraindicated),(2.maybe used together but with monitoring),(3.safe, or no interaction), but we also included the option (4.not sure) to give the respondents the chance to answer the question if they are only sure.

Table 4: Percentages of Correct responses by 4th year pharmacy students and pharmacy graduates regarding drug pair interactions.

Drug combinations	Correct* response	Percent(%) of Fourth-year Students who selected the correct response.	Percent(%) of Graduated respondents who selected the correct response.	Pearson Chi-square p-value
1.Amiodarone & Azithromycin	**1**	44.9	33.3	0.145
2.Captopril & Simvastatin	**3**	38.2	28.8	0.222
3.ACE inhibitors & Spironolactone	**2**	31.5	16.7	0.036
4.Theophylline & Ciprofloxacin	**1**	24.7	31.8	0.329
5. Sildenafil & Isosorbide Mononitrate	**1**	44.9	27.3	0.025
6.Clopidogrel & Ca+ Channel Blockers	**2**	21.3	16.7	0.466
7.Theophylline & Omeprazole	**3**	13.5	12.1	0.803
8.SSRIs(Fluoxetine) & MAOIs(Phenelzine)	**1**	40.4	28.8	0.134
9.Oral contraceptive & rifampicin	**1**	32.6	12.1	0.003
10.Atenolol & ranitidine	**3**	39.3	31.8	0.411
11.Bromocriptine & Pseudoephedrine	**2**	32.6	31.8	0.920
12. Acetaminophen & Clopidogril	**3**	32	30.3	0.431
Average		**32.99%**	**25.125%**	

*Rating scale: 1 : should not be used together (contraindicated), 2 : may be used together with monitoring, 3:safe or no interaction

In pair number 1 (Amiodarone & Azithromycin), the correct answer was (1.contraindicated), (44.9%) of 4th year students chose the correct answer, while only (33.3%) of graduated pharmacists selected the correct answer (**Figure8**). However, it should be noticed that the number of graduates, who were not sure, are much more (53.1%) in compare to pharmacy students(28.1%). Meaning that the number of graduates who picked the wrong answers (13.6%) is much smaller than that of pharmacy students(27%). However, Pearson Chi-square test showed that there was no significant difference (0.145).

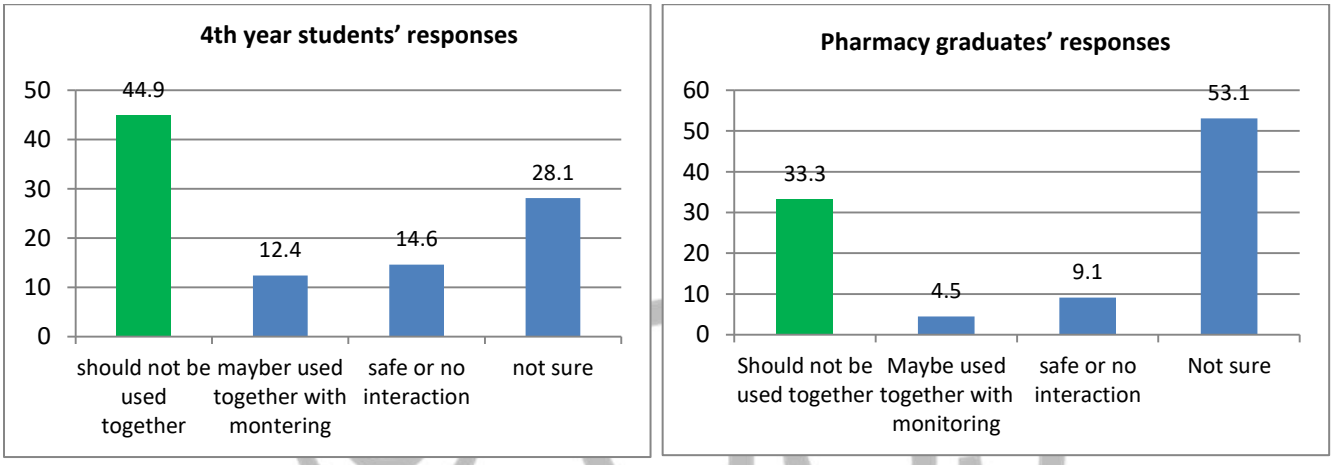


Figure 8: 4th -year pharmacy students and pharmacy graduates' responses regarding (Amiodarone & Azithromycin) combinations

In pair number 2(Captopril & Simvastatin), the correct answer was (3.safe, or no interaction). A Higher percentage of correct answers were obtained by 4th-year students (38.2%) in compare to graduated pharmacists (28.8%)(**Figure 9).** However, the number of graduates who were unsure, is much higher (45.5%) than those of 4th-year students (27%). Meaning that graduates who picked the wrong answers (25.7%), is slightly less than that of pharmacy students(35%). However, Pearson Chi-square test showed that there was no significant difference(0.222).

