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Impact of Clinical Pharmacist Educational Intervention on the Potential Drug-Drug Interactions in Surgical Intensive Care Unit

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ABSTRACT

ICU patients are at high risk of drug-drug interactions. In Middle East there is no sufficient data about the incidence of drug interactions. To explore the frequency and pattern of potential drug-drug interactions (PDDIs)and to study the impact of clinical pharmacist educational intervention on the (PDDIs) in surgical intensive care unit. A three phases study,phase (1) (pre-intervention phase)wasaretrospective cohort study of the frequency of potential DDIsin 500 prescriptions of patients in surgical ICU using Lexi-Interact interaction database. Phase (2) (intervention phase) involved the implementation of DDIs reducing measures. Phase 3 (post-intervention phase) was a prospective study of the frequency of potential DDIs in the 500 prescription collected after intervention phase (phase 2). A total of 2228 PDDIs were identified during phase 1 and 2139 PDDIs were identified during phase 3. In both phases most of the PDDIs encountered were of 'Moderate' severity (89%) of the PDDIs during the pre-intervention phase and 91.5% during the post-intervention phase were of risk rating C. There was no statistical difference between mean number of PDDIs in pre-intervention and post-intervention phases (*P*=0.859). There was no statistical difference in percent of PDDIs in the different degrees of severity between pre-intervention and post-intervention phase (Z=-1.4, *P*= 0.153). The present study demonstrated a relatively high frequency of occurrence of PDDIs among patients in surgical ICU. However, most of them were of minor-to-moderate clinical significance.

Keywords: Clinical pharmacist, intensive care, drug interactions.

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INTRODUCTION

The awareness of preventable medical errors was heighlighted in the Institute of Medicine's report ''To Err is Human, Building a Safer Health System,''[1]. Drug-drug interactions, a subclass of preventable medical errors, are particularly concerning because they are associated with an increase in patient morbidity and mortality [2]. A drug interaction takes place when the effects and/or toxicity of a drug are affected by another drug [3]. Although results may be positive (increased efficacy) or negative (decrease of efficacy, toxicity or idiosyncrasy), in pharmacotherapy they are usually unforeseen and undesirable [4]. It has become difficult for physicians and pharmaceutics to be familiar with all potential interactions with the continued development of new drugs and subsequent prescriptions with increasingly more complex combinations [5]. Drug–drug interactions (DDIs) in the intensive care unit (ICU) are associated with longer ICU stays, adverse drug events and end-organ damage[6,7]. Because of the large number of medications they receive and pharmacokinetic characteristics of the administered medicationscritically ill patients are at an increased risk of adverse drug events related to DDIs [8,9]. Drug–drug interactions software and clinical decision support software (CDSS) are recommended in the literature to aid prescribers and pharmacists in DDI identification [10]. Adverse drug reactions (ADRs) are very common in intensive care patients. It is difficult to quantify the true incidence of ADRs, butaccording to some studies it can approach 29.7 per 100 admissions[11]. Critically ill patients are commonly prescribed multiple medications that can potentially interact with each other. Drug-drug interactions may be responsible for 3% to 5% of all preventable in-hospital ADRs [12]**.** Another problem with DDI in the intensive care patients is potential loss of therapeutic efficacy leading to treatment failure. The incidence of DDI leading to treatment failure in medical intensive care unit (MICU) patients is unknown [13]. Not every healthcare provider can distinguish potential DDIs from ADRs, and take corrective measures accordingly. In a survey study, Glassman and his colleagues found that only 44% (ranging from 11 to 64%) of clinicians have correctly identified all drug–drug pairs[14]. A clinician's understanding of DDI can decrease the likelihood of ADR, safeguard patient safety, and avoid associated medicolegal problems. This study aimed to explore the pattern and frequency of potential drug-drug interactions as well as their risk rating and to study the impact of clinical pharmacist educational intervention on the pattern and frequency of potential drug-drug interactions (DDIs) in surgical intensive care unit.

PATIENTS AND METHODS

This three phases study was conducted at El-DemerdashUniversity Hospital, (Surgey unit, surgical intensive care unit) Cairo, Egypt through a period of 12 months. The study was approved by the ethical committee of faculty of pharmacy Ain Shams University. The study phases were phase 1 (pre-intervention phase), phase 2 (intervention phase), and phase 3 (post-intervention phase). During the study, all patients who were admitted to the surgical ICU were included. Lexi-Comp database (Lexi-Comp, Inc, Hudson, Ohio) was used to identify and analyze DDIs. Lexi-Comp database categorizes DDIs on the basis of their risk rating. It also provides the mechanism of the DDIs, clinical outcomes and management of the DDI. Risk rating for DDIs are defined by Lexicomp in table (1).

