ORIGINAL ARTICLE

Drug-drug Interaction Management in Internal Medicine Specialty

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Abstract

Aim: Many studies were conducted to ensure the role of clinical pharmacists in medication management and patient safety. However, there are no studies focused on drug interaction (DI) management in the Middle East hospitals. **Objectives:** The objectives of this study were to determine DI types, classify them according to their clinical significance, study their effect on the clinical outcomes, and raise recommendations about their management. **Materials and Methods:** Study Design - This prospective evaluation with descriptive analysis study conducted on 89 patients in the internal medicine department of a tertiary care hospital. Each DI was assessed using Lexicomp and Medscape DI databases, and based on its severity and its expected effect on the efficacy or toxicity of the treatment plan, certain interventions were provided to manage these DIs. The interventions included discontinuation of certain medications in case of severe interactions, monitoring of specific laboratory parameter such as international normalized ratio, potassium or digoxin serum levels, or changing certain drugs to another non-interacting one. **Results:** A total of 191 DIs were detected, 54.5% of them may increase the treatments' toxicities, and 45.5 % may decrease the treatment efficacy. Among the detected DIs, 33% required stopping one of the two drugs. About 29% of DIs required monitoring drug serum level or pharmacological effect. Pharmacokinetic interaction rate represented 67%. **Conclusion:** The results of this study emphasize the active role of clinical pharmacists in detecting and managing different types of DIs in internal medicine specialty. This is the first study that focuses on managing the DIs based on the patients' conditions.

Key words: Clinical pharmacy, drug interactions, internal medicine, pharmacodynamic interactions, pharmacokinetic interactions

INTRODUCTION

A drug-drug interaction (DDI) is defined as a decrease or increase in the clinical effect of a given drug due to interference by another drug, food, herbs, formulation excipients, containers, or environmental factors (such as tobacco). They are classified into three types: Pharmacokinetic (PK), pharmacodynamic (PD), and pharmaceutical.[1]

DDIs comprise a significant cause of morbidity and mortality worldwide as they may lead to adverse clinical events, result in decrease/inactivation of the therapeutic effect of a drug, and may enhance drug toxicity and indirectly compromise treatment outcomes and adherence.[2] Drug interactions (DIs) are one of the major therapeutic challenges to the treatment of inpatients.[3,4] The severity and frequency of the DIs are more prevalent when the patients are receiving multiple drugs.[5,6] Around 11.0% of patients may be found vulnerable for at least one DDI, and the chances of DDI increase nearly 40.0% among patients taking five drugs and >80% in patients taking seven or more medications.[4]

DIs can be classified into three types: PK, PD, and pharmaceutical. A PK interaction occurs when a drug alters the absorption, distribution, metabolism, and/or excretion of another. This results in an increased or decreased exposure to one or other drug. Most DDIs involve impaired drug elimination because of interference with hepatic metabolism, renal excretion, or transcellular transport.[7] A well-known PK mechanism is the interaction with the cytochrome P450 family. The PD interaction occurs when two drugs have similar mechanisms of action, for example, when two active substances compete for the same biological/physiological receptor or

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Received: 08-07-2017
Revised: 25-07-2017
Accepted: 31-07-2017

molecular target, *in vivo*. A pharmaceutical interaction may result from physical or chemical incompatibilities between two different drugs.[8] Regardless of the type of interaction, DIs may compromise treatment efficacy or increase drug toxicity, with serious clinical consequences; they can result in under-/over-dosing, the pharmacological effect can be boosted, or the drugs can become completely ineffective.[9]

Health-care clinical adverse outcomes are more likely if DDIs involve drugs with a low therapeutic index and elderly patients or patients with many comorbidities (renal, hepatic, impairment, etc.,). Polypharmacy in geriatric population is another factor which leads to increase in the rates of potential DIs.[7] The proportion of clinically significant DDIs ranges from 3% to 20% and is related to the number of medications taken by the patient. In a recent analysis of community prescribing in Scotland between 1995 and 2010, the proportion of adults prescribed ten or more drugs tripled while the proportion of potentially serious DDIs more than doubled. In a large prospective study of 18,820 patients, 6.5% of hospital admissions were related to an adverse drug reaction of which one in six was caused by a DDI.[10] These figures are likely to increase without preventive measures including prescriber education and clinical decision support tools.[7] There are limited data that reflect the clinical pharmacy service and its effectiveness in the secondary and tertiary care settings. Internationally, the role of the pharmacist is recognized in medication use review to ensure the element of medication safety in drug dispensing and administration.[11] The objectives of this study were (i) to determine the role of clinical pharmacists in identifying the types of DDI, classify them according to their clinical significance into contraindicated, serious, significant, and minor, and solve these DIs and (ii) to determine the incidences of PK and PD interactions and study their expected effect on increasing treatment toxicity or decreasing treatment efficacy. (iii) As a secondary objective, we compared between Lexicomp and Medscape DI software in the availability of DI information.