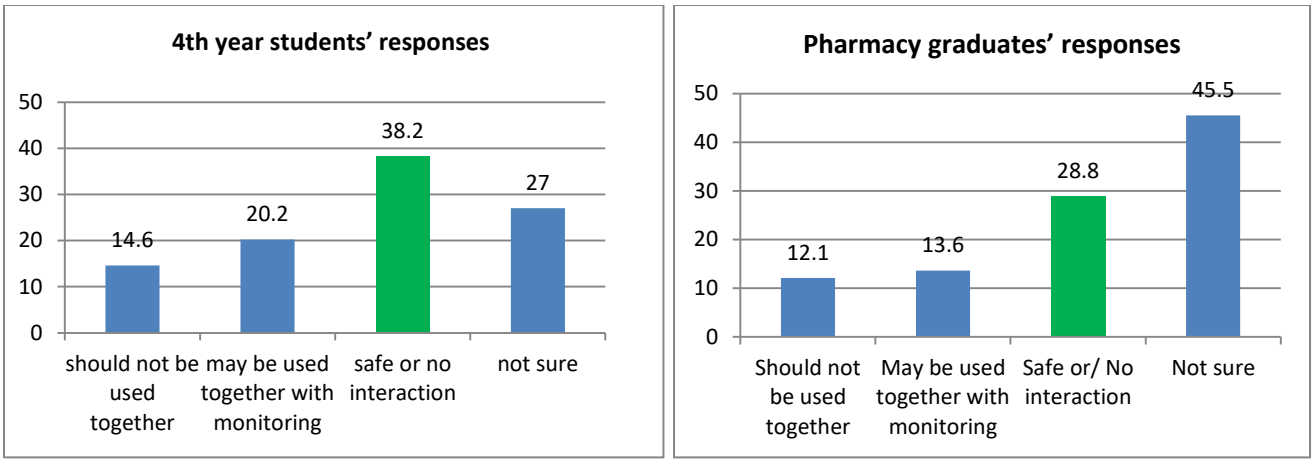


Figure 9: 4th- year pharmacy students and pharmacy graduates' responses to(Captopril & Simvastatin) combinations.

In pair number 3 (ACE inhibitors & Spironolactone) the correct answer was (2.maybe used together but with monitoring). (31.5%) of 4th- year students chose the correct answer, while only (16.7%) of graduated pharmacists did. As shown in the **Figure10**, the majority of 4th- year students' responses were (contraindicated and may be used together with monitoring) while the majority of graduates were unsure(45.5%). Pearson Chi-square test showed that there was a significant difference(0.036).

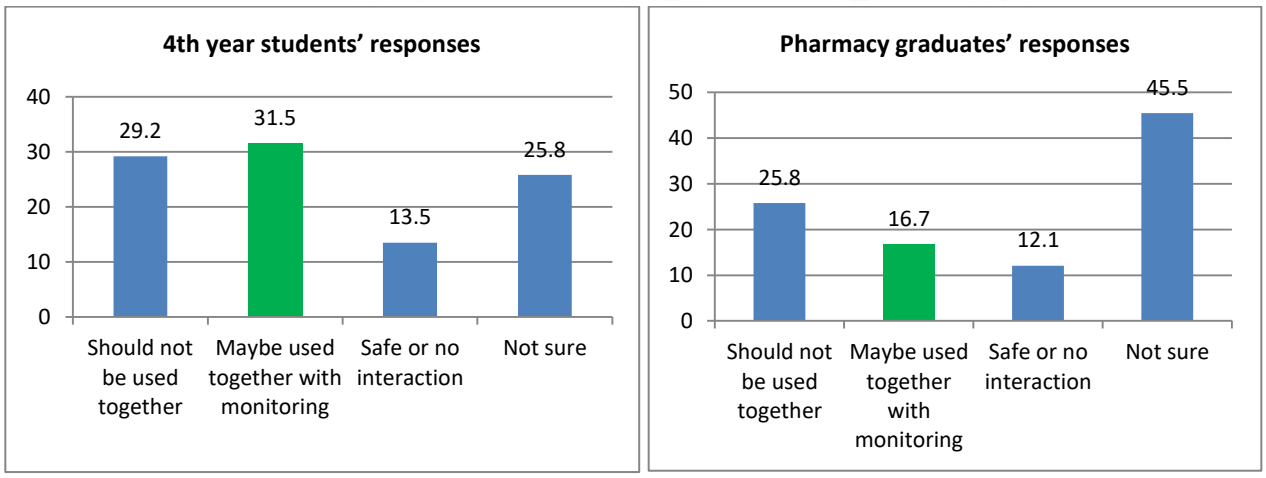


Figure 10: 4th- year pharmacy students and pharmacy graduates' responses to (ACE inhibitors & Spironolactone) combinations.

In pair number 4 (Theophylline & Ciprofloxacin) the correct answer was (1. contraindicated). (24.7%) and (31.8%) picked the correct responses for 4th -year students and graduates respectively(**Figure11**). The percentage of correct answers was low for both respondents. However, the graduates showed better responses than students. Pearson Chi-square test showed that there was no significant difference(0.329).

