ROLE OF PHARMACISTS IN CLINICAL RISK MANAGEMENT

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Summary

The focus of this thesis is on detecting and quantifying drug-related risks faced by in-patients in Singapore, followed by assessing and managing these risks from the perspective of a pharmacist. Currently, there are no formal local studies that investigate specifically into drug related problems (DRPs) and adverse drug reactions (ADRs) to evaluate the situation and to implement strategies to minimize the occurrence of these problems. To address the aforementioned conditions, this thesis attempted to establish the current level of risk that the patients were exposed to in the healthcare environment, as well as to ascertain the contributory factors for the increased risk. This was followed by an attempt to evaluate the clinical and economical impact on increased and systematic involvement by pharmacists in reducing these risks. Thereafter, a quantitative tool in assessing ADR with the view that risk of DRPs, namely ADR could be greatly reduced with a better instrument in an improved healthcare environment.

This thesis found that the DRPs detected in in-patients were mainly avoidable. With this knowledge of a more exact representation of the situation locally, it would then be possible to develop and implement strategies which would help in detecting, assessing and managing the situation of DRPs. This finding led the next step of the thesis to a follow-up study which studies the impact of regular pharmacist's participation in a physician-pharmacist review team. It was shown that with the presence of a pharmacist in a primary patient care review team, more DRPs (and even potential DRPs) were detected and were promptly averted. There was significant total drug cost savings during the study period (linearly projected as $42 000 annually)

when there was a pharmacist on board the review team. The cost-benefit ratio of such an arrangement was calculated to be 5.84. This positive ratio, on top of a net annual return of $42 000 in investing in a pharmacist to perform such monitoring tasks seemed to substantiate the cost-effectiveness for hospital administrators to endorse such pharmaceutical care services.

After evaluating the inclusion of a pharmacist into the regular ward round as a change in system to reduce clinical risk to the patients. The next study performed was to evaluate whether the existing tools for assessing and ascertaining risk is suitable or sufficient for the pharmacists to carry out the task efficiently. A thorough assessment of the available tools and the reality of readily available clinical data demonstrated the necessity to develop a simpler and user-friendlier tool to assist the pharmacists in the task. In this thesis, a new quantitative ADR causality scale was developed. A severity assessment scale for comparing the intensities of the severity of various ADRs was also produced and incorporated with the abovementioned ADR scale. This amalgamation provides a novel combined ADR causality and severity scoring system which will serve to give more practical value to the results obtained compared to the individual causality and severity scores. This scoring system could be utilized to facilitate ADR signal generation for general drugs or for targeted drugs. Its quantitative nature can also help clinicians, investigators and the regulatory authorities in case management when they are faced with limited time and resources. This scoring system will also be a useful tool for pharmacists in patient care review team for the purpose of detecting ADRs in the in-patients.

From the results obtained from these studies, it could be inferred that with a change in the workflow of the current healthcare system in Singapore and by equipping the pharmacists with user-friendlier tools (e.g. the algorithm developed in this thesis), it would be possible to allow the pharmacists to play a much bigger role in contributing to clinical risk management.

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List of Abbreviations

ABACUS – Alerts Based on ADRs' Causality and Severity

ADR – Adverse drug reaction

ADRAC – Adverse Drug Reaction Advisory Committee

CDA – Centre for Drug Administration

CI – Confidence interval

DRP – Drug related problem

FDA – Food and Drug Administration

SD – Standard deviation

TGA – Therapeutic Goods Administration

WHO-UMC – World Health Organization-Uppsala Monitoring Centre

List of Publications

A. Publications relating to research work from the current thesis

1. **Koh Y**, Yap CW, Li SC. A quantitative approach of using genetic algorithm in designing a probability scoring system of an adverse drug reaction assessment system. *Int J Med Inform*. 2006; **Submitted**.

2. **Koh Y**, Li SC. A new algorithm to identify the causality of adverse drug reactions. *Drug Saf.* 2005;28(12):1159-1161

3. **Koh Y**, Kutty FBM, Li SC. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. *Ther Clin Risk Manag*. 2005;1(1):39-48.

4. **Koh Y**, Fatimah BMK, Li SC. Therapy related hospital admission in patients on polypharmacy in Singapore: a pilot study. *Pharm World Sci*. 2003;25(4):135-137.

B. Publications from other projects not included in the current thesis

1. Luo N, **Koh Y**, Tan CH, Kua EH, Li SC. Drug utilization review of risperidone for outpatients in a tertiary referral hospital in Singapore. *Hum Psychopharm*. 2004;19(4):259-264

C. Conference Presentations (Oral Presentation)

1. **Koh Y**, Fatimah MK, Li SC. Prevalence of drug therapy related hospital admission and its association with polypharmacy and age of patients in Singapore. *Proceedings of European Society of Clinical Pharmacy 3rd Spring Conference on Clinical Pharmacy "Pharmaceutical Care: The Hospital - Primary Care Continuum"*, Portorož, Slovenia, 8 - 11 May 2002.

2. **Koh Y**, Chan CL, Li SC. Comparison of five established adverse drug reaction algorithms in a patient sample in Singapore. *Proceedings of European Society of Clinical Pharmacy 4th Spring Conference, "Clinical Pharmacy and the Ageing Patient"*, Lisbon, Portugal, May 14-17, 2003.

D. Conference Presentations (Poster Presentation)

1. **Koh Y**, Fatimah MK, Li SC. Prevalence of drug therapy related hospital admission and its association with polypharmacy and age of patients in Singapore. *Proceedings of 15th Singapore Pharmacy Congress*, Singapore, November 9-10, 2002.

2. **Koh Y**, Fatimah MK, Li SC. Prevalence of drug-related problems amongst hospitalised patients on polypharmacy in Singapore. Proceedings of ISPOR 9th Annual Conference, Arlington, West Virginia, USA, May 16-19, 2004. *Value in Health* 2004; 7(3): 372.

3. **Koh Y**, Yap CW, Li SC. Developing a quantitative scoring system for adverse drug reaction assessment using genetic algorithm. *Proceedings of ISPOR 2nd Asia-Pacific Conference*, Shanghai, China, March 5-7, 2006.

Chapter 1

Introduction

1.1 Overview

Risk management in the pharmaceutical sense is a term used to describe the process of actively identifying, assessing, communicating and minimizing the risks which may arise from using a drug.[1] Ideally, such processes which seek to establish and maintain a favorable benefit-risk balance in patients should take place at different stages of the life-cycle of a drug, from its development all the way to post-marketing surveillance of the drug used in the general population. Although drugs are meant to provide patients with relatively predictable beneficial effects, unfortunately they also have the potential to cause unexpected and unwanted effects. These unwanted effects may range from minor side effects to major debilitating effects, or in the worse case scenario, fatal consequence.

The term drug-related problems (DRPs) is used to describe these consequences which are different from the intended pharmacotherapeutic effect of the drugs involved.[2] However, this is only a brief and simplistic summary of what DRPs encompass. According to Strand *et al.*,[3] DRPs would include the following eight broad categories - adverse drug reactions (ADRs); untreated indication; drug use without indication; improper drug selection; using subtherapeutic dose of drug; excessive dose of a correct drug; drug interaction; and failure to receive drug.

The focus of this thesis is on detecting and quantifying these drug-related risks faced by in-patients in Singapore, followed by assessing these risks and managing them from the perspective of a pharmacist. In this chapter, an introduction to DRPs and ADRs would be provided (Section 1.2), followed by a brief review of work done to date for the management of DRPs and ADRs (Sections 1.3 and 1.4 respectively).

Thereafter, the rationale to assess the DRP and ADR situation in Singapore would be discussed (Section 1.5). With this in place, a list of research motivations is then generated (Section 1.6). These questions will be examined in the subsequent chapters with each chapter detailing the methodology, results and discussion of the individual studies embarked upon to answer each issue with the hope that the summation of the study results would shed some lights as how to minimize and manage drug-related risks from the perspective of a pharmacist.

1.2 Introduction to Drug-Related Problems (DRPs) and Adverse Drug Reactions (ADRs)

1.2.1 Drug-related problems

As briefly mentioned earlier, 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%.[4, 5] Due to their association with increased rates of morbidity and mortality, DRPs continue to be a major problem faced by healthcare institutions worldwide.[2, 6-8] Inappropriate prescribing of medications, ADRs and drug interactions may cause increased morbidity and mortality, and treating these iatrogenic complications further burdens the health care system.[6] This is in view of patients requiring more nursing care, more attention by the attending physician, and possibly additional drugs to treat the resulting adverse reaction or interaction.[7] All these inevitably lower the quality of life of the patient. Moreover, the extent and cost of drug related morbidity and mortality are of great importance to health care practitioners, administrators, patients and society as a whole.[2]

Many factors can contribute to the high prevalence rate of DRPs, but among these factors, polypharmacy and older age have often been identified as important risk factors.[4, 9, 10]

1.2.1.1 Causes of the various DRPs

As stated earlier in this chapter, there are 8 different types of DRPs. These are their associated causes, adapted for use in this dissertation[11]:

1. Adverse drug reaction
    a. The drug was administered too rapidly for this patient
    b. The patient is having an allergic reaction to this medication
    c. The patient has identified risk factors that make the administered drug too dangerous to be used
    d. The patient has experienced an idiosyncratic reaction to the administered drug
2. Untreated indication
    a. The patient has a new medical condition requiring initiation of new drug therapy but not receiving the drug
    b. The patient has a chronic disorder requiring continuation of drug therapy but is not receiving it
    c. The patient has a medical condition that requires combination pharmacotherapy to attain synergism/potentiation of effects
    d. The patient is at risk to develop a new medical condition preventable by the use of prophylactic drug therapy and/or pre-medication
3. Drug use without indication
    a. The patient is taking a medication for which there is no valid medical indication at this time
    b. The patient accidentally or intentionally ingested a toxic amount of a drug or chemical, resulting in the present illness or condition
    c. The patient's medical condition is better treated with non-drug therapy

   d. The patient is taking multiple drugs for a condition for which only single-drug therapy is indicated
   e. The patient is taking drug therapy to treat an avoidable adverse reaction associated with another medication

4. Improper drug selection
   a. The patient has a medical problem for which the administered drug is not effective
   b. Patient is allergic to the administered medication
   c. Patient is receiving a drug that is not the most effective for the indication being treated
   d. The patient has risk factors that contraindicate the use of the administered drug
   e. The patient is receiving a drug that is effective but not the least costly
   f. The patient is receiving a drug that is effective but not the most safe
   g. The patient has an infection involving organisms that are resistant to the administered drug
   h. The patient has become refractory to the present drug therapy
   i. The patient is receiving an unnecessary combination product when a single drug would be appropriate
5. Subtherapeutic dose
   a. The dosage used is too low to produce the desired response for this patient
   b. The patient’s serum drug concentrations are below the desired therapeutic range

c. Drug, dose, route, or formulation conversions were inadequate for the patient

d. Dose and interval flexibility (insulin sliding scales, “as needed” analgesics) were inadequate for the patient

6. Excessive dose

a. Dosage is too high for the patient

b. The patient’s serum drug concentrations are above the desired therapeutic range

c. The patient’s drug dose was escalated too rapidly

d. The patient has accumulated drug from chronic administration

e. Drug, dose, route, formulation conversions were inappropriate for the patient

f. Dose and interval flexibility (insulin sliding scales, “as needed” analgesics) were inappropriate for the patient

7. Drug interaction

a. The bioavailability of the drug is altered due to an interaction with another drug or food the patient is taking

b. The effect of the drug has been altered due to enzyme inhibition/induction from another drug the patient is taking

c. The effect of the drug has been altered due to displacement from binding sites by another drug the patient is taking

8. Failure to receive drug

a. The patient did not receive the appropriate drug regimen because a medication error (including prescribing, dispensing, administration or monitoring) was made

b. The patient did not comply (adherence) with the recommended directions for using the medication
c. The patient did not take the drug as directed owing to the high cost of the product
d. The patient did not take the drug as directed because of lack of understanding of the directions
e. The patient did not take the drug as directed because it would not be consistent with the patient's health beliefs

1.2.1.2 Influence of polypharmacy on DRP

Polypharmacy is defined as the use of multiple medications by a single patient and is commonly observed among geriatric patients.[4] The use of multiple medications has been shown to predispose patients to ADRs,[10, 12-15] drug-drug interactions,[4, 16, 17] and medication non-compliance,[18-20] particularly in the geriatric population.

Besides the undesirable clinical consequences for the patients, DRPs (mostly ADRs) also pose a significant financial burden to the healthcare system.[6] In a US study performed in 1992–1994, the estimated cost of treating reported adverse drug events among in-patients was US$1.5 million per year at a university-affiliated hospital.[21] Another more recent French study conducted in 1996–1997 showed the annual cost of drug-related hospital admission to a university hospital as €3.85 million per year.[22] Thus, reducing the use of unnecessary medicines and avoiding polypharmacy would be beneficial in aiding the reduction of healthcare cost beyond the confine of reduction in drug costs alone.

1.2.1.3 Influence of age on DRP

Amongst all the risk factors, advanced age has been associated with substantial increased risk of acquiring ADR.[23] A sevenfold increase in occurrence of ADRs from 3% to 21% has been shown to occur between patients aged 20–30 years and patients aged 60–70 years.[24] However, other researchers had argued that this propensity of older patients experiencing ADR was not well substantiated by epidemiological data.[13] Furthermore, the failure to control for important age-related covariates, e.g., clinical status of the patient, had also been cited as a limitation to the interpretation of many study results.[25] Some researchers had proposed that inappropriate medication in the elderly might pose a higher risk for acquiring ADR than advanced age as a sole risk factor.[26] Up to now, the issue of whether inappropriate drug use or advanced age should be considered the more important risk factor for causing 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.

1.2.2 Adverse drug reactions

Adverse Drug Reaction (ADR) is recognized as a major contributor in iatrogenic illness. ADRs are known to complicate management of existing disease, and affect patients' quality of life.[27] ADRs may also result in delay in cure of the original disease as well as inappropriate treatment of unrecognized drug-induced problems.[2, 8, 10, 27, 28] Epidemiological studies have indicated that the range of reported ADRs that occur during a hospitalization episode could vary from 1.5 to 43.5%.[29] The use of different definitions of ADRs coupled with the presence of different ADR reporting systems and the amount of emphasis placed on ADR reporting would all

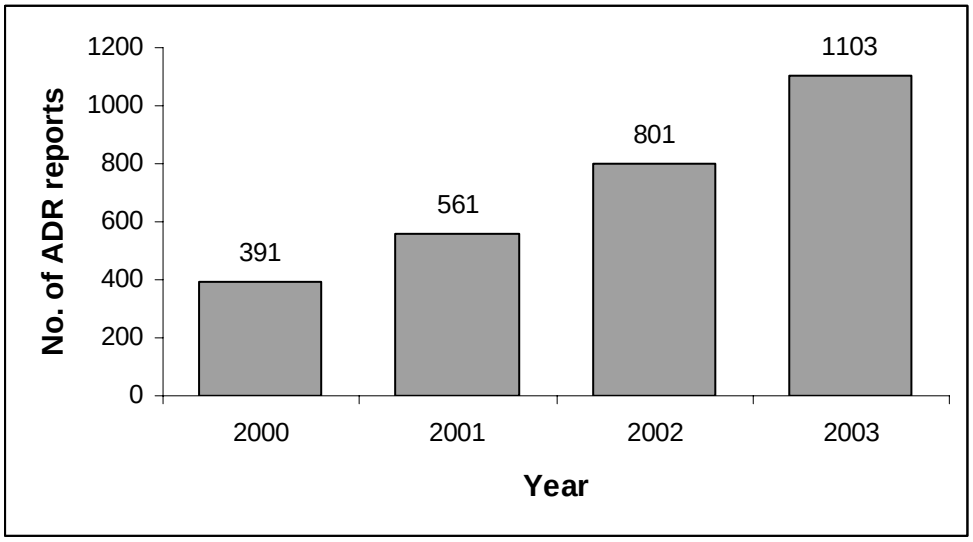
have contributed to this wide range. Nevertheless, the general consensus that ADR is a major problem encountered in clinical medicine is unchallenged.

Besides increased morbidity and mortality caused, the economic consequences of ADRs are often serious.[30] Data from both USA and Europe showed ADRs could impose a heavy financial burden on the healthcare system.[31-33] For instance, an American study estimated the average cost of treating reported adverse drug events occurring among in-patients amounted to US$1.5 million per year at an university-affiliated hospital,[21] while a study in a general hospital in France showed an estimated annual cost of treating adverse drug reaction to be €161 837.[31]

Hence, ADRs as one of the most important categories of iatrogenic illness, have significant medico-legal and economic ramifications.[34] This has brought on ADR reporting as a major initiative in contributing to maintaining drug safety at both the institutional and national level in many healthcare systems. The reporting of ADRs is of great importance for issuing alerts to reduce or prevent similar incidences. At the same time, consolidating all ADRs reports can generate signals which alert regulatory authorities to perform risk-benefit assessments for the drugs involved with the aim of safeguarding public health. In Singapore, data from the Pharmacovigilance Unit, at Centre for Drug Administration (CDA) (which is responsible for collating all ADR reports for the nation) showed a near 3-fold increase of ADR reporting from 391 cases in the year 2000 to 1103 cases in the year 2003 (Figure 1.1). This increase would substantially be due to a heightened ADR awareness as a result of the many promotion campaigns conducted by the Health Sciences Authority over the years and hence causing an increase in voluntary reporting. Nevertheless, the increase in ADR

reporting does highlight the need for a more effective way to assess ADR causality. The faster and more accurately a signal is identified, the sooner the appropriate remedial actions can be implemented. From the perspective of the regulatory authorities, a rapid and reproducible ADR identification will also translate to faster dissemination of alerts. This is especially important for serious ADRs.

Figure 1.1 Trends of local ADR reporting in Singapore



In many jurisdictions, pharmacovigilance is under the purview of the drug regulatory authorities.[35] Spontaneous reporting of suspected adverse reactions to drugs is currently the norm and backbone of pharmacovigilance internationally.[35] However, spontaneous reporting often produces only circumstantial evidence with uncertainties pertaining to the causal involvement of the drugs.[36] Therefore, further assessments are needed to confirm causality, identify risk factors, and also measure the occurrence frequency of ADRs. Besides causality, which is the likelihood of the suspected drug causing the ADR, another important criterion for assessing ADRs will be the severity. The ascertainment of these two criteria, will aid the regulatory authorities in evaluating the risks associated with the signals generated by ADR

reports, and making decisions on the necessary and most appropriate remedial measures. These may include the re-evaluation of the drug involved for the suitability of its approved indications, a requirement for additional special cautionary labels or changes in package inserts, or withdrawal of the drug. For the health-care professionals, this information can assist in the judgment of the risk-benefit in using the drugs to treat a condition.

1.3 Work done to date for the management of Drug-Related Problems (DRPs)

Despite the efforts of healthcare professionals in reducing DRPs, it is considered that a large proportion of these DRPs are preventable.[8] Although the influence of age and gender are inherent in DRPs and cannot be changed, the geriatrics and female patients will have to be monitored more closely to prevent DRPs from occurring or to detect the first signs of possible DRPs and manage them accordingly. Where polypharmacy is concerned, proper management of patients' drug therapy will help in risk minimization.

In the last decade, pharmacists have contributed to improvements in the areas of drug therapy and patient safety. There has been a paradigm shift from their traditional roles of distribution and dispensing of medications to the active involvement in the direct provision of pharmaceutical care.[37-47]

Pharmaceutical care implies communicating and reaching a consensus with physician regarding pharmacotherapy.[39] The pharmacists will be more involved in identification and solutions of problems related to drugs, and to prevent drug-related problems from occurring. Some of the interventions carried out by the pharmacists include advising of appropriate surgical antibiotic prophylaxis, performing pharmacokinetic monitoring, initiation and discontinuation of drug therapy, suggesting of alternative pharmacotherapy, as well as influencing the modification of drugs' dose, frequency and route of administration.[37, 39] Such pharmacist interventions strive to achieve a rationale and optimal use of drugs. For this to take place effectively,

pharmacists have to participate actively and coordinate with other health-care professionals in multidisciplinary care.[37, 39-44] Going on ward rounds as a member of the patient care team will allow the pharmacists to provide such services most efficiently.[40] The pharmacists will be able to intervene immediately when the need arises, rather than to spend time checking and correcting prescription orders after they have been sent to the pharmacy.

Such pharmaceutical care provision has been shown to reduce the number of adverse drug events and the length of hospital stay.[48] Other than signifying a lower rate of DRPs, all these reduction of adverse events and length of stay also translate to cost savings and cost avoidance in the medical institutions.[39, 41, 44] In 1997, Mutnick *et al.*[44] presented the results of 4648 interventions carried out by 50 pharmacists during a 9 months study at a 849-bed institution. These interventions were based on the pharmacist's evaluation of the patient, the condition involved, and the appropriateness of the drug therapy prescribed. Of these interventions, 87% were accepted by the medical staff, and these accepted interventions represent a net therapy cost saving of US$487,833, as well as a cost avoidance of US$158,563 achieved by preventing a potential net 371.9 additional hospital days. In a more recent study published in 2003, Galindo *et al.*[39] analyzed 3136 pharmacists' interventions that were collected prospectively for 6 months in a 330-bed acute hospital. The medical practitioners accepted 88.8% of these interventions and they represented a cost saving of €129,058.31.

1.4 Work done to date for the management of ADRs

To date, there are immense efforts in many countries to detect ADRs via various methods with the intention of distinguishing the real ADRs and incorporating safety nets to either prevent similar ADRs from occurring or to allow rapid identification of analogous ADRs. Such detections take place on different scales from within the institution,[49-51] to within the country,[52] and even across different countries in the world like what FDA and WHO-UMC are doing.[53, 54]

Within medical institutions, efforts to detect ADRs are usually through their own computerized systems. All health-care professionals (physicians, nurses, pharmacists) are encouraged to report ADRs detected to the hospital's pharmacy department.[49, 51, 55] Such spontaneous reports are captured in databases. In most cases, pharmacists or the hospital ADR review committees will evaluate the recorded ADRs to pick out trends in the reported ADRs. The information is then circulated to the prescribers with the intention of reducing future adverse reactions. When ADR management is done on a larger scale, it is too time consuming to have medical personnel going through each and every report to detect if the ADR is genuine and if an alert for a particular ADR needs to be disseminated. Hence, more comprehensive databases which are programmed to pick out ADR alert signals from data mining of huge number of reports are used.[53, 56, 57] These types of monitoring systems are generally organized at national level.

Where individual general practitioners are concerned, the relatively small number of cases that the doctor encounter would make the chance of arriving at worthwhile results too small.[30] Moreover, in cases of clinical practice where ADR

causality need to be determined immediately, or in organizations whereby computer data system is not as comprehensive, the traditional use of ADR algorithms[58-62] to identify causality of suspected drug still remains the most ideal. The presence of operational identification of ADRs incorporates an estimate of the certainty of the link between the untoward clinical event and the suspect drug. ADR algorithms are able to increase inter-rater agreement when assessing ADR causality,[58, 60] and also brings about better intra-rater reliability when assessing the ADR cases.[58]

Since the reason for going through the effort of detecting ADRs is to allow medical professionals to make the right diagnosis and to ensure safe usage of the drugs, it is important that information of established ADRs are passed on to the health care professionals as soon as feasible.[63] Hence, once these ADRs are detected, assessed for their causality and the causative drugs established, the alerts will be circulated in publications either within the institution or at national level to health care professionals. If the ADRs are considered to be of serious nature, there will even be alerts at international level. Depending on the level of seriousness and severity of these ADRs, regulatory bodies will decide whether to allow the continued use of these drugs. At the same time, the respective drug companies will have to evaluate if a recall for the offending drug is necessitated.

1.5 Why is there a need to assess DRPs and ADRs situation in Singapore?

As mentioned earlier in this chapter, to carry out risk management, there has to be risk identification, assessment, communication and minimizing the risks. So far, the published papers retrieved from the literature search on the topics of DRPs and ADRs are reports of studies carried out in other countries. There are no formal local studies that examine DRPs and ADRs to evaluate the situation and to implement strategies to minimize the occurrence of these problems. Although overseas studies would be useful to a certain extent, they may not be truly representative of local situation. Henceforth, the motivation for this study comes from wanting to identify and assess the most exact state of DRPs and ADRs in Singapore, as well as the risk factors faced locally that contribute to these problems. The hypothesis is that the situation here is very much similar to those in other developed countries. Once a more exact representation of the situation here is established and evaluated via such reviews, it will be possible to develop and implement strategies which will help improve the situation of DRPs locally.

1.6 Research motivations

In the current project, it is intended to adapt from the broad framework of risk management. The project will target its principle for detecting, assessing, and managing risks that occur during drug therapy.

There are a few research questions that the current thesis sets out to answer:

1. What is the current DRP situation in Singapore?
    a. Since DRPs have been shown to prevail in hospitalized patients, with polypharmacy and increasing age identified as two important risk factors,[10, 14, 15, 23, 24] the study would aim to find out what is the incidence of DRPs-associated hospital admission, and its correlation to polypharmacy and age (see Chapter 2). This will be a baseline study for analyzing if the incidence of drug therapy related admission to hospital in Singapore will be comparable to that occurring in other developed countries as reported above. In addition, the verdict of whether the DRPs are avoidable will provide a basis to derive suitable strategies to lower the incidence of these drug therapy related admissions.
    b. After establishing the incidence and type of DRPs that are prevalent during hospital admission, the thesis will examine the occurrence of DRPs amongst hospitalized patients on polypharmacy to complete the picture (see Chapter 3). When at that, other than wanting to verify the association of advanced age with developing ADRs in in-patient, the study also seeks to confirm the correlation between the female gender and occurrence of ADRs. This phenomenon has been reported in

overseas studies[28, 64, 65] and unless its incidence is established in Singapore, it will be difficult to substantiate the need to put forth the female gender as a risk factor for developing DRPs and ADRs. It is with the presence of a lucid guideline of the risk factors present that effective management measures can be implemented. The search for these risk factors will be the main intent.

2. Will the current system in the hospital benefit from the presence of physician-pharmacist review teams? Will DRPs and medication costs be reduced as a result of the presence of such a team?
    a. Having targeted to detect the risk factors involved in DRPs, the focus will now be to find out how pharmacists can make an impact in trying to reduce the occurrence of these DRPs. There is already an emerging trend in Singapore whereby hospital pharmacists are shifting towards a clinical role in improving the quality of medical care for patients. However, the prevalence of a low pharmacist-to-patient ratio coupled with the fact that pharmacist are still not relieved of the role of medications distribution and dispensing makes it difficult for a pharmacist to go on regular ward rounds as part of a primary patient care team. Here, the impact of pharmacists' participation in physician-pharmacist review teams will be studied. The research question would be to evaluate if such review teams can actually help in the detection of DRPs at its early stage and whether efforts can be implemented to minimize these DRPs or even eradicate them. If these potential DRPs can be intervened successfully, then the next step would be to verify if there is any reduction in pharmacy costs and decrease in length of stay

of patients when there is such active participation of pharmacists in doctors' ward rounds (see Chapter 4). Evaluating such potential cost-savings measures may also help to justify the cost-effectiveness for the hospital to endorse such services. Such studies were done in abundance elsewhere[39, 41, 44, 48] and without initiating this study, there will be no local data to justify the cost-effectiveness for the hospital to endorse such services and to allocate resources of them.