MATERIALS AND METHODS

Study design

This was a prospective evaluation with descriptive analysis study.

Patients

During a 3-month period, all patients admitted to the internal medicine department were enrolled in this study.

Inclusion criteria

Patients at any age group admitted to the internal medicine department and received at least three medications were included in the study. A total of 89 patients were enrolled in the study, and patients' demographics are shown in Table 1.

DI assessment methodology

The DDIs were recorded, and the nature of DI was assessed, i.e., the interaction is classified as PK or PD interaction. As a second step, the potential DIs identified in the study were classified by severity as contraindicated, serious, significant, and minor interactions. This classification of DI severity was done according to Medscape DI software classification system. Concerning DI's severity, interactions were classified as serious when they were life-threatening and required medical intervention, significant when they aggravated the patient's condition and required drug therapy change, minor when patients experienced any change in their clinical condition but did not require drug therapy change, and contraindicated when concomitant drug administration was not recommended. The detected DDI was analyzed by another DI software (Lexicomp). DIs were also categorized according to their expected effect on the therapeutic outcomes to: Interactions lead to increase in the treatment toxicity or interactions lead to decrease in the treatment efficacy based on their expected effects on the treatments' outcomes.

Physician's communication and follow-up

The investigator of this current study was a clinical pharmacy consultant who worked in the internal medicine department. If any DDI was detected during her rounds, the treating physician was contacted and informed to make the appropriate modifications in the treatment plan based on the clinical pharmacists' interventions.

Table 1: Characteristics of patients included in the study

Patients' characteristics	*N* (%)
Sex	
Female	39 (44)
Male	50 (56)
Age (years)	
Adults (12-65)	46 (51)
Elderly (>65)	43 (49)
Internal medicine specialty	
Neurology	21
Pneumology	19
Nephrology	16
Gastroenterology	13
Rheumatology	11
Others	9

Data analysis

During the study, a systematic analysis of all aspects of patient treatment was performed to detect potential DDIs. This review included all current patients' medications started during the current hospital admission or added to the patients' past medications. A data collection form was designed, on which the following variables were recorded: Age, sex, diagnosis, type of detected interaction, clinical significance of the detected interaction, the impact of the detected interaction on the toxicity and efficacy of the therapy, availability of information in two different DI checker software, detailed information about the mechanism of the detected DI and what action should be taken to manage this interaction (discontinue one of the interacting drugs, change to another alternative, or monitor specific clinical parameters), and the clinical pharmacists' interventions.

Clinical pharmacists' interventions in DDI management

Each DDI was assessed and based on its severity and its expected effect on the efficacy or toxicity of the treatment plan, and certain recommendations were done by the clinical pharmacist to manage these DDIs.

The clinical pharmacists' interventions (recommendations) were tailored based on the mechanism of the DI which was detected using Lexicomp and Medscape DI software. The interventions included discontinuing one of the interacting drugs if the interactions are severe. Other interventions included monitor specific laboratory parameter (international normalized ratio [INR], K level, or digoxin serum levels) or shifting certain drugs to another non-interacting one.

RESULTS

We analyzed data collected from 89 patients; 52% of whom were male and the rest were females. Patients' demographics are shown in Table 1. According to Medscape DI software, a total of 191 DDIs were detected; these interactions were classified according to their mechanism of interaction to: Interactions that may lead to an increase in the treatment toxicity or interactions that may lead to a decrease in the treatment efficacy. The clinical pharmacy interventions provided information to the treating physicians about the possible options to prevent these DIs. About 54.5% of the detected interactions would lead to an increase in the toxicity of drug regimens while 45.5% of them would lead to a decrease in treatment efficacy as shown in Table 2. Medscape DI software classify the different types of DDIs according to their severity or clinical significance into contraindicated, serious, significant, or minor; the numbers and percentages of these different types are shown in Table 2. Some of the detected DDIs were not found in the Medscape DI software

Table 2: The clinical significance, classification, and effects of different drug-drug interactions on the therapeutic outcomes