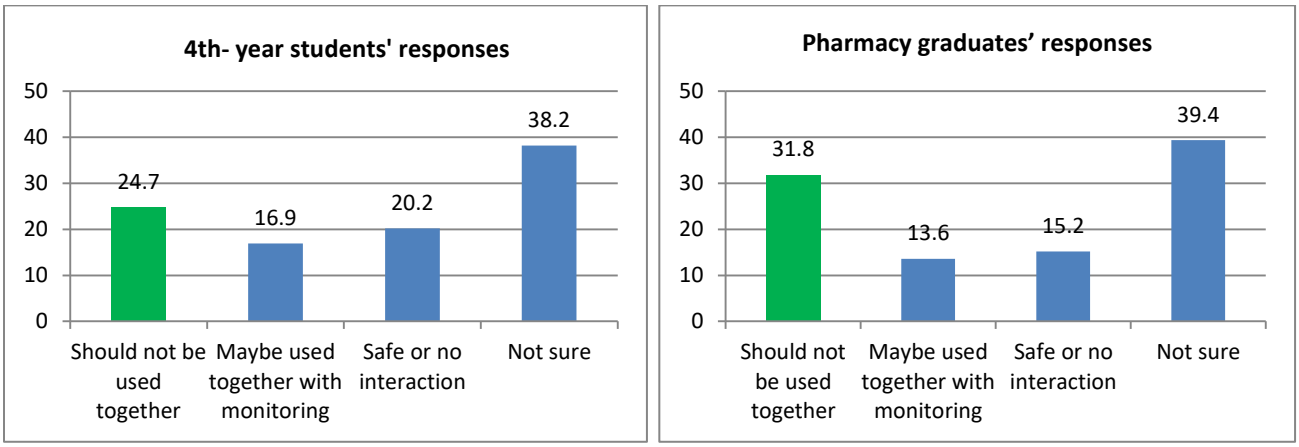


Figure 11: 4th- year pharmacy students and pharmacy graduates' responses to (Theophylline & Ciprofloxacin) combinations.

In pair number 5 (Sildenafil & Isosorbide mononitrate) the correct answer was (1. contraindicated). (44.9%) of 4th-year students chose the correct answer, while only (27.3%) of graduated pharmacists selected the correct answer. The students here showed better responses than graduates. Pearson Chi-square test showed that there was a significant difference(0.025).

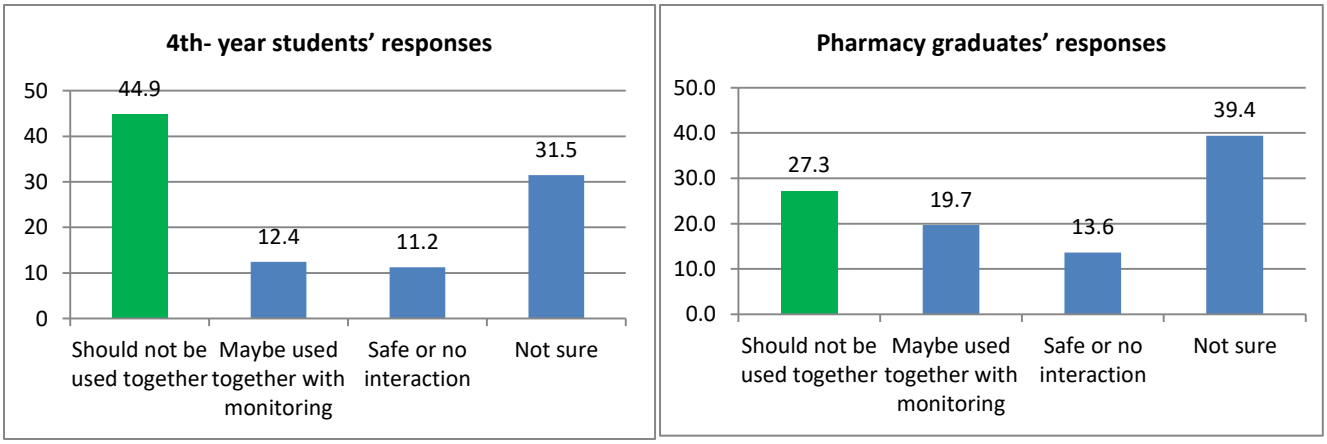


Figure 12: 4th- year pharmacy students and pharmacy graduates' responses to (Sildenafil & Isosorbide mononitrate) combinations.

In pair number 6 (Clopidogrel & Ca+ channel blockers) the correct answer was (2. maybe used together but with monitoring), (21.3%) of 4th year students chose the correct answer, while only (16.7%) of graduated pharmacists selected the correct answer. The percentage of correct answers was low among both respondents while the percentage of those who were unsure was high. Pearson Chi-square test showed that there was no significant difference(0.466).