3. Can the inadequacies present in some currently available ADR algorithms be improved upon? How can an ADR algorithm be further harnessed and developed into a functional and user-friendly tool in detecting and assessing ADRs?
    a. ADR is one big component of DRPs. In order to carry out comprehensive evaluation of DRPs, it is essential to have a good method of detecting and assessing ADRs as well. Currently, ADRs reporting within hospitals and even at national level are mostly done via spontaneous reporting. However, this is not the ideal method as it often produces only circumstantial evidence. A better method of accurately detecting ADR will be via causality algorithms.[66] These algorithms are preferred over clinical judgment for assigning ADR causalities because of their systematic approach in information acquisition, and thus help to improve the reliability of the assessments.[36, 58] However, due to the structure or data requirement of several commonly used algorithms, the problem of uncertainties pertaining to the causal involvement of the suspected drugs may remain unresolved. Therefore, the study question is to develop an

improved algorithm that can provide more consistent drug risk probability using information that are easily available to the physician or regulatory personnel (see Chapter 5).

b. For almost all existing ADR algorithms, each criterion in the algorithms was arbitrarily assigned weights based on its perceived importance. Such qualitative system is unable to determine the probability of the ADR causality based on the results obtained. If there is a probability scoring system, a quantitative likelihood of the ADR being caused by the suspected drug can be determined using such an algorithm. Noting the limitation of a qualitative approach to the existing ADR causality algorithms, the researcher would take up the challenge to develop a quantitative causality scoring system (see Chapter 6).

   For this quantitative scoring system, the power of genetic algorithm is harnessed. Genetic algorithm is a heuristic artificial intelligence algorithm that mimics some of the processes observed in natural evolution.[67] It is useful for the optimization of problems that require high demands on computational resources. Examples of such problems where genetic algorithms have been used are multi-disorder diagnosis,[68] determination of treatment doses for radiation therapy[69, 70] and patient scheduling.[71] With the development of a quantitative scoring system, the final score of the ADR algorithm can also be used as a measure of the probability of ADR causality.

c. However, the determination of ADR causality without establishing its severity may be reckoned as incomplete (see Chapter 7). With the

presence of both ADR causality and severity, it will be easier for health professionals to make decision on the management of ADR, as well as to decide on the benefit-risk ratio regarding further use of the drug involved. For that reason, the researcher sets to develop an assessment scale to determine the severity of ADRs (see Chapter 7). Following that, this severity assessment would be integrated with the ADR causality probability scale to give an overall score. To further improve the functionality of this score, they are classified into various alert zones. These zones will now provide users in settling on the most appropriate course of action to be taken following the particular ADR detection.

In each of the following chapters of the thesis, details of the studies which resulted from these motivations will be described.

Chapter 2

Therapy Related Hospital Admission in Patients on Polypharmacy in Singapore: A Pilot Study

2.1 Introduction

Publications have shown DRPs to be a common reason for hospital admission.[64, 72] Admittedly, many factors contribute to DRPs in patient management. However, among these factors, polypharmacy and older age have often been identified as important risk factors for patients suffering from DRPs.[4, 9, 10]

Polypharmacy is defined as the use of multiple medications by a single patient,[4] and this usually results from the prescription, administration, or use of more medications than is clinically indicated in a given patient.[9] This use of multiple medications can easily predispose patients to drug-related problems (DRPs) like adverse drug reactions (ADRs), drug-drug interactions, and non-compliance.[4]

ADRs incidences have been consistently shown to increase with the number of drugs taken.[4, 10] It has been shown that significantly more patients for whom four or more drugs had been prescribed were admitted to hospitals because of ADRs than patients receiving up to three drugs (11.1% vs. 3.6%).[64]

Besides higher risk of experiencing ADRs, the use of multiple medications also makes compliance with medication regimens more difficult.[4] This is evident in a study which showed that medication errors, largely made up of non-compliance, increased from about 15% when only one drug was prescribed to 25% when two or three drugs were prescribed. When more than four drugs were taken, errors exceeded 35%.[73]

Other than polypharmacy, advancing age has been shown to contribute to the substantial increase in risk of acquiring ADR, and hence increased risk of DRP-related hospital admission as well.[10] This is supported by data which showed a sevenfold increase in occurrence of ADRs from 3% in patients aged 20 to 30 years to 21% in patients aged 60 to 70 years.[24] However, this propensity of more older patients getting ADR may be due to higher risk of inappropriate medication rather than just advancing age as a sole risk factor.[13, 26, 74]

Hence, it can be seen from the above that polypharmacy can have adverse clinical consequences on the patients. In addition, the strain on health care cost is also substantial.[75] Nevertheless, although DRP-related hospital admission has been recognized as a healthcare problem, there has not been any formal research done in Singapore to study it systematically to date. As such, the correlations between DRPs with polypharmacy and age of patients have also not been examined and evaluated.

The current study intends to estimate the incidence of drug related admission to an acute care hospital in Singapore, and to evaluate its correlation to polypharmacy and age of the patients involved.

2.2 Method

A retrospective, cross-sectional study was carried out at Alexandra Hospital, a 404-bed acute care hospital in Singapore. In-patient case-notes and medication records were used for data collection. The patients were included in the study if they were in-patients on the last two Thursdays of November and December 2000, and had satisfied the criterion of being on polypharmacy.

In the study, polypharmacy was defined as the consumption of 5 or more medications. Different strengths of the same drug were counted as one item. However, formulations of the one drug that require different routes of administration were regarded as separate items. Combination drugs, that are drugs with more than one active ingredient in it, were regarded as a single item.

Each patient was characterized as having or not having a DRP on admission. Only definite cases of admission related to drug therapy were distinguished as having a DRP. If there was any uncertainty because of lack of supporting documents, then the case was classified as not having a DRP. Documentation by the admitting doctor was used to check for problems like non-compliance and lack of required drug therapy. Patients who required modifications to their drug therapy as a result of a newly diagnosed medical condition or worsening of an existing medical condition were not characterized as having a DRP on admission.

Definitions from Hallas *et al.* was used to evaluate the identified DRPs on/coincidental to admission for their contribution to hospital admission and their avoidability.[76] DRPs were classified as dominant reasons for hospitalization if they

were the main reason for admission. If there were other factors present which contributed to admission, then the DRP was classified as partly contributing.

The DRPs were deemed as avoidable if (i) they were caused by drug treatments which were obviously inappropriate or contraindicated; (ii) no measures were taken to counteract known adverse effects of the drug (e.g. extrapyramidal side effects of anti-psychotic drugs); (iii) patients were not compliant or were insufficiently educated about their medication. The DRP was classified as possibly avoidable if the patient's disease state was considered to be potentially changing, thereby resulting in the need for altered drug therapy. Unavoidable DRPs would be those that were unpredictable.

The main investigator (YK) was involved in checking for the presence of DRPs and the subsequent characterisation of these DRPs. Any need for confirmation of decisions was resolved with the other investigators.

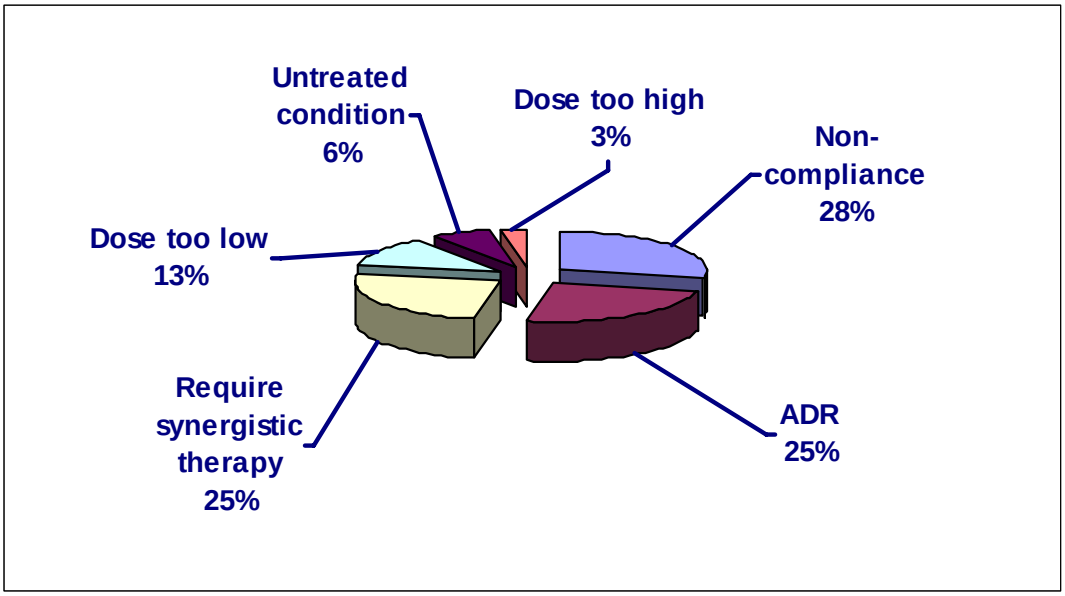
For data analysis, Chi-square test was employed to test for significant differences between the age of patients and their risk of getting DRPs. This test was also used to compare the risk of DRPs between patients on minor (5–9 drugs) and major polypharmacy (10 and more drugs). The *a priori* level of significance for all comparisons was $p<0.05$.

2.3 Results

There were 640 in-patients during the study period. Of these, 347 patients (54.2%) satisfied the criterion of being on polypharmacy. Their age ranged from 16 – 97 years old (mean ± SD: 66 ± 18 years), and 43% of the study subjects were female. The number of medications per patients ranged from 5 to 14 (mean ± SD: 7.4 ± 2.1). Geriatric patients (that is patients over the age of 65) made up 58.2% of our study population.

There were 32 cases (10.8% of study population) of DRPs which resulted in or coincidental to admission. In 71.9% of these cases, DRPs were the dominant reasons for hospital admission, and contributing factors for the reminder. Based on the criteria by Hallas *et al.*,[76] these DRPs were all avoidable and can be broadly classified into non-compliance (28.1%), adverse drug reactions (25%), require synergistic therapy (25%), dose too low (12.5%), untreated condition (6.3%) and dose too high (3.1%) (Figure 2.1).

Figure 2.1 Types and frequency of DRPs



For the 10 patients who required additional therapy, the existing medical conditions of nine of them may have been better controlled if synergistic drugs were added onto their current medication. The tenth patient was admitted as a result of syncope secondary to chronic anemia which was not treated with medication. Of the non-compliant patients, one of them had poor inhaler technique resulting in the exacerbation of his asthma problem. The remaining 8 patients were not compliant with their medication regime.

Among these DRPs, 52% were found in elderly patients (greater than 65 years old). However, statistical analysis showed that when corrected for the number of drugs used by the patients, the geriatrics did not appear to have a higher risk of acquiring DRP-related hospital admission as compared to the younger patients ($p = 0.574$).

Further analysis showed that there is a higher trend of DRP-related admission in patients on major polypharmacy as compared to those on minor polypharmacy (12.1% vs. 8.7%). In spite of this trend, there was no statistically significant difference between these 2 groups ($p = 0.454$).

2.4 Discussion

From the study results, 10.8% of the study population had DRPs which resulted in, or were detected on admission. This figure is lower than the 41% previously reported in Canada.[77] However, in the Canadian study, DRPs were reported for all elderly patients aged 65 and above, and the number of medications per patient ranged from 0 to 17 (average 5.7). In the present study, only patients with 5 drugs or more were recruited. Hence, DRPs present in patients consuming less than 5 drugs may have been missed. Moreover, the incidence of 10.8% was likely to be an underestimate due to the lack of comprehensive charting of medical and medication history upon patient admission.

Due to the retrospective nature of the study design, incomplete charting of history was a major limitation in our study. It hindered our ability to judge if a fall experienced by a patient was due to an accident, secondary to a medical condition, or secondary to an ADR. Moreover, information regarding chronic disease states, drug prescribing and compliance was not routinely gathered from the patient or recorded by the admitting doctor. Hence, the ability of the present study in identification of inappropriate drug therapy, lack of therapy and non-compliance was limited. This may further contribute to relatively low cases of admission related to drug therapy. Nevertheless, even an incidence rate of 10% for patients on polypharmacy to have DRP-associated hospital admission would be a case of concern for any health care system.

Considering the major causes of drug-related hospital admissions, non-compliance was the most common cause of DRP contributing to 28% of such hospital

admission. Eight patients were either non-compliant to their medications or diet, and one patient was not using his metered-dose inhaler properly. This would not be surprising as non-compliance had been strongly correlated with the number of medications given.[73] It had been reported as the main reason for most out-patient treatment failure, and cause of serious medical complications.[73]

Following non-compliance, adverse drug reactions also played an important role as one of the causes of drug-related hospital admissions (25%) in the current study. All the identified ADRs were found to be avoidable if the patients were monitored closely to ensure they were getting the optimum dosage of medication based on the status of their conditions, and if plasma drug concentrations were monitored. Thus, this is an area which needs to be investigated as ADRs are known to complicate existing disease, affect quality of life and may delay cure of the original disease.[10] Furthermore, ADRs may result in inappropriate treatment of unrecognized drug-induced problems.

Although the study results did not demonstrate any statistical significant difference between DRP-associated hospital admission between geriatrics and younger patients, the clinical importance of higher trend observed in geriatric patients may not be totally discounted. This could probably be due to the small sample size of the current study.

2.5 Conclusions

In conclusion, this baseline study suggests that the incidence of drug therapy related admission to hospital in Singapore would be comparable to that occurring in other developed countries. Of the major causes of drug-related hospital admissions, non-compliance was the most common cause of DRP, followed by ADRs. All the identified ADRs were found to be avoidable if the patients were monitored closely. This finding that the DRPs were mainly avoidable provides a basis to derive suitable strategies to lower the incidence of drug therapy related hospital admission.

Although the study results did not demonstrate any statistically significant difference in geriatric patients having higher DRP-associated hospital admission compared with younger patients, probably due to the small sample size of this current study, there is indeed a clinical importance of higher trend observed in geriatric patients. Effective management of medications taken by patients with special emphasis on the geriatrics should be incorporated into our future efforts.

Chapter 3

Drug-Related Problems in Hospitalized Patients on Polypharmacy: The Influence of Age and Gender

3.1 Introduction

Amongst the potential contributing factors of DRPs, the association between polypharmacy and the incidence of ADRs has been most widely studied and documented. Incidences of ADR have been consistently shown to increase in an exponential rather than a linear manner with the number of drugs taken.[10, 78-80] Furthermore, it was reported in another study that hospitalized patients who experienced an adverse reaction took twice as many drugs (12.5 vs. 6.3 drugs) as patients without ADRs.[78]

Besides the number of drugs prescribed, 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.[81-85] 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.[81]

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,[64, 65, 77, 86-88] or focused only on ADRs among hospitalized patients.[75, 78, 89] A more comprehensive study of DRPs in hospitalized patients would provide valuable insights for the healthcare professionals trying to reduce the incidence of DRPs.

Finally, 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 to 20 years ago,[64, 65, 75, 77, 78, 86-89] 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 optimizing intervention strategies according to needs and available resources.

In the current study, the researcher attempted to evaluate some of the aforementioned issues. As polypharmacy has been established to be associated with the increased occurrence of DRPs,[10, 18, 26, 87, 90] the main objectives were to investigate the occurrence of all DRPs (at admissions and while hospitalized) among hospitalized patients prescribed polypharmacy and evaluate the association of two risk factors, namely advanced age and female gender, with DRPs, especially ADRs.

Since advanced age had always been associated with higher incidence of DRPs,[15, 72, 78, 91] the researcher wanted to see if this trend could be confirmed or supported by local data. Also, female patients, being generally lighter in weight and smaller in build than their male counterparts (especially among Asians) but usually receiving the same drug doses, had been demonstrated to be more prone to ADRs in some studies.[28, 64, 65] This is most probably attributable to the exposure to higher dose per body weight for the females. It was postulated that this trend would be more pronounced for 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.

3.2 Methods

3.2.1 Study population

The study population used in this study is the same as that in Chapter 2. However, the emphasis for this chapter will be on drug-related problems acquired by the patients during their hospital stay, rather than those they presented with on admission to the hospital (Chapter 2).

As a recap, a retrospective, cross-sectional study was conducted in Alexandra Hospital - a 404-bed acute-care hospital in Singapore. In-patient case notes and medication records were used in our data collection. Subjects were included in the study if they were in-patients on the last two Thursdays of November and December 2000, and who satisfied the criteria of being prescribed polypharmacy (see definition below). 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 amongst these hospitalized patients.

3.2.2 Definitions

In this study, 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.[48]

For ADRs, 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 was used (WHO 1972).

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.

3.2.3 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.[92] DRPs experienced by the patients on admission and during their in-patient 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 any need for confirmation of the decision was resolved with the other investigators.

3.2.4 Classification of DRPs

DRPs were defined as inappropriate treatments, potential drug interactions, inappropriate dosages, unsafe drugs for patients, and ADRs experienced by the patients on admission and during their in-patient stay. ADRs which 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, the 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.[93]

The appropriateness of control was determined 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 (i.e., 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".

In assessing the appropriateness in the choice of drugs, Beer's explicit criteria were used to identify medications that were deemed unsuitable for use in elderly patients more than 65 years old.[94]

3.2.5 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, to evaluate the propensity to develop the events in these patient subgroups.

3.3 Results

3.3.1 Characteristic of population

There were 640 in-patients during the study period. Data were collected for 347 patients (54.2%) prescribed polypharmacy. Their age ranged from 16 to 97 years (mean 65.9 ± 17.7 years). Of the subjects recruited, 43% were female. Geriatric patients (patients more than 65 years old) made up 58.2% of our study population.

3.3.2 Medication profile

The number of medications per patient ranged from 5 to 14 (mean 7.4 ± 2.1). Paracetamol was the most commonly used drug (33.4%) followed by two laxatives, senna and lactulose (prescribed in 30.3% and 29.7%, respectively). A total of 181 patients (52.2% of our study population) were taking laxatives. Of which, 13 patients (3.7%) were on 3 laxatives and 80 (23.1%) on 2 laxatives simultaneously. The ten most commonly prescribed medicines are shown in Table 3.1.

Table 3.1 Ten most commonly prescribed drugs

Drug	Number of patients[a]	(%)[b]
Paracetamol	116	33.4
Senna	105	30.3
Lactulose	103	29.7
Sangobion	70	20.2
Aspirin	67	19.3
Isosorbide dinitrate	55	15.9
Potassium chloride	51	14.7
Amlodipine	50	14.4
Famotidine	50	14.4
Enalapril	42	12.1

[a]Patients who are receiving the drug
[b]The percentage of study population receiving the drug

3.3.3 DRPs during hospital stay

A total of 450 DRPs were seen in the 347 study patients. The types of DRPs identified during the study period included: (1) inappropriate treatment (comprises additional therapy required, unnecessary drug therapy, and use of inappropriate drug) – 33.1%; (2) potential drug interactions – 34.7%; (3) inappropriate dosages – dose too high or dose too low – 16%; (4) unsafe drug for patients – 10.4%; and (5) ADRs - 5.8% (Figure 3.1).

Figure 3.1 Drug-related problems and their number of incidences identified in patients during hospital stay

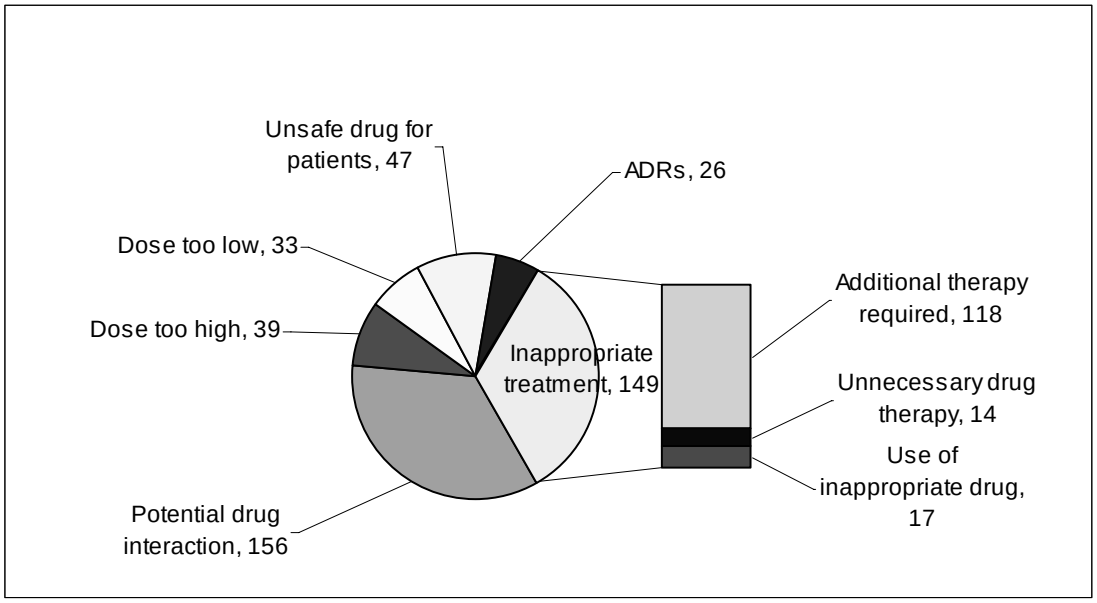
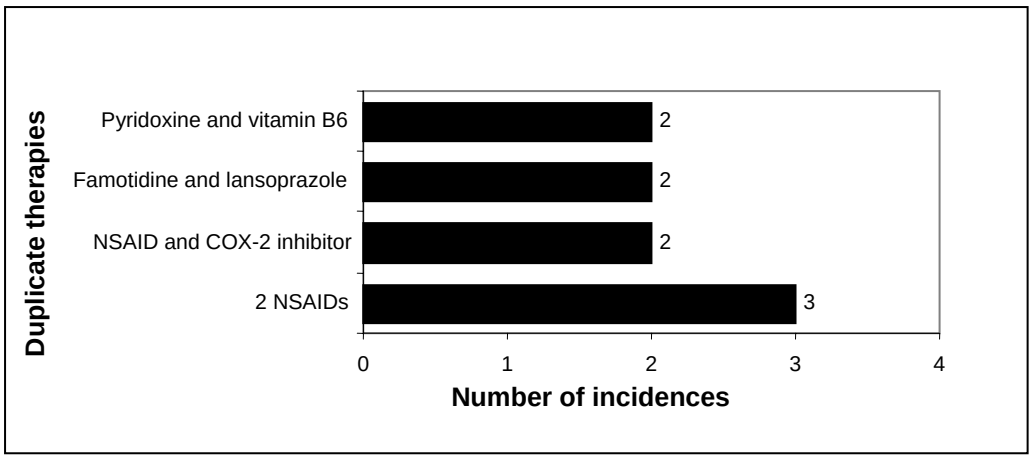


Figure 3.2 List of duplicate therapies



Of the 149 incidences of inappropriate treatment, 118 had an untreated condition that required additional therapy, with anemic patients (identified by their biochemistry results) making up 64.4% of this group. Another 9 patients would require additional drugs to improve the management of their existing medical conditions. For patients receiving unnecessary drug therapies, 5 had no recorded

medical indication for their prescribed medications and the remaining patients were prescribed duplicate therapies (Figure 3.2). Patients taking drugs not recommended for their conditions made up the remaining 17 cases of inappropriate treatment. Of these, 82.4% was due to usage of a particular drug when contraindicated (e.g. the use of propranolol in an asthmatic), and the rest due to using a drug when the condition was already refractory to it (e.g. using ciprofloxacin when culture and sensitivity results showed bacterial resistance) or when a particular drug was not even indicated for the condition (e.g. prescribing paracetamol for giddiness).

For inappropriate dosages, the cases encountered were wrongly prescribed dosages, inappropriate administration frequencies, or the serum drug concentrations were higher or lower than recommended ranges during therapeutic drug monitoring. For some patients, the dosages of their medications were deemed as too high when their abnormal hepatic or renal functions were taken into account (Table 3.2).

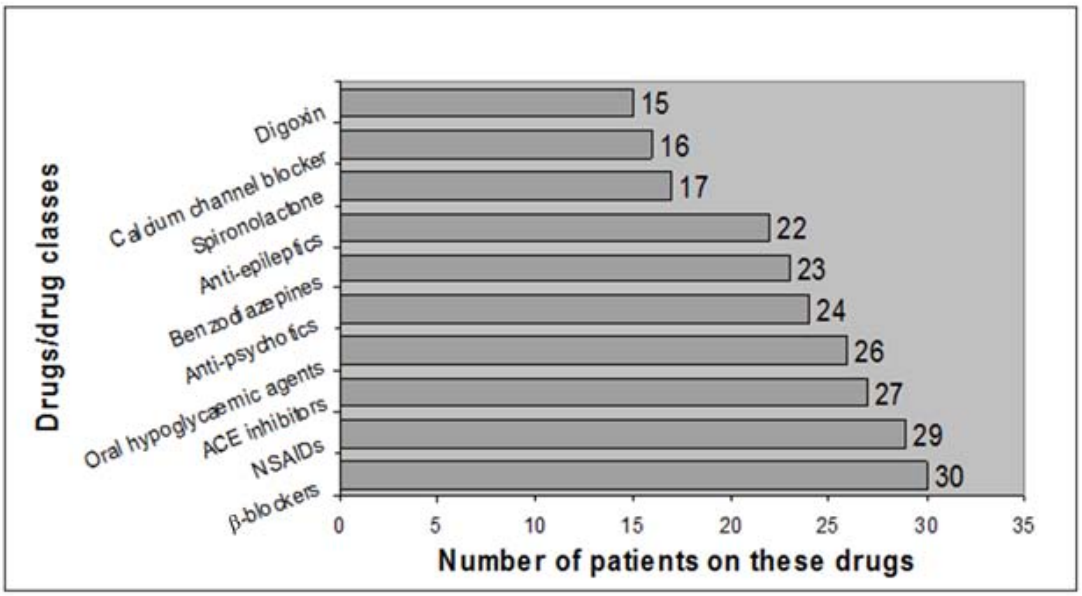
Table 3.2 Dose of medication too high for existing renal or hepatic function

Drug	Impaired function	Number of patients
Enalapril	Renal	4
Metronidazole	Hepatic	2
Allopurinol	Renal	1
Cefuroxime	Renal	1
Fluoxetine	Renal	1
Tolbutamide	Renal	1
Tramadol	Renal	1

Each combination of the drugs prescribed for the patients during their hospitalization were checked for potential interaction, and the top ten drugs/drug

classes that were most likely to be involved in causing drug–drug interactions are listed in Figure 3.3. The current study only managed to identify cases of potential drug interactions during hospital stay as the documentation of drugs which the patients were on prior to admission was not comprehensive for all the patients.