Drug information source documented the interaction, *N* (%)		Clinical significance*/action taken to solve the interaction, *N* (%)				Types of interaction, *N* (%)		Effect on therapeutic outcomes, *N* (%)	
Lexicomp	Medscape	Contraindicated	Serious interactions/use alternatives	Significant/monitor closely	Minor/not significant	NA	Pharmacokinetic	Pharmacodynamic	Increase in treatment toxicity	Decrease in treatment efficacy
191 (100)	147 (77)	7 (4)	56 (29)	55 (29)	30 (16)	44 (23)	129 (67)	62 (33)	104 (54.5)	87 (45.5)

*According to Medscape classification. NA: Not available in Medscape

(23%). The information about the mechanism of interaction and methods to prevent them was explained in another drug information reference which was Lexicomp. Figure 1 shows that 4% of the detected DDIs were contraindicated which required stopping one of the two drugs. Clarithromycin was involved in these two detected interactions, it was given empirically to treat community acquired pneumonia for these two patients, and it was given concurrently with indapamide in one case and with simvastatin in the other case. The clinical pharmacists' interventions were following up the culture and sensitivity reports and changing clarithromycin according to the detected microorganisms and monitor for any sign of toxicity. In these two previous interactions, it was easier to discontinue the empiric antibiotic than to discontinue the indapamide or simvastatin. Among the detected DIs, 29 % were labeled as serious DDIs, some of these interactions required change one of the two drugs, and others required close monitoring of specific clinical parameter. The details of different types, percentages, mechanisms, and clinical pharmacists' interventions regarding how to prevent these interactions are shown in Table 3. The majority of these interactions required monitoring of certain clinical parameters (example: INR or K level); the clinical pharmacist's responsibility was monitoring the laboratory tests for these patients on a daily basis to make sure that all the monitoring parameters are within the normal ranges. Other types of clinical pharmacists' interventions in this type of DIs were reducing drug doses or change some drugs to another drug from the same pharmacological category that may not induce the same interaction (example: Change from simvastatin to rosuvastatin to avoid the interaction with phenytoin). Significant interaction rate was 29% among all the detected interactions; these types of interactions required monitoring drug serum levels (phenytoin) or monitoring drug effect as shown in Table 3. The rest of interactions (30%) had minor clinical significance. PK interactions accounted for 67% of the detected interactions. These PK interactions may occur through change in the absorption, distribution, metabolism, or excretion of one of the interacting drugs, as shown in Table 3; the majority of the detected interactions in this current study were interactions affecting the serum level of one of the interacting drugs through increasing or decreasing its metabolism. Different mechanisms of PD interactions (33%) are also shown in Table 3. The physician acceptance rate to the clinical pharmacists' interventions was 78%.