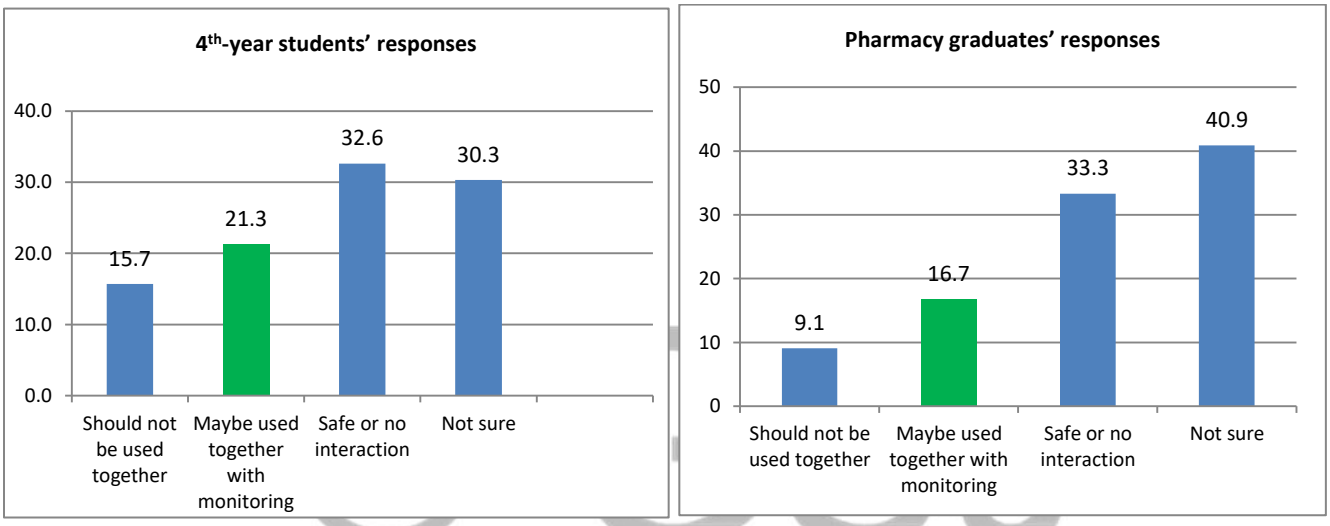


Figure 13: 4th- year pharmacy students and pharmacy graduates' responses to (Clopidogrel & Ca+ channel blockers)combinations.

In the pair number 7 (Theophylline & Omeprazole) the correct answer was (3.safe, or no interaction), (13.5%) of 4th year students chose the correct answer, while only (12.1%) of graduated pharmacists selected the correct answer. Both respondents showed low percentage of correct responses, however, more higher percentage of graduate who were unsure in compare to students. Pearson Chi-square test showed that there was no significant difference(0.803).

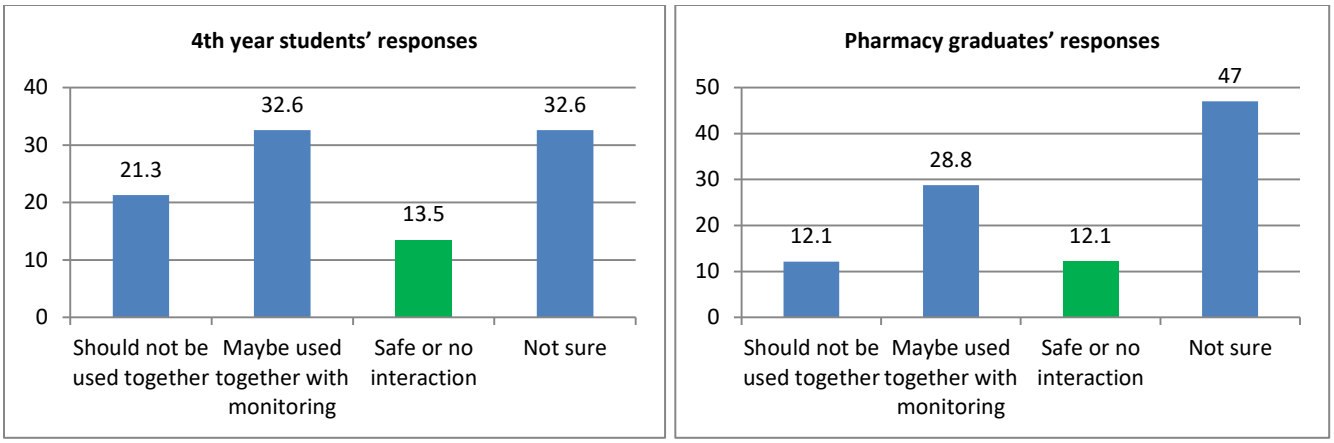


Figure 14: 4th- year pharmacy students and pharmacy graduates' responses to (Theophylline & Omeprazole)combinations.

In pair number 8 (SSRIs(Fluoxetine)&MAOIs (Phenelzine)) the correct answer was (1. contraindicated). The students picked more correct answers (40.4%) in compare to graduates(28.8%). On the other hand, the percentage of incorrect answers for both respondents were quit similar (23.6% and 27.3%) as 43.9% of graduates were not sure regarding their responses. However, Pearson Chi-square test showed that there was no significant difference(0.134).