Table 1: Risk rating for drug-drug interactions

Risk rating	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	No action needed	Data demonstrate that the specified agents may interact with each other,but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these 2 medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects.Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	Data demonstrate that the 2 medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, and choosing alternative agents.
×	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Phase (1) (pre-intervention phase) was a retrospective cohort study of the frequency of potential DDIs as well as their risk rating, and management in the last 500 prescriptions of patients in surgical ICU department of surgery, El Demerdash University Hospital before January 2014. A pilot study was conducted for two weeks prior to the commencement of the main study. This was to test the feasibility and practicability of the methodology, and to ensure

that there was a considerable number of drug-drug interactions that could be screened for using Lexi-Comp database. The patient age, sex, cause of admission, comorbidities, drug regimen and related parameters were entered in the designed structured patient profile form. DDIs were found using Lexi-Comp database. Data was analyzed using an Excel sheet and a 'pre-intervention report' was made. The pre-intervention report included the following: age, sex, cause of admission, comorbidities, potential DDIs in prescriptions, risk rating, mechanism of potential DDIs, and management. The report also listed the highest risk interaction found during the pre-intervention phase. Phase (2) (Intervention phase) involved the implementation of DDIs reducing measures by using educational methods of awareness to physicians (informational poster and booklet) as shown in figure 1 and 2 respectively. Phase (3) (post-intervention phase) was a prospective study of the frequency of potential DDIs as well as their risk rating in the 500 prescription collected after intervention phase (phase 2) to measure the impact of those drug-drug interactions reducing measures. Post-intervention phase was conducted identically as the pre-intervention phase. After completing the data collection, the impact and outcomes of intervention on the pattern and frequency of potential DDIs was found comparing both the pre and post intervention data.

Awareness step after investigating the PDDIs in the surgical intensive care unit in El-Demerdash University Hospital, group meetings were arranged with the physicians to illustrate the collected data of pre-intervention phase regarding the frequency, risk rating. Two meetings were performed; each of them was two hour duration. At the end of the second meeting booklets were given to the physicians. The informational poster was mounted on the unit board. The poster contained most potentially clinically significant drug-drug interactions in surgical ICU and their management based upon Lexi- Interact™ interaction database. The poster contained only management of PDDIs with risk rating × and D.

RESULTS AND DISCUSSION

Demographic data and patient characteristics:

The demographic data and characteristics of the patients in pre-intervention and post-intervention group are summarized in table (2). There was no significant difference between the two groups regarding gender, age, cause of admission to the surgical ICU and comorbidities (*p*-value > 0.05).

Table 2: The demographic data and patient characteristics of patients in the study groups

Parameter	**Pre-intervention group (N=191)**	**Post-intervention group (N=198)**	***p*-value**
Age (years): Median (range)	 50 (4-82)	 52 (4-90)	 0.414
Statistical test: Mann-Whitney test, *p*-value > 0.05: non-significant.			
Gender: Male: Number (%) Female: Number (%)	 94 (49.2%) 97(50.8%)	 103 (52%) 95 (48%)	 0.580
Statistical test: Chi square (χ^2) test, *p*-value > 0.05: non-significant.			
Admission cause: Number (%) POC Trauma Medical	 73 (38.2%) 50 (26.2%) 68 (35.6%)	 93 (47%) 44 (22.2%) 61 (30.8%)	0.218
Comorbidities:Number (%) Cardiovascular Metabolic Respiratory disease Renal disease Hepatic disease	N=115 53 (27.7%) 28 (14.7%) 25 (13%) 27 (14.1%) 20 (10.5%)	N=136 96 (48.5%) 75 (37.9%) 26 (13.3%) 32 (16.2%) 21 (10.6%)	0.08
Statistical test: Chi square (χ^2) test, *p*-value > 0.05: non-significant.			