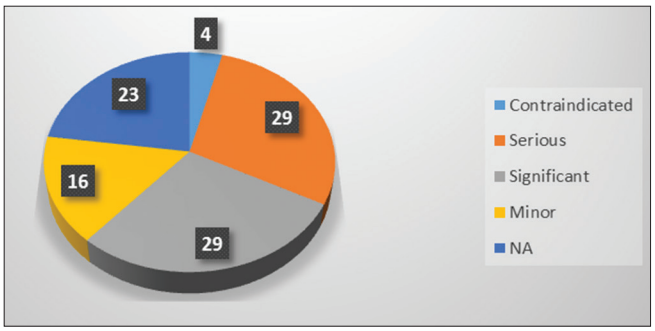

Figure 1: The clinical significance of the detected drug-drug interactions

DISCUSSION

Up to our knowledge, there are no studies conducted on DDIs focused on the recommendations for managing the detected interactions based on the patients' conditions. This is the first study concerned about providing recommendations about the different ways of solving these interactions based on the patients' investigations and laboratory data. The study detected a total of 199 DDIs and the clinical pharmacists' interventions succeeded in preventing and monitoring these interactions to prove the great impact of the clinical pharmacist as an effective member in the medical team. This current study was conducted in the internal medicine department because elderly patients in internal medicine departments are especially susceptible to many DDIs, due, among other factors, to the high number of drugs needed to treat their diseases. The clinical consequence of DIs involves interaction of two or more drugs either directly or indirectly and potentially alters its effectiveness and can increase the side effects. Weighing these risk factors, DIs may subsequently affect the severity of illness.[3] Identification of these factors is necessary to facilitate enhanced prescribing patterns. In reality, occurrence of DIs and associated risk is often not determined. In the current study, the prevalence of DIs was high in comparison with studies done in Iran, Ethiopia, Qatar, India, and Pakistan.[3-4,12-18] The current study was found to have the highest incidence of DIs. This is perhaps due to the involvement of clinical pharmacy services. Furthermore, it affirms the need for training for the medical staff and pharmacists to identify such events in day-to-day clinical practice. Moreover, these results highlight the need of clinical pharmacists in the ward setting to ensure the quality use of medicines and prove their role in direct patient care. All patients' files involved in this study showed at least one DI; Lees *et al.*[9] reported that only 92% of the patients included in their study suffered moderate-severe interactions. Popaand *et al.*[19] identified potential interactions in 75% of patients, but other authors have obtained lower figures, around 30-45%.[2,20,21] Van Leeuwen *et al.*[22] obtained potential DDIs in 46 % of patients treated with oral anticancer drugs (16% with major interactions). Clinically significance of the detected DIs is shown in Table 2 and Figure 1 which shows that 4% of the detected interactions were contraindicated according to the Medscape interaction checker classification, 29% were labeled with serious clinical significance, 29% were labeled with significant type and required close monitoring, and 16% were labeled with minor clinical significance. Lopez-Martin *et al.*[23] resulted in 35% serious DIs according to Lexicomp-interact and 27% according to Bot Plus. In relation to the detection of minor interactions, 85% of these patients presented category C interactions, according to Lexicomp-interact. The mechanism of the interactions previously described was PD in 33% of cases and PK in 67%; these rates were very similar to our

Table 3: The clinical significance, types and mechanisms of DDIs based on Medscape classification and the recommendations provided to solve these detected DDIs

The clinical significance of the detected DDIs	n.	Types	Mechanisms	Clinical pharmacists' recommendations
I. Contraindicated interactions				
Clarithromycin-Simvastatin	6	PK[#]	Clarithromycin will increase the simvastatin level through cyp 3A4	Change clarithromycin based on the C/S report and monitor for signs and symptoms of rhabdomyolysis
Clarithromycin-Indapamide	1	PD[+]	Both drugs will prolong the QT interval	Change clarithromycin based on the C/S report
II. Serious interactions				
Warfarin-Metronidazole	4	PK[#]	Metronidazole will increase the warfarin effect by decreasing the metabolism	Monitor INR closely and change metronidazole based on the C/S report
Omeprazole-Ketoconazole	2	PK[#]	Omeprazole will decrease the effect of ketoconazole by increasing the gastric pH	Change to IV omeprazole
Omeprazole-Carbamazepine	1	PK[#]	Carbamazepine will decrease the effect of omeprazole through cyp 2c19	No action should be taken (omeprazole is used for secondary prevention)
Metronidazole-Simvastatin	10	PK[#]	Metronidazole will increase the simvastatin level through cyp 3A4	Change metronidazole based on the C/S report
Phenytoin-Simvastatin	5	PK[#]	Phenytoin will decrease the effect of simvastatin through cyp 3A4	Change simvastatin to rosuvastatin to avoid the interaction
Clarithromycin-Digoxin	3	PK[#]	Clarithromycin will increase the level of digoxin through altering the intestinal flora	Monitor digoxin level and change clarithromycin based on the C/S report
Clarithromycin-Warfarin	6	PK[#]	Clarithromycin will increase level of warfarin by inhibiting the metabolism	Monitor INR closely and change clarithromycin based on the C/S report
Clarithromycin-Prednisolone	6	PK[#]	Clarithromycin will increase level of prednisolone through cyp 3A4	Change clarithromycin based on the C/S report
Diltiazem-Simvastatin	4	PK[#]	Diltiazem will increase the level of simvastatin through cyp 3A4	Reduce the simvastatin dose
Diltiazem-Tamsulosin	2	PK[#]	Diltiazem will increase the level of tamsulosin through cyp 3A4	Reduce the tamsulosin dose
Captopril-Azathioprine	1	PD[+]	Neutropenia due to pharmacodynamic synergism	Monitor closely for neutropenia
Captopril-Trimethoprim	2	PD[+]	Both drugs will increase the potassium level	Monitor K level
Captopril-Diclofenac	1	PD[+]	Both drugs will increase the renal functions' deterioration and increase the toxicity of each other Another mechanism: Diclofenac will decrease captopril effect by pharmacodynamic antagonism	Discontinue diclofenac
Furosemide-Amikacin	2	PD[+]	Nephrotoxicity will increase by pharmacodynamic synergism	Change amikacin to another antibiotic based on the *C/S report