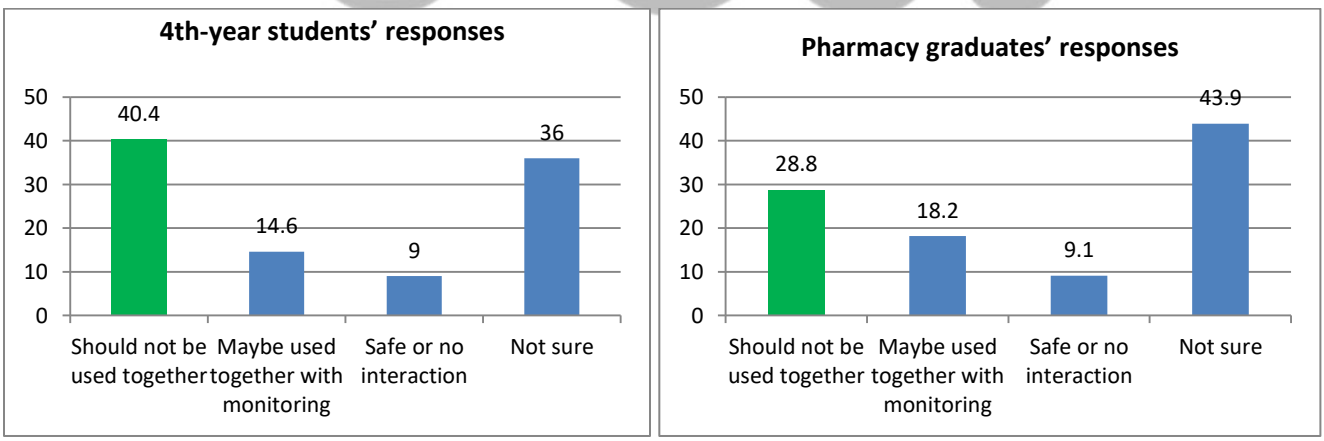


Figure 15: 4th- year pharmacy students and pharmacy graduates' responses to (SSRIs(Fluoxetine) &MAOIs (Phenelzine)) combinations.

In pair number 9 (Oral contraceptive & rifampicin) the correct answer was (1. contraindicated), (32.6%) of 4th year students chose the correct answer, while only (12.1%) of graduated pharmacist selected the correct answer. However, the percentage of graduates who were unsure was higher than those of

students. Meaning that the percentages of wrong answers were comparable for both respondents. Pearson Chi-square test showed that there was a significant difference between groups(0.003)

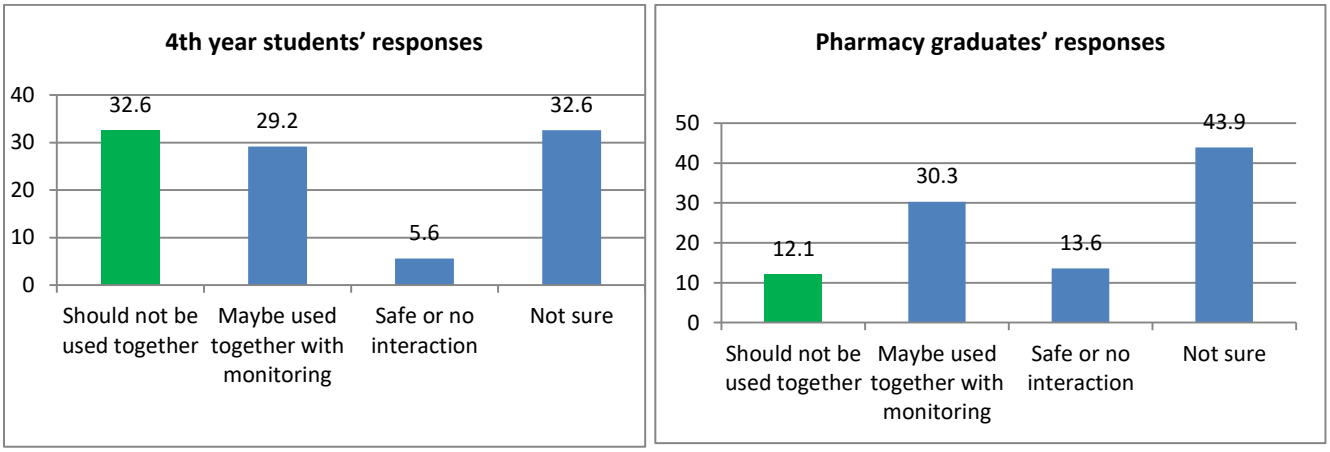


Figure 16: 4th- year pharmacy students and pharmacy graduates' responses to (Oral contraceptive & rifampicin)combinations.

In pair number 10 (Atenolol & ranitidine) the correct answer was (3.safe, or no interaction). 39.3% of 4th- year students chose the correct answer, while only (31.8%) of graduated pharmacists selected the correct one. However, The percentage of incorrect answers of graduates was far lower than those of the students, as high percentage of graduates were not sure regarding their responses in compare to students. Pearson Chi-square test showed that there was no significant difference(0.411).

