



DRUG RELATED PROBLEMS: A SYSTEMIC LITERATURE REVIEW

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ABSTRACT

Drug related problems are one of the problems on the patients; it leads to the prolonging of hospital stay, pharmaco-economic crisis and in some cases leads to the life-threatening condition. The goal of drug therapy is to achieve defined therapeutic outcomes and improve the patient's quality of life while minimizing the risk. But inappropriate use of drugs during disease management may lead to DRPs. Identification of common types of DRPs and common drugs involved in DRPs is an important component of drug therapy and contributes to the reduction of drug-related morbidity and mortality. Various classification systems are used to classify the DRPs and to identify the nature of DRPs. Majority of studies conducted at different countries and in groups of patients showed higher prevalence of DRPs and identified various drugs and drug classes involved in DRPs. Identifying the consequences of DRPs and determining its extent in hospitalized patients will minimize those outcomes and improve their quality of life. This review article explains an overview of drug-related problems.

Key Words:-DRPs, Pharmacoeconomics, Quality of life, Morbidity and Mortality.

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experiences or is liable to experience either a disease or symptom having a definite or assumed association with drug therapy (Irsa J *et al.*, 2015)

Classification of DRPs

The published literature on DRPs was reviewed systematically, as the following classifications,

Meyboom ABC of DRPs

He published a basic system for DRPs seen from a pharmacovigilance viewpoint. Each category has its own definition, but a general definition for DRPs was not given.

- Type A (drug actions) adverse effects
- Type B (patient reactions) adverse effects
- Type C (statistical) adverse effects (Meyboom RH *et al.*, 2002)

American Society of Hospital Pharmacists (ASHP) classification 1996

Medication with no indication, condition for which no drug is prescribed, medication prescribed inappropriately for a particular condition, inappropriate dose, dosage form, schedule, route of administration or method of administration, therapeutic duplication, prescribing of medication to which the patient is allergic, actual and potential adverse drug events, actual and potential drug-drug, drug-disease, drug-nutrient, and

INTRODUCTION

Drug related problems (DRP) can be defined as "an event or circumstance involving drug therapy that may actually or potentially interfere with desired health outcomes. Drug related problems (DRP) are very common in hospitalized patients. 10-30% of hospitalizations are directly related to drug related problems. DRPs may lead to decreased quality of life of patient, increased hospital stay, increased overall health care cost and even increase the risk of morbidity and mortality. In 1990 Linda Strand written about Drug related problem which occur when a patient

drug-laboratory test interactions that are clinically significant, interference with medical therapy by social or recreational drug use, failure to receive the full benefit of prescribed therapy, problems are arising from the financial impact of therapy, lack of understanding of the medication and failure of the patient to adhere to the regimen (Deffenbaugh J, 1996)

Cipolle/Morley/Strand classification

Need for additional therapy, unnecessary therapy, wrong drug, dosage is too low, adverse drug reaction, dose is too high and adherence problem (Strand LM *et al.*, 1990; Cipolle RJ *et al.*, 1998).

Granada consensus

Indication - Patient does not use the medicines needed, Patient uses medicines that he does not need. Effectiveness - Patient uses an erroneously chosen. Drug - Patient uses dose, interval, or duration inferior to the one needed. Safety -Patient uses a dose, interval, or duration greater than the one needed, Patient uses an agent that causes an adverse reaction (Consensus P, 1998; Grupo D, 2002).

Hanlon approach

Indication, effectiveness, dosage, correct direction, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and expense (Hanlon JT *et al.*, 1990; Schmader KE *et al.*, 1997).

Hepler-Strand classification

Untreated indications, improper drug selection, sub therapeutic dosage, failure to receive drugs, over dosage, adverse reactions, drug interactions and drug use without indications (Hepler CD and Strand LM, 1997).

Krska system

Potential/suspected adverse reactions, monitoring issues, potential ineffective therapy, education required, inappropriate dosage regimen, untreated indication, no indication, repeat prescription no longer required, inappropriate duration of therapy, discrepancy between dose prescribed and used, potential drug-disease interaction and other (Krska J *et al.*, 2002).