N; number of patients,POC; Post Operative Care

Phase 1: pre-intervention assessment

During the pre-intervention phase, 191 patients with 500 patient medication order were evaluated.Of these 500 evaluations, 404 evaluations revealed one or more potential drug-drug interactions.A total of 2228 potential DDIs were identified. According to the Lexi-Ineract™ ineraction database risk rating, most (89.2%) of the potential DDIs encountered were of class C type, and 6.4% were of classes × and D type.

Phase 3: post-intervention assessment

During the post-intervention phase, 198 patients with 500 patient medication order were evaluated.Of these 500 evaluations, 359 evaluations revealed one or more potential drug-drug interactions. A total of 2139 potential DDIs were identified. According to the Lexi-Ineractineraction database risk rating, most (91.5%) of the potential DDIs encountered were of class C type, and4.8% were of ofclasses × and D type.

Comparison of pre-intervention and post-intervention phases

There was a positive correlation between number of drugs and number of interactions per prescription in both phases, in pre-intervention phase r = 0.77 and in post-intervention phase r = 0.78, both are significant at 0.05 level (2-tailed).

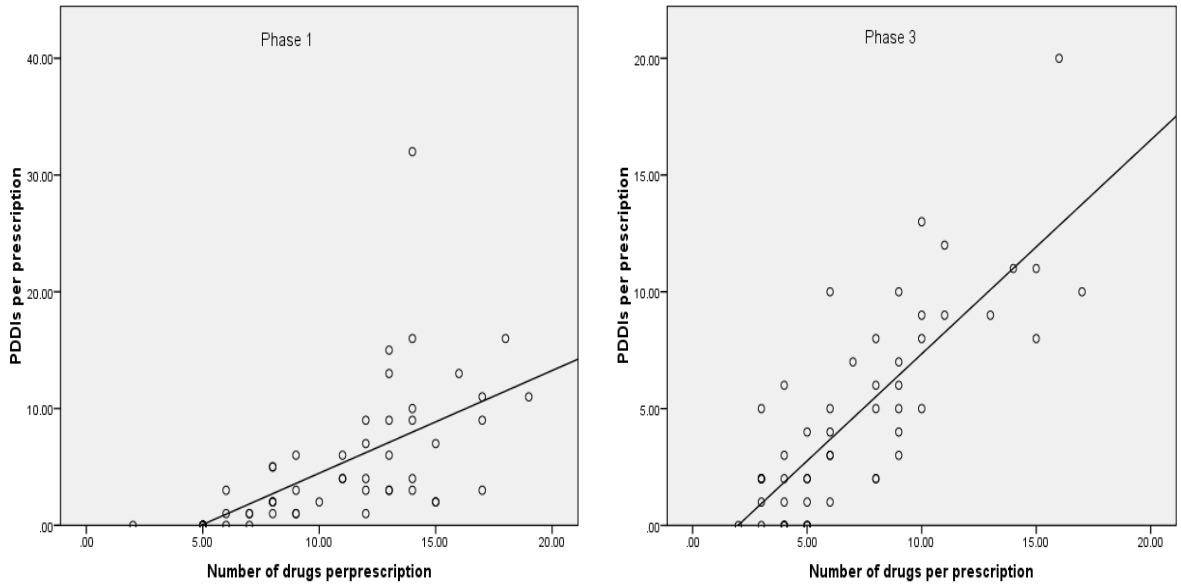

Figure.1: A scattered plot graph of number of drugs per prescription and number of potential drug drug interactions per prescription during phase 1 and phase 3

In pre-intervention phase, the average number of PDDIs per prescription was 5.1 interactions per prescription and standard deviation was 5.8, while in post-intervention phase, the average number of PDDIs per prescription was 4.7 interactions per prescription and standard deviation was 4.2. By comparing means using Mann-Whitney test it is concluded that there is no statistical difference between mean number of PDDIs in pre-intervention and post- intervention phases (p=0.859) at 0.05 level (2-tailed).

