INVESTIGATE THE MEDICATION RELATED PROBLEMS IN ADDIWANIYAH TEACHING HOSPITAL

A project

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Dedication

To whom Allah sent as mercy to the worlds

...

To the prophet Mohammed.....

TO my parents

To my family

To everyone I love.....

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This thesis would not have been possible without the blessing of God

I am heartily thankful to my supervisor, assistant teacher Ahmed M sultan, whose encouragement, guidance and support from the initial to the final level enabled me to develop an understanding of the subject.

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INTRODUCTION

1.1 Definition

Drugs are a dualistic therapeutic tool. They are intended to cure, prevent or diagnose diseases, signs or symptoms, but the shadow side is that improper use can be the cause of patient morbidity and even mortality. While in the 1960s the interest in adverse drug reactions increased greatly after the thalidomide disaster (which can be considered as the final trigger for the establishment of formal programs of drug approval and subsequent surveillance), only in recent years has attention shifted toward the problem of medication errors (1)

In general, problems related to the use of approved drugs can be summarized with the term “drug-related problems” (2).

When reviewing the literature on drug related problems (DRPs), one quickly discovers that most studies are difficult to compare because of variations in definitions and classification of DRPs (3,4) A uniform definition and classification system for drug-related problems would solve these difficulties.

Definitions: DRPs can be divided into intrinsic and extrinsic toxicity. Intrinsic toxicity is caused by the interaction of the pharmaceutical, chemical and/or pharmacological characteristics of the drug itself and the human biosystem. Intrinsic toxicity is therefore synonymous with adverse drug reactions (ADRs). An ADR is defined by the World Health Organization (WHO) as “any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function” (5). Previously unknown drug-drug interactions and lack of therapeutic effect (6) are included in this definition. Mechanistically there are two types of ADRs: Type A and Type B (2)

Type A reactions are pharmacological effects as much as therapeutic actions are, the essential difference being that they are unintended. Examples are constipation during the use of morphine and peptic ulcer induced by NSAIDs. Type Aeffects are by far the most prevalent. As a rule, there is a dose-response relationship: Type A ADRs are more frequent and more severe when higher doses are taken.

Type B reactions, in contrast, refer to the phenomenon that a medicine is well tolerated by the (vast) majority of users but elicits an idiosyncratic reaction in predisposed patients. Type B effects are often unexpected (i.e from pharmacology), rare and severe. Type B reactions have historically been the major reason for the withdrawal of medicines from the market. Characteristically there is no dose-response relationship. Type B effects are either immunological or nonimmunological forms of hypersensitivity and occur in patients with a predisposing condition, which is often unknown or unrecognized. Stevens - Johnson syndrome and anaphylactic shock are two examples of Type B reactions.

Extrinsic toxicity refers to the problems caused by the handling of the drug either by the healthcare professional or by the patient. The drug is not used in the proper way: a medication error has been made. A medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer (7). Therefore, medication errors do not necessarily need to result in harm to the patient. In contrast, ADRs always involve some form of harm. Known drug-drug both ADRs and medication errors (8-10).

1.2 Risk factors:

Drug-related problems (DRPs), which include adverse drug reactions (ADRs), unnecessary drug therapy, inappropriate choice of drugs, and untreated conditions, have been shown to prevail in hospitalized patients, with a reported incidence rate as high as 25%(11) . Undeniably, many factors can contribute to the high prevalence rate, but polypharmacy and older age have often been identified as important risk factors(12).

Polypharmacy is defined as the use of multiple medications by a single patient and is commonly observed among geriatric patients (13), drug–drug interactions (15), and medication noncompliance(16), particularly in the geriatric population.

Of the risk factors, advanced age has been associated with substantial increased risk of acquiring ADR (17). A sevenfold increase in occurrence of ADRs from 3% to 21% has been shown to occur between patients aged 20–30 years and 60–70 years (18). In addition, many studies have shown that a large number of emergency room visits and hospital admissions amongst older people could be attributed to iatrogenic syndromes associated with polypharmacy (19). Hence, polypharmacy plus old age could be considered a potent combination for ADRs to take place. The high risk of developing ADRs in patients with both risk factors was demonstrated when 35% of a study population of 167 older patients prescribed polypharmacy (taking 5 or more drugs) experienced a confirmed adverse drug event over a one-year period(20) However, other researchers had argued that this propensity of older patients experiencing ADRs was not being well substantiated by epidemiological data (21) .