(*Contd...*)

Table 3: (*Continued*)

The clinical significance of the detected DDIs	n.	Types	Mechanisms	Clinical pharmacists' recommendations
Furosemide-Gentamicin	2	PD+	Nephrotoxicity will increase by pharmacodynamic synergism Another mechanism: Increase the risk of hypokalemia	Change gentamycin to another antibiotic based on the *C/S report
Warfarin-Ceftriaxone	3	PD+	Ceftriaxone will increase the effects of warfarin and decreases the prothrombin activity	Monitor INR closely and change ceftriaxone based on the C/S report
Warfarin-Levothyroxine	2	PD+	Levothyroxine will increase the effects of warfarin by pharmacodynamic synergism	Monitor INR closely
III. Significant interactions				
Warfarin-Carvedilol	10	PK#	Both are substrates to CYP 2C9, 10 carvedilol effect may be increased	Monitor for decrease in blood pressure
Warfarin-Simvastatin	10	PK#	The effect of both of them may increase through CYP 3A4	Monitor for increased INR and rhabdomyolysis
Warfarin-Glibenclamide	1	PK#	Both are substrates to CYP 2C9, glibenclamide effect may increase	Monitor for hypoglycemia
Carbamazepine-Warfarin	1	PK#	Carbamazepine will decrease the warfarin's effect	Monitor INR closely
Phenytoin-Omeprazole	4	PK#	Omeprazole will increase the effect of phenytoin through CYP 2C9, 10	Monitor phenytoin level
Phenytoin-Metronidazole	10	PK#	Metronidazole will increase the effect of phenytoin through CYP 2C9, 10	Monitor phenytoin level and/or discontinue metronidazole
Phenytoin-Carbamazepine	10	PK#	Carbamazepine will decrease the effect of phenytoin through CYP 2C9	Monitor phenytoin level
Phenytoin-Lamotrigine	1	PK#	Phenytoin will decrease the effect of lamotrigine through decreasing its metabolism	Monitor for decrease of lamotrigine effect
Clarithromycin-Amlodipine	8	PK#	Clarithromycin will increase the level amlodipine through CYP 3A4	Monitor for decrease in blood pressure
$CaCO_3$-Metoprolol	1	PK#	Metoprolol effect will decrease due to decrease in the GI absorption	Monitor for increase in blood pressure and/or change $CaCO_3$ to sevelamer
$CaCO_3$-Levothyroxine	1	PK#	Levothyroxine effect will decrease due to decrease in the GI absorption	Monitor for increase in blood pressure and/or change $CaCO_3$ to sevelamer
Omeprazole-Warfarin	3	PK#	Omeprazole will increase the level of warfarin through Cyp 2C9/10	Monitor INR closely
Carbamazepine-Amlodipine	1	PK#	Carbamazepine will decrease the level of amlodipine by CYP 3A4	Monitor for increase in blood pressure
Carbamazepine-Lamotrigine	1	PK#	Carbamazepine will decrease the level of lamotrigine by increasing its metabolism	Monitor for decrease of lamotrigine effect

(*Contd...*)

Table 3: (*Continued*)