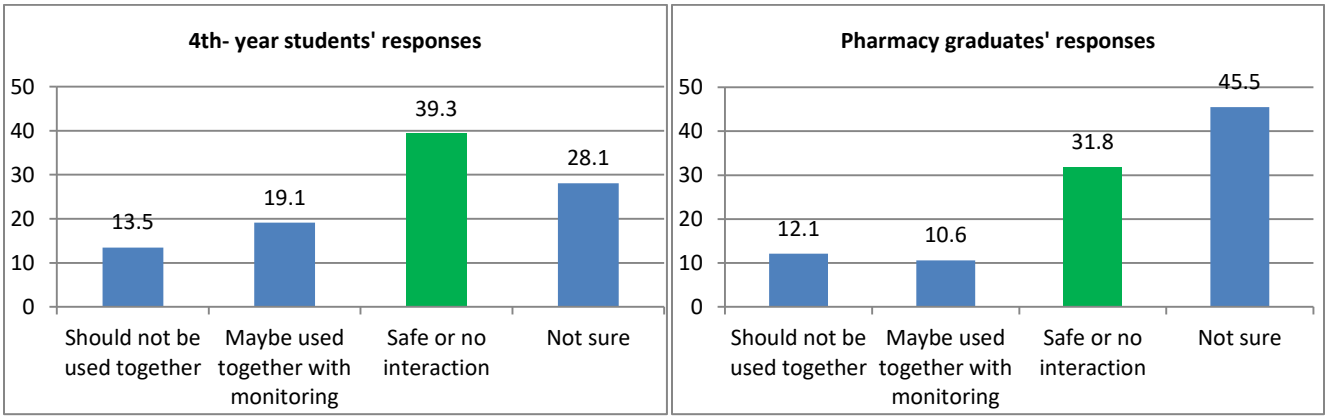


Figure 17: 4th- year pharmacy students and pharmacy graduates' responses to (Atenolol & ranitidine)combinations.

In pair number 11 (Bromocriptine & Pseudoephedrine) the correct answer was (2. .maybe used together but with monitoring). Both respondents (4th-year students and graduates) exhibited low correct responses(32.6% and 31.8 %respectively) in compare to unsure responses(44.9%% and 39.4% respectively). Pearson Chi-square test showed that there was no significant difference(0.920).

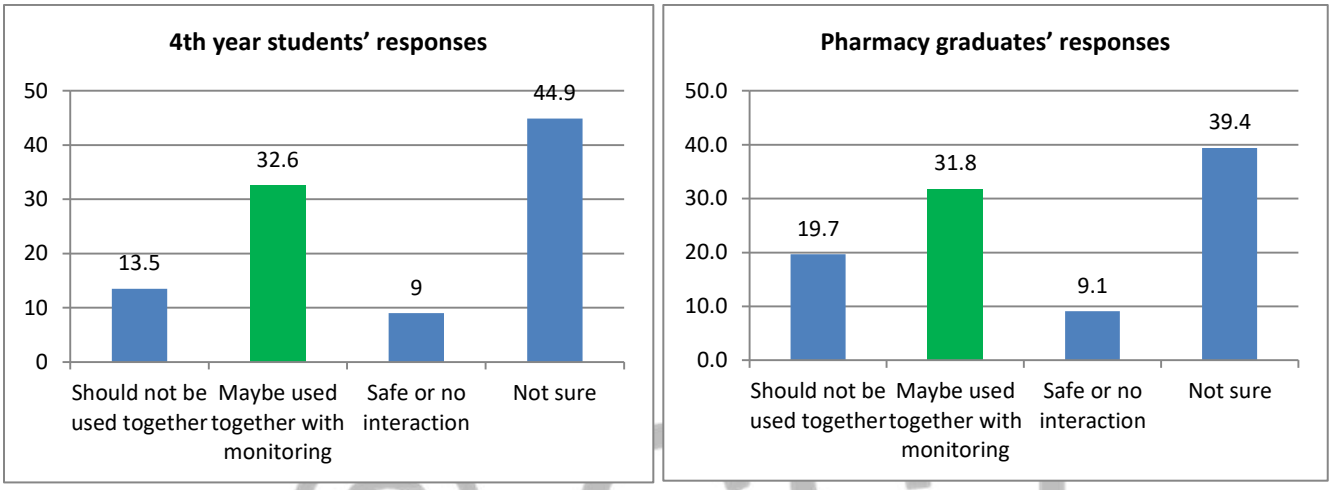


Figure 18: 4th- year pharmacy students and pharmacy graduates' responses to (Bromocriptine & Pseudoephedrine)combinations.

In pair number 12 (Acetaminophen & Clopidogril) the correct answer was (3.safe, or no interaction). 36% of 4th year students chose the correct answer, while only (30.3%) of graduates selected the correct answer. Pearson Chi-square test showed that there was no significant difference(0.431).