Furthermore, the failure to control for important age-related covariates (eg, clinical status of the patient) had also been cited as a limitation to the interpretation of many study results (22). Some researchers proposed that inappropriate medication in the elderly might pose a higher risk for acquiring

ADR than advanced age as a sole risk factor (23). Up to now, the issue of whether inappropriate drug use or advanced age should be considered the more important risk factor for developing DRPs remains unresolved. The resolution of this issue is of great relevance to the practice of clinical medicine, as it would allow physicians and pharmacists to focus more attention on patients with the "true" risk factors.

1.3 Adverse drug reacton ADR:

Incidences of ADR have been consistently shown to increase in an exponential rather than a linear manner with the number of drugs taken (24). For example, significantly more ADR-associated hospital admissions have been observed among patients prescribed four or more drugs than those receiving up to three drugs (11.1% vs 3.6%) (25).

In another study, it was reported that hospitalized patients who experienced an adverse reaction took twice as many drugs (12.5 vs 6.3 drugs) as patients without ADRs (26). Besides the undesirable clinical consequences for the patients, ADRs also pose a significant financial burden to the healthcare system (27)

Another interesting observation about the studies relating to DRPs is that there exists little data on comprehensive DRPs among hospitalized patients. So far, most studies published had addressed either the problem of drug-related admissions to hospitals (28), or focused only on ADRs among hospitalized patients (29). A more comprehensive study of DRPs in hospitalized patients would provide valuable insights for the healthcare professionals trying to reduce the incidence of DRPs.

Another issue that is pertinent to healthcare delivery and risk management is the impact of the numerous studies of DRPs on clinical practice. As most of the studies were performed between 10 and 20 years ago, it is unclear whether the

results and lessons learnt from these studies have any influence on changing clinical practices. An assessment of the current situation would assist the healthcare providers in optimising intervention strategies according to needs and available resources.

In the current study, we attempted to evaluate some of the aforementioned issues. As polypharmacy is associated with the increased occurrence of DRPs(30), our main objectives were to investigate the occurrence of all DRPs (at admissions and while hospitalized) among hospitalized patients prescribed polypharmacy, and to evaluate the association of two risk factors, namely advanced age and female gender, with DRPs and ADRs in particular. Since advanced age has always been associated with higher incidence of DRPs(31), we wanted to see if this trend could be confirmed or supported by our local data. Also, female patients, being generally lighter in weight and smaller in build than their male counterparts but usually receiving the same drug doses, had been demonstrated to be more prone to ADRs in some studies (32). This is most probably attributable to the exposure to higher dose per body weight for the females. We postulated that this trend would be more pronounced in our predominantly Asian female patients (who are generally even lighter in weight than Caucasian counterparts).

In addition to helping to resolve the abovementioned issues, the results from this study could provide baseline information quantifying the problem of DRPs among hospitalized patients receiving polypharmacy in Singapore, and contribute to the formulation and implementation of risk management strategies.

1.4 Unnecessary drug therapy:

Unnecessary drug therapy identified through assess the medical record especially compare of data symptoms, diagnosis, laboratory findings with drug prescription. Unnecessarry findings with drug prescription. Unnecessa drug therapy classified as following: no medical indication, additive/ recreational drug use, nondrug therapy more appropriate، duplicate therapy, and treating an avoidable adverse drug reaction. Unnecessary drug therapy was identifying through discussion forum involve clinical pharmacist and geriatric consultant. The medications which included in unnecessary drug therapy were classified and encoded according to MIMS.

1.5 Inappropriate prescribing:

Inappropriate prescribing is highly prevalent in older people and has become a global healthcare concern because of its association with negative health outcomes including adverse drug events (ADEs), hospitalization and healthcare resource utilization. In the general adult population, medicines are considered appropriate to prescribe when they have a clear, scientific evidence-based indication, are well tolerated in the majority of patients and are cost effective. However, in the older population, prescribing decisions are often made in the absence of scientific evidence generated by rigorous randomized controlled drug studies because older patients with complex and multiple co-morbidities are frequently excluded from such clinical trials. In addition, age-related physiological changes often result in altered pharmacokinetic and pharmacodynamic responses to medications, thereby reducing the tolerability of many medications in older compared with in younger patients.[1] Compounding this is the increasing prevalence of chronic illnesses that occurs with aging, leading to a greater requirement for the prescription of multiple medications. Such complex factors must be considered when determining the appropriateness of prescribing decisions in older patients.

