DRUG RELATED PROBLEMS ASSOCIATED WITH POLYPHARMACY: A LITERATURE REVIEW

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ABSTRACT

Any fluctuation from the intended beneficial effects of the drug results in drug related problems. The risk of development of drug related problems associated with polypharmacy increases with increase in age. Females are more vulnerable to these problems due to their lighter physique which can lead to ADRs. Polypharmacy can result in drug interactions, wastage of health budget, impaired quality of life of the patient, and confusion and mismanagement on the part of the physician. ADRs with polypharmacy in older age are more pronounced and effect badly the quality of life and cause drug related morbidities and mortalities. These also increase cost of therapy. The number of drugs is considerably more important in causing drug related problems as compared to age and gender. The number of drugs, doses used, drug related problems and total cost burden to patient can be reduced by pharmacist's interventions. These interventions also increases patient's adherence to therapy and improve quality of life.

INTRODUCTION

Drugs are used with an intention of particular outcomes, which can result in both beneficial as well as adverse effects. Any fluctuation from the intended beneficial effects of the drug results in Drug related problems (DRPs) (Johnson & Bootman). These various drug related problems may include untreated indication, improper drug selection, sub-therapeutic dosage, failure to receive drugs, overdose, adverse drug reactions, drug interactions and drug use without indication (Ernst & Grizzle, 2001; Khurshid, Zikria, Hamid, & Kumar, 2016). Various factors can cause DRPs in patients resulting in devastating effects which can even lead to death of the patients. Polypharmacy is the situation in which the patient is exposed to multiple drugs for multiple co-morbidities which usually exist in older individuals. As the patient is suffering from number of diseases like heart problems, diabetes, high blood pressure, asthma, liver disorders, kidney problems, CNS complications, psychiatric diseases, rheumatic fever, heart failure etc. So they have to take multiple drug therapy to treat all of these issues. In addition to this they sufferings. Our literature survey has revealed that in US also use many OTC products to treat their general older population polypharmacy is increasing. Older patients over the age of 65 years who are 15% of the total population have been observed to purchase most of medications in US (Geller & Zenick, 2005). One third of prescription medications and almost 40% of OTC medications are purchased by older population. Almost $3 billion are being spent on prescription medication by Americans. Older population is mostly victim of most of chronic morbidities as they have altered metabolism and compromised body functions. In this regard use of multiple drugs may lead to impaired elimination of drugs leading to drug accumulation in body that could be life-threatening.

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Polypharmacy also enhances the chances of adverse drug reactions and interactions, for example if a person is using two medicines the risk of adverse drug reaction (ADR) is 14%, this risk rises to 59% with five medicines resources. About 29% of all emergency department visits were drug related of these, 70% were curable, and as many as 25% resulted in hospital admission. Physicians and pharmacists collaboration is one approach to address on drug associated morbidity and to achieve therapeutic goals. Drug related problems (DRPs), which include unnecessary drug therapy, adverse drug reactions (ADRs), untreated conditions and inappropriate choice of drugs, have been shown to be prevalent in hospitalized patients, with a reported incidence rate as high as 26% (Steel, Gertman, Crescenzi, & Anderson, 1981; Stewart & Cooper, 1994). Indubitable, many factors can contribute to the higher prevalence rate, but polypharmacy and older age have been identified as important risk factors (Montamat & Cusack, 1992; Nolan & O'Malley, 1988; Steel et al., 1981). The use of four or more medicines by a patient, generally the adults of more than 65 years age has been shown to predispose patients to ADRs, (Beers & Ouslander, 1989; Chrischilles, Segar, & Wallace, 1992; Geller & Zenick, 2005; Hoigné, Lawson, & Weber, 1990; Inman, 1985; Nolan & O'Malley, 1988; Werder & Preskorn, 2003), drug-drug interactions and non-compliance of medication (UaBEW Bergman & B-E Wiholm, 1981; Gillum & Barsky, 1974; Ramsay & Tucker, 1981), particularly in the geriatric population. ADRs were found to be mostly linked with polypharmacy when studies on DRPs were conducted and it was seen that as the number of drugs increased the ADRs increased exponentially (Cadieux, 1989; Hurwitz, 1969; Hurwitz & Wade, 1969; Morgan, Dallosso, Ebrahim, Arie, & Fentem, 1988; Nolan & O'Malley, 1988). Apart from this, healthcare system also gets affected financially (Beers et al., 1992). In 1992–1994, a university-affiliated hospital in US, US $1.5 million per year was the estimated cost of ADRs treatment reported (Schneider, Mion, & Frengley, 1992). So, need of the hour is to reduce the number of unnecessary medicines to facilitate healthcare to reduce the cost as well as drug related drastic events in patients.

