



## The Impact Of Clinical Pharmacists' Interventions On Drug-Related Problems At The Military Hospital, Omdurman, Sudan

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**Abstract:** Clinical pharmacists can help to identify, solve and prevent drug-related problems (DRPs) through appropriate interventions. The objective of this retrospective study was to identify DRPs, their causes and to evaluate how the clinical pharmacists' interventions can impact on them in the medicine department at the Military Hospital, Omdurman, Sudan. A total of 100 files belonging to patients admitted between September 2018- March 2019 were analyzed in this study according to specific criteria, of which 170 Clinical pharmacists' Intervention (CPIs) were made, and 152 DRPs were identified. The most common DRP found was untreated indication (not prescribed drug but clear indication) accounting for 32.9% (n=50) of total studied cases, followed by sub-therapeutic dose 14.5% (n=22), and drug interactions 12.5% (n=19). Interventions were made by clinical pharmacists based on the type of DRP. The acceptance of intervening pharmacist suggestions was found to be 57.6% (n=98), the remaining 41.8% (n=71) of interventions were not accepted. The study highlighted that the participation of clinical pharmacists in the medical ward had a positive impact on optimization of drug therapy by reducing drug-related problems.

**Keywords:** Clinical pharmacist, Drug-related problems, acceptance, Clinical pharmacists' Intervention.

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## 1. INTRODUCTION

Previously, the concepts of clinical pharmacy were announced as “hot new trends” in the 1960s by pharmacy educators as a type of pharmacy practice, which is concerned with patients rather than drug<sup>1</sup>. Recently, clinical pharmacy is considered as a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention<sup>2</sup>. Clinical pharmacy was introduced in Sudan in 2001 as a subject in the Universities undergraduate pharmacy curriculum. Postgraduate clinical pharmacy education was started in 2004 as a “2-year” master program. Thereafter, postgraduate clinical pharmacy education expanded further, as several pharmacists started master degrees in clinical pharmacy programs. Unfortunately, the unavailability of suitable facilities, absence of resources, and unavailability of well-trained clinical pharmacists all challenge the progress of clinical pharmacy education in Sudan<sup>3</sup>. The role of Clinical pharmacists is to assess the status of the patient's health problems and determine whether the prescribed medications optimally meet the patient's needs and goals of care. Moreover, evaluate the appropriateness and effectiveness of the patient's medications. In addition to recognition of untreated health problems that could be improved or resolved with appropriate medication therapy, following the patient's progress to determine the effects of the patient's medications on his/ her health. Clinical pharmacists also consult with the patient's physicians and other health care providers in selecting the medication therapy that best meets the patients' needs and contribute effectively to the overall therapy goals. They also advise the patient on how to best take his or her medications, support the health care team's efforts to educate the patient on other important steps to improve or maintain health, such as exercise, diet, and preventive steps like immunization<sup>4</sup>. A cornerstone of clinical pharmacy is the identification, solving and prevention of drug-related problems (DRPs). DRP is defined as an ‘event or circumstance involving a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal therapeutic outcome’<sup>5</sup>. An actual problem has resulted in clinical manifestations (e.g. a drug-related rash, an adverse drug reaction), or therapy failure due to incorrect dosage. A potential problem is not manifested, but if left unresolved, it may lead to drug-related harm to the patient<sup>6</sup>. Categorization of DRPs can serve as a focus for developing a system for pharmacists to contribute significantly to positive patients' outcomes. Several research groups and organizations have developed their own systems for the classification of DRPs; including the Pharmaceutical Care Network Europe<sup>5</sup>, The American Society of Health-System Pharmacists<sup>7</sup> are perhaps the most well-known and used among pharmacists<sup>8</sup>. According to the classification scheme of the PCNEF version 5.01, five types of DRP exist including: ADRs, drug choice problem, dosing problem, drug use problem and interactions on which this study is based on. Clinical pharmacists can help to identify and resolve DRPs through appropriate interventions<sup>9</sup>. Examples of CPIs include advising patients of drug information and instructions for use or changing the drug prescription, dosage, formulation or regimen. In addition, if needed, CPs can also provide medication counselling and education for patients regarding ADR presentations and drug interactions<sup>10</sup>. In Sudan, many studies were done to assess the role of CPs, the self-perception of CPs regarding their roles in hospitals, how