In the last two decades, much has been written about the definition of medication appropriateness in older patients. A simplistic approach would be to define appropriateness in dichotomous terms, i.e. whether a drug is safe or unsafe in terms of its pharmaceutical properties, or whether or not it is cost effective to prescribe. However, such simple terminology is too restrictive given the complexity of prescribing decisions in older people. A more holistic definition of inappropriate prescribing should encompass the assessment of older persons' prescription medications in the context of their multiple co-morbidities, complex medication regimes, functional and cognitive status, treatment goals and life expectancy.

1.6 Aim of study:

We investigated the occurrence of DRPs and adverse drug reactions (ADRs) amongst hospitalized patients prescribed polypharmacy, and the association of advanced age and female gender in Addiwaniyah teaching hospital.

PATIENTS AND METHODS

2.1 Study population

We conducted a retrospective, cross-sectional study in a 187- bed acute-care hospital in Addiwaniya teaching hospital at Addiwaniya city. Inpatient case notes and medication records were used in our data collection. Subjects were included in the study if they were inpatients on the last two Thursdays of August and September 2016, and who satisfied the criteria of being prescribed polypharmacy. Thursday was chosen to ensure that the patients admitted over the weekend would have had their admitting medications checked or altered by the attending physicians. This would capture most DRPs (both causing admissions and those occurring during hospitalization) among these patients.

2.2 Definitions

DRP was defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome (33).

For ADRs, we used the World Health Organization definition which specifies an adverse reaction as a reaction which is noxious and unintended, and which occurs at dosages normally used for prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function(34).

Polypharmacy was defined as the daily consumption of 5 or more medications. Different strengths of the same drug were counted as one item. However, formulations of the one drug requiring different routes of administration were regarded as separate items. Combination drug, that is a drug with more than one active ingredient in it, was regarded as a single item(44).

2.3 Data collection

Patient's age, gender, principal diagnosis, concomitant disease states, medical history, concurrent medications and dosage, and medications taken prior to admission were recorded. Other data collected included biochemistry and hematology results, microbiological culture and sensitivity tests, and plasma drug concentrations when these were available.

Normal laboratory values for the hospital were used to determine the presence of abnormalities. Renal function was estimated from creatinine clearance(35). DRPs experienced by the patients on admission and during their inpatient stay, together with the suspected drugs were extracted from their medical records. To avoid inter-rater variation, the case notes and medication records of the patients were reviewed by one of the investigators and our research supervisor, and any need for confirmation of the decision was resolved with the other investigators.

2.4 Classification of DRPs

DRPs were defined as inappropriate treatments, potential drug interactions, inappropriate dosages, unsafe drugs for patients, and ADRs experienced by patients on admission and during their inpatient stay.

ADRs that occurred during the same period were characterized based on the drugs and drug class involved the manifestations of these ADRs, and the frequency of occurrence. Due to the retrospective nature of the study, ADRs and their potential causality drugs were extracted from patients' medical case

notes with no further evaluation and determination into the ADR causality. Based on the case notes, the patients' existing conditions were matched with their drug therapy.

Appropriate doses of drugs, appropriate drug indications, possible drug interactions, and ADRs were based on drug monographs in the 42nd edition of the British National Formulary (36)**.** The appropriateness of control was based on the physician's documentation of the patient's condition in the medical case notes, together with any available laboratory results.

For any documentation of a poorly controlled medical condition, the medication records were reviewed thoroughly to determine if the poor control was drug related (ie, if the patient was receiving adequate and/or appropriate medication at that time). Inappropriately controlled conditions due to lack of medications, or lack of synergistic medications, would be classified as "additional therapy required", while a drug was prescribed for no obvious indication would be classified as "unnecessary drug therapy".

2.5 Statistical analysis

Chi-square test was employed to test for significant difference between the age of patients, as well as the gender of patients and their risk of getting DRPs. Mann-Whitney test was used to test for significant difference between the number of medications taken and the risk of DRPs. In all comparisons, the level of significance was adopted as 0.05.