Advanced age is also a factor for ADRs (Gurwitz, Soumerai, & Avorn, 1990) as in patients with 20–30 years and 60–70 age, an increased risk of about seven folds in ADRs from 3% to 21% has been reported (Hurwitz & Wade, 1969). Iatrogenic syndromes due to polypharmacy may be a cause of many hospital admissions of a large number of elderly patients (Colt & Shapiro, 1989; Grymonpre, Mitenko, Sitar, Aoki, & Montgomery, 1988; Hanlon et al., 1997; Schneider et al., 1992; Stuck et al., 1994). According to a study 35% of a study population of 167 elderly patients suffered ADRs over a one year period due to both polypharmacy and old

and 83% with seven or more drugs (Geller & Zenick, 2005).

Drug related problems are a significant cause of hospital's emergency department visits and use o age (Hanlon *et al.,* 1997). Epidemiological data has not been able to demonstrate the ADRs in elderly significantly (Hoigné *et al.,* 1990). The risk for ADRs is more with inappropriate drugs than the advanced age according to some researchers (Lindley, Tully, Paramsothy, & Tallis, 1992). This debate for which one of either of them has high risk for DRPs has not produced any result even up to now, but an appropriate conclusion will be of great benefit to physicians and pharmacists to deal with patient in a better way. Furthermore, the comprehensive data on DRPs is quite less as most of research is either about hospital admissions due to adverse consequences of drugs (UaBEW Bergman & B-E Wiholm, 1981; Bero, Lipton, & Bird, 1991; Courtman & Stallings, 1995; Fattinger et al., 2000; Hallas et al., 1992; Prince, Goetz, Rihn, & Olsky, 1992) or about ADRs only (Brennan et al., 1991; Classen, Pestotnik, Evans, Lloyd, & Burke, 1997; Hurwitz & Wade, 1969). So a more detailed focused research work is needed. Now what is the impact of these researches on clinical practice is another question. We are unable to understand if results of these researches have any link with changing clinical practices as the age group of 10 to 20 years was selected for this. Need of the hour is to evaluate these problems to sort out some suitable solutions. Therefore, we have tried to evaluate these problems in our study work. Because of the fact that polypharmacy and DRPs are directly related (U Bergman & B-E Wiholm, 1981; Green, Mottram, Rowe, & Pirmohamed, 2000; Hallas et al., 1992; Lindley et al., 1992; Nolan & O'Malley, 1988). In this study we tried to sort out the DRPs in hospitalized patients and its relation with age and female gender. As the advanced age and DRPs are also directly related (Beijer & De Blaey, 2002; Hurwitz & Wade, 1969; McMillan, Harrison, Rogers, Tong, & McLean, 1986) so this study is also to evaluate this fact. Furthermore females are exposed to ADRs more than males (Fattinger et al., 2000; Veehof, Stewart, Meyboom-de Jong, & Haaijer-Ruskamp, 1999). The reason may be that females require higher dose than males. This review has summarized the drug related problems associated with polypharmacy and its risk factors.

Data source

A review of electronic databases "Polypharmacy and elderly" and "Drug therapy problems with Polypharmacy" was conducted. In this literature an association of DTPs with polypharmacy with further relation to gender, age, no. of medications for the period 1969 to 2013 was done. The study was conducted by

reviewing the articles from different online sites of relevant journals.

Objectives
In this literature review our objective is to correlate the drug related problems associated with polypharmacy with further relation to age, gender and number of medications.
It concludes that drugs prescribed for Type 2 Diabetes Mellitus is 53% prevalent in Females and 47% in males from various public and private hospital of Lahore as shown in the Figure 1. While it was more in 40-60 years age group than others.