doctors perceive and the obstacles that face them in implementing clinical pharmacy in hospitals. One study showed that the roles that were perceived by the majority of pharmacists as part of their tasks in hospitals in Sudan were identifying drug-related problems (100%, n= 51), providing drug-related information to healthcare workers by (96%, n= 47), and educating patients about their medicines (96%, n= 48)<sup>11</sup>. Another study found that doctors and nurses had a good acceptance of clinical pharmacists' interventions compared to senior doctors. Also, they found that the main obstacle the clinical pharmacist faced was their limited number, lack of support from health authorities, lack of job descriptions, lack of specific area in the patients' files for their intervention, and low salaries<sup>12</sup>. However, more studies in the field are needed to evaluate the impact of CPIs in decreasing the DRPs. The main aim of the present study was to evaluate the impact of clinical pharmacists' interventions on drug-related problems in the medicine department at the military hospital, Omdurman, Sudan. Moreover, determination of the percentage of DRPs identified by clinical pharmacists (adverse reactions, drug choice problem, dosing problem, drug use problem, and interactions) in the basis of pharmaceutical care network Europe foundation (PCNE) version 5.01. Also, identification of the frequency of interventions suggested by the clinical pharmacists at drug level, and at prescriber level. Assessment of interventions suggested by clinical pharmacists whether correct or not according to references. Finally, investigation of the outcome of clinical pharmacists' interventions whether DRPs are solved or not solved.

## 1. METHODS

### 2.1 Study Design, duration and settings

The present manuscript is a retrospective study, which was done in Medicine department at military hospital, Omdurman. The study duration was seven months from September 2018- March 2019.

### 2.2 Study Population, sample size and sample method

We checked files of patients admitted to the medicine department at the military hospital, Omdurman. We included files of patients admitted to the medicine department with clinical pharmacists' interventions at the military hospital, Omdurman from September 2018- March 2019. We excluded files of patients admitted to the medicine department without clinical pharmacists' intervention at the military hospital, Omdurman. One Hundred and seventy clinical pharmacists' interventions were collected from hundreds of patients admitted to the medicine department at military hospital, Omdurman. The sample was convenient, non-random sampling.

### 2.3 Data collection

Data were collected using a checklist composed of three parts: (drug related problems, clinical pharmacist interventions and the outcome of the intervention) based on the classification scheme of the Pharmaceutical Care Network Europe Foundation (PCNEF) version 5.01. The CPI were evaluated according to online references (Medscape, drugs.com, and ACCP guidelines 2017). Data were collected retrospectively from patients' files (including lab reports,

nephrology unit reports and medication profile).

2. STATISTICAL ANALYSIS

Variables were: Type of DRPs, Type of clinical pharmacists' intervention at drug level, Approval of clinical pharmacists' intervention by prescribers, Status of CPI according to references (whether correct or incorrect), status of the outcome of CPI (whether solved or not solved). Data were analyzed using a statistical package for social science (SPSS) version 16 and Excel 2010. Frequency and percentage were calculated and presented by pie, bar, and column charts.

3.1 Ethical Clearance

Joint ethical clearance was granted from the Ahfad University and the Military hospital (No. MsMH/2390). A consent was received from all study participants following the guidelines outlined in the Declaration of Helsinki. Patients' medical information and reports were kept confidential.

3.2 Expected Outcome

It is expected to find out a positive impact of CPIs which can help in achieving better therapeutic outcomes and improved patient care.

3.3 Limitations of the Study

The sampling was convenient. Moreover, Due to time restrictions, rounds were not attended. Also, the study is a uni-center study and hence it lacks the representation of the impact of CPIs in other hospitals and this is due to that in some hospitals clinical pharmacists were not available, lack of cooperation of some CPs and poor documentation of CPI because they were verbally suggested during rounds.

3.4 Strength of the study

Many studies were done to assess the role CPs, the self-perception of CPs regarding their roles in hospitals, however more studies in the field are needed to evaluate the impact of clinical pharmacist interventions in decreasing DRPs. The sample size of the study was hundred files of patients taken from seven month which is helpful to achieve better results. Open ended options in addition to the listed items were included in the data collection.