The relative risks of developing ADR and DRP for geriatric patients and female patients were estimated from the prevalence of these events compared with non-geriatrics and male patients, respectively.

Results:

3.1 significant potential drug interactions

Drug pair	Possible effects
Carbamazine+Omperazole	Decrease level effects of omperazole
Carbamazine+Dexamethasone	Decrease level effects of dexamethasone
Omperazole+Clopidogrel	Omperazole decrease effects of clopidogrel
Atenolol+Diazepam	Severe hypotension and heart failure occasionally
Carbamazipine+Diazepam	Affect hepatic /intestinal enzyme cyp3A4 metabolism

Table 1 significant potential drug interactions

3.2 Ten most commonly prescribed drugs

Drug	Number of patients	%
Ceftriaxone	103	55
Paracetamol	45	24
Flagyl	34	18
Aspirin	44	23.5
Lasix	54	28.8
Omperazole	48	25.6
Zantac	54	28.8
Heparin	40	21.3
Decadron	25	13.3
Avas	33	17.6

Table 2 ten most commonly prescribed drugs

3.3. Adverse drug reactions:

Drug class	drugs	Manifestations of ADRs	Number of patients
Nsaids	Aspirin	Epigastric pain with vomiting,gastric ulcer	2
Ace inhibitor	Enalapril	Decline renal function,postural hypotention	3
Antiepileptics	Phenytoin	Giddiness	3
Loop diuuretics	Frusemide	Dehydration	2
Ca-channel blocker	Amlodipine	Postural hypotention	1
Antibiotic	Ceftriaxone	Chest pain	3
Beta blocker	Propranolol	Asthma exacerbation	1
Statin	Simvastatin	Increase liver function test	1