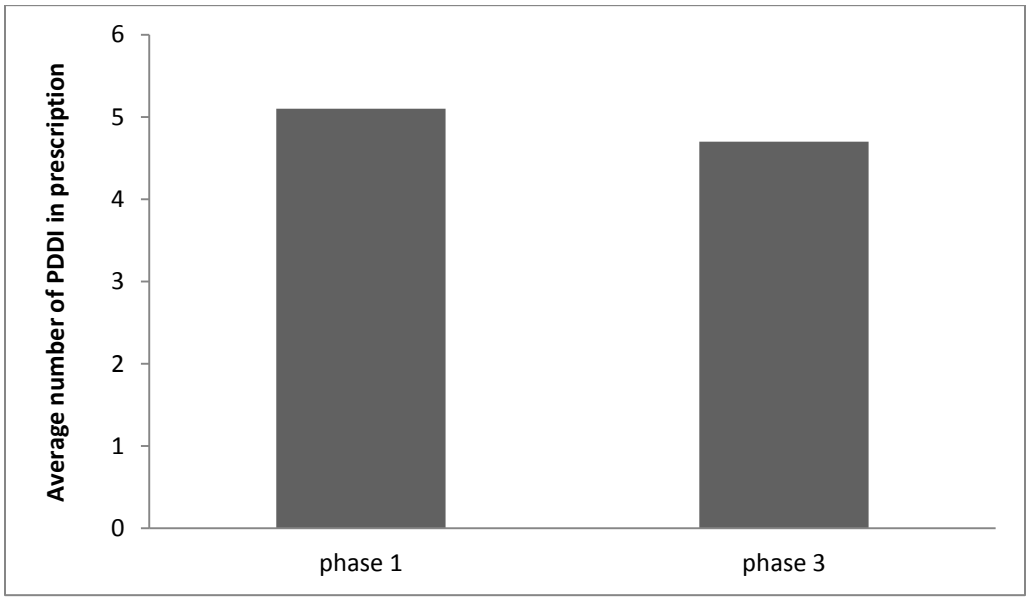

Figure.2: Comparison of the average number of PDDIs in prescriptions in phase (1) (pre-intervention) and phase (3) (post-intervention)

Table (3) shows Wilcoxon signed ranks test with no statistical difference in percent of PDDIs in the different degrees of severity between pre-intervention and post-intervention phase (Z=-1.4 ,*P*= 0.153) at 0.05 level (2-tailed). The frequency of the ten most common potential drug-drug interactions, identified through Lexi- Interact™ during the pre and post intervention phases is listed in table (4)

Table 3: Percent of interactions in the different degrees of risk rating of DDIs between pre-intervention and post-intervention phases

Degree of severity of DDIs	DDIs in pre-intervention phase (%)	DDIs in post-intervention phase (%)
×	0.7%	0%
D	5.7%	4.8%
C	89%	91.5%
B	3.9%	3%
A	0.8%	0.6%

DDIs; Drug Drug Interactions

Table 4: The frequency of the ten most common potential drug-drug interactions, identified through Lexi- Interact™ during the pre and post intervention phases

Pre-intervention phase Total DDI (n=2139)	Frequency (number)	Percentage (%)	Post-intervention phase Total DDI (n=2228)	Frequency (number)	Percentage (%)
Potassium chloride-tinzaparin	125	5.6	Potassium chloride-enoxaparin	97	4.5
Phenytoin-omeprazole	65	2.9	Capoten-nitroderm	58	2.7
Potassium chloride-enoxaparin	62	2.7	Capoten-enoxaparin	56	2.6
Acetaminophen-phenytoin	41	1.8	Enoxaparin-aspocid	49	2.2
Furosemide-phenytoin	38	1.7	Bisoprolol-nitroderm	47	2.1
Omeprazole-fluconazole	37	1.6	Potassium chloride-tinzaparin	44	2
Phenytoin-MgSO4	36	1.6	Bisoprolol-capoten	43	2
Furosemide-mannitol	35	1.57	Aldactone-enoxaparin	38	1.7
Capoten-enoxaparin	33	1.48	Aldactone-Potassium chloride	32	1.4
Capoten-Potassium chloride	33	1.48	Nitroderm-aspocid	30	1.4

Adverse drug reactions (ADRs) are very common in intensive care patients. Critically ill patients are commonly prescribed multiple medications that can potentially interact with each other. Results from the Harvard Medical Practice Study II disclose that complications related to use of drugs are the most common type of adverse events in hospital care (9% of the patients). Of the