3. RESULTS

Among 100 patient's files analyzed during the study period, 170 CPIs were determined and a total of 152 DRPs were identified in 93 patient's files, where each problem may have one intervention or more. The most common DRP found was untreated indication (not prescribed drug but clear indication) accounting for 32.9% (n= 50) out of 152 DRPs (Figure 1).

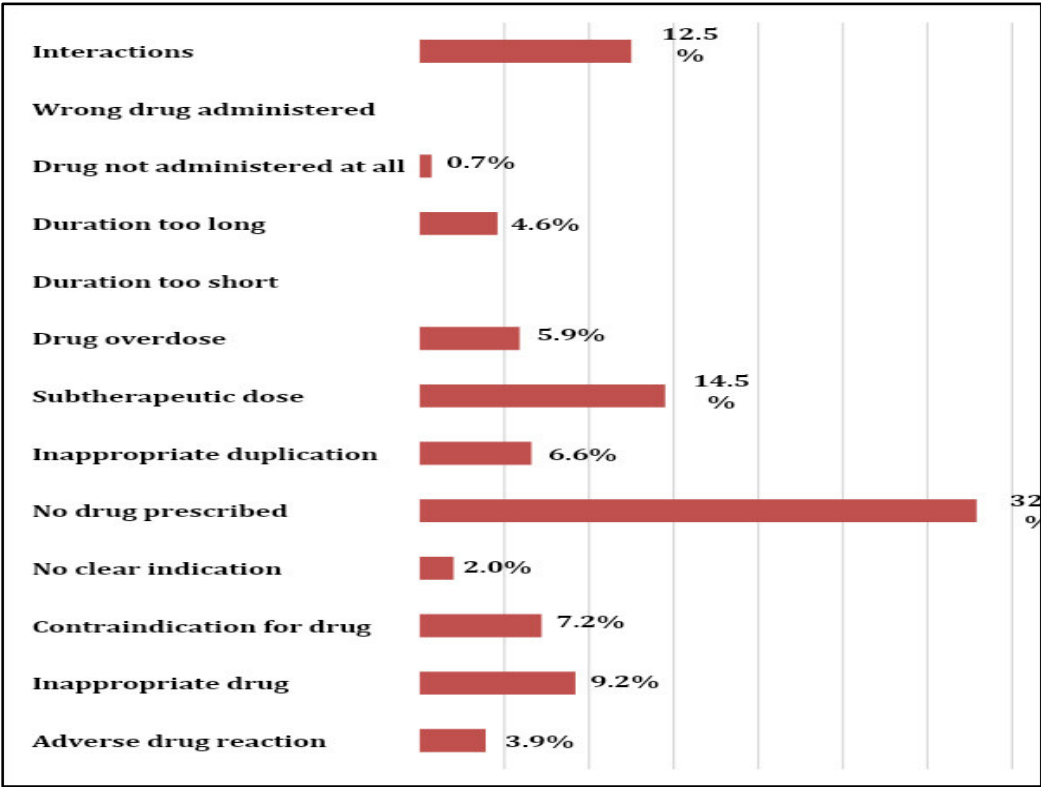
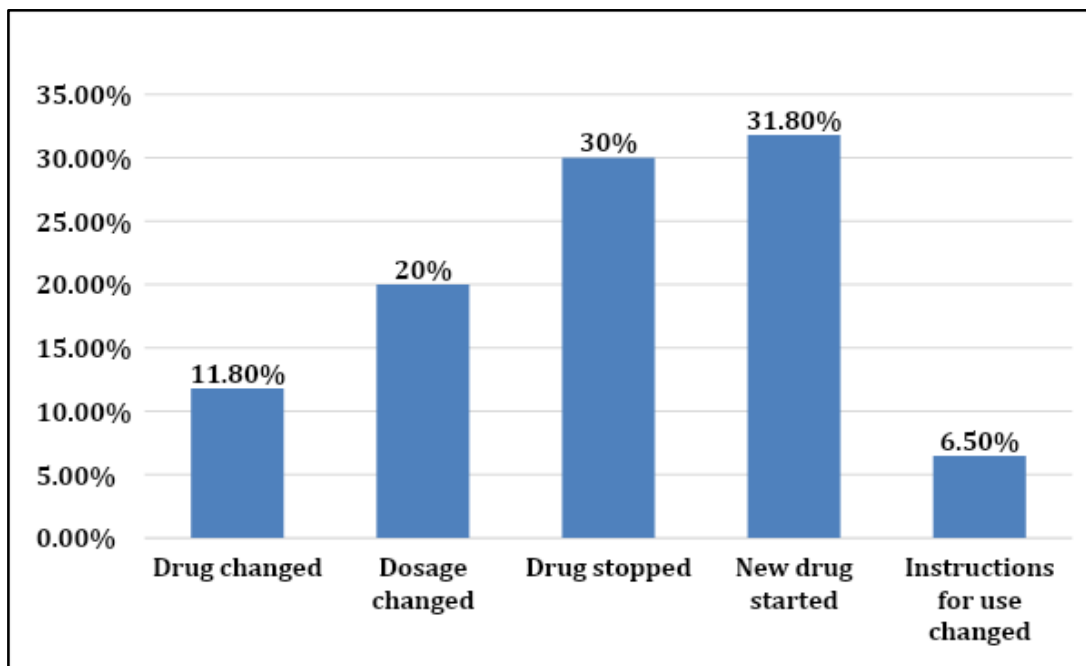