Figure 3.3 Ten drugs/drug classes that were most likely to be involved in causing drug–drug interactions



The 47 cases of unsafe drug for patients during hospitalization were identified based on Beer's criteria which documented the drugs unsuitable for use in patients more than 65 years old. Again, unsafe drug usage for patients on admission could not be identified due to limitation of documentation. Drug-pairs identified in the study that could give rise to potential severe interaction are shown in Table 3.3.

Table 3.3 Significant potential drug interactions

Drug pair	Possible effects
Atenolol + nifedipine	Severe hypotension and heart failure occasionally
Phenytoin + folic acid	Decrease plasma level of phenytoin
Simvastatin + erythromycin	Increase risk of myopathy
Simvastatin + warfarin	Enhanced anticoagulant effect
SSRI + valproate	Convulsion threshold lowered
Theophylline + calcium channel blocker	Possibly enhanced theophylline effect

With regards to the analysis of risk factors, there were no statistical correlations when age and gender were compared between patients with and without DRPs, both on admission and during hospital stay. However, based on Mann-Whitney test, the number of medications prescribed for the patients was not a risk factor for the presence of DRPs (p=0.119) during hospital stay, but it was a risk factor for patients with DRPs on admission (p=0.001).

3.3.4 ADR analysis

There were 34 cases of identified ADRs that occurred in 33 patients (one patient experienced two ADRs during the study period) (Table 3.4). Patients suspected of experiencing an ADR were taking a mean of 8.2 (± 2.6) different medicines compared with those not having an ADR on a mean of 7.3 (± 2.1) medicines (p=0.015). Of those who experienced ADRs, 60.6% were geriatrics. This formed about 10% of the geriatric patients in our study, and 36.4% of these geriatric patients were female.

Table 3.4 Identified cases of adverse drug reactions

Drug class	Drugs	Manifestations of ADRs	Number of patients
NSAIDs	Aspirin	Coffee ground vomitus	4
		Bleeding GIT	2
		Epigastric pain with vomiting	1
		Gastric ulcer	1
ACE inhibitor	Enalapril	Declining renal function	1
		Chronic cough with wheezing	1
		Postural hypotension	1
Antiepileptic	Carbamazepine	Hyponatremia	1
		Thrombocytopenia	1
	Phenytoin	Giddiness	1
	Valproate	Tremors	1
SSRI	Fluvoxamine	Hyponatremia	1
		Increased in INR	1
		Increased in liver function tests	1
	Fluoxetine	Hyponatremia	1
Loop diuretic	Frusemide	Dehydration	2
		Increased in liver function tests	1
Calcium channel blocker	Amlodipine	Postural hypotension	2
Anti-platelet	Ticlopidine	Generalized rash	1
		Decreased in hemoglobin	1
Analgesic / antipyretic	Paracetamol	Itch	1
Antiarrythmic	Procainamide	Anti-phospholipid syndrome	1
Antibiotic	Ethambutol	Generalized rash	1
Antipsychotic	Sulpiride	Extrapyramidal side effects	1
Beta-blocker	Propranolol	Asthma exacerbation	1
Fibrinolytic	Streptokinase	Rigors and facial flushing	1
Statins	Simvastatin	Increased in liver function tests	1
Sulphonylurea	Glipizide	Increased in liver function tests	1

Abbreviations: ADRs, adverse drug reactions; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin converting enzyme; SSRIs, selective serotonin re-uptake inhibitors; GIT, gastrointestinal tract; INR, international normalized ratio

Based on the results, the relative risk for geriatrics above 65 years in the current study to develop ADRs was 1.01 (95% CI: 0.52, 1.85), and the relative risk for female patients in developing ADRs was 0.79 (95% CI: 0.40, 1.55). However, when

the same analysis was performed for patients on major polypharmacy (10 or more drugs) the relative risks were 1.23 (95% CI: 0.36, 4.25) and 0.66 (95% CI: 0.21, 2.02), respectively, for geriatrics and female patients in developing ADRs.

The prevalence rates of developing DRPs and ADRs for the various patient subgroups during the study period are summarized in Table 3.5.

Table 3.5 Prevalence rates of developing DRPs and ADRs for the various patient subgroups

Patients	Prevalence rate (n/N)[a]		
	Polypharmacy	Minor polypharmacy	Major polypharmacy
DRP			
All study patients	72.0% (250/347)	70.2% (203/289)	81.0% (47/58)
Less than 65 years old with DRP	72.9% (102/140)	74.2% (89/120)	65.0% (13/20)
65–74 years old with DRP	71.6% (53/74)	67.3% (37/55)	84.2% (16/19)
75 –84 years old with DRP	69.0% (58/84)	64.3% (45/70)	92.9% (13/14)
85 years old and above with DRP	75.5% (37/49)	72.7% (32/44)	100% (5/5)
Female patients with DRP	41.2% (103/250)	37.4% (76/203)	57.4% (27/47)
Male patients with DRP	58.8% (147/250)	62.6% (127/203)	42.6% (20/47)
ADR			
All study patients	9.5% (33/347)	9.3% (27/289)	10.3% (6/58)
Less than 65 years old with ADR	15.7% (22/140)	16.7% (20/120)	10.0% (2/20)
65–74 years old with ADR	0% (0/74)	0% (0/55)	0% (0/19)
75–84 years old with ADR	6.0% (5/84)	2.9% (2/70)	21.4% (3/14)
85 years old and above with ADR	12.2% (6/49)	11.4% (5/44)	20.0% (1/5)
Female patients with ADR	27.3% (9/33)	29.6% (8/27)	16.7% (1/6)
Male patients with ADR	72.7% (24/33)	70.4% (19/27)	83.3% (5/6)

[a] n denotes number of patients experiencing the event, and N denotes the total number of subjects in the particular category

3.4 Discussion

Polypharmacy is an ubiquitous problem plaguing nearly all healthcare systems. Here, the occurrences of not only ADRs, but also all DRPs on admission and during hospitalization among patients receiving polypharmacy were investigated. An evaluation of the status and possibly the risk factors involved in DRPs would provide some basic information for working towards improving the current situation.

From the results, 63.4% of the study population (i.e., 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 only patients prescribed polypharmacy were recruited. Nevertheless, the high percentage of patients developing DRP here does highlight the need for more attention to the group of patients prescribed polypharmacy.

Henceforth, the DRPs experienced by the in-patient with emphasis on potential drug–drug interaction, appropriate dosages, and ADRs will be discussed, as these DRPs might have been preventable if physicians and pharmacists carried out proper checks.

The present analysis on DRPs showed that potential drug–drug interactions accounted for a substantial amount of potential drug toxicity (34.8%). Numerous drug combinations that resulted in modification of pharmacological action or in drug toxicity have been documented.[95] In the present study, 59% of possible drug-drug interaction occurred in geriatric patients. The drugs most implicated were β-blockers (namely, atenolol and propranolol), nonsteroidal antiinflammatory agents (NSAIDs)

(including aspirin, ketoprofen, diclofenac, and mefenamic acid), and angiotensin converting enzyme (ACE) inhibitors. This is consistent with published data citing that the average number of drug-drug interactions involving anticoagulants and antihypertensives were significantly higher than other drug groups.[96]

In addition, drug-pairs in this study that could give rise to potential severe interaction were also identified (Table 3.3). However, it must be acknowledged 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 drug interactions can affect patient's clinical outcome, quality of life, as well as contribute to unnecessary healthcare cost, the high prevalence rate (~30%) in this study would make this an important area requiring further investigation. As the study was carried out prior to the introduction of clinical pharmacist services at the study hospital, future pharmacists should focus on reviewing patients' medication charts and checking for potential drug interactions.

Another common aspect of DRPs is inappropriate dosages of medicines. Medication dosages were not adjusted for 11 patients with either renal or hepatic impairment. This made up 15.3% of all the patients receiving inappropriate drug dosages, and 2.4% of the entire DRPs in this study. Again, this might be an underestimation as the documentation in the patient's case notes was not very comprehensive and our judgment was based on available biochemistry reports. Moreover, there might be further cases of renal and hepatic impairment that were

missed during analysis. With proper monitoring, it is possible to substantially reduce such incidences.

ADR is another important subset of DRPs. Nearly 10% of in-patients 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.[33] 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.[89] Since the current 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 3.4), NSAIDs and ACE inhibitors were ranked the highest, closely followed by antiepileptics and serotonin-selective reuptake inhibitors (SSRIs). The drugs implicated in the present study are again quite similar to what has been reported.[77, 90] This congruency highlights that there is a rationale to focus more attention on patients prescribed certain drugs or drug classes.

In the attempt to identify risk factors, the study results supported published findings that the number of drugs taken by a patient is an important risk factor for ADRs. Definitely, the use of polypharmacy in patients is sometimes necessary to control or manage medical conditions. However, a patient may often be taking a multitude of medications because medications were used as substitutes for careful diagnostic manoeuvres or effective nonpharmacologic therapies.[23] Therefore, before

prescribing a medication, it is important to determine if the patient's condition is caused by a current medication. It defeats the purpose if additional agents are prescribed to deal with the symptoms of adverse drug effects and this in turn potentiates the problem of polypharmacy.

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.[91] The establishment and knowledge of the relative importance of various risk indicators would lead to better risk management strategy among different patient subgroups.

From the analysis for patients already receiving polypharmacy, it was found that geriatrics had a similar risk in experiencing an ADR compared with non-geriatrics. However, this relative risk was increased to 1.23 if only patients who were on major polypharmacy (10 drugs or more) were included. Although no statistically significant correlation between increasing age and increased likelihood of developing ADR was observed, this could be due to the small sample size.

Likewise, where gender comparison is concerned, the study results showed that female patients did not have a higher risk in developing ADRs when compared with male patients. This finding is contrary to those reported from Denmark,[87] and the Netherlands,[28] where the relative risk in developing ADRs for female patients was 1.57 (95% CI: 1.15, 2.14) and 1.46 (95% CI: 1.09, 1.75), respectively. However, there were some differences in patient characteristics between the studies. In the Danish

study, a total of 1999 patients of all ages, regardless of whether they were receiving polypharmacy or not were recruited.[87] 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, the current study 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.

3.5 Conclusions

In summary, several observations could be drawn from the study results:

1. The study results established that the situation of drug therapy related problems in hospitalized patients receiving polypharmacy in Singapore is comparable to that occurring in other developed countries. One important interpretation of this would be that although the problem of DRP has 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, the study 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 show higher risk of developing DRP, but this may be confounded by the inclusion criteria. A similar trend was observed in the developing of ADRs.
3. The results 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.

Based on these findings, the researcher would advocate applying the 20/80 principle in business management into clinical risk management here. 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), most of these DRPs could be minimized or prevented. The researchers believe that with such an approach, the rampaging problem of DRPs could be dampened.

Chapter 4

The Impact on the Clinical and Economic Outcomes among In-Patients by a Physicians-Pharmacists Review Team

4.1 Introduction

Drug-related problems (DRPs) are consequences which are different from the intended pharmacotherapeutic effect of the drugs involved.[2] Due to their association with increased rates of morbidity and mortality, DRPs continue to be a major problem faced by healthcare institutions worldwide.[2, 6-8] Inappropriate prescribing of medications, ADRs and drug interactions may cause increased morbidity and mortality, and treating these iatrogenic complications further burdens the health care system.[6] This is in view of patients requiring more nursing care, more attention by the attending physician, and possibly additional drugs to treat the resulting adverse reaction or interaction.[7] All these inevitably lower the quality of life of the patient. Moreover, the extent and cost of drug related morbidity and mortality are of great importance to health care practitioners, administrators, patients and society as a whole.[2]

Despite the efforts of healthcare professionals in reducing DRPs, it is considered that a large proportion of these DRPs are preventable,[8] In the last decade, pharmacists have contributed to improvements in the areas of drug therapy and patient safety. There has been a paradigm shift from their traditional roles of distribution and dispensing of medications to the active involvement in the direct provision of pharmaceutical care.[37-47]

There are many definitions of pharmaceutical care.[39, 48, 97, 98] However, despite the slight difference in definition, one common fundamental element is that pharmaceutical care implies communicating and reaching a consensus between the patients and physician or other healthcare professionals regarding pharmacotherapy.[39]

With such a shift in approach in health care delivery, the pharmacists will need to go beyond their traditional roles of dispensing and distributory function and be very much more involved in the identification and solutions of problems related to drugs, and to prevent drug-related problems from occurring. Some of these interventions carried out by the pharmacists would include advising of appropriate surgical antibiotic prophylaxis, performing pharmacokinetic monitoring, initiation and discontinuation of drug therapy, suggesting of alternative pharmacotherapy, as well as influencing the modification of drugs' dose, frequency and route of administration.[37, 39] Such pharmacist interventions strive to achieve a rationale use of drugs, and pharmacists actually have carried out most of these either regularly or sporadically. However, for this to take place effectively and systematically, pharmacists have to participate actively and coordinate with other health-care professionals in multidisciplinary care.[37, 39-44] Going on clinical ward rounds as a member of the patient care team will allow the pharmacists to provide such services most efficiently.[40] The pharmacists will be able to provide real time response or consult and intervene immediately when the need arises, rather than to spend time checking and correcting orders after they have been sent to the pharmacy.

The provision of pharmaceutical care can reduce the number of adverse drug events and the length of hospital stay.[48] All these would translate to cost savings and cost avoidance in the medical institutions as well as for the patients.[39, 41, 44] The quantum of the cost savings could be quite substantial and has been estimated by several overseas studies. In 1997, Mutnick *et al.* presented the results of 4648 interventions carried out by 50 pharmacists during a 9 months study at a 849-bed institution.[44] These interventions were based on the pharmacist's evaluation of the

patient, the condition involved, and the appropriateness of the drug therapy prescribed. Of these interventions, 87% were accepted by the medical staff, and these accepted interventions represent a net therapy cost saving of US$487,833, as well as a cost avoidance of US$158,563 achieved by preventing a potential net 371.9 additional hospital days.

In a more recent study published in 2003, Galindo *et al.* analysed 3136 pharmacists' interventions that were collected prospectively for 6 months in a 330-bed acute hospital.[39] Of the recommendations made by the pharmacists in their interventions, 88.8% was accepted by the medical practitioners and financially they represented a cost saving of €129,058.31.

In Singapore, hospital pharmacists are starting to play a more significant role in improving the quality of medical care for patients by actively identifying and solving DRPs. Although participation of pharmacists on ward rounds in hospitals is relatively common, there is a lack of regular schedule for participating in ward rounds in conjunction with a primary patient care team. However, the clinical and financial impact of the inclusion of a pharmacist as a regular member of team doing the clinical ward round has not been evaluated or studied. This stems from the fact that a low pharmacist-to-patient ratio still prevails here, and the pharmacists are over-worked just dealing with the traditional role and function of distribution and dispensing of medications, thus preventing many of them from participating as a regular member of the clinical ward round team. Nevertheless, pharmacists do perform routine reviews of patients' medication records to check their drugs, dosing regimen, drug compatibility, drug-drug/food interactions, etc as part of their drug distribution

responsibility. On occasions when DRPs or potential DRPs were identified when going through patient's medication or medical record, the pharmacists would approach the primary care team to alert them about the problem and suggest a solution for it.

Since economic constraints dictate that the impact of all such pharmacist services on patient care be demonstrated to ensure the cost-effectiveness and best use of pharmacist services and manpower, this study aimed to investigate the impact of the pharmacist's participation in a physician-pharmacist review team. If the current study is able to demonstrate the reduction in pharmacy costs and decreased length of stay of patients with the active participation of pharmacists as regular member in doctors' ward rounds, it would further enhance the roles of pharmacists in the care and clinical management of patients. Evaluating the cost-savings as a result of the successful interventions made by these physician-pharmacist review teams will also help to justify the cost-effectiveness for the hospital to endorse such services. Hence, the information obtained from this study would be able to lay the groundwork to allow further streamlining of clinical pharmacist services and how they can be provided more efficiently. This would also assist in allocating of valuable resources from the management perspective, and lead to further improvement in clinical and economic outcomes in patients.

4.2 Methods

The prospective, controlled study was carried out in Alexandra Hospital, an acute care hospital (440 beds) in Singapore. In Singapore, 80% of hospital care is provided by the publicly funded health care institutions which include Alexandra Hospital.

Four wards were chosen for this study, serving both as the control and study arms. These wards were chosen as a result of their similarity in patient-mix (gender and age group), as well as discipline-mix (all belonged to general medicine discipline). General medicine discipline was chosen for this study because patients in this discipline made up a large portion of the hospital in-patient population.

Due to the constraint in the number of in-patient pharmacists available to participate daily in this pilot study of physician-pharmacist review team during the study period, a maximum of only two pharmacists could participate in the study at any one time. Hence, only one or two wards can be studied each time. This was a trade-off after considering the number of available pharmacists at the study site and the number of pharmacists required to handle day to day pharmacy operations like distribution of drugs to the wards and dispensing of medications to discharged patients.

The enrolment target for this study was at least 660 patients, i.e. 330 patients each in the control and study groups. This sample size was derived based on biostatistical calculations as follows. If there were 300 patients in each group, at an *a priori* alpha level of 0.05 and power of 80%, a difference in response rate of 25%

could be detected. That would translate to having a significant difference if the length of stay was reduced by at least 0.93 days; if the difference in pharmacy cost was at least S$275; and if the difference in hospital charge was at least S$1000 (before any form of government subsidy). This worked out to a total of 600 patients from both groups. However, in order to accommodate drop-outs (see next paragraph) where the drop-out rate was estimated at 10%, the recruitment number was increased to 660 patients.

The inclusion criterion for this study was patients who were admitted as in-patient in the selected wards on the stipulated days of study. Patients who died, changed medical discipline, transferred out of the ward/hospital, absconded from the hospital or were discharged at own risk (meaning patients who asked for discharge even when the physicians feel that they are not ready for that) were excluded from the analysis.

4.2.1 Study group

During the study period from January 2005 to April 2005, the in-patient pharmacists who were involved would participate in ward rounds together with the medical team on a daily basis, except on weekends, in the selected wards. Prior to the rounds, the pharmacist reviewed all patient profiles and relevant data, including the progress and consultation notes, and note down any modification of drug regimen to be recommended. They also interviewed patients with regards to their drug history and drug allergy profile when required. The relevant information would be highlighted to the physician teams during ward rounds. For newly admitted patients (during the night), the pharmacist would visit them with the physicians. The

pharmacist would take this chance to evaluate the drug treatment given to the new patients and suggested relevant changes, if any. Any existing or potential drug related problems would also be identified by the pharmacist and highlighted to the medical team.

4.2.2 Control group

The control group was run independently from the study group. During the same period, the other wards that were matched with the study group in terms of patient-mix and specialty-mix were used as control. The difference in the control group was that pharmacists did not attend ward rounds with the medical team. Nevertheless, services that were already provided by the pharmacists still continued as per normal. Hence, the pharmacists would still review in-patient medication records independently for any existing or potential drug related problems, as well as sub-optimal pharmacotherapeutic regime. These were highlighted to the medical team either via telephone call or by pasting a note in the medication/medical records for the relevant medical teams to follow-up on.

In order to reduce bias due to different working patterns and clinical experience, the four pharmacists who participated in this study were rotated between the study and control group. At any one time, there was only one pharmacist and one study ward involved due to shortage in manpower. However, one control ward would always run concurrently with a study ward.

4.2.3 Types of interventions

The types of interventions carried out by the pharmacists in both the study and control group were tabulated in Table 4.1.

Based on the type of intervention carried out, the percentage of recommendations for the intervention accepted by the physicians would also be examined. Concurrently, the financial impact of these interventions would also be evaluated.

Table 4.1 Type of interventions carried out by pharmacists during the study

A. Review drug administration dose regimen

Examples

1. Wrong dose
2. Wrong dosage form/strength
3. Wrong frequency/rate
4. Wrong duration
5. Wrong route
6. Inappropriate duration of administration – medication to be stopped but not off.
7. Convert from IV to oral
8. Recommendation for blood levels of drugs to be taken

B. Identify adverse drug reactions and suggest alternatives

C. Review drug selection indications

Examples

1. Drug used without medical indications (discontinue drug)
2. Inappropriate drug chosen (drug substitution)
3. Therapeutic duplication
4. Drug allergy
5. Patient prescribed a drug that should not be given because of his medical condition
6. Drug interactions
7. Financial impact (drug too expensive, suggest drug substitute)

D. Indication without drugs e.g.

Untreated medical conditions (addition of drug or other therapy)

E. Follow-up on incomplete medication history

F. Provide drug information to physician

G. Information provided for administration/therapy

4.2.4 Data collection

During the study period, patients' demographic data as well as information on the types of interventions by pharmacists and the size of each patient's hospital discharge charge were collected. These data were collected from:

1. Records in patients' in-patient case-notes and in-patient medication records for data like patients' demographics, the types and number of medications patients were on as well as the patient's length of stay.
2. Therapeutic intervention recording forms used by the pharmacy department (See Figure 4.1). These documentations by the pharmacists would provide the details of the type of interventions they initiated and whether these were accepted by the physicians.
3. Patient's hospital charge provided by the finance department. This was for getting information on the drug cost for each patient, as well as the total hospitalization charge of the patient.

Figure 4.1 Therapeutic intervention recording forms used by the pharmacy department

Therapeutic Intervention Documentation

Alexandra Hospital Pharmacy Department

Date	Person contacted (Dr / SN)
Type of intervention*	Accepted / Not Accepted
IC no. Ward / bed	Patient name
Intervention(s) done & outcome(s)	
Cost incurred / saved	

4.2.5 Outcome measures

The effects of pharmacist's participation in a physician-pharmacist review team were assessed with three measures:

1. length of hospital stay,
2. total pharmacy costs incurred by patients during their stay in the hospital; and

3. total hospital costs incurred by patients during their stay in the hospital.

These three factors were ascertained in both the study and control groups, and a comparison was made.

The rationale for choosing these outcomes was based on the premise that at the population or group level, any improvement in clinical outcomes would be reflected in the overall length of stay, and any financial and economic impact of the intervention would be reflected in the total drug cost and the final hospital charge (which would also included laboratory costs and other procedure costs).

However, since the nature of interventions carried out by pharmacist would mainly concern drug-related problems, the immediate impact would logically be more observable in overall drug cost between the two groups. Hence, the impact on the drug cost would be the major outcome variables in this study. The other two outcomes would be considered as secondary outcome variables as there are many other factors that may influence them. Those influencing factors would be discussed in the discussion section of this chapter.

4.2.6 Analysis

The average length of stay for the patients in each group was calculated by taking the mean of the number of hospital stay of the individual patients.

To calculate the mean drug cost for the study group, the total drug cost over the length of stay for each patient was used to derive the drug cost per day. Based on

the drug costs calculated for all the patients, an average drug cost per day was calculated.

Using the average drug cost per day and average length of stay for the study group, the total mean drug costs per patient in the study group ($Cost_{study}$) was calculated. The calculation to get the drug costs per patient in the control group ($Cost_{control}$) was performed likewise.

The formulae used for calculations are shown in Table 4.2. From the above, the total cost savings (if any) between the study and the control groups could be calculated.

In order to calculate the total cost savings for the study group where the total hospital charges to the patient is concerned, the average hospital charges per patient in each group was first determined. The difference between the average hospital charges between the control group and the study group would give the hospital charge savings per patient in the study group. The total hospital charge savings of the study group can be calculated using the difference in hospital charges as mentioned above multiplied by the number of patients in the study group (See Table 4.3). However, in order to accommodate the difference in level of subsidy that are being provided by the government to the different classes of patients, the hospital charges for each patient was adjusted to reflect the true level before government subsidy. Our study encompassed patients from class B2 wards, as well as class C wards. Currently, class B2 patients are given a 65% government subsidy on their charges, whereas class C are given a subsidy of 80%.

Table 4.2 Calculating cost savings in study group over control group

For study group:

For each patient, take total drug cost / length of stay to get drug cost per day, $DrugCost_{day(study)}$.

Based on all the drug cost per day, take an average drug charge per day $AvDrugCost_{day(study)}$.

Use the $AvDrugCost_{day(study)}$ x average length of stay of the group to get drug cost for the study group, $Cost_{study}$.

For control group:

For each patient, take total drug cost / length of stay to get drug cost per day, $DrugCost_{day(control)}$.

Based on all the drug cost per day, take an average drug charge per day $AvDrugCost_{day(control)}$.

Use the $AvDrugCost_{day(control)}$ x average length of stay of the group to get drug cost for the control group, $Cost_{control}$.

Therefore, drug cost savings per person $Cost_{savings} = Cost_{control} - Cost_{intervention}$

Total drug cost savings in study group = $Cost_{savings}$ x number of people in study group

Table 4.3 Calculating hospital charge saving in study group over control group

Total mean hospital charges per patient in the study group, $HospChargel_{study}$ = Sum of hospital charges of all the patients in the study group / number of patient in the study group
Likewise, total mean hospital charges per patient in the control group, $HospCharge_{control}$ = Sum of hospital charges of all the patients in the control group / number of patient in the control group
The mean hospital charge savings per patient, $HospCharge_{savings} = HospCharge_{control} - HospCharge_{study}$
Total hospital charge savings in study group = $HospCharge_{savings}$ x number of people in study group

In order to quantify the financial impact of the inclusion of a pharmacist in the regular clinical ward round team, the drug cost savings per patient, cost-benefit ratio, as well as the net annual return on the investment of a pharmacist in such physician-pharmacist review teams were also calculated. The formulae and the cost used to calculate these values are detailed as in Table 4.4.