Mackie classification

Appropriateness, unnecessary therapy, no indication apparent, untreated indication, safety, adverse reaction, clinically significant drug interactions, contraindication, ineffective therapy, in appropriate choice of therapy, in appropriate formulation or delivery, in appropriate dose or dosing schedule, admitted non-adherence, monitoring required and miscellaneous (Krska J, *et al.*, 2001).

National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) taxonomy of medication errors

The medication is in control of the health care professional, patient or consumer, dose omission, improper dose, wrong strength/concentration, wrong drug, wrong dosage form, wrong technique (includes inappropriate crushing of tablets), wrong route of administration, wrong rate (probably relating to administration), wrong duration, wrong time, wrong patient, monitoring error (includes contraindicated drugs), deteriorated drug error (dispensing drug that has expired) and other (Mackie CA, 2002).

PAS coding system

The PAS coding originally was developed to document patient's questions on their drug therapy not to classify DRPs. Problems, assessment, and solutions are classified separately. This system no longer exists due to its inability to support in the classification of DRPs (<http://www.nccmerp.org/aboutmederrors.htm>)

Pharmaceutical Care Network Europe (PCNE) system (version 4.0)

Adverse reaction(s), drug choice problem, dosing problem, drug use and administration problem, interactions and other (Van MJW and Tromp TF, 1997).

Problem-intervention documentation (PI-Doc)

Unsuitable drug choice, unsuitable use by the patient, unsuitable dosage, drug-drug interactions, adverse reactions, other (www.pcne.org/dokumenter/PCNE%20scheme%20V400.htm; Schaefer M, 2002).

SHB-SEP classification

Patient initiative doubts or insufficient understanding (also second opinion), question about drug use (dosage/advice/way of use), worries about complications/adverse reactions, self-care advice, advice on medical aids, information request (general/disease/complaint/disorder), pharmacy team initiative administration, alterations in prescription (not based on medication-surveillance signal), evaluation as result of a consultation by invitation and evaluation without patient consultation (Schaefer M, 1995).

Westerlund system

Uncertainty about aim of the drug, drug duplication, drug-drug interactions, contraindications, therapy failure, adverse effect, under use of drug, over use of drug, other dosage problem, difficulty swallowing tablet/capsule, difficulty opening drug container, other problem of administration /handling and other (Proposals for adaptation of the SEP-codes, 2003; Westerlund T, 2002).

Prevalence of DRPs

The prevalence of drug related problems varies through different studies. Some reported higher number with a prevalence of more than 70 %, while others reported a relatively lower number (less than 30 %) (Göteborg, 2002). A study done to identify drug related problems ,the most commonly identified DRPs were non-conformity to guidelines or contra-indication (29.5%) followed by improper administration (19.6%), drug interaction (16.7%) and over dosage (12.8%) (Westerlund T *et al.*, 1996). In Another study The most frequent types of interventions given by clinical pharmacists were changed drug, drug stopped, prescriber informed, changed dose and drug started (Mohammed B, 2000). A study showed 81% of the patients had DRPs. The DRPs most frequently recorded were dose-related problems (35.1% of the patients) followed by need for laboratory tests (21.6%), non-optimal drugs (21.4%), need for additional drugs (19.7%) and unnecessary drugs (16.7%). A prospective study shows that most frequently identified DRPs were: drug interactions (21%), untreated indications (18%), over dosage (16%) and drug used without a valid indication (10%) (Bedouch P *et al.*, 2000). A Study on drug related intervention stated that most and frequent DRPs underlying interventions were unnecessary drug therapy 36 (24.2%), need for additional drug therapy 34 (22.8%), and noncompliance, 29(19.5%). The most frequent intervention type was change of dosage or instruction for use 23 (15.4%) (Trine R *et al.*, 2000). The result of a study in Indonesia shows that the most commonly presented problems were drug use without indication or unnecessary drug therapy and wrong drug (Blix H *et al.*, 2004). According to a retrospective study the most common DRPs encountered were insufficient awareness of health and diseases (26%), drug choice problems (23%), dosing problems (16%) and drug interactions (16%) (Bertrand G *et al.*, 2001). From the six classes of DRPs addressed by one study, 103 (32.6%) cases were related to untreated indication or need for additional drug therapy and 49 (15.5%) cases were related to high medication dosage. Unnecessary drug therapy in 49(15.5%) cases, low medication dosage in 44 (13.9%) cases, and ineffective drug therapy in 42(13.3%) cases and noncompliance in 31 (9.8%) cases was the least prevalent DRP (Mekonnen A *et al.*, 2001). A study done to identify drug related problems and resolve them by providing pharmaceutical care, Lack of understanding of the therapy by 33 patients (28.7%) was the major pharmaceutical care issue identified and this was addressed by patient education. This was followed by presence of drug–drug interactions in 11 prescriptions (9.6%), 11 patients (9.6 %) failed to adhere to the therapy on economic grounds, 3 patients (2.61%) had medical conditions for which there was no medicine prescribed (Fita R *et al.*, 2008). A report from a sample of elderly patients had revealed that need for additional drug therapy was the most common DRP identified, followed by low