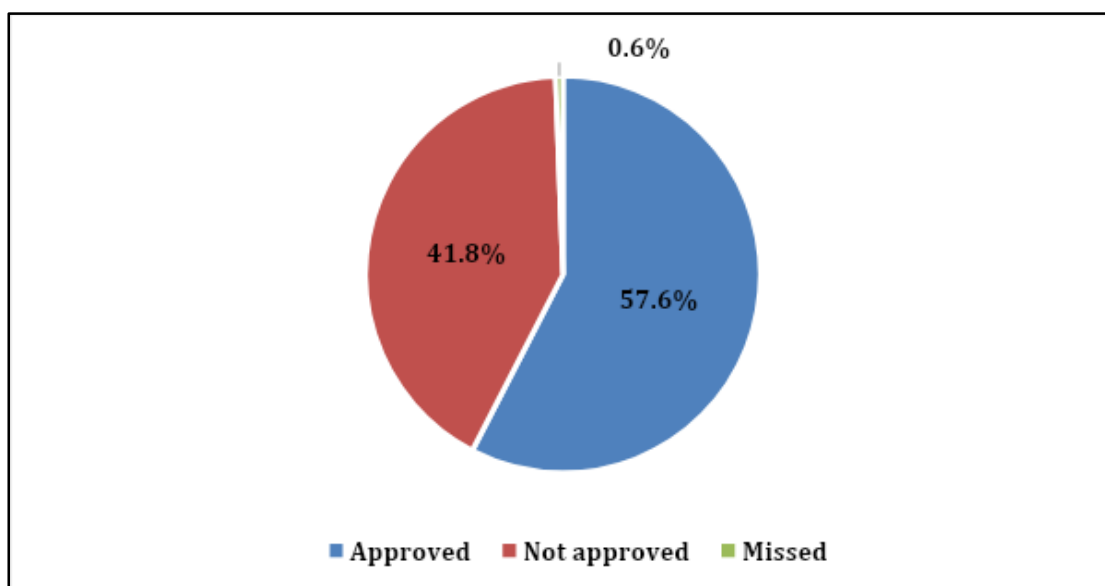
Fig 1: Type of Drug-related problems (y-axis) identified by CPs (n=152) in percentage: x-axis.

Interventions were made by clinical pharmacists based on the type of DRP. Most frequent intervention was starting a new drug 31.8% (n= 54), which was done for untreated indications, where no drug prescribed but clear indication (Figure 2).