Table 4.4 Calculating the net annual return on investment in one pharmacist

Cost of pharmacist working on the study arm:

Average annual salary for one pharmacist = S$36,000 (this figure is obtained from the Human Resource Department of Alexandra Hospital)

Proportion of time spent each day on this intervention work = 20% (about 1.5 hours out of 8 hours; based on the actual time spent by the pharmacist in a clinical ward round)

Number of months which the study took place = 4 months (one third of a year)

Hence, total cost of employing the pharmacist to do the study for 4 months

= [(S$36000 / 3] x 20%

= S$2,400

Calculation of Cost-Benefit Ratio

1. Based on savings in drug costs, cost-benefit ratio = total drug cost savings in study group / $2400
2. Based on savings in hospital charges, cost-benefit ratio = total hospital charge savings in study group / $2400

Net annual return on investment in one pharmacist

1. Based on savings in drug costs = Total annual drug cost savings in study group – Annual cost of employing a pharmacist
2. Based on savings in hospital charges = Total annual hospital charge savings in study group – Annual cost of employing a pharmacist

A sensitivity analysis was also performed to test the robustness of the conclusion from the data obtained in this study. The sensitivity analysis was performed by evaluating the different cost-benefit ratios obtained by using the extreme values in cost differences between the control and study groups.

4.3 Results

A total of 795 patients (388 in control group and 407 in study group) were enrolled in the current study.

However, there were 23 and 46 patients in the control and study group, respectively who were subsequently excluded from the study as they fell into the exclusion criteria which were stated earlier under the methods section.

A breakdown of why these patients are excluded can be seen in Table 4.5. With that, 726 patients were left for the data analysis segment of this study, 365 in the control group and 361 in the study group.

Table 4.5 Reasons for eventual exclusion from the study

Reasons	Control group (n = 23)	Study group (n = 46)
Absconded from the hospital	1	2
Patient requested for discharge even when the physicians feel that they are not ready for discharge	1	4
Change of discipline	2	12
Change of ward	9	11
Transferred to another hospital	5	7
Patient died during study	5	8
Missing medication records at time of data collection	-	2

The patient populations for both groups were comparable. The age range for the control group was 18 – 80 years old (mean: 52.5 years old; SD: 15.8) and 44.0% of the patients were female. In the study group, the ages of the patients ranged from 16 – 100 years old (mean: 51.1 years old; SD: 17.0 years old) and 47.3% of the patients were made up of females. All these patients were from the medical discipline and there were no significant difference between the two groups where patients' age (p=0.989) and gender (p=0.374) were concerned.

4.3.1 Average length of Stay

The average length of stay of the control group was 5.26 days (SD = 5.10 days; range 1 – 34 days) and that of the study group was 5.02 days (SD = 5.60; range 1 – 44 days).

The difference in length of stay between the two groups was 0.24 days more in the control group and this is statistically not significant (p = 0.550). The above data are summarized in Table 4.6.

Table 4.6 Patient population in the two groups

	Control group (n = 365)	**Study group (n = 361)**
Age range/years (Mean; SD)	18 – 80 (52.5; 15.8)	16 – 100 (51.1; 17.0)
Percentage of females/%	44.0	47.3
Range of length of stay/days (Mean; SD)	1- 34 (5.26; 5.10)	1 – 44 (5.02; 5.60)

4.3.2 Interventions carried out during the study period

An analysis of the data collected showed that a total of 202 interventions were performed during the study period, of which 15 came from the control group and 187 were from the study group. This worked out to about 0.13 interventions per day in the control group and 1.56 interventions per day in the study group.

The most common intervention carried out by the pharmacists in the control group was correcting erroneous drug dosage prescribed, while the most common intervention carried out by the pharmacists in the study group were to prevent presence of untreated condition (i.e. indication without drugs) (20.6%), to ensure complete medication history taking (12.8%) and to ensure the most appropriate drug was chosen for the patient (10.6%).

Of the recommendations from these interventions, 100% from the control group (all 15 interventions) and 96.3% from the study group (180 out of 187 interventions) were accepted by the physicians. There is no statistically significant difference between the acceptance rates for the two groups ($\chi^2 = 0.582$). A breakdown of the accepted interventions for the control and study groups is shown in Figures 4.2 and 4.3, respectively.

Following these interventions, the number and types of DRPs prevented can be seen in Figure 4.4 (for control group) and Figure 4.5 (for study group). Hence, the number of drug related problems prevented in the study group was about 11 times more than that in the control group.

Figure 4.2 Types of intervention performed in the control group (n = 15)

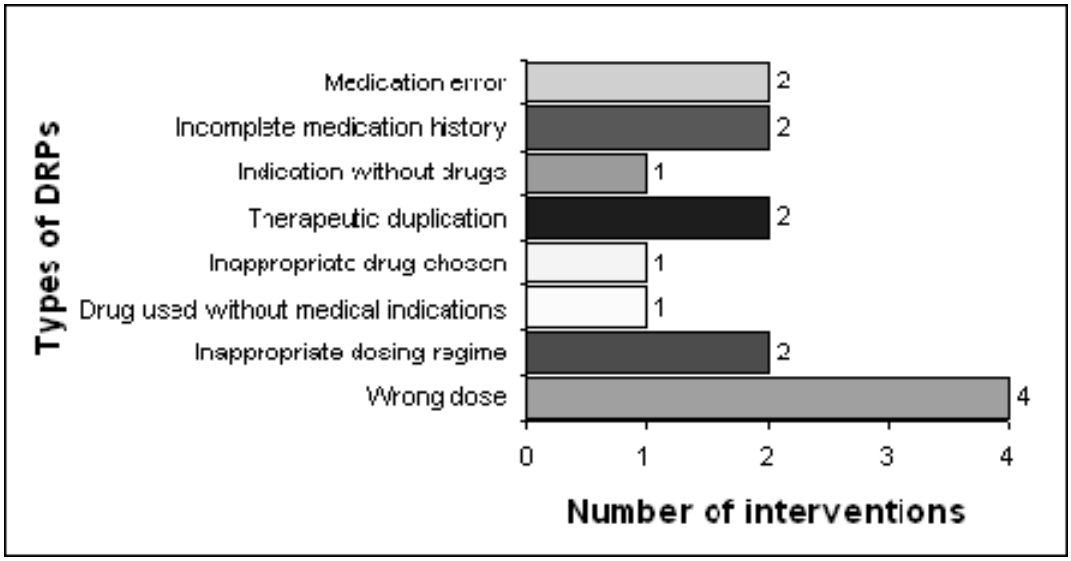


Figure 4.3 Types of intervention performed in the study group (n = 180)

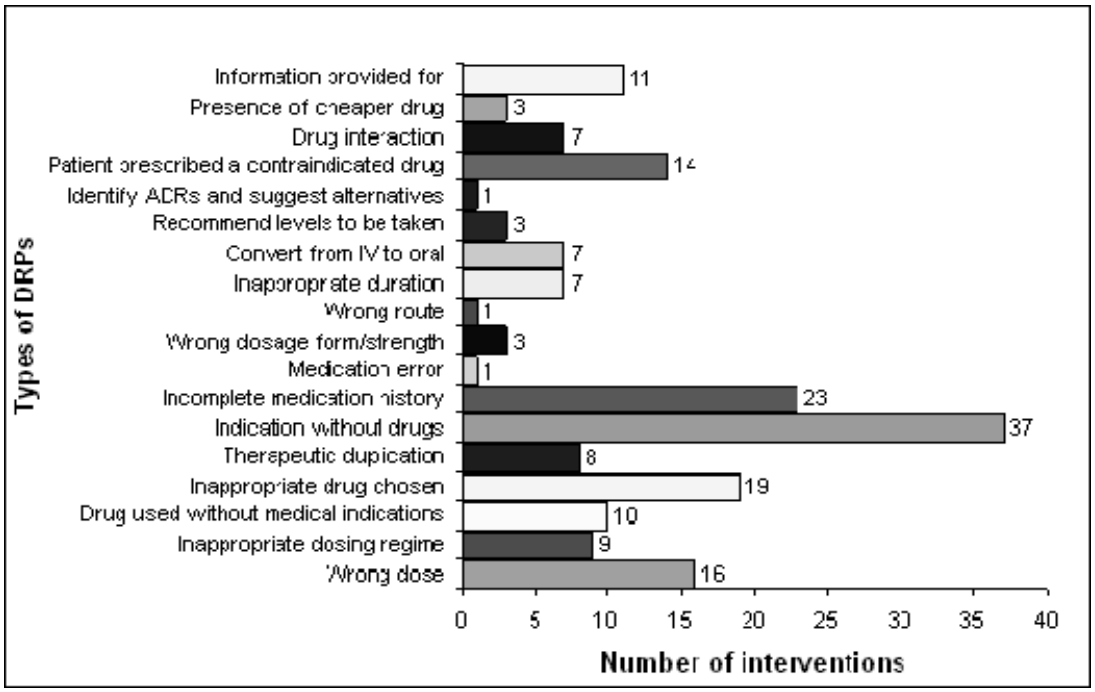


Figure 4.4 Types of drug related problems prevented in the control group (n = 15)

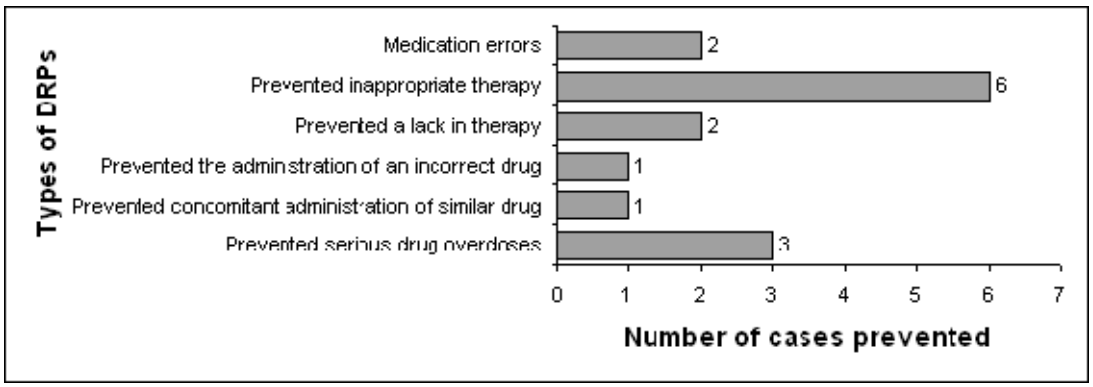
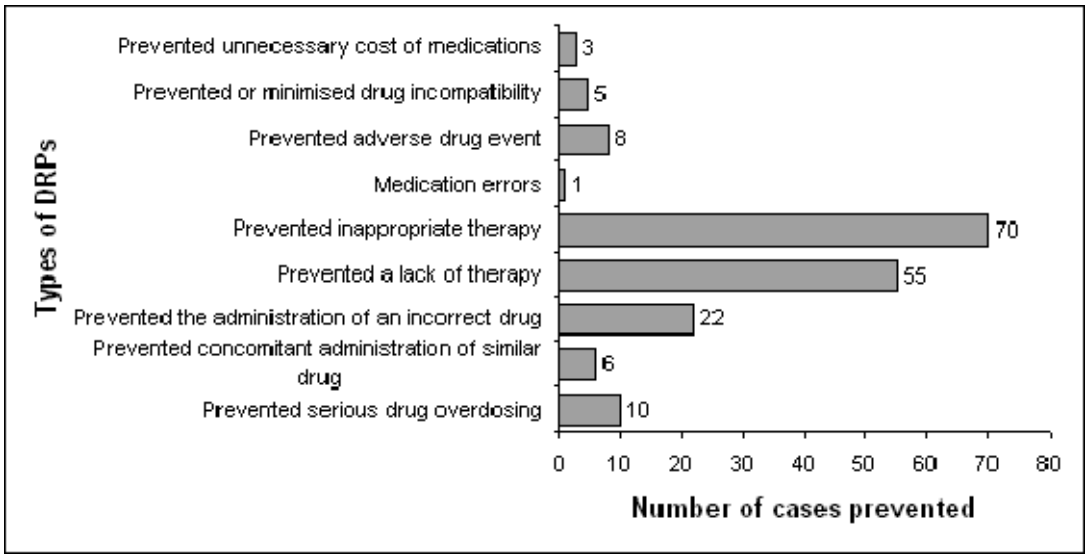


Figure 4.5 Types of drug related problems prevented in the study group (n = 180)



4.3.3 Costs analysis

In the control group, the total mean drug cost per patient was S$158.02 (95% CI: S$137.09 – S$178.95), as opposed to a mean of S$119.03 (95% CI: S$103.29 – S$134.78) in the study group. Based on this, the cost savings of S$38.99 (95% CI: S$12.84 – S$65.14) per patient in the study group as compared to the control group was statistically significant (p=0.004).

Hence during the 4 months of study, the total drug cost savings in study group was S$14,036.40. The drug costs used in these calculations were actual drug costs prior to any form of subsidy. Such costs reflect more accurately the value of drug resources consumed than do subsidized charges.

Where hospital charges were concerned, the researchers worked entirely on the charges which had been corrected for subsidy. Hence based on the charges to the patients before subsidy, the average total hospital charge per patient in the control group was S$2,364.52 (SD: S$3,264.46; range: S$168.57 – S$45,655), whereas that in the study group was S$2,180.16 (SD: S$2,966.16; range: S$165.23 – S$26,947.95). Even though the difference between the two groups is not statistically significant (p=0.426), there is a trend in favour of the study group. Based on the difference in mean charge sizes, a saving of S$66,373.20 in the study group during the 4-month study period would be realized. This would still represent a sizeable amount of savings for the study group.

Based on an average annual salary of S$36,000 for one pharmacist, the service of a pharmacist in the review team would help bring about a cost-benefit ratio (based on savings in drug costs) of 5.85. With a simple linear projection using the total drug cost savings in 4 months, the drug cost savings on an annual basis will work out to be S$42,109.20. Hence, the net annual return on investing in one pharmacist to perform such a function based on total drug cost savings would be S$34,909.20.

When the above calculations were performed using the savings in hospital charge, the cost-benefit ratio derived would be 27.66, and the corresponding net

annual return (based on savings in hospital charge) on investing in a pharmacist to perform such clinical service would be S$191,919.60.

4.3.4 Sensitivity Analysis

The above cost-benefit ratios were calculated based on the pharmacist spending 20% of the total working hours participating in the review team. If a conservative estimation is made by keeping the drug cost savings achieved annually constant, but to vary the time spent by the pharmacist instead, the cost-benefit ratios calculated can be seen in Table 4.7. This table presents a series of sensitivity analyses that was carried out using extreme values obtained from the 95% confidence interval of the total drug cost savings. As such, the worst-case and best-case scenarios of having a pharmacist on board the review team were hypothetically tested out.

Table 4.7 Sensitivity analysis of cost-benefit ratio based on drug cost savings

% of pharmacist's total work time	Total drug cost savings (S$)	Annual total drug cost savings (S$)	Cost-benefit ratio*
20	38.99 (Base case)	42,109.20	5.85
20	12.84 (Worst case)	13,867.20	1.93
20	65.14 (Best case)	70,351.20	9.77
30	38.99	42,109.20	3.90
30	12.84	13,867.20	1.28
30	65.14	70,351.20	6.51
40	38.99	42,109.20	2.92
40	12.84	13,867.20	0.96
40	65.14	70,351.20	4.89
50	38.99	42,109.20	2.34
50	12.84	13,867.20	0.77
50	65.14	70,351.20	3.91

*Calculated based on the formula given in Table 4.4

In interpreting the estimated cost-benefit ratio, a ratio larger than 1 demonstrates that it is beneficial to have the pharmacist as part of the review team. From the sensitivity analyses performed, there are two cost-benefit ratios in the afore table that are smaller than the value 1. In the first instant, it may seem that it is not always cost effective to have a pharmacist on board the review team under those circumstances. However, a Monte Carlo simulation of 10,000 trials showed that in the case when the pharmacist spent 40% of his or her working hours doing clinic rounds (i.e. double the amount of time as observed during the study period), the

probability of a cost-benefit ratio of less than one occurring is only 0.95%. In other words, 99.05% of the time, it will still be cost effective to have a pharmacist under those circumstances. When a similar Monte Carlo simulation is performed for the case assuming the pharmacist spent 50% of the working hours doing clinical rounds (i.e. two and a half times that observed in the study), the probability of a cost-benefit ratio being above the value 1 still stands at 92.74%.

The above sensitivity analyses showed that even when a conservative estimate is made by keeping the drug cost savings achieved annually constant and increasing the amount of time spent by the pharmacist on clinical involvement, the cost-benefit ratios were still favourable. Thereby, it is still beneficial to have the pharmacists on physicians-pharmacists review teams.

In the case of evaluating the robustness of cost-benefit ratios calculated from the total hospital charge savings, sensitivity analysis was only performed on the extreme values in the 95% confidence interval for the total hospital charge savings per patient between the two groups. The results obtained are presented in Table 4.8.

Table 4.8 Sensitivity analysis of cost-benefit ratio based on hospital charge savings

% of pharmacist's total work time	Hospital charge savings (S$)	Annual hospital charge savings (S$)	Cost-benefit ratio*
20	184.37 (Base case)	199,119.60	27.66
20	-270.31 (Worst case)	-291,934.80	-40.55
20	639.05 (Best case)	690,174.00	95.85

*Calculated based on the formula given in Table 4.4

The calculated possible cost-benefit ratios ranging from negative to positive values would mean that it would not always be cost-effective to include a pharmacist in the team. Using an approach for estimating the probability of such non cost-effective events occurring, Monte Carlo simulation of 10,000 trials was once again performed. The results obtained showed that the probability of having a cost-benefit ratio less than 1 (meaning not cost-effective) would be 30.56%. In other words, the probability of having a cost-benefit ratio of more than 1 will be around 70% even when difference in total hospital charges between the two groups are compared.

4.4 Discussion

In the past two decades, the pharmacy profession has undergone a paradigm shift where the main role in the healthcare industry is concerned. Instead of spending the majority of their working hours preparing and dispensing medications, pharmacists are beginning to focus more on evaluating drug regimens and prospective monitoring of patients' responses to drug therapy.[99] The pharmaceutical care concept described by Hepler and Strand is gaining greater acceptance in today's healthcare industry.[48] Today, in many countries, pharmacists are participating more actively in the delivery of health care, and are beginning to take joint responsibility for the outcomes in drug therapy. Hence, other than fulfilling the traditional role of ensuring that the correct drug product is delivered to the correct patient in a timely manner, the role of the pharmacist has expanded to include many scopes of pharmaceutical services. Furthermore, pharmacists nowadays do not only work independently but also form close and complementary working relationships with physicians, nurses and other paramedical personnel in delivering optimal drug therapy to the patients.[97]

From the study results, the pharmacists carried out a total of 202 interventions, 96.5% of the recommendations from these interventions were accepted by the physicians. This high rate of acceptance showed that the suggestions made by the pharmacists were valued as beneficial for the drug therapy of the patients in Singapore. As shown by the breakdown of the accepted interventions as presented in Figures 4.2 and 4.3, it can be seen that more interventions were carried out when there was active pharmacists' participation during clinical ward rounds together with other health care professionals (1.56 interventions per day for just the ward involved in the study) as compared to when the pharmacists do reviews of the patients' medical and

medication records on their own (0.13 interventions per day for the matched control ward). This is important to highlight that under the operational mode of the current system, pharmacists in Singapore hardly have the time to do proper intervention work to help improve patient outcomes. Moreover when going on ward rounds as a team, the pharmacists would have clearer information and therefore better understanding of the patients' medical conditions, what were the treatment plans for the individual patients and what were the monitoring parameters which the physicians were laying out for the patients as compared to reading the medical case-notes as certain documentation may not be comprehensive enough. Hence, if the pharmacists had any suggestions or recommendations to make about the drug regime for the patients they could raise it during the rounds itself. Physicians might be more receptive to such suggestions when they hear it in person and have a chance to clarify any doubts they have with the pharmacists rather than when the pharmacists leave notes in the medication records for the physicians to read and approve. The current study results reinforced the findings from overseas studies that more effective interventions could be carried out by the pharmacists during such rounds since they would have a chance to find out more about patients' past and existing conditions.[37, 39-44] With the better understanding, the pharmacist would be able to make more meaningful and relevant recommendations regarding the patient's pharmacotherapy. This is evident from the difference in sheer number of interventions carried out by the study and control groups.

The type of interventions carried out by the pharmacists in the control and study groups during the study period reinforces the above inference. From Figure 4.2, correcting of wrong drug dosage was the most common drug problem that the

pharmacists in the control group identified and intervened on. This may be because without any extensive background knowledge of the patients, their medical conditions and all, there is limitation to how much the pharmacists can intervene. Singling out wrong dosage may be one of the easier and most obvious interventions in such a scenario. However, as can be seen in Figure 4.3, the types of intervention performed by the pharmacists in the study group were a lot more varied and extensive. The most common drug related problem intervened upon by the pharmacists in the study group was ‘Indication without drugs’. This meant that the patients had existing medical conditions that can be relieved or treated by a drug but the patients were not prescribed the required medication. Some of these untreated medical conditions were anaemia, gastric discomforts, cough, presence of phlegm and asthmatic patients who were not given a reliever inhaler to use when they experienced their asthma exacerbations. There were also cases of patients who had medications ceased prior to undergoing medical procedures but their medications were not restarted after they had undergone the procedures. One example was a patient who had to cease his metformin tablets before taking an IV contrast media. However, the physicians did not re-start his metformin doses after he had completed his procedure.

The second most commonly intervened problem by the pharmacists in the study group was ‘incomplete medication history’. In such cases, the patients had previous medical follow-up with private clinics, polyclinics or other hospitals’ specialist clinics. These patients were not aware of what medications they were prescribed prior to the admission. The physicians treating these patients did not retrieve their previous medication histories and were either prescribing empiric medications or simply treating the conditions which the patients were warded for

without regards for their other existing medical conditions. The pharmacists were there to assist in getting patients' previous medication records and ensure that the patients had their usual supply of medicines even when they are warded. This, as well as the previous problem of medical conditions without an appropriate drug do require a great deal more interaction with the patients or the physicians, and would have been difficult and in fact close to impossible to be identified by the pharmacists if they had not gone for the rounds with the physicians.

'Inappropriate drug chosen' was the third most common intervention performed by the pharmacists in the study group. With the chance to be present when the physicians were examining the patients and with first hand knowledge of what the physicians intend to treat the patient for, the pharmacists could recommend an even more appropriate choice of therapy for the patient if the physicians happened to select otherwise. An example of such a case during the study was when the physician gave only a cough suppressant to a patient who had very thick phlegm. The pharmacist suggested for the patient to be prescribed a mucolytic agent and only to be given the cough suppressant at night to ensure good sleep.

As mentioned, there were more types of drug related problems intervened by the pharmacists in the study group compared to that in the control group. Two of the more common drug related problems that were seen in the additional list that occurred only in the study group included 'patient prescribed a contraindicated drug' and 'information provided for administration/therapy'. Once again, these two problems would not have been easy to recognize if not because the pharmacists were around when the physicians were examining the patient and deciding on drug therapy.

‘Patient prescribed a contraindicated drug’ made up 8% of the total interventions performed in the study group. Though this percentage may not be high, dire consequences might have occurred if these were not identified. Likewise, without the intervention of ‘information provided for administration/therapy’ carried out by the pharmacists, there may be a lack of efficacy of the treatment prescribed.

Following these interventions, the drug related problems that were prevented as a result could be seen in Figures 4.4 and 4.5 for the control group and study group, respectively. As mentioned, the number of drug related problems prevented in the study group is about 11 times higher than that in the control group. In the study group, the top three problems that were prevented were, in descending order, ‘prevented inappropriate therapy’ (39%), ‘prevented a lack of therapy’ (31%) and ‘prevented the administration of an incorrect drug’ (12%). These preventions could be translated to ensuring optimal drug therapies for the patients and their associated medical conditions. In fact, lack of therapy of a regime or the administration of an incorrect drug is very detrimental to the patients’ health as they can either worsen existing medical condition or even cause fatalities. On the whole, such prevention helped the patients to achieve a better quality of life.

The three types of drug related problems that were prevented only in the study group but not in the control group were ‘prevented adverse drug event’ (4%), ‘prevented or minimized drug incompatibility’ (3%) and ‘prevented unnecessary cost of medications’ (2%). Although the number of adverse drug events prevented was small, it is of no doubt important due to the possibly dreadful consequence which the patient may suffer, not forgetting the additional costs involved in managing the

adverse events. Pharmacists in the team could also perform immediate recommendation for a cheaper drug alternative if they felt that both drugs had equal beneficial effects on the patients. This would help the patient save on unnecessary drug costs.

Although the number of drug related problems detected and problems prevented in the study group were higher in the study group, this did not seem to impact significantly on the average length of stay between the two groups - 5.26 days in the control group versus 5.02 days in the study group. There was essentially no significant difference in the average length of stay between these two groups. However, this observation would not necessarily be interpreted as a lack of impact on clinical outcomes by the interventions carried out by the pharmacists. In clinical practice, the length of stay in the hospital may also be influenced by other factors such as discharge protocol and policy, availability of step-down facilities etc. which would not be immediately be affected by any of the improved outcomes due to interventions by the pharmacists.

Therefore, although it was reported that there was no significant difference in the length of stay between the two groups, this lack of difference might be due to inherent nature of the healthcare delivery system. Even though the pharmacists had reduced the occurrence of DRPs in the study group, discharge policies and clinical pathways which the physicians adhered to were not changed immediately as a result of this study. The impact of the interventions carried out by pharmacists, which might realize in improved outcomes in the patients, would require a much longer time to be translated into changes in clinical protocol and policy.

Despite the fact that there was no difference in the average length of stay, it was found that during the 4 months of study, the total drug cost savings achieved in the study group was S$14,036.40. Although there was no statistically significant difference in total hospital charges between the two groups, there is a trend in favour of the study group which could be estimated to result in a cost saving for the study group of S$66,373.20. However, what would be more informative for the health administrators and providers would be the cost-benefit ratios estimated from the results of the current study. When the cost-benefit ratios of having a pharmacist in such physician-pharmacists review team in helping to bring drug costs down was estimated, the cost-benefit ratio of having a pharmacist on board was valued to be 5.85 based on savings in drug cost between the two groups. This positive ratio, coupled with the net annual return of S$34,909.20 in investing in one pharmacist to perform such tasks makes it worthwhile and justifiable to employ pharmacists to do such monitoring as their main duties.

In this study, due to other work commitments the pharmacists only spent about 20% of their working hours monitoring patients' drug regimes and counter-suggesting more optimal drug therapies. With lesser allocation of time to perform other tasks like distribution and dispensing of medications, as well as with better pharmacist-to-patient ratio, there could be even more considerable drug costs savings for the patients. Indeed, when a conservative estimate of keeping the drug cost savings achieved annually as a constant, but varying the time spent by the pharmacist in monitoring patients' drug therapies was done as per sensitivity analysis presented in the results section, the cost-benefit ratio attained was still maintained above 1. Actually, the probability that the cost-benefit ratios would dip below 1 as calculated by Monte

Carlo simulation was between 0.95 to 8% only, demonstrating that the intervention by pharmacists is more than likely to produce good return for investment for the healthcare system. Thus, other than just direct drug cost savings, this will also translate to drug costs savings for the government as most patients were receiving subsidized medications. Moreover in this study, improvement in the health related quality of life (HRQoL) as a result of the patients as a result of better management of their drug therapies was not studied. With a probable improvement in the HRQoL due to reduced DRPs, patients will benefit much more from such pharmaceutical care.