dosage accounting for 32% and 23% respectively (Zaman H and Fun W, 2003). A study done on drug related problems the most commonly identified drug-related problems were drug interactions (37%), over dosage (28%), non-conformity to guidelines or contra-indications (23%), under dosage (10%) and improper administration (2%) (Tigabu B, *et al.*, 2001). A prospective, observational and interventional study carried out to assess clinical pharmacist intervention on drug related problems, in this study a total of 71 drugs related problems were identified from 49 patients. Most of the DRPs observed in this study resulted from inappropriate drug dosing (25.4%) followed by drug selection (23.9%), drug interaction (21.1) and ADR (12.7). Majority of the clinical pharmacist recommendations were on drug discontinuation (29.6%) and drug dose change (22.5%) (Gopal K *et al.*, 2004). A cross-sectional study in Iran indicated 262 errors were detected from 132 patients. Wrong frequency 71 (27%), forgetting to take 37 (14.1%), wrong selection of drug 33 (12.5%), drug interactions 26 (9.9%), forgetting to discontinue 25 (9.5%) and inappropriate dose adjustment in renal impairment 25 (9.5%) were the most common types of errors (Rao D *et al.*, 2007).

Causes

Drug or Dose selection

The cause of the DRPs related to the selection of the drug and or dosage schedule is related to wrong drug selection, dosage selection, more cost–effective drug available.

Information

It includes instructions for use or taking unknown drug, patient unaware of reason for drug treatment, patient has difficulties in reading or understanding patient information form or leaflet, patient unable to understand local language, lack of communication between health care professionals.

Drug use process

It includes inappropriate timing of administration and or dosing intervals, drug under used or under administered, drug over used or over administered, therapeutic drug level not maintained, drug misused, patient unable to use drug as directed.

Patient/psychological

It includes patient forgets to take drug, patient has concerns with drugs, patient suspects adverse effects, patient unwilling to carry financial costs, to change drugs, to adapt life style.

Pharmacy (logistics)

It includes prescribed drug not available, prescribing error (only in case of slip of the pen), dispensing error (wrong drug or dose dispensed) (AlHajje A *et al.*, 2012).