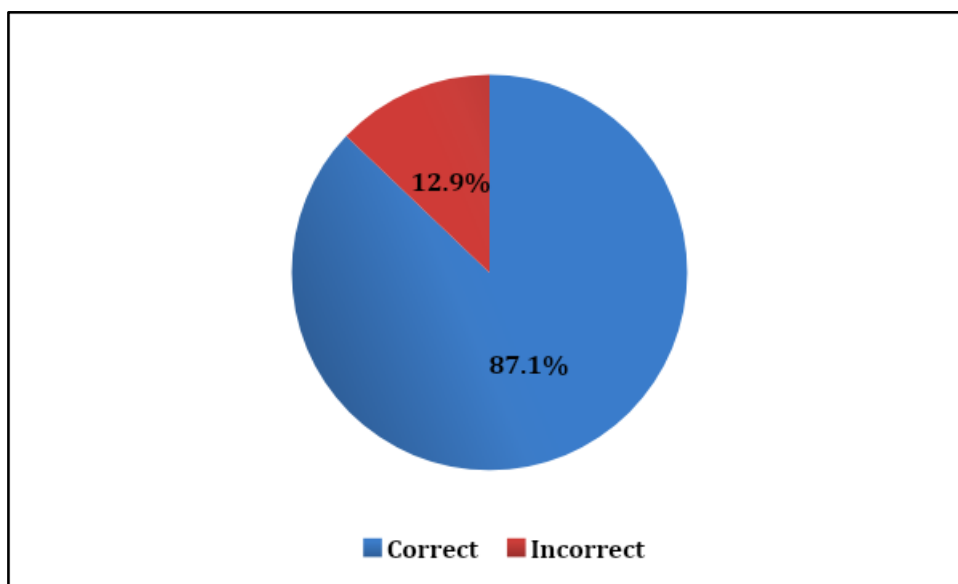
**Fig.2 : Type of clinical pharmacists' intervention (x-axis) at drug level (n=170) shown in percentage: y-axis.**

The acceptance of intervening pharmacists' suggestions were found to be 57.6% (n= 98), on the other hand 41.8% were not accepted (Figure 3).



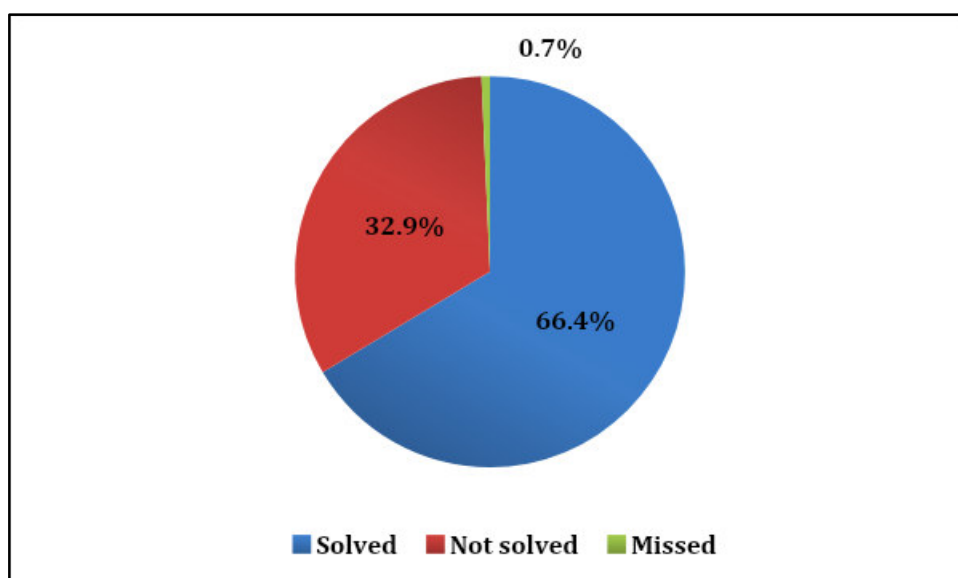
**Fig 3: Percentage of approved clinical pharmacists' intervention at prescriber level (n=170).**

Interventions provided by clinical pharmacists were mostly correct 87.1% (n= 148). Incorrect interventions were 12.9% (n= 22) and they were all fortunately rejected showing the awareness and knowledge of physicians (Figure 4).



**Fig 4:Percentage status of CPI according to references (n=170)**

Out of 152 DRPs, 66.4% (n= 101) were solved by interventions suggested by clinical pharmacists, while 32.9% were not solved (Figure 5).