hospitalized patients 2-3% experience reactions specifically caused by pharmacological interactions. In intensive care units (ICU) studies have disclosed that potential drug interactions may occur in 44.3 to 95% of patients. However, studies are scarce and limited, regarding the real assessment of their clinical values[5]. Considering that patients in the ICU often are aged and have physiological alteration, summing up to unfavorable clinical conditions for drug metabolism such as shock, renal failure and hepatic disease, it might be inferred that relevance of potential interaction, even if not very significant, is relevant for prevention of undesirable adverse effects.The results of this study confirm this finding. In pre-intervention phase a total of 2228 PDDIs were found, but only 6.4 % of them were classified as severe (grade × and D in Lexi-Interact™ interaction database). In Egypt there is a lack of an effective screening system for detecting DDIs both at the level of prescribing by physicians and also at dispensing from community pharmacies. Almost all prescriptions are handwritten. Usually patient's medication history can be accessed through manual observation of patient's prescriptions and all DDIs have to be identified manually. The present study observed that polypharmacy was common. In our study, the number of interactions increased with an increase in the number of drugs prescribed, in accordance with the results of previous studies[13,15]. The use of a computerized drug interaction surveillance system may be a helpful tool to identify and prevent drug interactions of clinical significance. However, a common problem with these systems is that they identify a large number of drug-drug interactions with unclear clinical significance or irrelevance, which can lead clinicians to alert fatigue [16]. This highlights the importance of our study in elucidating the most significant alerts, not necessarily the most common alerts, in providing data for developing a clinical drug interaction surveillance system. Lexi-Interact™ interaction database was used to identify and provide consistent and objective analysis of potential drug-drug interactions. This database was chosen because it is accessible and highly used by practitioners. When evaluating DDIs, one primary concern was the clinical significance or level of severity of the interaction. Significance relates to the type and magnitude of the effect and subsequently, the necessity of monitoring the patient or altering the therapy to avoid potentially adverse consequences. Although a large number of DDIs were detected in this study, only 6.4% of them were considered to be most potentially clinically significant during the pre-intervention phase. The majority of the DDIs were of moderate significance, where monitoring of the DDI was sufficient and concomitant use of precipitant and object drugs was not harmful. Egger et al likewise reported that the majority of DDIs found in their study were of moderate severity (n = 281, 69.9%)[17]. Although a few studies have documented that potentially significant DDIs were highly

prevalent, the number of DDIs associated with potentially relevant clinical consequences was relatively low and rare[17,18]. Our results regarding the percentage of potential interactions of significance level × and D revealed a total of 142 interactions (6.4%) during the preintervention phase. Of the 142 interactions 15 (10.5%) of significance level × and 127 (89%) of significance level D. Our results are lower than findings reported from a study conducted in the US in medical intensive care patients, which repoted that 25 interactions (14.3%) were considered clinically significant by the critical care pharmacist, 4 (16%) were of significance level X, and 21 (84%) were of significance level D[13]. Our values are almost similar to the findings reported from a study conducted in the US, which reported 7.3% of Major DDIs in a surgical intensive care unit[19]. An appropriate approach to the management of DDIs should be based on identifying the potential DDIs and then taking the necessary measures, such as therapeutic drug monitoring or dose adjustment, to reduce the likelihood of clinically relevant consequences. In accordance with the results of our study, a study from Malaysia carried out in combined ICU reported that more than half of the study patients were still administered the same drugs found to be involved in clinically significant DDIs (Type-D and Type-C) after a pharmacist intervention was carried out[15]. The most common potential DDIs observed during the pre-intervention phase were between potassium chloride-tinzaparin (5.6%), followed by phenytoin-omeprazole (2.9%), and KCl-enoxaparin (2.7%). Unlike in our finding, a study done in a surgical ICU in US found that the most common DDIs were between neuromuscular blockers- aminoglycoside antibiotics, followed by digoxin- quinidine, and potassium-spironolactone[19]. In a prospective analysis of 18 820 patients, aspirin with warfarin, aspirin with other NSAIDs, combinations of diuretics or the concomitant use of diuretics and ACEIs, digoxin toxicity through co-prescription of interacting drugs were the common causes for admission to the hospital due to ADRs[20]. During the post-intervention phase, the most common potential DDIs identified were between potassium chloride-enoxaparin (4.5%), followed by capoten-nitroderm (2.7%), and capoten-enoxaparin (2.6%). Cardiovascular drugs are also of particular concern because several of these were also identified as frequently occurring interactions during post-intervention phase. Similar to our findings, a study from England reported cardiovascular drugs as the major drugs involved in ADRs [20]. In cardiovascular diseases, polypharmacy cannot be ignored. For example the recent JNC VII guidelines recommendspolypharmacy in managing diseases like hypertension [21]. Moreover, conditions like hypertension are associated with other concurrent complications that might increase the risk of potential DDIs.