The sensitivity analysis based on the total hospital charge was not as extensively performed because the total hospital charge savings would not have been as reflective of the impact of the study as compared to the total drug cost savings. Total drug cost savings would be insightful of a direct impact as the interventions made by the pharmacists were mainly concerning DRPs and hence would have immediate effect on the drug costs. On the other hand, while such intervention might also impact the total hospital charge, it may be less pronounced as sometimes, laboratory tests and other procedures would be based on clinical pathways and treatment protocols which would not be immediately affected. Nevertheless, the sensitivity analysis carried out for the total hospital charge savings did show a favourable trend when there was the presence of a pharmacist in the review team. The results of the Monte Carlo simulation demonstrate that even when total hospital charge was concerned, the inclusion of a pharmacist was likely to result in positive return of investment with a probability of more than 70%.

In conclusion, although the task of pharmacists in ensuring the safe and rational use of drugs in a managed care environment is not a new one, the findings from the current study supported the observations that the participation of pharmacists in physician-pharmacist review teams did demonstrate the potential quantum in reduction in drug costs, as well as has the possibility of improve the quality of life for in-patients. Another important finding from the current study is inferred from the relatively low number of interventions carried out by the pharmacists in the control group. Besides the reasons mentioned previously, it would also indicate that under the workload and arrangement of the current system, the pharmacists are left with very little time to carry out other functions besides those of dispensing and distribution. With such potential, hospital administrators should consider decreasing the pharmacist-to-patient ratio, as well as employing pharmacists to perform more pharmaceutical care roles to bring about better management of pharmacotherapy, result in more savings in drug costs, as well as to bring about better quality of life for the patients.

Chapter 5

Development of a New Algorithm to Identify the Causality of Adverse Drug Reactions

5.1 Introduction

To assess causality, differential diagnosis of adverse drug events can be achieved with the use of clinical judgments and/or algorithms.[66] Both have their advantages and disadvantages. In practice, clinical judgment is usually the first step in the identification of any adverse drug event. However clinical judgment is not calibrated and the decision-making process is not explicit. Hence, it is neither transparent nor replicable,[100] resulting in high levels of intra-rater and inter-rater disagreement.[58, 101, 102]

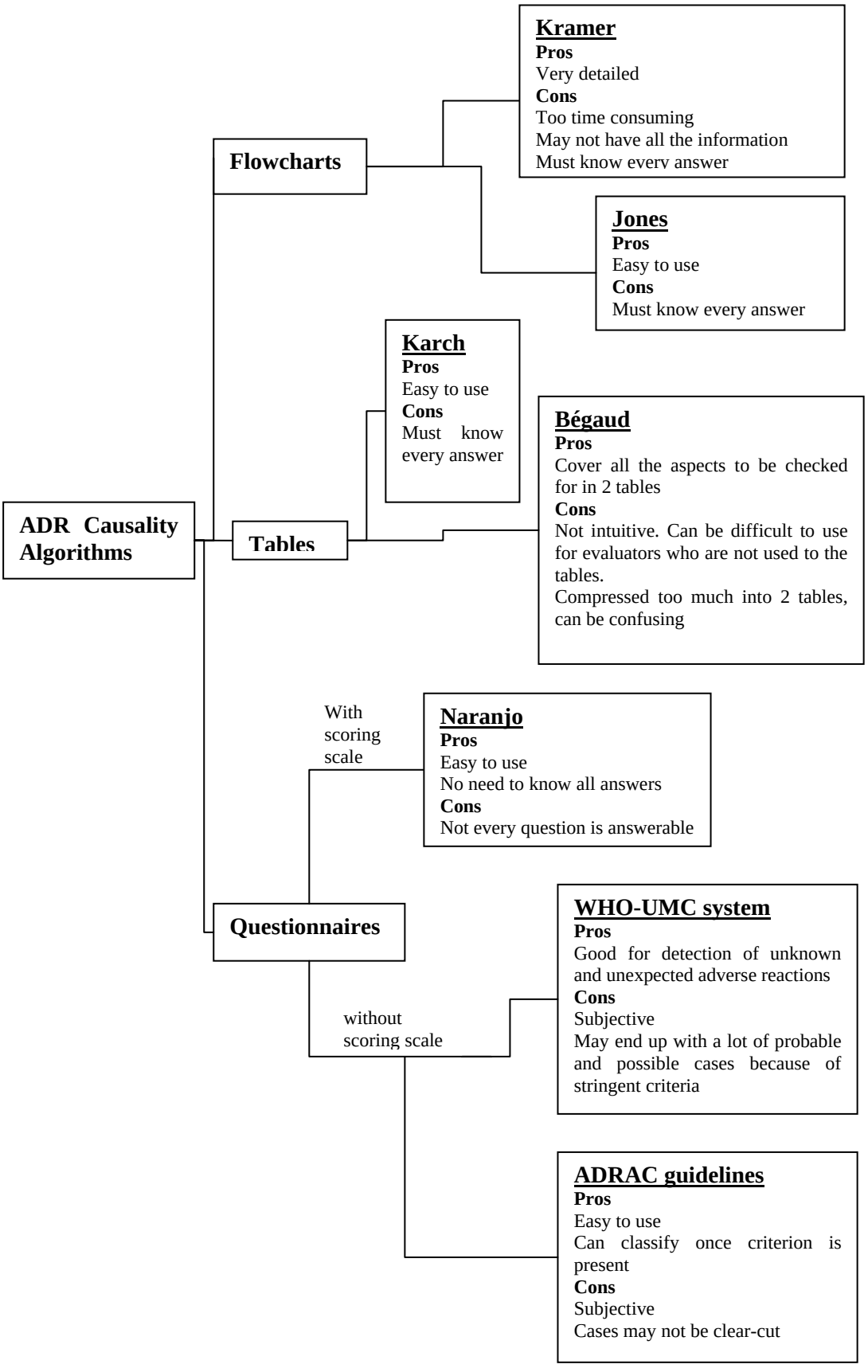
Algorithms, on the other hand, are either flow-charts or questionnaires that attempt to determine drug causation in the occurrence of an ADR by checking the temporal association between drug administration and the onset of the adverse drug event. The systematic approach in information acquisition helps to improve the reliability of assessments and increase inter- and intra-rater agreement.[36, 58] Generally, the use of algorithms will provide more consistent results especially in the regulatory settings where the evaluator would not have the opportunity to observe the suspected ADR event first-hand. In the case of clinical settings, the use of an algorithm will augment clinical judgment.

Several algorithms for evaluating adverse drug events have been published.[58-62] These algorithms are used to assign a probability (e.g. definite, probable, possible, or unlikely) to an event thought to be an adverse drug event. However, several comparative studies had shown that different algorithms might sometimes disagree in the assigning of probability of risk to the same data set.[103-105]

The incongruence of outcomes as reported may be explained by the different structure and approach used in these algorithms. The seven established ADR algorithms, namely, Karch's,[59] Kramer's,[60] Jones',[61] Naranjo's,[58] Bégaud's,[62] World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system[106] and the guidelines used by the Adverse Drug Reaction Advisory Committee (ADRAC) in Australia[107] which the current study would use for comparison can be broadly divided into three types: flow charts, tables and questionnaires. The advantages and disadvantages of these algorithms are summarized in Figure 5.1.

Some of the existing algorithms, e.g. Kramer's, require too much information and are therefore more suited for academic research work rather than for clinical or regulatory use. Others have their own disadvantages that make them less user-friendly (Figure 5.1). Due to these reasons, there is a need to develop an algorithm to suit the needs of the Pharmacovigilance Unit in Singapore. Hence, in this study, the attempt was to develop a new ADR causality algorithm to incorporate the strengths of these existing ones, and yet well adapted for the use of clinicians and regulatory authorities without the need for extra clinical information than those already routinely collected. In other words, the present study intends to produce an ADR causality assignment algorithm that is "friendly" and practical for both clinicians and drug regulators.

Figure 5.1 Categories of various algorithms

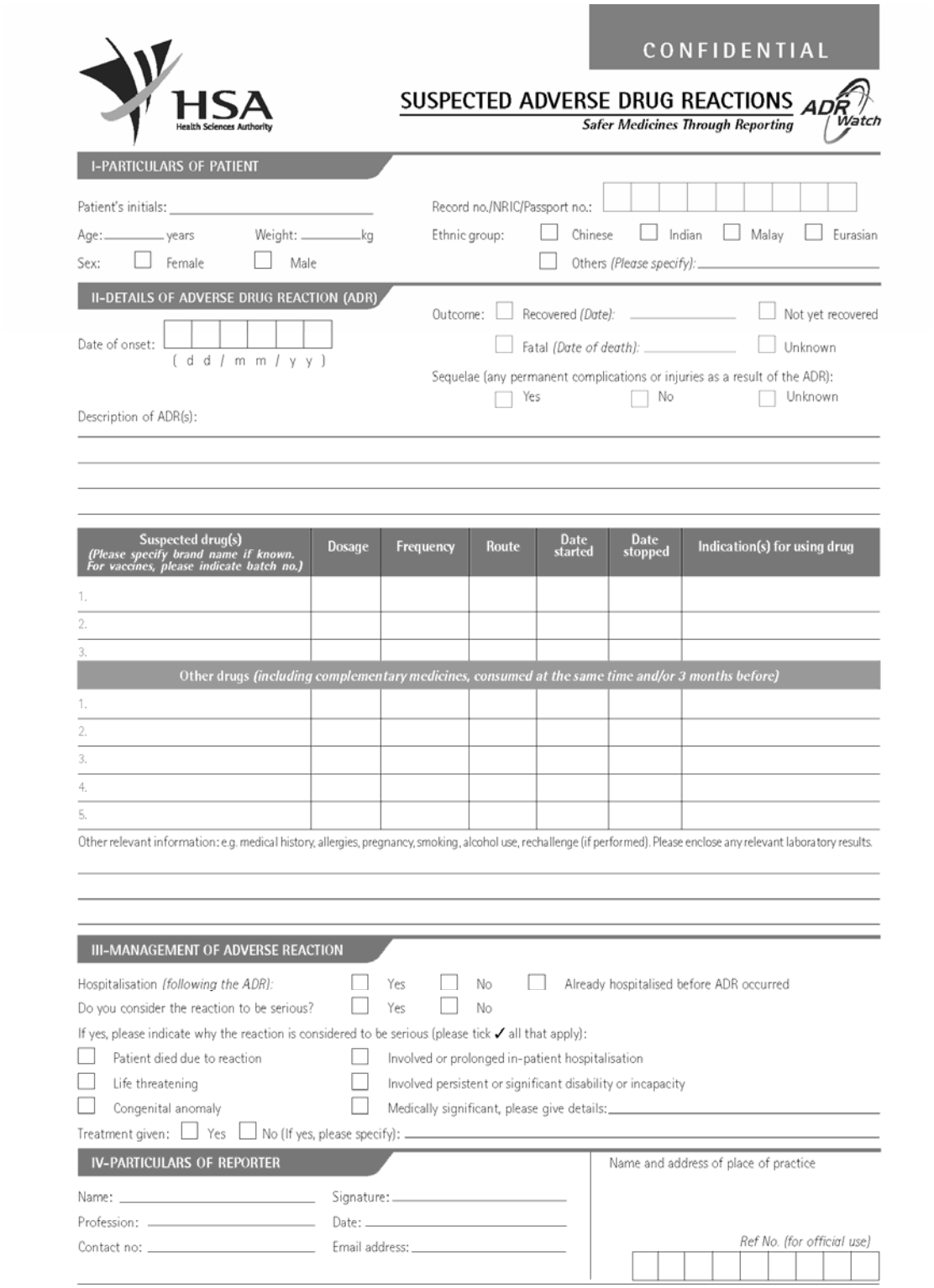


5.2 Methods

5.2.1 Development of the new algorithm

In developing the new algorithm, the ADR reporting form used by CDA when soliciting voluntary reports (Figure 5.2), were used as a basic platform to formulate the questions. This is to ensure that the questions for the new algorithm can be answered from the information routinely collected. With this approach, the resulting algorithm will be of practical use and impose minimal extra burden on information collection. The amount and types of information required in the form used by CDA is similar to those required by Medwatch (FDA)[108] in USA and Therapeutic Goods Administration (TGA)[109] in Australia. The information currently being collected include temporal effect between drug use and onset of ADR (derived from start date of suspected drug and date of onset of ADR); dose of suspected drug administered; objective evidences (e.g., laboratory results) contributing to confirm the adverse event; any similar reaction experienced by patients previously; effect upon stopping suspected drug; any re-challenge; any pre-existing or possibly new medical conditions that could have resulted in such an event; and any outstanding laboratory results to support the adverse event.

Figure 5.2 ADR reporting form used by CDA



CONFIDENTIAL

HSA Health Sciences Authority

SUSPECTED ADVERSE DRUG REACTIONS

Safer Medicines Through Reporting

ADR Watch

I-PARTICULARS OF PATIENT

Patient's initials: _____ Record no./NRIC/Passport no.: ☐☐☐☐☐☐☐☐☐☐

Age: _____ years Weight: _____ kg Ethnic group: ☐ Chinese ☐ Indian ☐ Malay ☐ Eurasian

Sex: ☐ Female ☐ Male ☐ Others *(Please specify)*: _____

II-DETAILS OF ADVERSE DRUG REACTION (ADR)

Outcome: ☐ Recovered *(Date)*: _____ ☐ Not yet recovered

Date of onset: ☐☐☐☐☐☐☐☐ (d d / m m / y y) ☐ Fatal *(Date of death)*: _____ ☐ Unknown

Sequelae (any permanent complications or injuries as a result of the ADR):

☐ Yes ☐ No ☐ Unknown

Description of ADR(s):

Suspected drug(s) *(Please specify brand name if known. For vaccines, please indicate batch no.)*	Dosage	Frequency	Route	Date started	Date stopped	Indication(s) for using drug
1.						
2.						
3.						
Other drugs *(including complementary medicines, consumed at the same time and/or 3 months before)*						
1.						
2.						
3.						
4.						
5.						

Other relevant information: e.g. medical history, allergies, pregnancy, smoking, alcohol use, rechallenge (if performed). Please enclose any relevant laboratory results.

III-MANAGEMENT OF ADVERSE REACTION

Hospitalisation *(following the ADR)*: ☐ Yes ☐ No ☐ Already hospitalised before ADR occurred

Do you consider the reaction to be serious? ☐ Yes ☐ No

If yes, please indicate why the reaction is considered to be serious (please tick ✓ all that apply):

☐ Patient died due to reaction ☐ Involved or prolonged in-patient hospitalisation

☐ Life threatening ☐ Involved persistent or significant disability or incapacity

☐ Congenital anomaly ☐ Medically significant, please give details: _____

Treatment given: ☐ Yes ☐ No (If yes, please specify): _____

IV-PARTICULARS OF REPORTER

Name: _____ Signature: _____

Profession: _____ Date: _____

Contact no: _____ Email address: _____

Name and address of place of practice

Ref No. (for official use) ☐☐☐☐☐☐☐☐☐☐

From this platform, preliminary questions answerable from the ADR reporting form were derived. These questions were matched against the 56 questions used in

Kramer's algorithm,[60] the standard for comparison in our study because of the comprehensive nature of this algorithm. Those questions from Kramer's algorithm which cannot be answered using information available on the ADR reporting form were eliminated. The remaining questions in Kramer's algorithm were then summarized to form main questions and reconciled with the 9 initial questions to arrive at the modified questions for the new algorithm.

The scores were developed based on the importance of the various questions in determining if the suspected drug had indeed brought about the ADR. For each of the 8 questions, the options which contribute to the suspected drug being a causative agent for the ADR would receive a higher score compared to the options which did not support the drug as being the sole agent in bringing about the ADR. For more important questions (like temporal effect, presence of influence from existing clinical condition, use of antidotes and presence of re-challenge), the options which push the case towards positive association with the suspected drug will get higher weights compared to other, though important but not as crucial, questions. This is similar to the way Naranjo *et al.*[58] described how the scoring system of their published algorithm was developed.

To determine the cut-off points for the different causality categories for the new algorithm, the distribution of theoretical "Unlikely", "Possible", "Probable" and "Definite" cases in Naranjo's and Kramer's algorithms were analyzed. These two algorithms were chosen because they share a similar answering format to the new algorithm under development, i.e., the questions required a 'Yes', 'No' or 'Do Not Know' type of answer. The researcher analysed the theoretical cases which can be

generated from these two algorithms and study the percentages of these theoretical cases which fall into these 4 separate categories and modeled against the same percentage range to develop the cut-off points for these 4 categories in the new algorithm.

The first step involved determination of the total number of possible case combinations for both algorithms. For Naranjo's algorithm, there are ten questions and each question has three possible answers, giving a total number of 3^{10} = 59,049 case combinations. Kramer's algorithm has a total of 56 questions, of which only 15 questions would be needed to arrive at a causality for most suspected ADR cases. Of these 15 questions, two have three possible answers whilst the rest have two. Thus, the total number of case combinations is 3^2 x 2^{13} = 73,728 cases. The "cut-off" scores of the two algorithms were then applied to their theoretical case combinations and the percentage of "Definite" cases in these two algorithms was found to be less than 2%, whereas the percentages of "Probable", "Possible" and "Unlikely" cases range from 7% to 26%, 54% to 61% and 17% to 32% of the total number of cases, respectively. Hence, an arbitrary cut-off of 1% of cases with the highest scores as "Definite", the next 9% for "Probable", and the following 60% for "Possible" and the last 30% as "Unlikely" were set and applied to the new algorithm. In the new algorithm, there are eight questions and each question has three possible answers. However, Questions 5 and 6 in this algorithm are inter-related; if the answer to Question 5 is not unknown, the answer to Question 6 must be unknown to prevent logical contradiction. Likewise, if the answer to Question 6 is not unknown, the answer to Question 5 must be unknown. Thus the total number of possible case combinations for our algorithm is 3^8 – (3^6 x 2 x 2) = 3645. To determine the appropriate cut-off for the definite case, the

scores from all the theoretical case combinations were analyzed and approximately 1% of the cases (n=31) has a score of at least 12. Thus "12" was used as a cut-off in the new algorithm to differentiate between definite and probable cases. The other cut-offs are found in a similar manner.

5.2.2 Testing of the new algorithm

For testing the newly developed algorithm, anonymized ADR reports collected by the Pharmacovigilance Unit in the Centre for Drug Administration (CDA), Health Sciences Authority, Singapore were used. This unit in CDA is the national body in Singapore responsible for all pharmacovigilance and ADR monitoring activities. The anonymized ADR reports were voluntary reports consolidated from hospitals and clinics in Singapore during the period of January to August 2002.

To test the new algorithm, ADR causality score was first assigned to the usable cases by using the new algorithm together with seven different established algorithms – Kramer's,[60] Naranjo's,[58] Karch's,[59] Jones',[61] Bégaud's,[62] the guidelines used by the Adverse Drug Reaction Advisory Committee (ADRAC) in Australia[107] and the WHO-UMC causality assessment system.[106] The results obtained from the various algorithms were translated into 4 categories of causality (Unlikely, Possible, Probable and Definite). 'Unclassified', 'Unassessable', and 'Unclear' categories in ADRAC guidelines were all re-grouped under the 'Unlikely' category for ease of comparison. These resulting categories from each algorithm were matched against the outcomes obtained with Kramer's algorithm,[60] the "gold" standard in this study to compare the relative performance of all the algorithms. To avoid inter-rater variation, only one of the investigators was involved in testing the algorithms. Any need for

confirmation of decisions was resolved with the other investigators. The clinical evaluators at the Pharmacovigilance Unit in the Centre for Drug Administration, Health Sciences Authority, Singapore were approached for their expert opinions whenever necessary.

For all these comparisons, the percentages of congruency between the algorithms were then calculated. The 95% confidence intervals were obtained using exact binomial calculations.

5.3 Results

Using information available from the ADR reporting form used locally by CDA, 9 potential questions were derived for the new ADR algorithm (Table 5.1). After matching these questions with the 56 questions in Kramer's algorithm, the new algorithm was consolidated with a set of 8 questions and the scores for their possible options as present in Table 5.2. In the final version, the question regarding the presence of laboratory tests results was removed because this information is seldom reported in spontaneous ADR reporting forms.

Table 5.1 List of "answerable" questions

	Questions
1	Any temporal effect between drug and ADR?
2	Suspected drug known to have this effect?
3	Appropriate dosage (for general population) was used?
4	Reaction confirmed by objective evidence?
5	Improvement upon de-challenge?
6	Patient had such reaction before?
7	Any re-challenge?
8	Present medical condition or other medical condition may have given rise to this reaction?
9	Any outstanding laboratory test results?

Table 5.2 List of questions with scores for our new ADR algorithm

		Yes	No	Do Not Know	Not applicable
1	Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?	2	-4	0	-
2	Has the adverse reaction been associated with the suspected drug before?	2	-2	0	-
3	Could this adverse reaction be due to an existing clinical condition?	0	4	0	-
4	Is there any over-dose of the suspected drug?	2	0	0	-
5	If the drug was discontinued, did the adverse reaction improve? (if the drug brought about irreversible changes, please classify as “Do Not Know”)	1	-2	0	0
6	If the drug was NOT discontinued, did the reaction resolved on its own?	-2	0	0	0
7	Did the reaction improve when specific antagonist/antidote was administered?	4	0	1	0
8	Did the adverse reaction recur when the suspected drug was discontinued and re-administered again?	4	-2	0	0
	Total score:				

The final cut-offs for the categories can be seen in Table 5.3. This new algorithm was then tested with the data set from CDA as described.

Table 5.3 Cut-off scores for our algorithm

Categories	Sores
Definite	≥12
Probable	8-11
Possible	0-7
Unlikely	<0

During the study period of January to August 2002, there were 518 ADR reports collected by the Pharmacovigilance Unit at CDA. Of these, 68 reports were not usable (including 18 reports not related to ADR; 11 reports due to complementary medicines which were not intended to be used for developing our new algorithm; 39 reports with missing essential information). The remaining 450 usable cases were used for the testing of our newly developed algorithm, as well as for the comparative study with the established algorithms.

The seven established algorithms mentioned were applied to the 450 usable cases. The assigned causalities were all translated into four different categories which were then compared against that obtained with Kramer's algorithm. Results from this comparison are shown in Table 5.4 (for absolute number of cases in the different causality classification) and Table 5.5 (for percentage of congruency with Kramer's algorithm). The comparison of percentage of congruency between the different algorithms is presented in Table 5.6.

Table 5.4 A comparison of the different causality classification of the 450 ADR reports

Algorithm	**Definite**	**Probable**	**Possible**	**Unlikely**	**Unclassifiable**
Kramer	12	370	64	4	0
Our new algorithm	13	367	70	0	0
ADRAC	4	436	10	0	0
Jones	0	248	21	0	181
Karch	4	236	1	35	174
Naranjo	4	391	54	1	0
WHO-UMC	3	196	175	1	75
Bégaud	4	226	165	55	0

Table 5.5 Results from comparative study of the various algorithms against Kramer's

Algorithm	% of Congruency	95% CI
Our new algorithm	98.44	96.82 – 99.37
Naranjo	94.67	92.17 – 96.55
ADRAC	84.44	80.76 – 87.67
Jones	56.44	51.72 – 61.08
Bégaud	55.33	50.61 – 59.99
Karch	52.22	47.49 – 56.92
WHO-UMC	45.11	40.45 – 49.84

Table 5.6 Comparison of percentage of congruency (%) between the different algorithms

	Kramer	New algorithm	Naranjo	ADRAC	Jones	Bégaud	Karch	WHO-UMC
Kramer	100.00	98.44	94.67	84.44	56.44	55.33	52.22	45.11
New algorithm	98.44	100.00	94.44	84.67	56.44	54.44	51.11	44.89
Naranjo	94.67	94.44	100.00	89.78	57.11	55.11	53.56	45.11
ADRAC	84.44	84.67	89.78	100.00	54.89	51.56	53.33	44.22
Jones	56.44	56.44	57.11	54.89	100.00	52.89	88.89	53.33
Bégaud	55.33	54.44	55.11	51.56	52.89	100.00	57.11	70.44
Karch	52.22	51.11	53.56	53.33	88.89	57.11	100.00	52.00
WHO-UMC	45.11	44.89	45.11	44.22	53.33	70.44	52.00	100.00

Of the established algorithms, Naranjo's showed the highest percentage of congruency (94.67%) as compared to Kramer's. This is then followed by guidelines used by ADRAC (84.44%), Jones' (56.44%), Bégaud's (55.33%), Karch's (52.22%) and WHO-UMC causality assessment system (45.11%) in descending order. The results obtained with the new algorithm was 98.44% (95% CI: 96.82 – 99.37) congruent to the results from Kramer's algorithm.

5.4 Discussion

In the process of developing a new ADR algorithm, first and foremost, the format had to be decided upon. It was decided against flow-chart or table format because once the evaluator could not answer any questions in these formats, they would find it almost impossible to proceed further with the algorithm to arrive at the final ADR causality of the suspected drug. Where guidelines or assessment criteria were concerned, the researchers were not in favor of using that as a format for the new algorithm due to presence of evidence that using such guidelines were neither reproducible, valid nor accountable.[100]

After the formulation of the questions, the scoring system similar to that used by Naranjo *et al.*[58] was adopted. The rationale being that the user can just answer each question in the algorithm to the best of his or her ability and sum up the score for all the questions. This total score will then be translated into causality categories. However, Naranjo's algorithm could not be used without modifications because of the presence of questions like whether the reaction appeared when a placebo was administered, or if there was any increase in severity of the reaction when the drug dose was increased and any decrease in severity when the drug dose was decreased. Most of the time, it is impossible to answer these questions because it is not a common practice to use placebos clinically. In addition, in the case of a likely ADR, the suspected drug most likely would have been discontinued pending further investigation, instead of an upward or downward adjustment of the drug doses. The perpetual answer of "Do Not Know" to these two questions will tend to lower the total score obtained for a suspected drug hence affecting an accurate final causality assignment. Upon checking the ADR reporting forms by Medwatch[108] and

ADRAC,[109] it was found that information required to answer these questions are also not solicited in these forms. Hence, these 2 questions may be seen as redundant in present day clinical context and may not be necessary in an ADR algorithm.

Hence, to minimize the problem of having unanswerable questions most of the time, the approach used in the current study was to derive a set of "answerable" questions first. Based on the information usually collected from ADR reporting forms and comparison with the questions from Kramer's algorithm, the final set of eight questions was obtained. Although this is only two questions lesser than Naranjo's algorithm, the questions are more answerable based on the information available when an ADR report is made. This new algorithm was then subjected to testing and comparison study.