Drugs Associated With DRPs

According to the study in Jimma iron, calcium, vitamins and other supplements were the most frequent drugs involved in DRPs 30(20.1%), followed by antibiotics 22 (14.8%). A cross-sectional study identify that antimicrobials, angiotensin converting enzyme inhibitors (ACEI), vitamins & minerals and beta blockers are the commonest drug classes that were involved in DRPs. According to the study on the drugs with highest risk rate in causing DRP were warfarin, digoxin and prednisolone. The drug groups causing most DRPs were antithrombotic agents, NSAIDs, opioids and ACE inhibitors. The study in Beirut, Lebanon reported cardiovascular drugs were the most frequently causing DRPs (44%), followed by anticoagulants (17%) and corticosteroids (14%). Similarly in the Grenoble University Hospital DRPs appeared most frequently for cardiovascular drugs, central nervous system drugs, and gastrointestinal agents (Satish K *et al.*, 2013). The study conducted in the Grenoble University Hospital, France reported that 429 different drugs were associated with DRPs. Cardiovascular drugs were the most frequently implicated agents (22.2%), followed by anti-infective (13.3%), analgesic / anti-inflammatory drugs (11.3%), gastrointestinal drugs (11.2%), psychotropic drugs (9.6%) and antithrombotic agents (6.3%) (Mohammad A *et al.*, 2013). Similar result was also found in a study done at Jimma university specialized hospital to assess medication prescribing errors (Annemie S *et al.*, 2009). A study done to indicate the most frequently involved drugs in DRPs were tramadol, antidepressants and acenocoumarol, for drug interactions calcium-vitamin D, for untreated indications statins and aspirin, proton pump inhibitors and paracetamol for over dosage, proton pump inhibitors and aspirin for drug used without indication. A retrospective cross-sectional study shows that drugs mostly causing DRPs were B-blockers (atenolol and propranolol), NSAIDs (aspirin, ketoprofen, diclofenac, and mefenamic acid), and angiotensin converting enzyme inhibitors (Bosma L *et al.*, 2007). Aspirin, clopidogrel, simvastatin, amlodipine and metformin were the most frequently implicated drugs for DRPs in type 2 DM patients with hypertension (Agalu A *et al.*, 2011). Common drug-drug interactions identified in the southern Indian study involve drug interaction between digoxin and amiodarone, digoxin with calcium channel blockers, diuretics and corticosteroids, drug interaction with sucralfate. The Iranian study showed cardiovascular medications were the class with the highest number of errors 83 (31.6%), after which gastrointestinal agents 41 (15.6%) had the highest rank. Hormonal medications were the class with the lowest frequency of error.

Predictors of DRP Occurrence

A retrospective cross-sectional study in Singapore, no statistical correlations were observed between age and gender with developing DRPs. An

increased number of medications were associated with higher risk for patients with DRPs on admission, but not for inpatients with DRPs. According to the study, independent factors which predicted the occurrence of DRPs in the study population were sex, age, polypharmacy, and drug-drug interactions. From all covariates studied, females were 1.95 times more likely to have DRPs than males. Patients, who took ≥ 5 drugs/day on average, were 5.23 times more likely to have DRPs than patients who took < 5 drugs/day on average. The Danish study showed that the number of drugs at admission and the number of Clinical or pharmacological risk factors were both independent risk factors for the occurrence of DRPs, whereas age and gender were not. According to the southern Indian study drug related problems were more commonly seen in patients aged above 60 years (53.10 %). According to the study done in Jimma, Patients who took five or more drugs per day on average were 5.96 times more likely to have unnecessary drug therapy problems than patients who took less than five drugs per day on average (Yvonne K *et al.*, 2005).

Risk Factors for DRPs

Recent research on DRPs and ADR has identified several categories of risk factors that may be used to identify patients who are susceptible to DRPs and ADRs. These categories include specific medications, certain categories of drugs and patient health status. Specific medications that are potential risk factors include Digoxin, Warfarin, Lithium, and Chlorpropamide. Another study on risk factors for Drug Related Problems said that some high risk drugs (such as anticoagulants and insulin), polypharmacy, communication issues between health care professionals, patient education and renal impairment were the most eliciting risk factors possibly leading to DRPs (Matsoso M *et al.*, 2009). A study on patient risk factors for developing a drug-related problem in a cardiology ward, the risk factors for developing DRPs were polypharmacy, female sex and first admission (Tigabu B *et al.*, 2009). According to a study, home intravenous therapy, multiple drug regimens to treat multiple chronic diseases, increased acuity of non-hospitalized patients and increased longevity have placed elderly patients at increased risk for drug related problems (Carole P *et al.*, 2009).

Different variables are potential risk factors for the development of drug related problems in hospitalized children. Therefore, different variables were reported by different published literatures. For example, in a large prospective study in UK and Saudi was reported that, polypharmacy and transferred admission (another hospital or ward) were potential risk factors for the occurrence of drug related problems (Urbina O *et al.*, 2015). However, a review article on drug-related problem in children with chronic kidney disease study showed that, prolonged hospitalization, number of medicines prescribed and in

children undergoing dialysis, were risk factors for the development of DRPs (Patrick N and Catania P, 1998). However, Hong Kong study reported that, the number of prescribed drugs and certain infectious and parasitic diseases were potential risk factors for occurrence of DRPs (Rashed AN *et al.*, 2001). Another study shows that poly pharmacy was found to be a potential risk factor for developing drug related problems in stroke patients (Ibrahim N *et al.*, 2013). And similar result was obtained in medical wards of TikurAnbessa specialized hospital, Ethiopia (Rashed AN *et al.*, 2013).