**Fig 5: Percentage status of the CPI outcome (n=152)**

#### 4. DISCUSSION

Our main aim of the study was to evaluate the impact of clinical pharmacists' interventions on drug related problems in the medicine department at military hospital, Omdurman. Also, to determine the percentage of DRPs identified by clinical pharmacists. Our results showed that the most common DRP found was untreated indication (not prescribed drug but clear indication). Agents not prescribed mostly were supplements (vitaferrol, iron supplement, potassium chloride, etc.), and antibiotics e.g., doxycycline after malaria course. This was followed by sub-therapeutic dosage, and then drug interactions which may be due to lack of physician's knowledge about the pharmacokinetic and pharmacodynamics properties of the drug<sup>13</sup> also poly-pharmacy and the combination of various drug classes might have contributed to the high prevalence of drug interactions<sup>14</sup>. Most of these interactions were pharmacokinetic interactions that led to change or cessation of drugs e.g.

enzyme inhibitors like ceftriaxone and sodium valproate interact with warfarin leading to massive bleeding. Improper drug selection (inappropriate drug) was mostly observed in patients who may develop stress induced ulcer during the hospitalization period and in the treatment of pneumonia whether hospital (HAP) or community acquired (CAP) e.g. for CAP, CPs suggested (clarithromycin + ceftriaxone) instead of (clarithromycin + ceftazidim), while contraindications mostly occurred among drugs administered for patients with heart, liver and renal problems like diclofenac Na, meannitim hydrochloride and vancomycin, respectively. The occurrences of other problems included inappropriate duplication of therapeutic group or active ingredient e.g., lisinopril and captopril, and amlodipine 10mg and amlodipine 5mg, respectively. Inappropriate duplication was followed by long duration of treatment that was common in the course of antibiotics. These were followed by drug overdose and then ADR's, which may be due to age factor, poly-pharmacy, drug administration with narrow index,

decreased renal elimination and the use of oral anticoagulants and diuretics<sup>15</sup>. Other minor problems were drug without indication (no clear indication for drug use) and no administration of drug, which occurred for one patient only, where the patient received no slow potassium tablets although it was prescribed. There was no DRP attributed to short duration of treatment and wrong drug administration during the study. This finding is in contrast to A. Chandrakanth I, *et al* (2013), and Javedh Shareef, *et al* (2014) where drug interaction was the most DRP<sup>14,15</sup>. Interventions were made by clinical pharmacists based on the type of DRP. The most frequent intervention was starting a new drug, which was done for untreated indications, where no drug prescribed but clear indication. This observation coincides with the study conducted by Al-Hajje AH, Atoui F, Awada S, *et al*, (2012) where addition was (31%)<sup>16</sup>. Drug discontinuation (drug stopped) was due to drug without indication, inappropriate duplication, long duration of treatment, and improper drug selection, ADR, drug interactions, and contraindications. The last three problems also contributed to the change of drug by for example, changing pantoprazole to H2 blocker (ranitidine) as prophylaxis for stress ulcer was mostly observed to avoid incidence of infection by *clostridium difficile*. Dosage change was done for sub therapeutic dose, ADRs, and drug overdose as well. Other interventions include change of usage instructions that were specifically frequency change for lactulose and antibiotics. This besides some files included monitoring, counselling and reviewing of medications. According to ACCP guidelines<sup>17</sup>, Medscape and drugs.com, interventions provided by clinical pharmacists were mostly correct 87.1%, revealing the awareness, knowledge and impact of clinical pharmacists in optimization of drug therapy. For incorrect interventions it was about 12.9% and they were all fortunately rejected showing the awareness and knowledge of physicians. The acceptance of intervening pharmacists' suggestions was found to be 57.6%, this finding is similar to a study by Shareef J, *et al* (2016) where 58% of interventions were accepted<sup>15</sup>. A study by Javedh Shareef, *et al*. (2014) also showed high acceptance of CPIs 96.21%<sup>15</sup>. All of the accepted interventions led to change in drug therapy, this was observed from the next day medication profile. Mostly accepted interventions where dosage change and drug change, and this may be due to the fact that most physicians believe that clinical pharmacists possess more knowledge about dosing and drug interactions. One documentation was missed, where the clinical pharmacist suggested adding a potassium supplement or diet rich in potassium for a hypokalemic patient because of insulin therapy, no document shows whether this suggestion was approved or not. The remaining of the interventions were not accepted which may be due to the guidelines used by physicians differ from those used by clinical pharmacists. At the military hospital, physicians are using British guidelines while clinical pharmacists are using American guidelines. Another reason is the intervention may be correct but without proper references to strengthen the suggestions provided. Another reason may be the suggestions provided were thought to be insignificant by the physicians. Moreover, the effect of medical representatives in promoting one product rather than other. For example, physicians were preferring using Pantodac. It is known that (pantoprazole) for stress ulcers as prophylactic while clinical pharmacists were always suggesting H2 blocker to prevent the incidence of infections by *colistredium difficil* followed by treatment with pantoprazole.