Table 3 identified cases of adverse drug reactions

3.4 List of duplicate therapies.

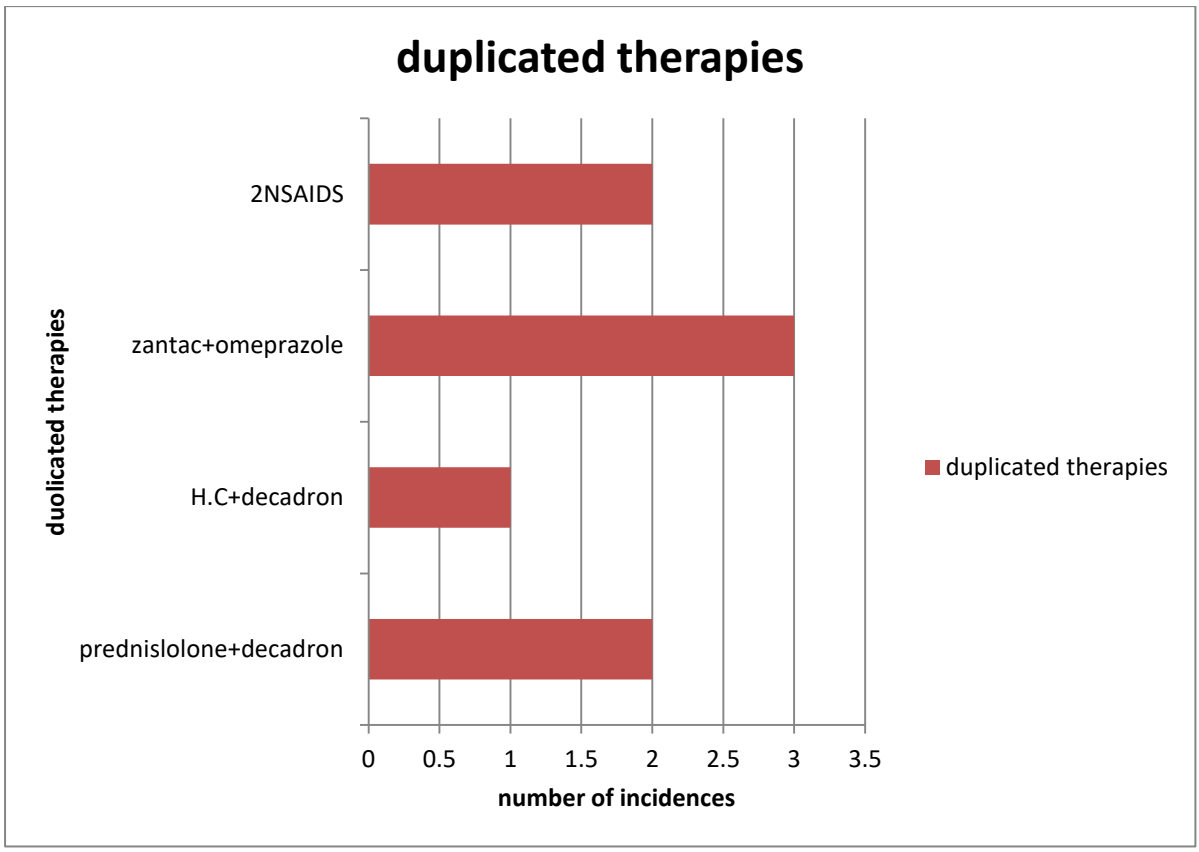

Figure 1 **List of duplicate therapies**

3.5 Drug-related problems and their number of incidences identified in patients during hospital stay.

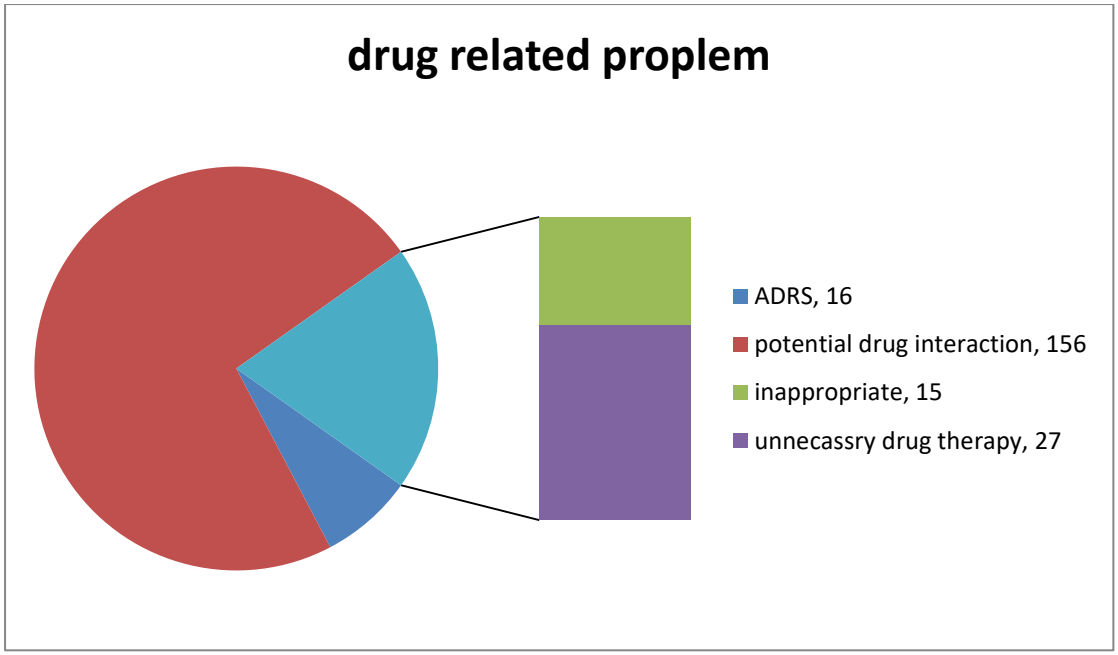

Figure 2 drug-related problems and their number of incidences identified in patients during hospital stay

Discussion:

Polypharmacy is a ubiquitous problem plaguing nearly all healthcare systems. Here, we investigated the occurrence of not only ADRs, but all DRPs during hospitalization among patients receiving polypharmacy. An evaluation of the status and possibly the risk factors involved in DRPs would give us some basic information for working towards improving the current situation.

From our results, comparatively**,** 63.4% of our study population (ie, approximately 3 out of 5 patients) had at least one DRP, albeit theoretical or actual, during their hospitalization. However, there was no equivalent comparison found in the published literature since we recruited only patients who were prescribed polypharmacy. Nevertheless, the high percentage of patients developing DRP here does highlight the need for more attention to the group of patients prescribed polypharmacy.