In this study, the percentage of congruency, that is, the percentage of cases which had exactly the same causality assignments, was used to evaluate the comparative performance of all the algorithms against Kramer's algorithm. From the results obtained, it can be seen that compared with the other six established algorithms, Naranjo's algorithm showed the most agreement with Kramer's, followed by ADRAC's, Jones', Bégaud's, Karch's and WHO-UMC's in descending order. On the other hand, the results obtained using the new algorithm managed to reach 98.44% congruency with Kramer's algorithm.

The relatively poor performance of several established algorithms such as Jones', Karch's and WHO-UMC's algorithm was due to the presence of substantial unclassifiable cases, ranging from 16.7% (WHO-UMC) to 40.2% (Jones'). Hence,

these three algorithms are not particularly suited for clinical use based on the type of information from our ADR reports. In addition, WHO-UMC's algorithm assigned 163 cases as 'Possible' instead of 'Probable' causality like Kramer's (See Table 5.7), contributing further to its low congruency with Kramer's algorithm.

Table 5.7 Actual number of ADR cases with the same causality assignment as that by Kramer's algorithm

		Kramer's algorithm			
		Definite	**Probable**	**Possible**	**Unlikely**
New algorithm	**Definite**	12	1	0	0
	Probable	0	367	0	0
	Possible	0	2	64	4
	Unlikely	0	0	0	0
Naranjo	**Definite**	4	0	0	0
	Probable	8	370	13	0
	Possible	0	0	51	3
	Unlikely	0	0	0	1
ADRAC guideline	**Definite**	4	0	0	0
	Probable	8	370	58	0
	Possible	0	0	6	4
	Unlikely	0	0	0	0
Bégaud	**Definite**	4	0	0	0
	Probable	8	218	0	0
	Possible	0	142	23	0
	Unlikely	0	10	41	4
Karch	**Definite**	4	0	0	0
	Probable	8	228	0	0
	Possible	0	1	0	0
	Unlikely	0	9	23	3
	Unclassifiable 174				
Jones	**Definite**	0	0	0	0
	Probable	12	236	0	0
	Possible	0	2	18	1
	Unlikely	0	0	0	0
	Unclassifiable 181				
WHO-UMC	**Definite**	3	0	0	0
	Probable	7	189	0	0
	Possible	1	163	11	0
	Unlikely	0	1	0	0
	Unclassifiable 75				

As mentioned above, compared with other established algorithms, the new algorithm managed to achieve a higher congruency with Kramer's algorithm (98.44%). Although it may be argued that this would be expected as this only demonstrates the conceptual equivalence between the two algorithms, the high level of congruency does show that the new "short" algorithm can achieve quite respectable results as a very comprehensive one. Another pertinent question to ask at this juncture would be: "What if both Kramer's and the new algorithms were both wrong?" The answer to this question can be found by examining the numbers of definite cases assigned by the various algorithms (Table 5.4). In pharmacovigilance, the ability to identify "definite ADR cases" is of paramount importance. The comparative results showed that the new algorithm and Kramer's algorithm have lower threshold than other algorithms in triggering off warning signals, i.e. in assigning of "definite" cases. The lower threshold represents a more conservative approach that would be acceptable in the context of public safety. Hence, with this short algorithm, it was felt that it provides ease of use and requires lesser time to get a causality assignment for the suspected drug. Although patient-unrelated factors such as the quality of data documentation and the medical knowledge of the assessors are likely to influence the assessment outcomes, the presence of such an algorithm is nevertheless still valuable for improving the ADR reports by focusing on pertinent information, particularly the dates concerning drugs and events. On the whole, this will be useful from both clinical practices as well as from drug-regulation perspectives. Even though this new ADR drug causality assessment is developed to cater for local needs, there is no reason why it could not be used in other regions which are looking for a simple and easy method to assign ADR causality.

Having developed the basic algorithm, more time needs to be spent in improving on the questions to ensure ease of understanding and to make sure that there is minimal ambiguity for the person using the algorithm. The scoring system can be further refined so as to increase the sensitivity of this algorithm scale.

5.5 Conclusion

By evaluating the advantages and disadvantages of several established algorithms for assigning ADR causality, a simple algorithm that requires no extra data collection than those routinely collected in most ADR reporting forms have been developed. In terms of performance, the new “short” algorithm can achieve similar result with a much more comprehensive algorithm. In addition, the algorithm adopts a lower threshold in assigning “definite” ADR cases than most established algorithms, a feature that may be desirable in the context of public safety. In conclusion, a short algorithm that provides ease of use and is less demanding on time required in getting a causality assignment for a suspected drug has been developed. This algorithm would provide clinicians and drug regulators with a handy tool to assign ADR causality.

Chapter 6

A Quantitative Approach of using Genetic Algorithm in Designing a Probability Scoring System for Adverse Drug Reaction Assessment

6.1 Introduction

The detrimental effects of adverse drug reactions (ADRs) contributing to major problems like morbidity, mortality and high cost of patient care have been well established.[8, 50, 101] In order to effectively manage and minimize ADRs, it is necessary to have more precise and accurate assessment of the causality of the ADRs as well as predictors for likely occurrence of ADRs. In the former case, the challenge lies in determining the probability that the suspected drug is the actual cause of the ADR.

To date, spontaneous adverse drug reactions' reporting is the backbone of most pharmacovigilance centres,[35, 110] medical institutions and clinical trials.[111] These spontaneous reports will give rise to signals which alert the regulatory authorities or the physicians about the dangers posed by the suspected drugs involved. The major problem encountered here is the differentiation between "signals" and "noise". Studies have been done to evaluate the impact of these signals detected from spontaneous ADR reporting data.[56] Generally speaking, such signals will be useful and be less problematic for national pharmacovigilance units that collect huge amount of spontaneous ADR reporting and hence have a large database of ADR reports to determine the significance of the signals. However, for countries with smaller population and hence lesser spontaneous reports, or medical institutions and pharmaceutical companies conducting clinical trials on yet to be marketed drugs, this method may not be the most ideal. Furthermore, for impact analysis of signals detected from spontaneous ADR reporting described by Waller *et al.*,[56] the scoring for strengths and weaknesses of the evidence (which is the drug causality of the ADR) is said as based on judgment of the overall quality of the series of case reports received. This would still lead to the problem of inter- and intra-rater disagreement on causality

since there is substantial subjective element in the judgment process. Hence, it is of importance to develop a system capable of assessing the spontaneous reports that is not only more objective but at the same instance able to predict the likelihood that a signal is a true signal. In other words, it should possess the same properties as a good screening test.

In the current practice of assessing any suspected ADRs, drug causality can be determined by using either clinical judgments or algorithms.[66] Although always the first and unavoidable essential step in ADR detection and assessment, clinical judgments often have low inter- and intra-rater agreements because of implicit decision-making process.[58, 101, 102] Algorithms on the other hand, are structured operational systems for the identification of ADRs. Hence theoretically, using algorithms to evaluate the causality of ADRs make the evaluation less arbitrary, more objective and also produces higher inter- and intra-rater agreements.[58]

Several algorithms have been developed in the late 1970s and early 80s. For these algorithms, weights were arbitrarily assigned to the various criteria in questionnaires based on their perceived importance, and validity of the algorithms was checked based on the degree of agreement between the algorithm-derived results and experts' opinions. Although giving arbitrary weights to criteria is a qualitative way of determining the causality of an ADR and a good guide for assigning causality, this qualitative nature also means that it is not possible to determine the probability (or likelihood) of the ADR causality based on the results obtained.

To help overcome the above problems, a robust yet easy to use ADR algorithm that could offer a more objective way to determine ADR causality as well as the probability of the causal relationship should be developed. With a probability score, when the algorithm is applied to a suspected ADR situation, it gives a quantitative likelihood of the ADR being caused by the suspected drug. This will allow a quantification of ADR signals for small pharmacovigilance centres without large databases. At the same time, it will also be extremely useful for application in clinical practice, as well as in clinical trials for new drugs where there may be unprecedented ADRs. For large national pharmacovigilance centres, a quantitative ADR algorithm can be incorporated into their current system to get an even more accurate impact analysis of their ADR data from spontaneous reporting.[52, 56]

Nevertheless, the new algorithm should not be designed just purely for academic purpose but attain a level of balance between scientific rigor and at the same time, simple enough for use in clinical or regulatory setting. Henceforth, the criteria used by the algorithm in assessing the probability that an ADR is caused by the suspected drug should be determinable based on routinely collected data. On top of that, like any other scientific measuring instruments, high reproducibility and validity are also essential attributes for a good ADR algorithm.

Currently, Bayesian Adverse Reaction Diagnostic Instrument (BARDI), is an algorithm which is able to determine the probability of ADR causality.[112] BARDI calculates the probability of ADR causality using six components: (1) prior odds, which is the ratio of the drug-attributable risk and non drug-attributable risk based on epidemiologic information, and (2) five likelihood ratios, which are (a) patient history,

(b) timing of ADR with respect to drug administration, (c) characteristics of the ADR, (d) drug de-challenge and (e) drug re-challenge. A major advantage of BARDI is its ability to incorporate any new information regarding the drug, patient or ADR into the probability assessment of the ADR causality. However, this is time-consuming and there are considerable difficulties in determining the prior odds ratio and likelihood ratios. Hence, there is a need to develop an algorithm that has the pros of both ease of use and ability to give a probability of the ADR causality.

Table 6.1 The eight criteria used in our algorithm

1	Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?
2	Has the adverse reaction been associated with the suspected drug before?
3	Could this adverse reaction be due to an existing clinical condition?
4	Is there any over-dose of the suspected drug?
5	If the drug was discontinued, did the adverse reaction improve? (if the drug brought about irreversible changes, please classify as “Do Not Know”)
6	If the drug was NOT discontinued, did the reaction resolved on its own?
7	Did the reaction improve when specific antagonist/antidote was administered?
8	Did the adverse reaction recur when the suspected drug was discontinued and re-administered again?

In the previous chapter, the development of a new algorithm with 8 criteria for assigning ADR causality with the purpose of balancing scientific rigor and applicability has been reported (Table 6.1). The preliminary results showed that the new algorithm can perform better in detecting and assigning causality of ADRs compared with several well established algorithms.[113] Using the insights on the limitation of qualitative approach in assigning weightage, the scoring system of the algorithm has been further improved using the genetic algorithm approach so that the

final score can also be used as a measure of the probability of ADR causality. Genetic algorithm is a form of artificial intelligence and its use in the medical field has been published.[68-71] This chapter reports the developmental process and the performance of the improved algorithm.

6.2 Methods

6.2.1 Development of the scoring system

The intention was to identify several ADR cases with known ADR causality probability values as reference points for the development and testing of the scoring system. However, it would be too time-consuming to establish a scoring system that satisfy all these reference points through an exhaustive search of all possible scoring systems by systematically varying all the scores in the scoring system. Thus genetic algorithm was used to find a suitable scoring system.

Theoretically, the new scoring system should assign a higher probability to 'Definite' ADR cases than other causality categories. With this, seven rules (Table 6.2) which define all possible combinations of 'Definite' ADR cases were identified. By identifying all possible combinations of 'Definite' ADR cases, it will be possible to test the new scoring system to determine whether it satisfies this condition. The seven rules were identified based on a review of cases where the suspected drugs were considered to have definite causality effect in the reported ADRs. These cases were picked out based on retrospective inspection of all the ADR reports by a panel of experts from the regulatory body Centre for Drug Administration, CDA (the FDA equivalent in Singapore).

Table 6.2 Rules that define 'Definite' cases

Rule	Criteria to fulfil for each rule
1	- Presence of temporal effect - ADR improve with de-challenge and recur with re-challenge - No antidote/antagonist is given
2	- Present of temporal effect - ADR responds to antidote/antagonist administered - If a re-challenge is performed, result must not be negative
3	- Presence of temporal effect - Not due to any existing clinical condition - Presence of drug overdose which improve upon de-challenge - If a re-challenge is performed, result must not be negative
4	- Presence of temporal effect - ADR has been associated with the suspected drug before - Not due to any existing clinical condition - Improvement of ADR upon de-challenge - If a re-challenge is performed, result must not be negative
5	- Presence of temporal effect - ADR recur on re-challenge - ADR may or may not improve when antidote/antagonist is administered *(This rule cover for ADR resulting from excipients used in the formulation of the drug)*
6	- Unknown temporal status - ADR respond to antidote/antagonist - ADR recur upon re-challenge
7	- Unknown temporal status - Not due to any existing clinical condition - ADR improve with de-challenge - ADR recur upon re-challenge

Table 6.3 Rules that define 'Probable' cases

Rule	Criteria to fulfil for each rule
1	- Unknown temporal status - Existing clinical condition - ADR improve with de-challenge and recur with re-challenge - No antidote/antagonist is given
2	- Unknown temporal status - ADR responds to antidote/antagonist administered - If a re-challenge is performed, result is unknown
3	- Unknown temporal status - Not due to any existing clinical condition - Presence of drug overdose which improve upon de-challenge - If a re-challenge is performed, result is unknown
4	- Unknown temporal status - ADR has been associated with the suspected drug before - Not due to any existing clinical condition - Improvement of ADR upon de-challenge - If a re-challenge is performed, result is unknown
5	- Unknown temporal status - ADR recur on re-challenge - ADR does not improve when antidote/antagonist is administered
6	- Presence of temporal effect - Not due to any existing clinical condition - Presence of drug overdose - Effect of de-challenge is unknown - No antidote/antagonist given - No re-challenge
7	- Presence of temporal effect - ADR has been associated with the suspected drug before - Not due to any existing clinical condition - Effect of de-challenge is unknown - No antidote/antagonist given - No re-challenge

Although it will be useful to have a set of similar rules to define 'Probable', 'Possible' and 'Unlikely' ADR cases, it is difficult to classify all the remaining ADR cases into these three categories. Thus, only some rules which defined some

combinations of 'Probable' ADR cases were identified (Table 6.3). These rules were identified by slight modification of the rules for 'Definite' ADR cases. For example, if a rule for 'Definite' ADR cases contains a criterion which implicate the drug as a causative agent (Rule 2 in Table 6.2), changing that criterion to a 'Unknown' or 'Not Applicable' option will change the rule from defining 'Definite' ADR cases to defining 'Probable' ADR cases (Rule 2 in Table 6.3).

Table 6.4 ADR cases with known probability values

Rule	Criteria to fulfil for each rule	Probability
1	- Presence of temporal effect - ADR has been associated with the suspected drug before - Not due to any existing clinical condition - Presence of drug overdose - ADR respond to antidote/antagonist - ADR recur upon re-challenge	1
2	- Unknown temporal status - ADR may not have been associated with the suspected drug before - Unknown existing clinical condition - Unknown drug dose - Effect of de-challenge is unknown - If antidote/antagonist given, effect is unknown - If a re-challenge is performed, result is unknown	0.5
3	- No temporal effect - ADR has not been associated with the suspected drug before - Existing clinical condition - No drug overdose - Effect of de-challenge is unknown - Result of re-challenge is negative	0

In addition to identification of rules for 'Definite' and 'Probable' ADR cases, several ADR cases with known probability values were also identified (Table 6.4). The known probability values are 1, which corresponds to ADR cases where all the

criteria implicate the drug as a causative agent, 0.5, which corresponds to ADR cases where all the criteria are either 'Unknown' or 'Not Applicable' options, and 0, which corresponds to ADR cases where all the criteria exclude the drug of any possible causal effect.

The scores in the new scoring system were determined with the help of genetic algorithm[67] which is shown schematically in Figure 6.1. It comprises of four phases: initialization, evaluation, exploitation and exploration. The initialization phase involves constructing an initial population of scoring systems. Typically, the population size used in genetic algorithms is in the range of 50 to 500. In our study, we tentatively used an initial population of 300 randomly generated scoring systems.

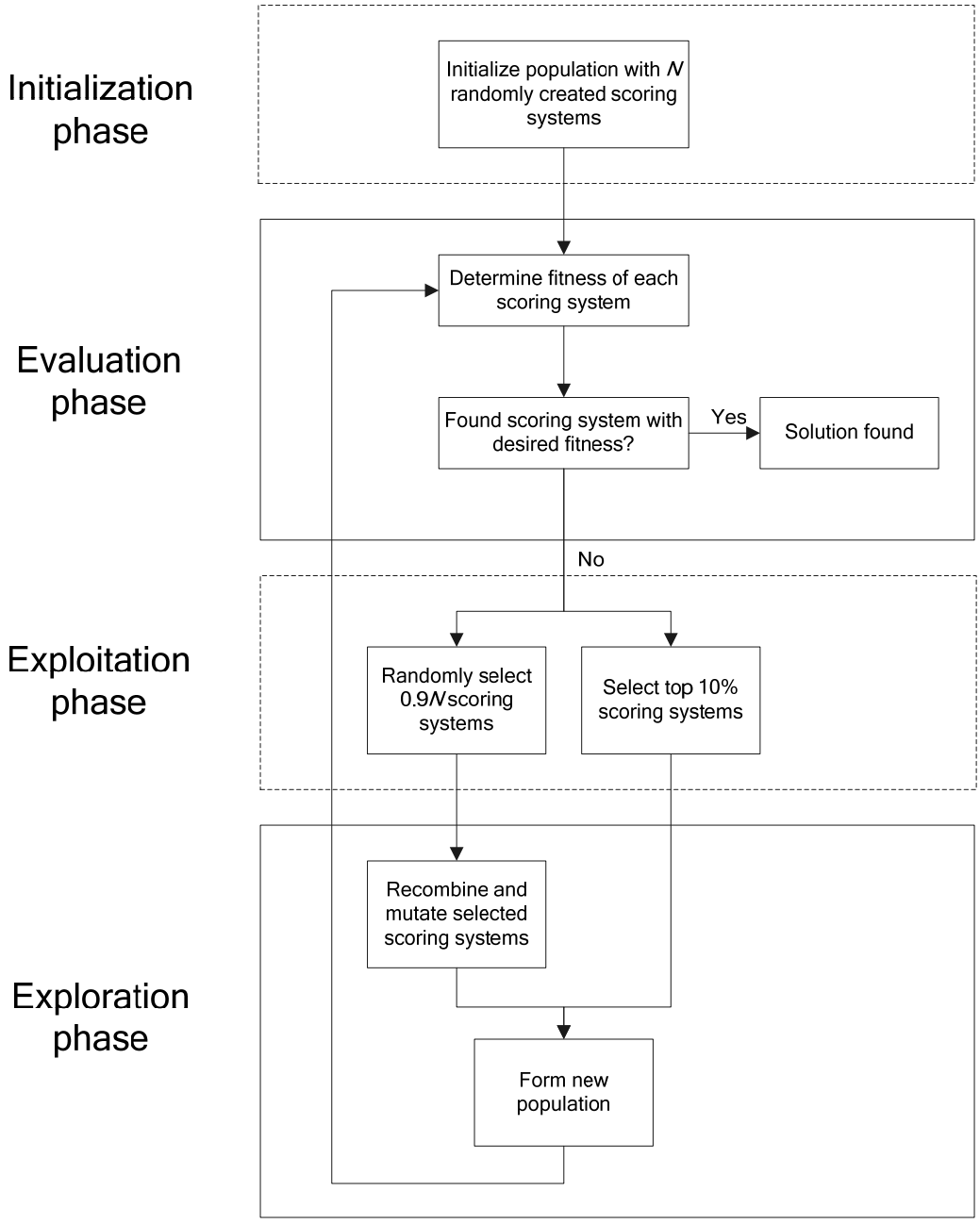
During the evaluation phase, each scoring system is evaluated by calculating its fitness score. The fitness score indicates how well a scoring system satisfies all the reference points and is calculated by using the following formula:

$$F = \frac{N_{Tdef}}{N_{Tdef} + N_{Fdef}} + \frac{N_{Tpro}}{N_{Tpro} + N_{Fpro}} + \frac{N_{TP1}}{N_{P1}} + \frac{N_{TP0.5}}{N_{P0.5}} + \frac{N_{TP0}}{N_{P0}}$$

where N_{Tdef} is the total number of 'Definite' ADR cases defined by the rules in Table 6.2, N_{Fdef} is the total number of 'Not definite' ADR cases which have higher or equivalent total score as 'Definite' ADR cases. N_{Tpro} is the total number of 'Probable' ADR cases defined by the rules in Table 6.3, N_{Fpro} is the total number of these 'Probable' ADR cases which have a probability value below 0.5. N_{P1}, $N_{P0.5}$, and N_{P0} are the total number of cases which should have an ADR probability of 1, 0.5 and 0

respectively and N_{TP1}, $N_{TP0.5}$, and N_{TP0} are the actual number of these cases that have these probabilities. Thus a scoring system that satisfy all the reference points will have a fitness score of 5 and if one is found, then further processes are stopped and the scoring system will be validated to ensure it is useful. Otherwise, the genetic algorithm proceeds to the exploitation phase.

Figure 6.1 Schematic diagram of how genetic algorithm works



In the exploitation phase, the scoring systems are ranked in terms of their fitness score and higher ranked scoring systems are selected more frequently to replace the bottom 90% of the current population. This method was used because the basic assumption in genetic algorithm is that scoring systems with higher fitness scores will have higher probability of producing scoring systems with even higher fitness scores, leading eventually to scoring systems which have the desired fitness scores. The exploitation phase helps to increase the average fitness scores of the population as multiple copies of high ranking scoring systems are more likely to be retained. However, this will also reduce the diversity of the population. This problem will be solved by the exploration phase.

The last phase of genetic algorithm, exploration, is used to introduce variation into the new population. Recombination and mutation are two events that occur during exploration. In recombination, two different scoring systems exchange some of their scores with each other. This creates two new scoring systems and may result in major improvement in fitness if the right fractions are joined together. During mutation, individual scores in the scoring systems may change to another randomly selected value. The role of mutation is to maintain diversity in the population by ensuring different scores have equal chance to be included in a scoring systems. Since recombination and mutation are random processes, there is a slight possibility that scoring systems with high fitness scores may change to new scoring systems with lower fitness scores as a result of the exploration phase. Thus the top 10% of the population are not subjected to the recombination and mutation process in order to ensure that scoring systems with high fitness scores are not removed accidentally.

After the exploration phase, the genetic algorithm returns to the evaluation phase and the cycle repeats until the desired scoring system is found.

Once the new scoring system has been established, the probability of ADR causality for an ADR case can be calculated using the following formula:

$$P = \frac{S - S_{\min}}{S_{\max} - S_{\min}}$$

where S is the total score of the ADR case, S_{min} and S_{max} is the minimum and maximum possible score of the scoring system respectively (Table 6.5).

Table 6.5 New scoring system for the algorithm

		Yes	No	Do Not Know	Not Applicable
1	Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?	49	0	36	-
2	Has the adverse reaction been associated with the suspected drug before?	1	0	0	-
3	Could this adverse reaction be due to an existing clinical condition?	0	7	1	-
4	Is there any over-dose of the suspected drug?	2	0	0	-
5	When the drug was discontinued, did the adverse reaction improve within a reasonable period of time?	14	0	7	7
6	When the drug was NOT discontinued, did the reaction resolved on its own?	0	1	0	0
7	Did the reaction improve when specific antagonist/antidote towards the suspected drug was administered?	17	0	1	1
8	Did the adverse reaction recur when the suspected drug was discontinued and re-administered?	33	0	17	17
	Total score, S:				
	Probability, P = (S - 8) / 108:				

Causality categories

Definite: $0.75 \leq P \leq 1$ ($S \geq 89$)
Probable: $0.63 \leq P < 0.75$ ($76 \leq S \leq 88$)
Possible: $0.50 \leq P < 0.63$ ($62 \leq S \leq 75$)
Unlikely: $0 \leq P < 0.50$ ($S \leq 61$)

6.2.2 Testing of new scoring system

In order to test the ability of this newly derived scoring system to assign causality probability, 4 different ADR cases, with varying amount of information available, were selected from the pool of ADR reports (see Chapter 5). The description of these 4 cases can be seen in Table 6.6. The probability value derived after subjecting each case through the new scoring system should tell us the likelihood that the ADR is caused by the suspected drug.

Table 6.6 ADR cases with varying amount of information available

ADR case 1 A 19 year old female presented with scattered macular discrete red rashes 1 day after a lignocaine gel was applied to her buccal cavity prior to a tooth extraction. Patient had not recovered from the rash 5 days after the initial onset. It is not known if the patient was taking any other medications concurrently or if she has history of drug allergy. Causality assessment for lignocaine Total score, S = 0 + 1 + 7 + 0 + 7 + 0 + 1 + 17 = 33 Probability of causing ADR = (33-8)/108 = 0.231
ADR case 2 A 30 year old female patient, with no known drug allergy, presented with alopecia areata a few days after taking a single dose of fluconazole 150mg for the treatment of vaginal candidasis. Patient recovered from the condition 1 month after the single dose ingestion. Causality assessment for fluconazole Total score, S = 36 + 1 + 7 + 0 + 7 + 0 + 1 + 17 = 69 Probability of causing ADR = (69-8)/108 = 0.565
ADR case 3 A 61 year old male patient was prescribed naproxen 275mg per oral for treatment of toothache. Following the first dose of naproxen, he developed peri-orbital swelling, wheezing and hoarseness of voice. IV hydrocortisone and nebulisation were given to treat his wheezing and patient recovered. Patient had previous allergies with paracetamol and phenylbutazone. Causality assessment for naproxen Total score, S = 49 + 0 + 7 + 0 + 14 + 0 + 1 + 17 = 88 Probability of causing ADR = (88-8)/108 = 0.741
ADR case 4 A female patient who has been taking rofecoxib for 6 months for the treatment of knee osteoarthritis experienced low platelet count. Platelet count returned to normal following a de-challenge, but decreased again when therapy was re-introduced. Therapy with rofecoxib was subsequently discontinued. The patient had a medical history of stroke and has the following concurrent medical conditions: atrial fibrillation, dementia, ischaemic heart disease. Causality assessment for rofecoxib Total score, S = 49 + 1 + 7 + 0 + 14 + 0 + 1 + 33 = 105 Probability of causing ADR = (105-8)/108 = 0.898

Although the aim is to produce a scoring system which provides ADR probability rather than a qualitative causality assessment, it is still important to make sure that the algorithm developed in this work is able to perform at least as well as

previously published algorithms in determining the causality of the suspected drug. However, a direct comparison is not possible since previous algorithms give categories of causality while the present algorithm gives only a probability value. Thus probability cut-off values need to be established to convert probability values to causality categories so that comparison with previous algorithms can be made. The probability cut-off values to differentiate between 'Definite' and 'Probable' ADR cases and between 'Probable' and 'Possible' ADR cases can be obtained by analyzing the probability values of the 'Definite' and 'Probable' ADR cases which have been identified in Tables 6.2 and 6.3. A probability cut-off value of 0.5 is used as a lower limit for 'Possible' ADR cases as it corresponds to a situation where there is no information available to implicate or exclude the drug of any possible causal effect.