CONCLUSION

There was a direct link between polypharmacy and occurrence of DDIs. The present study demonstrated the leading role of clinical pharmacist in the detection of PDDIs. In our study most of the interactions were found to be very common and potentially significant. We identified major and contraindicated potential drug-drug interactions occurring in surgical ICU patients. Implementation of a computerized drug-drug interaction surveillance system, based on interaction severity, could use the data described in this study as a foundation to develop a knowledge base. The study also demonstrated that educational interventions can minimize the frequency of DDIs of significant clinical importance (class× and D). These educational activities didn't remove all the risks and ICU patients at the hospital are still subjected to significant drug-drug interactions, though at lower rate and severity than before intervention. This calls for more pharmacists' involvement in the medication use process to improve patient safety.

RECOMMENDATIONS

The actual impact on adverse clinical outcomes from interactions were not investigated in this study. Thus, to what extent the pharmacist educational activities decreased interactions actually result in clinical benefit needs to be investigated.

REFERENCES

1. Brown A, Patterson DA. 2001. To err is human. In: Proceedings of the First Workshop on evaluating and architecting system dependability.
2. Smithburger PL, Kane-Gill SL, Seybert AL. 2010. Drug-drug interactions in cardiac and cardiothoracic intensive care units. Drug Safety 33:879-888.
3. Jankel CA, Speedie SM. 1990. Detecting drug interactions: a review of the literature. Annals of Pharmacotherapy 24:982-989.
4. Streetman DS. 2000. Metabolic basis of drug interactions in the intensive care unit. Critical care nursing quarterly 22:1-13.
5. Hammes JA, Pfuetzenreiter F, Silveira Fd, Koenig Á, Westphal GA. 2008. Potential drug interactions prevalence in intensive care units. Revista Brasileira de Terapia Intensiva 20:349-354.
6. Plaza J, Alamo M, Torres P, Fuentes A, López F. 2010. [Drug interactions and adverse events induced by drugs used in an intensive care unit]. Revista medica de Chile 138:452-460.
7. Moura C, Prado N, Acurcio F. 2011. Potential drug-drug interactions associated with

prolonged stays in the intensive care unit. Clinical drug investigation 31:309-316.

8. Lima REF, Cassiani SHDB. 2009. Potential drug interactions in intensive care patients at a teaching hospital. Revista latino-americana de enfermagem 17:222-227.
9. Reis AMM, Cassiani SHDB. 2011. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics 66:9-15.
10. Smithburger PL, Buckley MS, Bejian S, Burenheide K, Kane-Gill SL. 2011. A critical evaluation of clinical decision support for the detection of drug-drug interactions. Expert opinion on drug safety 10:871-882.
11. Dubaybo BA, Dingell JD. 2005. Adverse Drug Reactions in the ICU Lessons Learned. CHEST Journal 128:1100-1101.
12. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, Hallisey R, Ives J, Laird N, Laffel G. 1995. Systems analysis of adverse drug events. JAMA 274:35-43.
13. Rivkin A, Yin H. 2011. Evaluation of the role of the critical care pharmacist in identifying and avoiding or minimizing significant drug-drug interactions in medical intensive care patients. J Crit Care 26:104. e101-104. e106.
14. Glassman PA, Simon B, Belperio P, Lanto A. 2002. Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. Medical care 40:1161-1171.
15. Hasan SS, Lim KN, Anwar M, Sathvik BS, Ahmadi K, Yuan A, Kamarunnesa MA. 2012. Impact of pharmacists' intervention on identification and management of drug-drug interactions in an intensive care setting. Singapore medical journal 53:526-531.
16. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. 2005. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 293:1223-1238.
17. Egger SS, Drewe J, Schlienger RG. 2003. Potential drug–drug interactions in the medication of medical patients at hospital discharge. European journal of clinical pharmacology 58:773-778.
18. Glintborg B, Andersen SE, Dalhoff K. 2005. Drug-drug interactions among recently hospitalised patients–frequent but mostly clinically insignificant. European journal of clinical pharmacology 61:675-681.
19. Oeser DE, Polansky M, Thomas N, Varon J. 2003. Incidence of major drug interactions and associated adverse drug events in a surgical intensive care unit. Internet J Pharmacol 2.

20. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. 2004. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329:15-19.
21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT. 2003. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560-2571.