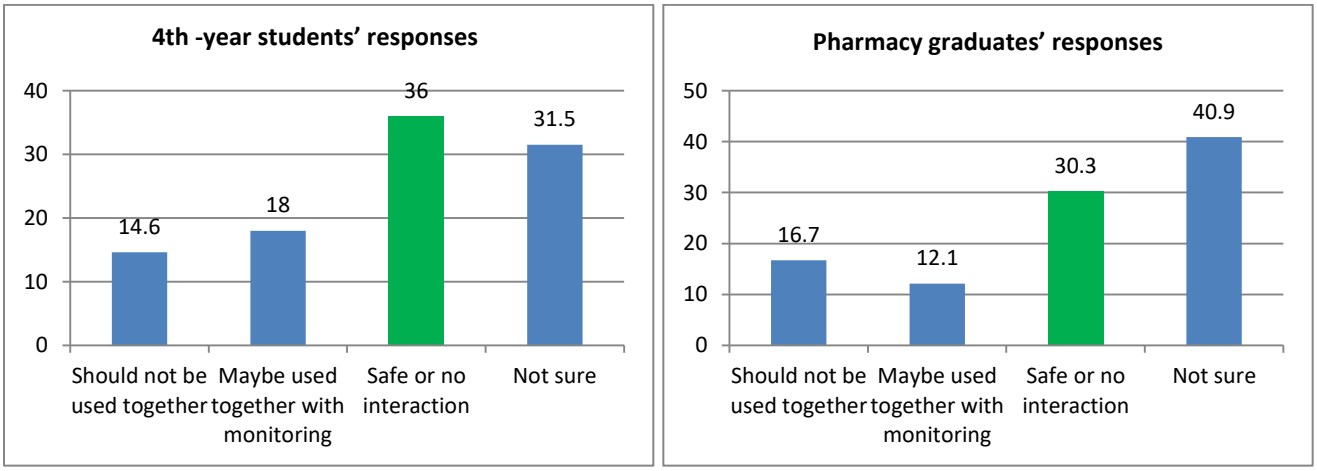


Figure 19: 4th- year pharmacy students and pharmacy graduates' responses to (Acetaminophen & Clopidogril)combinations.

DISCUSSION:

The ability to identify potentially harmful drug interactions is a vital component of a pharmacist's work. This study compare DDI knowledge between 4th year pharmacy students and pharmacy graduates. To our knowledge, this study is the first evaluation of pharmacy students' and graduates ability to identify DDIs in Libya.

Regarding the question that examine the ability of respondents to recognize the DDI mechanisms, both groups of respondents' showed similar responses, which is not completely correct. Most of the answers include only pharmacodynamics and pharmacokinetics interactions and missed pharmaceutical interactions. Pharmacy graduates picked up more correct responses in compare to 4th- year students. However, chi square test showed that the result was statistically non-significant (p=0.2). According to **(Hincapie, *et al*. (2012)** most of the studies have focused on the pharmacokinetic and pharmacodynamics drugs interactions but the data on pharmaceutical interactions was very limited. The reason why regarding this issue is believed that pharmaceutical interactions are not dangerous and rarely cause adverse complications.

The results from questionnaires that assess the knowledge of respondents regarding drug pairs interactions showed that 4th- year pharmacy students correctly identified 32.99% of the drug combinations in compare to pharmacy graduates who are correctly identified 25.125% of drug combinations. However, this results suggest that knowledge of DDIs is generally poor in compare to a similar study by **Saverno *et al*.,(2009)** that assessed the ability of third- and fourth-year pharmacy students to categorize the severity of drug interactions. The study showed that they could correctly categorize 52% to 66% of drug interaction pairs presented to them.

Additionally, a similar study revealed that senior pharmacy students and practicing pharmacists were able to correctly categorize 66% of drug-interaction pairs in 2-drug prescription profiles presented to them **(Weideman *et al*.,1999)**.

Nevertheless , DDI knowledge appeared to be higher in 4^{th-} year pharmacy students in compare to pharmacy graduates. 4th- year Pharmacy students correctly identified 32.99% of all drugs pairs. While pharmacy graduates correctly identified 25.125% of all the drugs pairs. However, the chi square test showed that there was no statistically significant difference in the percentage of correct responses between the groups (p=0.076).

Of the 4interactions categorized as those that should not be used together or /contraindicated, (1.Amiodarone & Azithromycin, 5. Sildenafil & Isosorbide Mononitrate, 6.Clopidogrel & Ca+ Channel Blockers,8.Fluoxetine & Phenelzine, 9.Oral contraceptive & rifampicin), the majority of 4th year students identified more correct answers in compare to graduates, and the chi square test showed that the difference was statistically significant (p=0.0347).

That difference in results may be linked to that pharmacy students' knowledge retention of DDIs is still new from pharmacology courses intended on 3rd year class as well as in clinical pharmacy courses in 4th year class. The other reason may be that graduates prefer using DDI checker software rather than relying on their current knowledge and information. According to **Gilligan *et al*.,(2011),** DDIs' knowledge appeared to be higher 1 year after the educational session. However, a study by **(Hincapie, *et al*., 2012)** found that pharmacy and medical students' ability to identify DDIs is still poor even after 1 year of the educational session. Additionally, another study by **(Warholak, *et al*., 2011)** revealed that the health professional students ability to categorize DDIs was low. Similar study by (**Alrabiah *et al*., 2019**) showed that knowledge of community pharmacists about DDIs was inadequate.