Drug related problems
There is linear relationship between DRPs and number of drugs used by single patient. A study conducted by L.M. Strand and his colleagues in 1990, classified the DTPs in to different categories according to which the pharmacist is to maintain a list of DTPs for each patient, this list then helps the other pharmacists to know about the patient's DTPs and clinical condition as well.
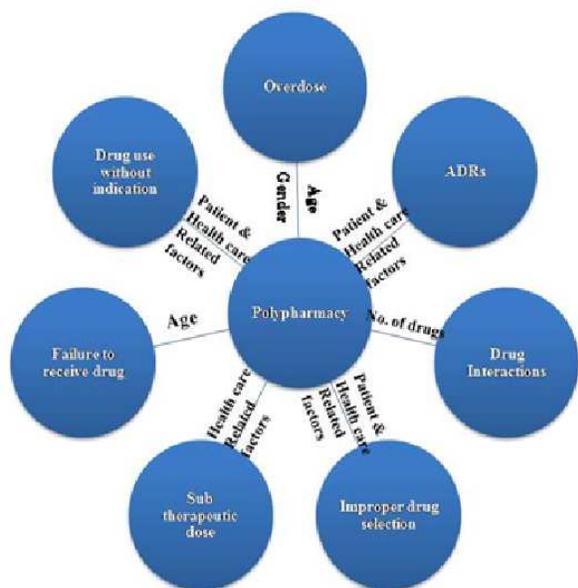
Figure 1: Drug related problems associated with Polypharmacy and related factors

Polypharmacy
Polypharmacy is the un-necessary and excessive use of OTC as well as prescription medications. In research studies polypharmacy is defined in different ways by different researchers, like it is the concomitant use of five or more drugs, it is use of more drugs than indicated, or the use of two or more drugs for the treatment of same

condition (Viktil, Blix, Moger, & Reikvam, 2007). Polypharmacy increases the chances of adverse drug reactions, drug-drug interactions, prescribing cascade, and therapy costs as shown in Figure 1.

Drug realated problems associated with polypharmacy with reference to age
With advanced age altered pharmacokinetics and pharmacodynamics are major factors to consider when talking about polypharmacy. Older individuals respond to medication differently, and medication effects may be varied and less predictable. Pharmacokinetics means how the body absorbs, distributes, metabolizes and eliminates a medication (Geller & Zenick, 2005). Physiological changes related to aging influence the pharmacokinetics in the way that little changes occurring in drug absorption and elimination of fat soluble drugs may be prolonged due to increased body fat and reduced renal elimination. The risk for developing ADRs and drug-drug interactions increases with polypharmacy. It also decreases patient's quality of life. Pharmacodynamics describes the effect of medication on the patient and how it interacts at its receptor sites. There are many patient related and health care provider related factors responsible for DRPs.

Patient related factors
Patient related factors are physiological changes, co-morbidities, psychomotor retardation, self-medication and little social support.

Health care provider related factors
Health care provider related problems may include inappropriate prescribing, multiple physician's consultancy and inability of care providers to review the medications regularly.

Drug related problems associated with polypharmacy with reference to gender
In gender comparison many studies have shown that male patients are at higher risks of developing ADRs than the female patients. But these studies do not match with the studies conducted by Denmark and the Netherlands which have shown that female patients are more prone to develop ADRs demonstrating the risk in female to be 1.57 and 1.46 given by Denmark and Netherland, respectively. So, for the purpose of studying the gender related DRPs associated with polypharmacy, the two studies are used more probably. In Danish study, 1999 patients are included of about all ages without considering that whether they are on polypharmacy or not. In Dutch study, 2185 geriatrics were studied which were receiving polypharmacy. In the above two mentioned studies, the correlation between female

gender and risks for the development of ADRs was more as compared to male gender. So, it can be concluded on the basis of aforesaid studies that the risks of ADRs development are more in female patients (Koh, Kutty, & Li, 2005).

Drug related problems associated with polypharmacy with reference to number of drugs
A study is conducted on the basis of number of drugs without considering the age and it was found that half of the patients under observation were taking more than 5 drugs thus according to the definition, showing the polypharmacy. The fraction of elderly patients taking more than 5 drugs is much higher. It was shown that 66% were taking 5 or more drugs, 46% were taking more than 7 while 21% were on 10 or more drugs. In another study, it was found that more than 60% patients were found to use 5 or more drugs when admitted to rheumatic wards. But the above study is not satisfactory as we also have to consider the DRPs with reference to the number of drugs. Another study was conducted, which showed that as the number of drugs increased, the occurrence of DRPs per patient also increased linearly. So, DRPs risks increased with the addition of each drug linearly for complete range of drugs i.e. 1 to more than 11 drugs. Hence the increased risks of DRPs may affect health of the patient seriously and thus a great threat to the life. The DRPs reported in the study were mostly major or moderate with reference to clinical significance.