Testing of the algorithm with this new scoring system was performed on 37 'Definite' ADR cases. These 37 cases were taken from a total pool of 468 ADR reports received by the Pharmacovigilance Unit in CDA during the period of September 2002 and March 2003. As mentioned in the previous chapter, this unit is the national body in Singapore managing ADR monitoring. The ADR cases were classified as 'Definite' cases based on retrospective inspection of all the ADR reports by experts from CDA. These cases were classical ones which displayed positive temporal effects, and they were known adverse effects of the offending drugs involved. This test would enable a determination on how rigorous the new algorithm is in picking out 'Definite' ADRs resulted from the suspected drugs. Concurrently, seven other algorithms (namely, Naranjo,[58] Kramer,[60] Karch,[59] Jones,[61] Bégaud,[62] ADRAC's guidelines[107] and WHO-UMC causality assessment[106]) were applied to these 37 'Definite' ADR cases to help assess how the new algorithm compare to these

existing ones in terms of percentage accuracy in picking out these similar 'Definite' cases.

6.2.3 Developing of appendix for existing algorithm

An appendix is included in the algorithm to help increase inter-rater agreement. This appendix aims to clarify the meaning of the criteria so that the amount of ambiguity when applying the algorithm will be very much reduced. To test the effectiveness of this appendix, 3 evaluators (all qualified pharmacists with experience in clinical settings) were asked to apply the algorithm to evaluate 50 randomly selected ADR reports, first without the appendix and then re-evaluated the same cases 3 months later with the appendix. This three-month lag was to ensure that the evaluators have forgotten their previous experience with the cases.

For each rater, the percentage difference for each criterion between the absence and presence of the appendix was calculated. A high percentage difference would support that the appendix did create an impact in the way the rater graded the criterion. However, we have to check whether this difference translates to an actual increase in the inter-rater agreement or have no impact on it. This inter-rater agreement will be tested using Kappa statistics using SPSS Version 12.0.[114]

To test the content validity of our algorithm, we carried out a sensitivity and specificity analysis. A similar analysis was performed using the guidelines adopted by ADRAC. These analyses would allow a comparison of performance between our algorithm and an existing algorithm.

6.3 Results

The optimum scores for each of the possible answers for the 8 criteria derived for the algorithm are shown in Table 6.5. Probability cut-off values of 0.75 and 0.63 were found to be differentiating between ‘Definite’ and ‘Probable’ ADR cases and between ‘Probable’ and ‘Possible’ ADR cases respectively. These probability cut-off values correspond to total scores of 89 and 76 respectively. The probability cut-off value for classifying ‘Possible’ and ‘Unlikely’ ADR cases was fixed at 0.5 and this correspond to a total score of 62.

The results obtained from the 4 different cases (Table 6.6) showed that this new scoring system is able to differentiate the ADR probabilities based on the information provided in standard ADR reporting forms. A probability of 0.231 in Case 1 showed that the adverse reaction presented in the patient presented is most likely not to be due to the drug thought to be involved. On the other hand, a probability score of 0.898 in Case 4 showed that there is very high likelihood that rofecoxib is the offending agent which resulted in the episodes of thrombocytopenia in the patient.

When this new version of the algorithm was applied to the 468 ADR reports from CDA, of which 37 reports had ‘Definite’ causality, 83.8% of the 37 cases were identified as ‘Definite’ by the algorithm, and the specificity of the new algorithm was 71.0%. The sensitivities and specificities of the other seven algorithms are shown in Table 6.7.

Table 6.7 Sensitivity and specificity comparison of various existing algorithms

Algorithms	Sensitivity (%)	Specificity (%)
New algorithm	83.78	71.00
Naranjo	16.22	98.84
Kramer	8.11	99.30
Karch	16.22	99.07
Jones	0	100.00
Bégaud	5.41	100.00
ADRAC	21.62	98.38
WHO-UMC	2.70	99.07

The newly added appendix for the algorithm is shown in Table 6.8. The results obtained from comparing the difference in individual criterion between the algorithm with and without the appendix can be seen in Table 6.9. Fifty cases were evaluated by each of the three rater and the results showed that Criterion 2, followed by 3, 4 and 5 displayed the most changes in descending order.

Table 6.8 Appendix for new algorithm

Criterion and part of criterion to note	Explanation
Criterion 1 "Reasonable time interval"	- Refers to time present for drug to act in body - If the reaction comes on only after 5 half lives of the drug has passed since time of drug withdrawal, then it is considered as no temporal effect.
Criterion 2 "Adverse reaction been associated with the suspected drug before"	- Based on official reference (BNF, Micromedex, USPDI, etc) - If *not sure* whether such a reaction has been reported, please use 'Do Not Know' instead of 'No'.
Criterion 3 "Could this adverse reaction be due to an existing clinical condition?"	- Existing clinical condition refers to condition which patient already has. Do not anticipate for possible clinical conditions which patients *may* have. - If *not sure* what clinical condition the patient has, please use 'Do Not Know' instead of 'No'.
Criterion 4 "Any over-dose of the suspected drug"	- 'Over-dose' here is inclusive of diminished elimination of the suspected drug as a result of drug interaction with another concomitant drug, or reduced renal or hepatic function.
Criterion 5 "If the drug was discontinued, did the adverse reaction improve within a reasonable period of time?"	- When the drug is discontinued and a specific antagonist/antidote is given concurrently, please select the option 'Do Not Know' - If the drug brought about irreversible changes (e.g., organ failure), please select the option 'Do Not Know' - "Within a reasonable period of time" indicates that the option 'No' should only be used after at least 5 half lives of the drug has passed.
Criterion 7 "Specific antagonist/antidote towards the suspected drug"	- E.g., Digibind for digoxin, Vitamin K for warfarin, acetylcysteine for paracetamol - *Not* referring to treatment given to relieve symptoms of ADR
Criteria 5 to 8	- Please use 'Not Applicable' when the mentioned actions were not taken

Table 6.9 Percentage differences in grading each criterion before and after the introduction of the appendix (n=50)

	Criteria in algorithm							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Rater 1	8%	24%	22%	14%	16%	10%	0%	0%
Rater 2	8%	28%	28%	14%	12%	8%	4%	0%
Rater 3	10%	24%	24%	14%	6%	8%	4%	0%
Average	8.7%	25.3%	24.7%	14.0%	11.3%	8.7%	2.7%	0.0%

Table 6.10 Inter-rater agreement of the algorithm

	Kappa values		
	Between rater 1 & 2	**Between rater 1 & 3**	**Between rater 2 & 3**
Before addition of appendix	0.617	0.660	0.483
After addition of appendix	0.965	0.898	0.931

The Kappa values obtained from the inter-rater studies are presented in Table 6.10. All the Kappa values of each inter-rater pair were significant at $p<0.001$. From the table, it shows that with the addition of an appendix to explain how to grade the various criteria for the algorithm, the range of Kappa values increased from 0.483 – 0.660 to 0.898 – 0.965.

6.4 Discussion

In this study, genetic algorithm was used to generate the scores for the algorithm which was developed in the previous chapter, with the resultant final scores being quantitative instead of qualitative. Genetic algorithm is used in this study because the total number of scoring systems that have to be explored in order to find one which fulfils all the different reference points is too large to be practically done. Artificial intelligence methods like genetic algorithm are able to search through the vast pool of scoring systems in a reasonable time by rapidly eliminating those scoring systems which are obviously unsuitable and concentrating the search efforts on those scoring systems which have the potential to fulfil the different reference points. When this new algorithm is applied to specific ADR cases, the evaluator is now able to determine the probability of the involvement the suspected drug and the resultant ADR. This feature would be very informative in clinical decision making when the physicians can have more concise estimate of the likelihood of a drug causing an ADR. Besides its clinical applicability, this new algorithm is especially useful for regulatory agencies, as well as of great value in drug companies when conducting clinical trials.

The contribution of our new algorithm to clinical risk management would be particularly pronounced in allowing more rapid signal detection for new drugs and for rare ADRs. Undeniably, pharmacovigilance units in countries with large number of ADR reports can perform signal selection by using statistical parameters in impact analysis which quantitatively compare combinations of drugs and adverse events against the background of the database.[115] A quantitative ADR algorithm like the one developed in this study, can be incorporated into the ‘Scoring for strengths and

weaknesses of the evidence' segment to further increase the robustness of the existing analysis.

As for pharmacovigilance units in countries with smaller population and hence smaller number of consolidated reports, the knowledge of the likelihood of any received ADR reports caused by a suspected drug would allow the regulatory agency to use this information to warn prescribers as appropriate. Whereas in clinical trials, the ability to detect definite ADRs in Phase II and Phase III trials would provide invaluable information in deciding whether to continue with the trials as well as issuing extra caution for continuing trials. Extrapolating this to post-marketing surveillance studies (Phase IV trials), the acquiring of a quantitative ADR signal to pick up rare but definite ADRs will help to alert the drug companies on the need of withdrawing the offending drugs from the market, or to put in extra cautionary labels regarding the use of the drugs.

Other points about the new algorithm worth discussing are its sensitivity and specificity, and its performance against other algorithm used. From the results, the congruency between this new version of the algorithm and that of expert opinion is 83.8%, about 60% higher than using the current CDA algorithm (adapted from guidelines used by ADRAC). Also comparing with the other established ADR algorithms (Table 6.7), the new version of the algorithm has the highest sensitivity of 83.8% and lowest specificity of 71.0%. Therefore, using the new algorithm will result in more cases with definite ADRs being classified correctly. However, the seven algorithms are more superior in weeding out the non-definite ADR cases due to their higher accuracies in assigning 'Not definite' to ADR cases that are indeed not caused

by the suspected drug. Hence, our algorithm takes on a more conservative stand of suspecting that there is definite drug causality involved. From the public health perspective, this would be a desirable feature if an ADR algorithm is viewed as a screening test. This would be congruent with the concept of "Sn-N-out" of using screening test in the clinical setting.

Other than adopting a quantitative scoring method, an appendix was also added to the new algorithm with the purpose of reducing any possible ambiguity when applying the algorithm and to further reduce inter-rater disagreement. Even though the algorithm has already provided a specific sequence of steps to ensure reproducible results, without this appendix to clarify potential ambiguity resulting from the questions, judgmental intermediates may occur in the sequence thus altering the end results. The results showed that 2 criteria (Criteria 4 and 5) had more than 10% change in their selected options ('Yes', 'No', 'Do Not Know', 'Not Applicable') between the absence and presence of the appendix, and another 2 criteria (Criteria 2 and 3) had more than 20% change. A Kappa analysis carried out for inter-rater agreement showed that the agreement between raters were better (0.898 – 0.965) with the presence of the appendix, indicating an improvement in clarity after the appendix was added in.

In conclusion, the refining of the scoring system to reflect a quantitative scale and the addition of an appendix have helped to make the previously developed algorithm (see Chapter 5) more sensitive, and reduced the variability when used by different users. These strengths will give this algorithm an extra advantage when used by clinicians, regulatory agencies or drug companies to generate alerting ADR signals.

Using a quantitative method of assessing causality will also mean that rare ADRs and new ADRs that have not been documented can more readily be detected since a quantitative score can tell more precisely the likelihood of ADR causality. Therefore, by using a quantitative approach, a simple and easy to use ADR algorithm which would contribute to clinical risk management was developed.

Chapter 7

A Systematic Approach of Identification and Classification of Adverse Drug Reactions: **A**lerts **B**ased on **A**DRs' **C**a**u**sality and **S**everity **(ABACUS)**

7.1 Introduction

Adverse drug reactions (ADRs) are an unfortunate but often inevitable drug related problem in pharmacotherapy. Hence, ADR reporting is a major initiative in improving drug safety at both the institutional and national level in many healthcare systems with, pharmacovigilance forming part of drug regulation in many jurisdiction.[35] As mentioned in previous chapters, spontaneous reporting of suspected adverse reactions to drugs is currently the backbone of such pharmacovigilance.[35] However, this is not the ideal method as spontaneous reporting often produces only circumstantial evidence, with uncertainties pertaining to the causal involvement of the drugs.[36] Further assessments, which include measuring frequency, identifying risk factors and explaining the mechanisms of the ADRs, are therefore needed in order to allow a more definite confirmation of causality.

As discussed previously, clinically speaking, the most important criterion for assessing ADRs is its causality, which is the likelihood of the suspected drug causing the ADR. Such differential assessment of ADRs can be achieved with the use of clinical judgments alone or in combination with algorithms.[66] Algorithms are a set of questionnaires that determine drug causation in the occurrence of an ADR by checking the temporal association between drug administration and the onset of the adverse drug event. The use of algorithms help to improve the reliability of assessments, decrease inter- and intra-rater disagreement,[58] and give a better guide in making complex clinical decisions than clinical judgment alone.[100] However, one of the major drawbacks is that most commonly used algorithms use a qualitative approach in assessing ADR causality. In the previous chapter, we reported the development of a simple ADR assessment algorithm with a quantitative scoring

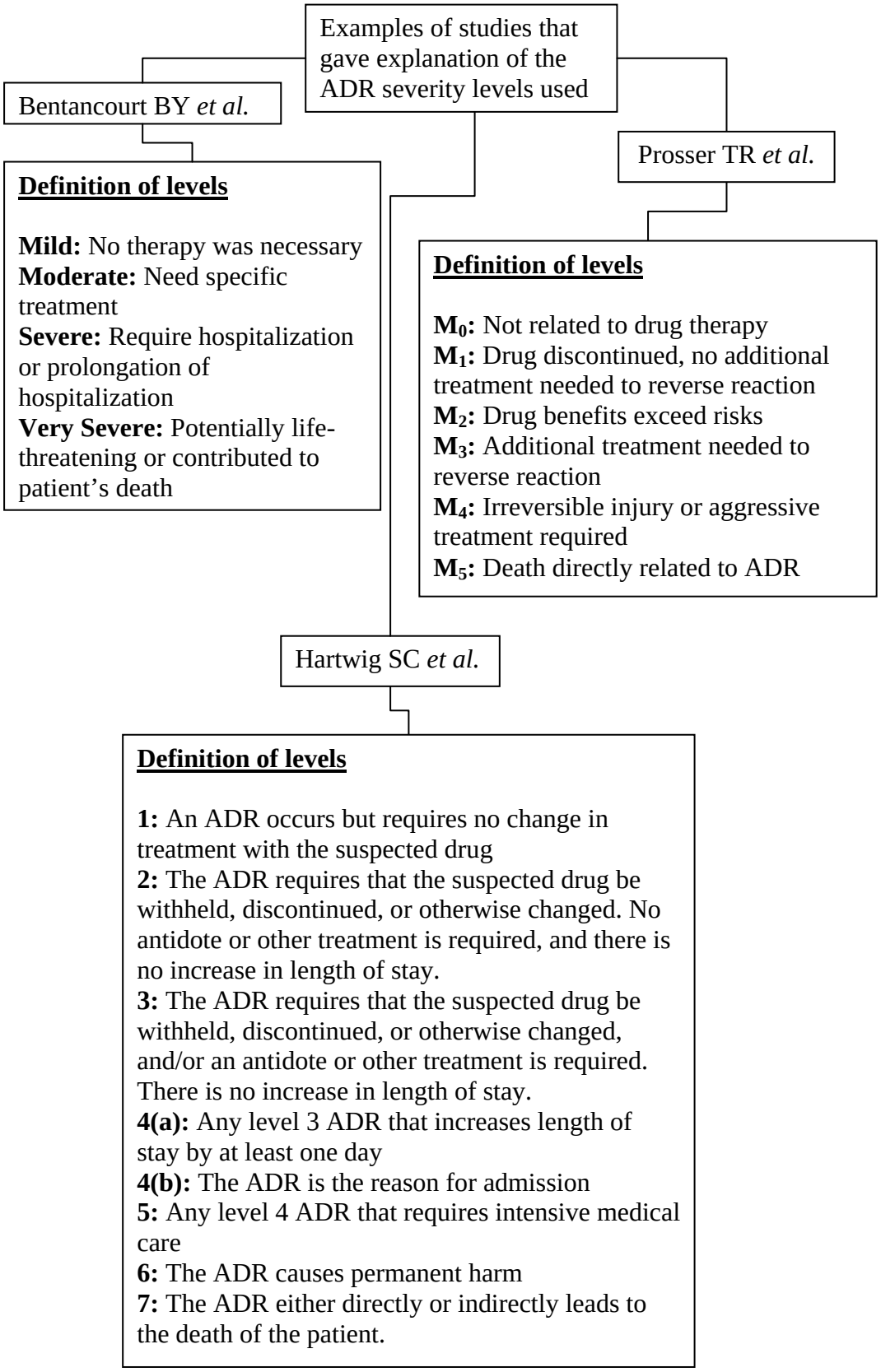
system based on the genetic algorithm, an artificial intelligence approach. The results from applying the algorithm showed that this algorithm could provide the decision maker with the likelihood of a reported ADR being caused by the suspected drug, thus allowing a more informed and accurate differentiation between signals and noises. Additionally, the new algorithm has demonstrated good sensitivity as a screening test for suspected ADRs.

Regardless of whether an ADR algorithm is using the conventional qualitative approach or the quantitative approach as provided by our algorithm reported in previous chapters, it can only provide information of the possible causality (or even likelihood) of a drug in the occurrence of an ADR. However, information on how severe the ADR may be is lacking from the assessment when using such algorithms. In order to give the most appropriate response to any reported ADR, it is imperative that both the likelihood of causality as well as the severity of the ADR be known and correlated. For example, it would still be appropriate to initiate the "alert" response when an ADR with higher level of "severity" but low to moderate probability of causality is encountered.

This raises the issue of the definition of severity for ADR reporting. Based on the definitions provided by World Health Organisation – Uppsala Monitoring Centre (WHO-UMC), the term 'severe' is used to describe the intensity of a specific event. That is, if the event is mild, moderate or severe.[116] This is unlike seriousness, which is based on either outcome or action criteria, and serves as a guide for defining regulatory reporting obligations.[116] From literature search, several published studies related to ADR detection, reporting and prevention also mentioned that ADR severity

were being investigated.[117-120] Unfortunately, different researchers have their own method of defining the various levels of severity. Some researchers do mention how they define the various levels (Figure 7.1), whereas some don't. The literatures cited in Figure 7.1 are definitely not exhaustive; there are many other publications which used their own definition when assessing the severity levels of adverse reactions or side effects from pharmacotherapy.[121] In 2001, Loke *et al.* did a literature review to study details on the severity of the reported ADRs.[121] For ADRs with severity reported, they investigated how these severity scales were defined. From their search, it was found that the severity levels used in many studies were not defined. The severity scales used were broadly classified as 'Mild', 'Moderate' and 'Severe' ADRs. So far, we only came across one study which used a scoring system to determine the severity level of the ADRs.[122] In that study, Dormann *et al.* used a questionnaire with 11 criteria and each criterion was assigned a different weightage to assess ADR severity. Based on the total score derived from the questionnaire, different intensities of severity were then assigned.

Figure 7.1 Some severity assessments which define the severity levels used



From these published severity assessments, the obvious and logical trend is that all of the studies attempted to classify the ADR severities into scales of increasing intensity. However, the various assessments had different number of intensity levels - Dormann *et al.* had 3,[122] Bentancourt BY *et al.* had 4,[118] Prosser TR *et al.* had 6,[119] and Hartwig SC *et al.* had 8 levels.[123] Nevertheless, these severity assessments of ADRs will not be useful if they were used independently. As previously mentioned, an ADR of high severity is not meaningful if the cause of the ADR is not known. Hence, there is a need for both drug causality and ADR severity to be determined concurrently. With the knowledge of both causality and severity of the suspected ADR, it would serve to aid regulatory authorities in making decisions on whether the drug causing the ADR should be re-evaluated for the suitability of its indicated use, or should there be special cautionary labels which the manufacturers need to put in for the particular drug. For the clinicians, this information can assist in judging the risk-benefit ratio of using the drugs involved in ADRs to treat a condition, or whether an alternative drug should be used. In the case of drug trials, this knowledge would facilitate the investigators or the sponsor companies in deciding if there is a need to break the code for a blinded-study, to increase trial monitoring or even to halt the conduction of the trial.

In this chapter, an attempt to develop a severity assessment scale that is straightforward to use and accurate in presenting the severity of ADRs is reported. This severity assessment scale would be incorporated into the previously reported ADR causality assessment scale (see Chapter 6). The fundamental approach is to combine both ADR causality and severity analysis to give an overall assessment which is presented as various "alert" zones. This approach is to increase the utilitarian

factor of this combined causality and severity assessment in helping the user determine the appropriate course of action to be taken, following the particular ADR detection.

Once the combined assessment is developed, an online version of the assessment to help users with the calculation of scores and assignment of alert zones will be made available.

7.2 Methods

7.2.1 Approach in Designing the Severity Scoring System

In order to construct a severity assessment scale, the first step was to develop a number of categories with increasing intensities of severity. After that, a particular score was given to the different levels of severity, with the lowest for the level with the least severity and ascend at regular interval to reach a highest score for a lethal ADR. This assigned score was an arbitrary number and its absolute value is not important. The importance lied with the relative scale between the different levels of severity. That is, a higher score would represent a more intense severity for the adverse reaction experienced.

To give more meaning and function to the severity scores, they were combined with the scores derived from an ADR causality probability algorithm which was reported in previous chapter (see Chapter 6) to form a combined scoring and assessment system. This combined scoring system from both the causality and severity assessment scales would be translated into three different colour zones – green, amber, and red.

Green zone would signify that the ADR is mild or most probably not even due to the suspected drug. There is not need to place too much emphasis or resources into an ADR that is classified under the green zone. Amber refers to an ADR that has a higher level of severity and coupled with the fact that it is of higher probable drug causality, medical personnel or regulatory authorities need to continue to monitor the use of the offending drug. For the red alert zone, the ADR is of a severity that is high

enough for the authorities to stop using the offending drug, or to completely withdraw the use of the drug.

7.2.2 Rules for Assigning Severity Scores

In order to produce the combined system, some rules for different scenarios had to be determined. These rules should be universally accepted as logical to assign different ADR cases with varying causality and severity scores into one of the three colour zones.

For Rule 1, when an ADR is determined as 'Definite' based on the previous probability scoring system that was reported in the earlier chapter (See Table 7.2, Part 1), and if the patient requires intensive care, experience irreversible harm or death, such an ADR case will immediately be admitted into the red alert zone.

Rule 2 will denote that if ADR is of 'Definite' causality but the patient only need out-patient attention or require in-patient care (but excluding intensive care), these cases will be classified under the amber alert zone. These "amber alert" cases would require further observation to determine how should the offending drug be dealt with. This allowance was made for 'Definite' causalities with requirement for both in-patient and out-patient care to address the fact that patients with the same ADR may present with symptoms of different severity, and physicians may react to them in different manner where the decision of keeping them warded is concerned.

For Rule 3, 'Definite' ADR causalities that do not require any form of intervention will be deemed to fit into the green alert zone. With the above 3 rules, all 'Definite' ADR cases can be classified into the three zones.

For 'Probable' and 'Possible' causality cases, they will be considered as under the red alert zones if they give rise to irreversible harm or fatality (Rule 4).

If the 'Probable' and 'Possible' cases require intensive care, then they will be admitted into the amber alert zone (Rule 5). Though these ADRs are severe enough to require intensive care, the fact that there is doubt if the ADR is caused by the suspected drug once again puts them into the "observe and manage" category.

'Unlikely' ADR causality cases that result in irreversible harm to the patients will be classified under the amber alert zone for further observation to evaluate if there is a more intimate causality relationship between the drug and the ADR (Rule 6).

However, if the ADR is 'Unlikely' and if patient does not suffer from irreversible harm or fatality, then this will be classified into the green alert zone (Rule 7). . It is difficult to determine logically the appropriate zone alert for 'Probable' or 'Possible' ADRs with patients requiring only out-patient or in-patient treatment. So, the final zone alert for these cases will be determined based on an analysis of all the different rules and not on direct logic. Thus, with Rules 6 and 7, all 'Unlikely' ADR cases can be classified into one of the three alert zones.

7.2.3 Constructing the Border between the Different Alert Zones

A chart which summarized the above rules for the various scenarios would then be developed. 200 x 6 = 1200 data points were generated by varying the causality scores from 0 to 1, at intervals of 0.005 and by varying through the six severity level. The data points were then classified into one of the three zones using the seven rules shown above. Data points that are not classifiable based on the seven rules are removed. The remaining points are plotted on a chart with severity scores on the y axis and causality scores on the x axis. Each point is coloured based on its zone alert classification.

Since some of the original 1200 data points are unclassifiable and thus removed, there will be gaps in the chart. These gaps are filled by extrapolating from those data points which can be classified. This chart will provide a visual aid to users in determining the appropriate alert zone when the severity score and causality score is known. This is to help the user in determining the alert zones after they have determined the drug causality and severity of the ADRs. It will also help to classify those cases which cannot be classified through logic.

A final score is then calculated from the severity score and causality score by taking the average of the two scores. Using this final score, different priorities can be assigned to different cases that are in the same alert zone. For example if two cases are in the amber zone and case A has a final score of 0.471 and case B has a score of 0.571, then case B should receive more attention than case A since it is nearer to the red zone than case A.

7.2.4 Development of online version of new algorithm

At the same time, an online version of this combined scoring and assessment system was developed. The objective of this is to provide the user with an easily accessible and simple to use tool for determining the alert zone of ADR cases. The online version also provides a checking mechanism to detect any inconsistencies in the ADR report.

7.2.5 Testing of the New Algorithm

With the newly merged causality and severity scoring system, 10 ADR cases with varying drug causality were used to illustrate how this assessment system can be used. The ADR cases were taken from ADR reports received by the Pharmacovigilance Unit in the Centre for Drug Administration (CDA), Health Sciences Authority, Singapore, during the period of January 2002 and March 2003. As previously reported, this unit is the national body in Singapore handling ADR monitoring.

7.3 Results

With reference to existing severity scales used by various researchers,[56, 122, 123] an assessment scale with 6 different severity levels, denoted as S1 to S6 (Table 7.1) was developed. These levels are meant to show increasing intensities of the ADRs since the levels from S1 to S6 demonstrates ascending requirement for more dire measures to manage the ADR. The arbitrary scores assigned to the different levels can be seen in Part 2 of Table 7.2. The scores start from 0 for the severity with the mildest intensity and increase in steps of 0.2 for each increasing level of severity. When the ADR is fatal, the severity score will be the highest at 1.