Of the 3 drug pairs that categorized as (may be used together without monitoring), 28.46% of the 4th year pharmacy students has the ability to correctly categorized the interactions. while only 21.7% of the pharmacy graduates correctly identified them. However, the difference between groups was non-significant(p=0.777) . Additionally , of the 4 drugs pairs categorized as (safe), 30.75% and 25.75% of 4th - year students and graduates respectively gave the correct answer. However, respondents' answers were not significantly different between groups (p=0.517).

Of all the drug interaction pairs in the questionnaire, the pairs receiving the most correct responses by students (44.9% and 44.9%) belong to (Amiodarone & azithromycin) and (sildenafil & isosorbide mononitrate). The drug pair least likely to generate correct severity responses from the graduates (12.1%) was Oral contraceptive & rifampicin.

On other hand, the results of questionnaires, that assess knowledge of respondents' regarding interactions of drugs with low therapeutic index (e.g. digoxin and warfarin), revealed that the knowledge was very good for both 4th-pharmacy students and graduates. That may indicate that DDIs courses incorporated into pharmacy college curriculum have contributed for both respondents' ability to correctly categorize the drug interactions of LTIs.

Moreover, there was a significant difference in the percentage of correct responses between groups (p=0.000129). This means graduates show better responses in compare to 4th-year students which may be contributed to the recurrent prescription in pharmacy practice, familiarity and learning of drugs with low safety. In addition, many serious adverse drug reactions were expected as results from the interaction of drugs with low therapeutic index and that will take the attention of many pharmacists in duty.

In a study by **Warholak, *et al*.,(2011)** to assess DDI knowledge of students and practicing pharmacists, showed that the drug combination (digoxin/ clarithromycin) appeared to be more challenging for the student than for the practicing pharmacists. This could indicate that those who have experienced this interaction in practice showing better knowledge than others. However, a study by **Al-Arifi*, et al.*, (2016)** suggests that health care professionals' (including pharmacists in duty) knowledge of warfarin-drug interactions was inadequate.

From these results, background information of both students and graduated pharmacists, focused more on the low therapeutic index drug interactions and to lesser extent on severe DDIs, while ignoring DDIs that may be used together with monitoring.

In a question asked both students and graduates do pharmacists have a duty to warn or report for DDIs , the majority of students said Yes (56.5%), while the majority of pharmacy graduate said No (39.4%). Pharmacist is the bridge between doctors and patients who counsels and advice the patient to minimize the adverse effects of the drug and maximize the desired effect of the drugs. The basic duty of a pharmacist is to check prescriptions from physicians before dispensing the medication to the patients to ensure that the patients don't receive the wrong drugs or take an incorrect dose of medicine **(Sinha, 2014).**

From the safety viewpoint, the pharmacist has the legal duty to warn about potentially harmful drug interactions. The warning should be directed to the prescribing physician in a manner that will increase the chances of avoiding the drug interaction **(Burns and Kelly, 2002)**.

However, from these result, most of graduated pharmacists did not know that it is their responsibility to report or warn prescribers about DDIs. That may be possibly because of low confidence in their background information. Poor pharmacists' knowledge and weak confidence regarding Drug

interactions may be correlated with inadequate curriculum of pharmacy school that qualify the graduates for this job.

The majority of 4th year pharmacy students reported that their primary source of DDI knowledge was their undergraduate study. Therefore, this study recommend the need for more comprehensive , focused education devoted to the area of DDIs in the pharmacy curriculum. While pharmacy graduates reported that pharmacy practice was the main source of DDI knowledge. However, the knowledge of the graduates according to this study showed less preferable response in compare to students.

Pharmacy students and graduates should receive more educational programs of DDIs to offer an appropriate patient counseling and best therapeutic outcomes. Clearly, educational programs such as continued drug interactions courses, practical pharmacy workshops and web resources are required. These should be followed by studies assessing their effectiveness in terms of pharmacists' knowledge and patient outcome.

CONCLUSION:

The background information of both students and graduated pharmacists was generally poor and focused more on the low therapeutic index drug interactions. However, they focusing more on severe DDIs, while ignoring DDIs that may be used together with monitoring.

This study found that DDIs knowledge of pharmacy students showed statistically significant responses in compare to graduates. However, this finding does not showed any significant difference between 4th year pharmacy students and pharmacy graduate in regard to identifying drugs pair that may be used together with monitoring. Therefore, these finding recommended to implement DDI course material into pharmacy curriculum in Benghazi university which may prepare pharmacy students and pharmacists for better practice, and has the potential to increase the quality of patient care. Community pharmacist should have specific courses in drug interactions to cover the most possible interactions that can be seen in this setting.

LIMITATION :

This study has many limitations. It anticipated that the student DDI knowledge assessment could be sufficiently provided by questionnaire. Also it assumed that, pharmacy students would have been exposed to DDI knowledge listed in the questionnaire in their curriculum. Additionally, The students were not permitted to use drug-interaction compendia to help them with their answers, but this is not an accurate reflection of real-world pharmacy practice.

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