Flaherty studied the relationship of the number of drugs used and the related problems which affected the health of patients (Flaherty, Perry III, Lynchard, & Morley, 2000). The study showed no difference between the patients receiving polypharmacy i.e. using five or more than five drugs, at home or at hospital. However when the number of drugs increased to seven or more or equal to 10, then the risks of DRPs also increased either in home care patients or in hospitalized patients. Another study related to Lawlor (Lawlor, Patel, & Ebrahim, 2003) showed that the elderly patients were mostly affected by the chronic diseases and the multiple pathological conditions rather than polypharmacy. So, the number of drugs increment had a strong impact on the DRPs and hence polypharmacy is also associated with the increased risks of DRPs. Study analysis showed that there are greater risks of DRPs (Blix *et al.,* 2004) which include clinical and pharmacological risks, associated with increased number of drugs. Similarly, in the patient using several drugs concomitantly, drug monitoring should be performed regularly for that patient. However, the risk factors associated with the polypharmacy cannot be accurately studied in a hospital and hence a research is needed to be performed on it.

The polypharmacy is usually associated with the appearance of ADRs in the patients. ADRs are defined by the Taber's cyclopedic medical dictionary as, undesired side effects or toxicities caused by the administration of concurrent medications they may potentiate or antagonize the effects of each other. The degree of ADRs is not always same; it may be mild or even fatal. There is another study i.e. Laser and Hoot Martin study who reported that hospital admissions of 20-25% patients of 'over 65 age group' are due to the adverse drug events. Adverse drug events are usually the result of drug-drug interactions while this interaction may occur at pharmacokinetic or pharmacodynamic level. Pharmacokinetic interactions occur due to the alteration of absorption, distribution, metabolism or excretion of a drug by another drug when given concomitantly while pharmacodynamic interactions are produced when a drug's effect is either inhibited or potentiated by another drug administrated at the same time. The drugs with the narrow therapeutic index e.g. digoxin, theophylline etc. require monitoring after administration as the risks of life-threatening toxicity are more.

Intervention
Polypharmacy has greatly increased the health care cost. As, it is associated with increase in direct cost i.e. spend on medication itself, and the indirect cost i.e. the additional expenses (visits to specialists, an emergency care and admission to hospital) thus, resulting in increased annual cost (Geller & Zenick, 2005). Polypharmacy is leading towards hazardous effects on society. Patients are affected because of more side effects than positive effects of these medications. The number of patients admitted to the hospitals and health care cost are also increased to treat these side effects. For solving these problems some interventions are needed. These interventions include decreasing medicines so that ADRs, DTPs and drug costs can be controlled and patient compliance to medication can be increased. In literature review, it is revealed that many studies, though still not enough, have been conducted to focus on pharmacist's intervention in the field of polypharmacy. A study showed that there is a reduction in average number of drugs prescribed from 5.7 to 4.4 (22.8) and 35% of these patients receive reduced dose of at least one of their medications (Schrader *et al.,* 1996).

Mostly the older patients are chronic medication users, for such patients, adherence to the therapy is essential to get desirable outcomes so special interventions are required in this regard. Many of the investigators have concluded that patient education regarding their knowledge about the purpose and mode of effect of

medications, such interventions have improved patient's adherence to their therapy (Rollason & Vogt, 2003). Pharmacist's intervention leads to a reduction in total cost of therapy by reducing number of drugs, dose of drugs and number of hospitalization.

CONCLUSION

It is concluded that polypharmacy is continued to be a significant issue and little research has been conducted regarding the methods to access polypharmacy. The risk of development of drug related problems associated with polypharmacy increases with increase in age, female gender due to their lighter physique, and the number of drugs taken by patients. It results in number of drug-drug interactions, drug-disease interaction, increases the risk of hospitalization, unnecessary expenses, time wastage, embarrassment on the part of the patient, and confusion and mismanagement on the part of the physician. A more comprehensive and focused research is needed to be done.

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