Around 66.4% of DRPs were solved by interventions suggested by clinical pharmacist, this observation is in consistency to a study by Muhammad Umair Khan, *et al*. (2014) which showed CPI were successful in solving DRPs<sup>18</sup>. By observation, ADRs, no administration of the drug and drug without indication were completely solved. Other problems that have been mostly solved were untreated indications (no drug prescribed but clear indication), sub therapeutic dose and interactions. This result was achieved by analyzing laboratory reports, nephrology unit reports and physician replaying notes. Problems were solved due to the effectiveness of clinical pharmacist interventions and cooperation of physicians with clinical pharmacists. A previous hospital based observational cross-sectional study performed during 2015- 2016 in Spain, showed that the involvement of clinical pharmacists in the multi-disciplinary teams facilitated the detection and solution of DRPs, which included many disease categories, mainly allergy, renal impairment, obesity and polypharmacy<sup>19</sup>. It was observed that all correct and approved interventions contributed in solving problems except one was missed, where the clinical pharmacist suggested adding potassium supplement or diet rich in potassium for a hypokalemic patient because of insulin therapy. The outcome of this intervention was not determined because the patient's potassium level of the next days was not documented. On the other hand, around 32.9 % of problems were not solved, this was due to the rejection of interventions by some prescribers and hence no change in drug therapy occurred. One problem was not solved due to ineffective CPI where the clinical pharmacist recommended to stop metformin for a diabetic patient that has renal problem without changing it to the other proper medication. In a previous study at the general Hospital in the Jazan region, Saudi Arabia in 2016, only 17.5% of the clinical pharmacists interventions were rejected, compared with 29.7% rejections in 2017<sup>20</sup>.

## 5. CONCLUSION

The present study highlighted that the participation of clinical pharmacists in the medical ward had a positive impact in optimization of drug therapy by reducing drug related problems. Furthermore, the well acceptance of interventions by physicians can infer that clinical pharmacists' interventions were highly relevant. Interventions were mostly correct, which indicates the awareness, knowledge and positive impact of clinical pharmacists in achieving better patient care that can lead to improved quality of care and drug therapy. Therefore, clinical pharmacy services could contribute to a rationalization of drug therapy and may eventually lead to more medication safety.

## 6. LIST OF ABBREVIATIONS

ACCP : American College of Clinical Pharmacy  
 CPs : Clinical Pharmacists  
 CPI : Clinical pharmacists' Intervention  
 DRPs : Drug Related Problems  
 PCNE : Pharmaceutical Care Network Europe Foundation

## 7. AUTHOR CONTRIBUTIONS STATEMENT

Nada Rashad Farrag Eltaib, Najla Idriss Abdurhman Ahmed and Hala Mahamed Elnasif are responsible for the study research conception and design concept, Data acquisition, Drafting of the manuscript, Critical revision of the manuscript, Administrative, technical, or material support

and Approval of the final manuscript. Ashraf Nabeel Abdalla, Yosra Zakariyya Y. Alhindi and Sahar Mohy A. Elashmony were responsible for the Statistical analysis, Data analysis and interpretation and Supervision.