The Need for evaluating DRPs

The Swedish social board has developed recommendations of when and how medication should be performed. According to SOSFS 2012:9 all patients above 75 years old with 5 or more drugs must be offered a medication review. DRPs are expensive for the society, but at the same time the resources to prevent them are limited. Identifying associated factors to DRPs could be interesting for further investigation of who should be offered a medication review. Categorization of DRPs is important to get an overview of what types of problem that most frequently occur (Cellin AT *et al.*, 2012).

Approaches to enhance the quality of drug therapy

Physicians and pharmacists have complementary and supportive responsibilities in providing optimal drug therapy. To achieve this goal, and to ensure that patients receive consistent information, patients, pharmacists and physicians must work cooperatively and in partnership with each other. This requires effective communication, respect, trust, and mutual understanding of each other's complementary responsibilities.

The Physician's Responsibilities

Physicians and pharmacists recognize the following responsibilities in drug therapy as being within the scope of physicians' practice. Some responsibilities may overlap with those of pharmacists (see The Pharmacist's Responsibilities). 1) Assessing health condition, diagnostic diseases, the need for drug therapy and providing curative, preventive, moderate and punitive drug therapy in consultation with patients and in collaboration with care givers, pharmacists and other health care professionals. 2) Working with patients to set therapeutic goals and supervise progress toward such goals. 3) Monitor and assess response to drug therapy, progress toward therapeutic goals and patient compliance towards the therapeutic plan. 4) Furnish specific information to patients and caregivers about diagnosis, indications, treatment goals, and the action, benefits, risks and side effects of drug therapy. 5) Providing and sharing information and advice about disease and drugs with patients, caregivers, health care providers and the public. 6) Keep adequate records of drug

therapy for each patient. 7) Ensuring safe procurement, storage, handling, preparation, distribution, dispensing of drugs. 8) Care must be provided in accordance with lawmaking, in an atmosphere of privacy and patient confidentiality must be maintained. Care also should be provided in accordance with accepted scientific and ethical standards and procedures.

The Pharmacist's Responsibilities

Evaluating the patients' drug-therapy record ("drug profile") and reviewing prescription orders. Examples include possible contraindications, drug interactions or therapeutic duplication, allergic reactions and patient non adherence to treatment. Ensuring safe procurement, storage, preparation, distribution and dispensing of pharmaceutical products. Discussing actual or potential drug-related problems and the purpose of drug therapy with patients in consultation with caregivers, physicians and health care providers when appropriate. Monitor drug therapy to identify drug related problems or any interventions. Advising patients and caregivers on the selection and use of nonprescription drugs and the management of minor symptoms. Directing patients to consult their physician for diagnosis and treatment when required. Pharmacists may be the first contact for health advice. Notifying physicians of actual or suspected adverse reactions to drugs and when appropriate report such reactions to health authorities. Providing specific information to patients and caregivers about drug therapy. This information may include the name of the drug, its purpose, potential interactions or side effects, precautions, usage, methods to promote compliance to the treatment plan and any other health information appropriate to the needs of the patient. Providing and sharing general and specific drug-related information and advice with patients, caregivers, physicians, health care providers and the public. Maintaining adequate records of drug therapy to facilitate the prevention, identification and management of drug related problems. Maintaining a high level of knowledge about drug therapy through critical appraisal of the literature and continuing professional development (Cellin AT *et al.*, 2012).

CONCLUSION

A DRP is an event or circumstance involving drug therapy that actually or potentially interfere with desired health outcomes. In our review, various types of DRP classification systems were explained, among all systems PCNE version 4.0 comes closest to the defined requirements. Prevalence of DRPs were vary among different studies, most studies reported that Drug – interactions were the most common types of DRP identified followed by drug use without indication and ADRs. Polypharmacy was found to be the potential risk factor for developing DRPs and cardiovascular drugs are the most commonly associated drugs in DRPs. Early

detection and documentation of DRPs improve therapeutic outcomes. Developing and adopting the guidelines regarding the drug administration; dispensing and prescribing would minimize the DRPs.

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CONFLICT OF INTEREST

No interest

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