The clinical significance of the detected DDIs	n.	Types	Mechanisms	Clinical pharmacists' recommendations
Cefuroxime-Ranitidine	6	PK#	Ranitidine will decrease the level of cefuroxime by increasing the gastric pH	Change cefuroxime to augmentin
Fluconazole-Prednisolone	1	PK#	Fluconazole will increase the level of prednisolone through CYP 3A4 metabolism	Discontinue prednisolone (completed 5 days in status asthmatics)
Allopurinol-Warfarin	1	PD+	Allopurinol increases effects of warfarin	Monitor INR closely
$CaCo_3$-Amlodipine	3	PD+	$CaCO_3$ will decrease the effect of amlodipine by pharmacodynamic synergism	Monitor for increase in blood pressure and/or change $CaCO_3$ to sevelamer
$CaCo_3$-Nifedipine	2	PD+	$CaCO_3$ will decrease the effect of nifedipine by pharmacodynamic synergism	Monitor for increase in blood pressure and/or change $CaCO_3$ to sevelamer
$CaCo_3$-Lisinopril	5	PD+	Lisinopril effect will decrease	Monitor for increase in blood pressure and/or change $CaCO_3$ to sevelamer
IV. Minor interactions				
Metronidazole-Amlodipine	7	PK#	Metronidazole will increase the level of amlodipine through CYP 3A4	Monitor for decrease in blood pressure
Metronidazole-Clarithromycin	2	PK#	Metronidazole will increase the level of clarithromycin through CYP 3A4	Change clarithromycin to azithromycin
Phenytoin-Amlodipine	6	PK#	Phenytoin will decrease the level of amlodipine CYP 3A4	Monitor for increase in blood pressure
Phenytoin-Furosemide	7	PK#	Phenytoin will decrease the level of furosemide by decreasing the GI absorption	Monitor for decrease in furosemide efficacy
Phenytoin-Levothyroxine	3	PK#	Phenytoin will decrease the level of levothyroxine by increasing its metabolism	Monitor for decrease in levothyroxine efficacy
Phenytoin-Acetaminophen	1	PK#	Phenytoin will decrease the level acetaminophen by increasing its metabolism	Discontinue acetaminophen, the patient was free of pain
Phenytoin-Topiramate	1	PK#	Topiramate will increase the level of phenytoin by decreasing its metabolism	Monitor phenytoin level
Digoxin-Carvedilol	1	PD+	Both of the two drugs increase the potassium levels	Monitor digoxin level
Fluconazole-Amikacin	1	Unknown	Fluconazole will decrease level of amikacin by unknown mechanism	Monitor amikacin level
Warfarin-Paracetamol	1	Unknown	Increase in the effect of warfarin by unknown mechanism	Monitor INR closely

*C/S report: Culture and sensitivity report, #PK: Pharmacokinetics, +PD: Pharmacodynamics, GI: Gastrointestinal

results as shown in Table 2. Another study conducted by Albadr *et al.*[24] concluded that 47 % of the detected DIs were PD and 53% were PK. This study used similar methodology, and the incidences of PK and PD interactions were similar to our results. However, their study did not consider the interventions for managing these detected DDIs. The clinical pharmacists' interventions in this current study succeeded in preventing and managing many of the detected DDIs in many internal medicine specialties as shown in Table 3. Description of the effect of DIs on the therapeutic outcomes is shown also

in Table 1, 54.5% of the detected DIs may lead to increase in the treatment toxicity, and 45.5% may lead to decrease in treatment efficacy. Lopez-Martin *et al.*[23] studied the effect of DIs on the therapeutic outcomes in cancer patients and found that 80.3% of the detected were related to treatment toxicity and 19.7% to efficacy. Clinical pharmacists' interventions succeeded to prevent and manage many of the detected DDIs as shown in Table 3, and the degree of acceptance by the attending physician after communication of the need for treatment modification was very high. Similar results were obtained by de Maat *et al.*[25] who concluded that the advice of a clinical pharmacist was effective in the studied setting. Their study was conducted on HIV patients and focused only of infectious specialty. The novelty of this current study is: It focused on many internal medicine specialties and the patients included in this current study were treated from neurology, pneumology, nephrology, gastroenterology, rheumatology, and other internal medicine diseases. The fact that the pharmacist is a member of the hospital multidisciplinary internal medicine team could have contributed to obtain the high rate of interventions acceptance. Detection of interactions in elderly and internal medicine patients plays a key role in the management of the pharmacotherapy in these patients, not only by the high incidence found, but also by the consequences they may have. Clinical pharmacists are uniquely trained in therapeutics and provide comprehensive drug management to patients and members of the health-care team. In addition to this, their demonstrated capacity to review the patient's drug list and their knowledge about detection and management of interactions makes the pharmacist as the most qualified professional to develop this task. However, further studies are needed to establish the incidence and impact of DIs in other medical specialties to professionals realize the magnitude and importance of this topic.

CONCLUSIONS

The outcomes of clinical pharmacists' interventions in decreasing the treatment toxicity and increasing its efficacy had led to improve the health-care clinical patients' outcomes as decreasing morbidity and mortality together with decrease in the expected treatment costs. Further study will be conducted to estimate the impact of these interventions in the expected treatment costs. In conclusion, this current study emphasizes the active role of clinical pharmacists in detecting and managing different types of DIs in internal medicine specialty. Intensive monitoring of each prescription by the clinical pharmacist and further providing DDI alerts to the prescribers in internal medicine ward can be helpful to avoid negative outcome of these DDIs.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Source of Support: Nil. **Conflict of Interest:** None declared.