## 8. FUNDING

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## 11. REFERENCES

1. Ibrahim OM, Ibrahim R. Perception of physicians to the role of clinical pharmacists in United Arab Emirates (UAE). *Pharmacology & Pharmacy*. 2014 Aug 7;5(09):895.
2. Randy P, McDonough, American College of clinical pharmacy, the definition of clinical pharmacy, *Pharmacotherapy*, 2008; 28(6):816-7.
3. Mohamed SS. Current State of Pharmacy Education in The Sudan, *Am J Pharm Educ*. 2011; 75:65a
4. American Society of Health-System Pharmacists. ASHP guidelines on a standardized method for pharmaceutical care. American Society of Health-System Pharmacists. *American Journal of Health-System Pharmacy*. 1996 Jul 15;53(14):1713-6.
5. PCNE. [Internet] PCNE Classification for Drug-Related Problems V5.01. [cited November 2021]. available at: <http://www.pcne.org>. 2006
6. Dahal PR, Venkataraman RA, FULORIA PC. Assessment of clinical pharmacist intervention in tertiary care teaching hospital of Southern India. *Asian J Pharm Clin Res*. 2013;6(2):258-61.
7. Krska J, Jamieson D, Arris F, McGuire A, Abbott S, Hansford D, Cromarty J. A classification system for issues identified in pharmaceutical care practice. *International Journal of Pharmacy Practice*. 2002 Jun 1;10(2):91-100.
8. Abraham RR. Drug related problems and reactive pharmacist interventions for inpatients receiving cardiovascular drugs. *International Journal of Basic Medical Sciences and Pharmacy (IJBMS)*. 2014 Jan 26;3 (2).
9. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. New York: McGraw-Hill Education; 2014 Mar 22.
10. Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Begaud B. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *European journal of clinical pharmacology*. 2000 May 1;56(2):181-6.
11. Gurwitz JH, Field TS, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Edmondson AC, Bates DW. Incidence and preventability of adverse drug events in nursing homes. *The American journal of medicine*. 2000 Aug 1;109(2):87-94.
12. Chandrakanth1, Mrs. P. Alekhya. Dr. U. Kishan, Dr. B.V.S Lakshmi. Impact of clinical pharmacist on drug related problems. *Indo American Journal of Pharmaceutical Research* 2015; Vol 5, Issue 15, ISSN NO: 2231-6876.
13. Javedh Shareef, Sandeep B1, C S Shastri. Assessment of Drug Related Problems in Patients with Cardiovascular Diseases in a Tertiary Care Teaching Hospital. *Journal of Pharmaceutical Care* 2014; 2(2): 70-76.
14. Kaufmann CP, Stämpfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. *BMJ open*. 2015 Mar 1;5(3):e006376.
15. Shareef J, Fernandes J, Samaga L. Assessment of clinical pharmacist interventions in drug therapy in patients with diabetes mellitus in a tertiary care teaching hospital. *Diabetes Metab Syndr* 2016 Apr-Jun; 10(2):82-7.
16. Al-Hajje AH, Atoui F, Awada S, Rachidi S, Zein S, Salameh P. Drug-related problems identified by clinical pharmacist's students and pharmacist's interventions. *In Annales pharmaceutiques francaises* 2012 May 1 (Vol. 70, No. 3, pp. 169-176). Elsevier Masson.
17. Shannon W. Finks *et al*, ACCP Updates in Therapeutic: *pharmacotherapy preparatory Review and Recertification Course*. American college of clinical pharmacy, 2017; volume 2
18. Khan MU, Ahmad A. The impact of clinical pharmacists' interventions on drug related problems in a teaching based hospital. *Int J Pharm Clin Res*. 2014;63(63):276-80.
19. Garin, N., Sole, N., Lucas, B. *et al*. Drug related problems in clinical practice: a cross-sectional study on their prevalence, risk factors and associated pharmaceutical interventions. *Sci Rep*. 2021; 11, 883.
20. Babelghaith SD, Wajid S, Alrabiah Z, Othiq MAM, Alghadeer S, Alhossan A, Al-Arifi M, Attafi IM. Drug-Related Problems and Pharmacist Intervention at a General Hospital in the Jazan Region, Saudi Arabia. *Risk Manag Healthc Policy*. 2020; 13:373-378.

## 9. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests.

## 10. DATA AND MATERIALS AVAILABILITY

All data associated with this study are present in the paper.