Our analysis on DRPs showed that potential drug–drug interactions accounted for a substantial amount of potential drug toxicity **(**73%). The drugs most implicated were Carbamazine, Omperazole Dexamethasone**,** Clopidogrel, Atenolol and Diazepam**.**Numerous drug combinations that resulted in modification of pharmacological action or in drug toxicity have been documented (37).

In addition, we also identified drug-pairs in our study that could give rise to potential severe interaction (Table 1)**.**We acknowledge that the judgment here is based on theoretical consideration. In clinical practice, some of these combinations may still be used, but the patient will need to be closely monitored for manifestations such as lack of therapeutic efficacy or toxicity, especially for drugs whose therapeutic effects may be diminished or augmented when used in

those combinations. As the study was carried out prior to the introduction of clinical pharmacy services at the study hospital, future pharmacists should focus on reviewing patients' medication charts and checking for potential drug interactions.

ADR is another important subset of DRPs. Nearly 10% of inpatients were found to have an ADR, which is higher than the ADR incidence of 6.7% found in the meta-analysis of 39 prospective studies from US hospitals(39). However, it was in line with the report from another study showing 10%–20% of hospitalized patients experiencing at least one ADR during their hospital stay (40). Since our study was carried out only on patients prescribed polypharmacy, the only inference that could be drawn was that the ADR incidence was probably comparable to international figures.

In evaluating the drugs frequently implicated in ADRs (Table 3), Antiepileptics and ACE inhibitor were ranked the highest, closely followed by NSAIDs and Loop diuretics**.** The drugs implicated in the present study are again similar to what has been reported (41). This congruency highlights that there is a rationale to focus more attention on patients prescribed certain drugs or drug classes.

The study also attempted to estimate the relative risk of developing ADRs using the age and gender of patients as risk factors. So far, we know of only one study that determined the relative risk of age (as a risk factor) in developing ADR in patients on major polypharmacy(42).The establishment and knowledge of the relative importance of various risk indicators would lead to better risk management strategy among different patient subgroups.

From our analysis for patients already receiving polypharmacy, we found that geriatrics had a similar risk in experiencing an ADR compared with non-geriatrics. However, this relative risk was increased to 1.4 if we included only patients who were on major polypharmacy (10 drugs or more). Although we did

not manage to see any statistically significant correlation between increasing age and increased likelihood of developing ADR, this could be due to our small sample size. Likewise, where gender comparison is concerned, our results showed that female patients did not have a higher risk in developing ADRs when compared with male patients.

In the Danish study, a total of 1999 patients of all ages, regardless of whether they were receiving polypharmacy or not were recruited (43). For the Dutch study, 2185 geriatric patients (65 years and older) prescribed polypharmacy were recruited, and polypharmacy was defined as long-term use of 2 or more drugs. In comparison, our inclusion criteria for polypharmacy, defined as 5 or more drugs, had restricted the number of eligible patients during the study period. The much bigger sample sizes in the previous two studies allowed them to be more sensitive in detecting the correlation between female gender and the risk of developing ADRs.

Conclusions:

Several observations could be drawn from the study results.

1. Our results established that the situation of drug therapy related problems in hospitalized patients receiving polypharmacy in Addiwaniyah teaching hospital in Addiwaniyah city is comparable to that occurring in other developed countries. One important interpretation of this would be that although DRPs have been studied and reported for the past twenty years, lessons and experiences from these studies have not exactly been translated into effective management of these problems. Further investigations are required to see what the underlying problem is in the current healthcare operating system that is causing this failure.

2. Regarding risk factors, our results showed that among patients with polypharmacy, age and gender may not be as important as the number of drugs prescribed as predictors of experiencing a DRP. In our case, neither older nor female patients showed a higher risk of developing DRPs. A similar trend was observed in the developing of ADRs.

3. We also showed that the drugs causing DRPs in this study are similar to those in overseas studies. Through identifying drugs that are most likely to cause DRPs, healthcare professionals could spend more time monitoring patients prescribed these drugs.

4. By identifying and properly managing the small percentage of high-risk patients (such as those with risk factors for developing DRPs and those prescribed drugs commonly associated with DRPs), we would be able to minimize or prevent most of these DRPs. We believe that with such an approach, the rampaging problem of DRPs can be at least dampened.

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