Table 7.1 Our new severity assessment scale

Severity category	Descriptions
S1	Offending drug may or may not be withheld, no treatment required
S2	Offending drug to be withheld, out-patient treatment is required
S3	Offending drug to be withheld, in-patient treatment is required
S4	Intensive care is required but patient does not suffer any disability
S5	Patient suffer irreversible harm (including physical disability)
S6	Patient died as a result of the reaction (either directly or indirectly)

This severity assessment scale will be used together with the quantitative algorithm for ADR causality which was developed earlier (see Chapter 6). The combined scoring system can be seen in Table 7.2. Part 1 of Table 7.2 enables the algorithm to identify the probability that a particular ADR is indeed caused by the suspected drug. Part 2 of this table on the other hand provides the newly developed severity scale with the corresponding severity score which was mentioned earlier.

To obtain the combined score for both causality and severity, the average of the two scores attained by running Part 1 and Part 2 through a given ADR case or report was used. The formula for calculation of the final score is provided in Part 3 of Table 7.2. The chart in Part 4 is to help determine the alert zone for the ADR. The vertical axis of the chart denotes the different severity levels, whereas the horizontal axis represents the causality probability. With both the causality probability value, calculated from Part 1 of Table 7.2, and the corresponding severity level, the user will be able to locate the intersection point on the chart and determine the alert zone which the ADR will be assigned.

Table 7.2 Combined ADR causality and severity scoring system

	Part 1: ADR Section (Appendix A should be used concurrently)				
		Yes	**No**	**Do Not Know**	**Not Applicable**
1	Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?	49	0	36	-
2	Has the adverse reaction been associated with the suspected drug before?	1	0	0	-
3	Could this adverse reaction be due to an existing clinical condition?	0	7	1	-
4	Is there any over-dose of the suspected drug?	2	0	0	-
5	If the drug was discontinued, did the adverse reaction improve within a reasonable period of time?	14	0	7	7
6	If the drug was NOT discontinued, did the reaction resolved on its own?	0	1	0	0
7	Did the reaction improve when specific antagonist/antidote towards the suspected drug was administered?	17	0	1	1
8	Did the adverse reaction recur when the suspected drug was discontinued and re-administered?	33	0	17	17
	Circle the relevant option for each question and add up the score for Part 1				
	Total score, T:				
	Probability, P = (T - 8) / 108:				

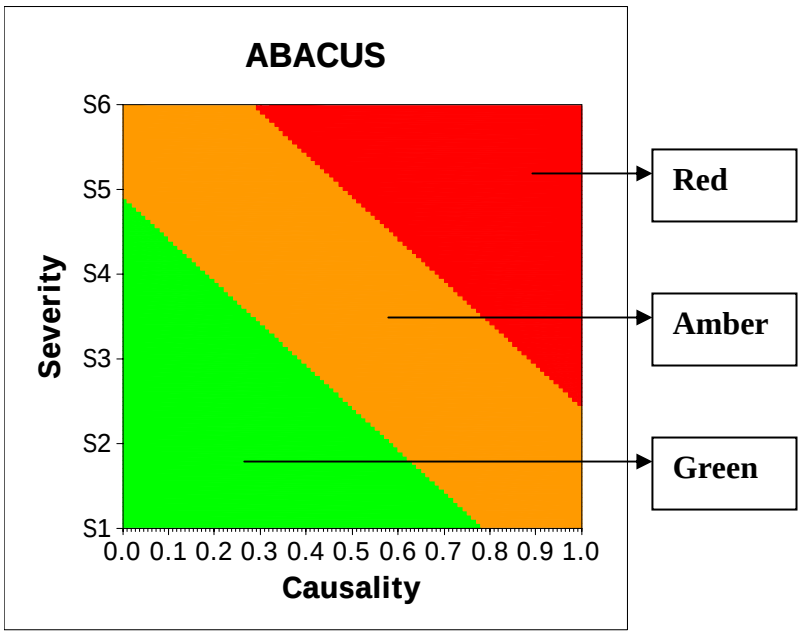
Causality categories: Definite: $0.75 \leq P \leq 1$; Probable: $0.63 \leq P < 0.75$; Possible: $0.50 \leq P < 0.63$; Unlikely: $0 \leq P < 0.50$

Part 2: Severity Section		
Severity category	**Description**	**Score**
S1	Offending drug may or may not be withheld, no treatment required	0.0
S2	Offending drug to be withheld, out-patient treatment is required	0.2
S3	Offending drug to be withheld, in-patient treatment is required	0.4
S4	Intensive care is required but patient does not suffer any disability	0.6
S5	Patient suffer irreversible harm (including physical disability)	0.8
S6	Patient died as a result of the reaction (either directly or indirectly)	1.0

PART 3: FORMULA FOR FINAL SCORE, F

Average score of Part 1 and Part 2:
(P + S) / 2 = F

Part 4: Chart to help determine alert zone

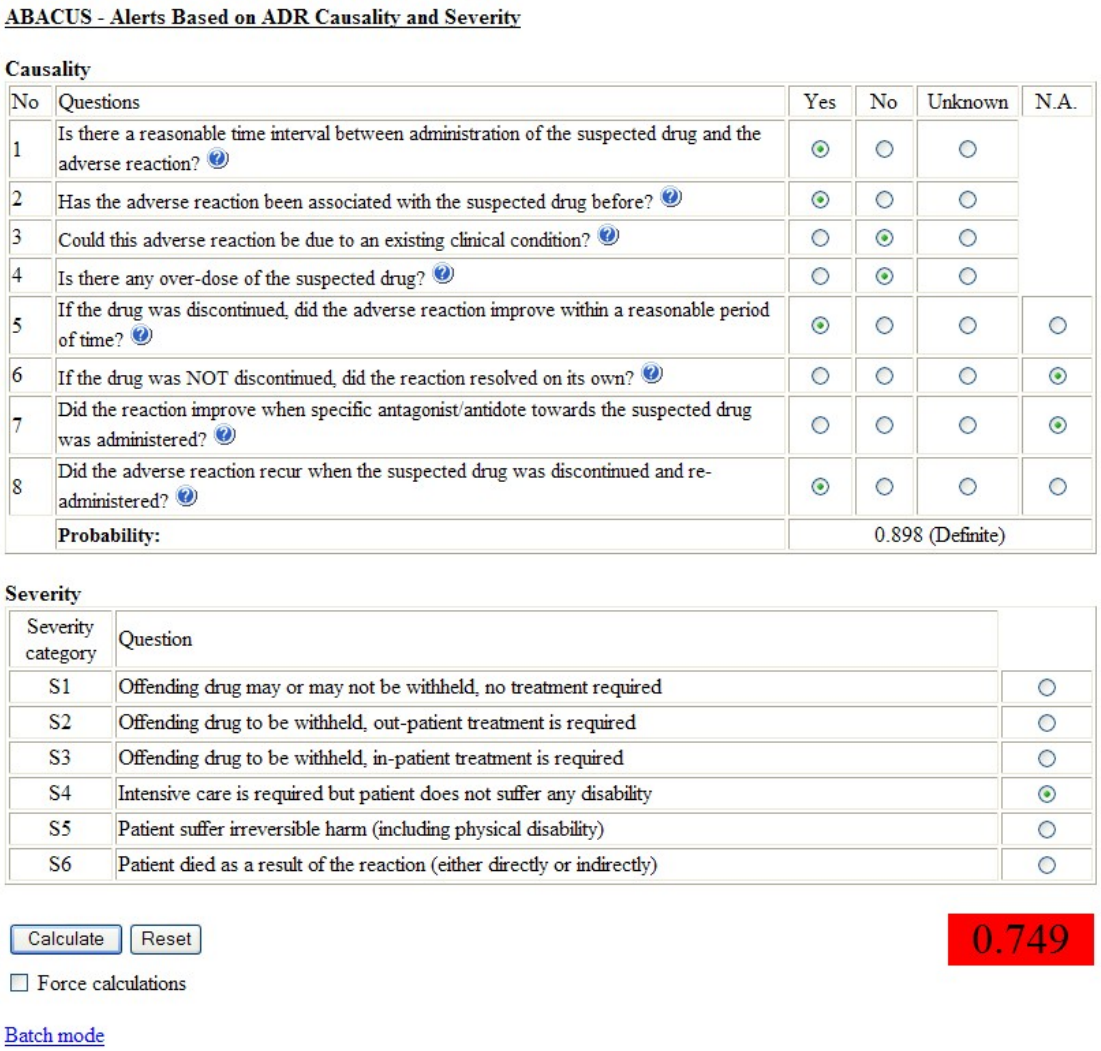


Appendix A

Criterion and part of criterion to note	Explanation
Criterion 1 "Reasonable time interval"	- Refers to time present for drug to act in body - If the reaction comes on only after 5 half lives of the drug has passed since time of drug withdrawal, then it is considered as no temporal effect.
Criterion 2 "Adverse reaction been associated with the suspected drug before"	- Based on official reference (BNF, Micromedex, USPDI, etc) - If *not sure* whether such a reaction has been reported, please use 'Do Not Know' instead of 'No'.
Criterion 3 "Could this adverse reaction be due to an existing clinical condition?"	- Existing clinical condition refers to condition which patient already has. Do not anticipate for possible clinical conditions which patients *may* have. - If *not sure* what clinical condition the patient has, please use 'Do Not Know' instead of 'No'.
Criterion 4 "Any over-dose of the suspected drug"	- 'Over-dose' here is inclusive of diminished elimination of the suspected drug as a result of drug interaction with another concomitant drug, or reduced renal or hepatic function.
Criterion 5 "If the drug was discontinued, did the adverse reaction improve within a reasonable period of time?"	- When the drug is discontinued and a specific antagonist/antidote is given concurrently, please select the option 'Do Not Know' - If the drug brought about irreversible changes (e.g., organ failure), please select the option 'Do Not Know' - "Within a reasonable period of time" indicates that the option 'No' should only be used after at least 5 half lives of the drug has passed.
Criterion 7 "Specific antagonist/antidote towards the suspected drug"	- E.g., Digibind for digoxin, Vitamin K for warfarin, acetylcysteine for paracetamol - *Not* referring to treatment given to relieve symptoms of ADR
Criteria 5 to 8	- Please use 'Not Applicable' when the mentioned actions were not taken

The online version of the combined scoring system can be found at http://staff.science.nus.edu.sg/~phalisc/abacus/ (Figure 7.2). The usage of the online scoring system is very simple. The user will input the options ('Yes', 'No', 'Do not know', 'Not applicable') to the various criteria for individual ADR reports by clicking the relevant radio buttons. At the same time, the user will have to input the severity level of the ADR. On clicking the 'Calculate' button, the probability of the ADR causality of the suspected drug will be calculated. Simultaneously, the alert zone of the ADR will be determined and presented in a box which the ADR causality will be presented. The background of this box will reflect a corresponding 'Green', 'Amber' or 'Red' colour. The online assessment system also has a batch job option. The user can input the options to the various criteria for several ADR reports on a Microsoft Excel spreadsheet, and then copy and paste these data onto the text box provided on the webpage. The alert zone for each of these ADR reports will then be given to the user on another text box.

Figure 7.2 Online version of combined scoring system



ABACUS - Alerts Based on ADR Causality and Severity

Causality

No	Questions	Yes	No	Unknown	N.A.
1	Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?	◉	○	○	
2	Has the adverse reaction been associated with the suspected drug before?	◉	○	○	
3	Could this adverse reaction be due to an existing clinical condition?	○	◉	○	
4	Is there any over-dose of the suspected drug?	○	◉	○	
5	If the drug was discontinued, did the adverse reaction improve within a reasonable period of time?	◉	○	○	○
6	If the drug was NOT discontinued, did the reaction resolved on its own?	○	○	○	◉
7	Did the reaction improve when specific antagonist/antidote towards the suspected drug was administered?	○	○	○	◉
8	Did the adverse reaction recur when the suspected drug was discontinued and re-administered?	◉	○	○	○
	Probability:	0.898 (Definite)			

Severity

Severity category	Question	
S1	Offending drug may or may not be withheld, no treatment required	○
S2	Offending drug to be withheld, out-patient treatment is required	○
S3	Offending drug to be withheld, in-patient treatment is required	○
S4	Intensive care is required but patient does not suffer any disability	◉
S5	Patient suffer irreversible harm (including physical disability)	○
S6	Patient died as a result of the reaction (either directly or indirectly)	○

Calculate Reset 0.749

☐ Force calculations

Batch mode

The case description of the 10 chosen ADR cases used for illustrating the application of the combined causality and severity scoring system are presented in Tables 7.3 and 7.4. The figures 'Probability of Causality' column were determined from Part 1 of Table 7.2.

Table 7.3 Actual cases to illustrate use of combined causality and severity scoring system (first part)

Case	Case description	Probability of Causality	Severity Level	Total Score and Alert Zone
1	A patient developed muscle ache whilst taking pravastatin 20mg every night. The muscle ache went away when the pravastatin was withdrawn.	0.574 (Possible)	S1	0.287 Green
2	A 45 year old patient presented with light-headedness and raised creatine kinase and aldolase after a single dose of sildenafil citrate. The patient was hospitalized and hydrated. He recovered eventually.	0.620 (Possible)	S3	0.51 Amber
3	A male patient was on a complementary medicine which contained ephedrine for many months before he presented with vomiting, increased drowsiness and jaundice. A diagnosis for acute liver failure was made by the attending physician.	0.620 (Possible)	S5	0.710 Red
4	Patient with no known drug allergy developed pruritus after taking clarithromycin 1gm per day for 8 days.	0.639 (Probable)	S1	0.320 Green
5	Patient developed oedema of the face after ingesting a single dose of 40mg omeprazole for gastroesophageal reflux disease. Patient recovered 2 days after discontinuing omeprazole.	0.741 (Probable)	S2	0.471 Amber

Table 7.4 Actual cases to illustrate use of combined causality and severity scoring system (second part)

Case	Case description	Probability of Causality	Severity Level	Total Score and Alert Zone
6	Patient developed generalized erythematous, pruritic rash, as well as shortness of breath and involuntary irregular jerking of upper and lower limbs after receiving 100mg of intravenous paclitaxel for ovarian carcinoma. Patient recovered after drug was removed.	0.741 (Probable)	S3	0.571 Amber
7	Patient developed bronchospasm and collapsed airways upon receiving intravenous Iohexol for urography. He was intubated and ventilated in the intensive care unit and treated with adrenaline. Patient recovered.	0.741 (Probable)	S4	0.671 Red
8	Patient developed a mild, transient rash around the face and arms, with some slight pruritus upon receiving 120ml of intravenous Ioparmro for CT scan of the abdomen. Patient recovered within a few hours.	0.750 (Definite)	S1	0.375 Green
9	A 51 year old male patient presented with an intense urge to fall asleep without warning within 1 – 2 hours after consuming 100mg of piribedil. This symptom resolved when piribedil was withdrawn but recurred upon re-challenge.	0.843 (Definite)	S1	0.422 Amber
10	Patient presented with low platelet count after taking rofecoxib 25mg daily for 6 months to manage her osteoarthritic knee. Her platelet count returned to normal following a de-challenge but decreased again when rofecoxib therapy was re-introduced. Therapy with rofecoxib was subsequently discontinued.	0.898 (Definite)	S4	0.749 Red

7.4 Discussion

The main purpose for this study is to develop a severity assessment scale to compare the intensities of severity of various adverse drug reactions. This scale was then incorporated with a previously developed quantitative ADR causality scale (see Chapter 6) to give a combined ADR causality and severity scoring system. The idea of such a combined scoring system is to give more practical value to the results obtained compared to the individual causality and severity scores.

For the severity assessment scale, 6 different severity levels which are distinctly different from each other were used. This is done with the intention of providing the user with well-defined severity categories so that there will be no ambiguity in interpreting the severity of the reactions.

Each level was represented with a code (S1, S2, S3, S4, S5 and S6) and a corresponding score. This is to minimize confusion with terms like 'Mild', 'Moderate', 'Severe' since they are subjective and very much relative to a particular starting point. These severity levels and scores may not be of much significance on their own, but when coupled with the probability score from the ADR causality algorithm, a specific level of alert can be tagged onto the drug suspected to cause the ADR. The quantitative scoring system adopted can also aid in triage where there is a need to prioritize cases for management. This is evident in the cases which are presented in Tables 7.3 and 7.4.

From Tables 7.3 and 7.4, based on the cases and the resultant alert zones, it can be observed that although drug causality were the same, dissimilarities in severity

levels resulted in the cases being assigned to different alert zones. Hence, even though the cases have the same causality, they will still warrant different levels of attention. This can be seen in case 2 and case 3. They share exactly the same probability score for ADR causality but because case 3 has a higher level of severity since it required intensive care treatment compared to case 2 which only required in-patient attention, case 3 is classified into the red zone compared to case 2 which goes into the amber zone.

The combined scoring system which was developed can also be used quantitatively. This can be exemplified in case 5 and case 6. Even though both are in the amber zone, a higher score for case 6 compared to case 5 indicates that the drug involved in case 6 should receive a higher priority for further investigation or other actions since it is a step closer to the red alert zone compared to case 5.

Another important point that can be demonstrated using the cases assessed is that a 'Definite' ADR may not be as severe as a 'Possible' or 'Probable' ADR (See case 3, 7 and 8 in Tables 7.3 and 7.4). Hence, in a situation when there is a need to prioritize management of cases, those in the red alert zones should be dealt with first despite it having a lower causality score than another ADR in the green or amber zones.

Hence, with this combined ADR causality and severity scoring system, important information like whether a drug is likely to cause an adverse reaction and whether it is dangerous enough to be withheld or necessitate further investigation on its potential dangers can be obtained. This will be useful from medical practice and

clinical trials points of view, as well as from drug-regulation aspect. For the clinicians, this scoring system serves as a fast and convenient way of identifying true and hazardous ADRs. In the case of clinical trials, when the adverse effects of a drug are not yet well established, using such a scoring system can bring about more efficient management of the possible ADRs and prompt decisions can be made with regard to discontinue the trials or in less drastic measures, to just provide additional precautionary labels for the drug involved. Where drug regulatory authorities are concerned, having such convenient method of ADR identification and classification can be a preliminary step leading to further inquiry or dissemination of nation-wide alerts. This will be especially useful in small pharmacovigilance centres that do not have access to vast amount of ADR data and hence more difficult to produce signal alerts from ADR reporting data.

The online version of the combined scoring and assessment system has some features incorporated into it to aid in its user-friendliness. A 'Help' icon is provided at the end of each criterion. The 'Help' icons provide information that is present in the appendix section of the ADR causality portion. The user will just have to roll the cursor over the icon to get a dialog box giving relevant instructions to reduce possible ambiguities to the question to be answered. Another added feature in this online version is its ability to detect any inconsistencies in the ADR report. For example, if the option for Question 5: "If the drug was discontinued, did the adverse reaction improve within a reasonable period of time?" is chosen as 'Yes', and that for Question 6: "If the drug was NOT discontinued, did the reaction resolved on its own?" is chosen as 'Yes' as well, the algorithm is programmed to highlight both options and inform the user that there are inconsistencies in the ADR report. The user

can roll the cursor over the highlighted options to get a dialog box giving the reasons for the suspected inconsistencies and instructions for correcting the inconsistencies.

7.5 Conclusion

In conclusion, a combined ADR causality and severity assessment system has been developed, including an online edition. Such a system can be utilized to help a clinician, principle investigator or even regulatory authority to determine the course of action to be taken, following a particular ADR detection. With its quantitative nature, the scoring system can also aid clinicians in their case management when there is limited time and resources. With further fine tuning and more extensive testing, it would provide a handy tool for healthcare deliverers, drug regulators and clinical trial coordinators in risk management.

Chapter 8

Overall Conclusion

8.1 Major findings

In this finale chapter, a summary of the major findings which were presented in the past chapters will be given.

First, a recap of the research questions to show the original intent of the project:

1. What is the current DRP situation in Singapore like? Is it different from the situation as reported in overseas studies?
2. Will the patients being managed under the current system in the hospital benefit from the presence of physician-pharmacist review teams? Will DRPs and medication costs be reduced as a result of the presence of such a team? What would be the impact of such a team on the clinical and economic outcomes among in-patients (who supposedly would be more susceptible to DRPs due to the more severe nature of their medical conditions and hence would also consume more valuable healthcare resources)?
3. Can the inadequacies present in some currently available ADR algorithms be addressed and improved upon? How can an ADR algorithm be further harnessed and develop it into a functional tool for detecting and assessing ADRs?

In essence, the main objective of the project was to evaluate whether pharmacists can contribute significantly with a review of managing risk among patients within the current healthcare system in Singapore.

In order to answer the aforementioned questions, the authors have performed a study that attempted to establish the current situation as to the level of risk that the patients were exposed to in the healthcare environment, as well as to ascertain the contributory factors for the increased risk. This was followed by an attempt to evaluate the impact, both clinically and economically, on increased and systematic involvement by pharmacists in reducing these risks. After evaluating the impact of the system, the authors also proceeded to develop a quantitative tool in assessing ADR with the view that risk of DRPs, namely ADR could be greatly reduced with a better tool in an improved healthcare environment.

These studies yielded the following findings:

1. Chapter 2 of this thesis was intended to be a baseline study of the current situation in Singapore. The results obtained from this initial baseline study of risk assessment suggest that the incidence of drug therapy related admission to hospital in Singapore is comparable to that occurring in other developed countries. Of the major causes of drug-related hospital admissions, non-compliance was the most common cause of DRP, followed by ADRs.

   More importantly, all the identified ADRs were found to be avoidable if the patients were monitored closely. This finding that the DRPs were mainly avoidable provided a basis to derive suitable strategies to lower the incidence of drug therapy related hospital admissions. Although the results obtained did not demonstrate any statistically significant difference in DRP-associated hospital admission between geriatrics and younger

patients, probably due to the small sample size of the study, there is indeed an observed increased trend among geriatric patients which would be of clinical importance.

2. Once again, the next study which was reported and detailed in Chapter 3 investigated the DRPs in local hospitalized patients, so by and large, this was another risk assessment study in the local context. The results from this study established that the situation of drug therapy related problems in the group of patients receiving polypharmacy is again comparable to that occurring in other developed countries. One important interpretation of this would be that although the problem of DRP has been studied and reported for the past twenty years, lessons and experiences from these studies and different countries have not exactly been translated into effective management of these problems. With regards to risk factors identified, results from the study 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 the case of the study, neither older nor female patients have been reported as predictor of increased risk of developing DRP. However, this observation may be confounded by the inclusion criteria imposed by the study design. Nevertheless, the results from the study did show that the drugs causing DRPs locally are similar to those in overseas studies.[77, 90] With this finding, healthcare professionals could at least pay more attention in monitoring patients prescribed these drugs.

Based on these abovementioned findings, the researchers would advocate applying the 20/80 principle in business management into clinical risk management. By identifying and properly managing the small percentage of patients with high risks for developing DRPs and those prescribed drugs commonly associated with DRPs, strategies can be created to minimize or prevent most of these DRPs. It is believed that with such an approach in resource optimization, the rampaging problem of DRPs can be at least dampened.

3. The next study carried out in this thesis as reported in Chapter 4 was to evaluate whether the involvement of a pharmacist as a regular member in clinical ward round would be a cost-effective strategy in risk management under the current healthcare system. Upon investigating the impact of the pharmacist's participation in a physician-pharmacist review team, the study showed that although the average length of stay in the group with a pharmacist in the patient care team was not significantly shorter than the group without a pharmacist, other benefits were reaped from the presence of a pharmacist. With the presence of a pharmacist, more drug related problems were detected and these problems were therefore promptly averted. The total drug cost savings during the 4-month study period when there was a pharmacist on board such a primary patient care team was S$14,036.40 and the calculated cost-benefit ratio of such an arrangement was 5.84. On top of this positive ratio, a net annual return of S$42,109.20 in investing in a pharmacist to perform such monitoring tasks seems to substantiate the cost-effectiveness for the hospital administrators to

endorse the inclusion of a pharmacist to provide such pharmaceutical care services. The total hospital charge savings during the 4-month period on the other hand was also substantially high at S$66,373.20, and the cost-benefit ratio from this is 27.66. The benefits to the patients would even be much greater if the impact on quality in life caused by the potential DRPs were taken into consideration.

However, the finding from the study also demonstrated that under the current healthcare structure at the public institutes, the pharmacists are too over-burdened with the role and function of dispensing and distribution of medicine, and would not be able to have the time to perform other functions in a persistent and regular manner.

4. In Chapter 5 of the thesis, after evaluating the impact on risk management by involving a pharmacist as a regular member of clinical ward round, the authors proceeded to evaluate whether the currently available tools in assessing ADR need improvement so that the pharmacist in the team would be better equipped to deal with the demands of their new role. The rationale for the study was based on the finding from the baseline study (as presented in Chapter 2) that ADR was one of the most common cause of hospital admissions and most of the ADRs were avoidable. Therefore, a simple and reliable ADR assessment algorithm would be a handy tool for the pharmacist as a regular member of the clinical ward round team.

By evaluating the advantages and disadvantages of several established algorithms for assigning ADR causality, a simple algorithm that provides ease of use and requires no extra data collection than those routinely collected in most ADR reporting forms was developed. In terms of performance, the new and shorter algorithm can achieve similar result as compared with a much more comprehensive algorithm. In addition, the new algorithm adopts a lower threshold in assigning “definite” ADR cases than most established algorithms, a feature that may be desirable in the context of public safety. On the whole, this algorithm would provide pharmacists, clinicians and drug regulators with a handy tool to assign ADR causality.

5. In Chapter 6, a study was carried out to further fine-tune the newly developed algorithm so that the pharmacists or other healthcare professionals can be more certain about the likelihood of the ADR being caused by the suspected drug. This was achieved by, further refining the scoring system of the newly developed algorithm using genetic algorithm to reflect a quantitative scale. The further addition of an appendix also helped to make the algorithm more sensitive, and reduced the variability when used by different users. These strengths will give this algorithm an extra advantage when used by clinicians, regulatory agencies or drug companies to generate alerting ADR signals. Using a quantitative method of assessing causality will also mean that rare ADRs and new ADRs that have not been documented can be more readily detected since a quantitative score can indicate more precisely the likelihood of ADR

causality. Therefore, by using a quantitative approach, a simple and easy to use ADR algorithm which would contribute to clinical risk management was produced.

6. In Chapter 7 of the thesis, a further study was performed to incorporate another important feature in assessing ADR to make the newly developed algorithm a more useful tool in risk management.

   A severity assessment scale for ADRs was developed to objectively compare the intensities of the severity of various ADRs. This scale was then incorporated with the quantitative ADR causality scale which is mentioned above. This amalgamation provides a novel combined ADR causality and severity scoring system which will serve to give more practical value to the results obtained compared to the individual causality and severity scores. Herewith, information like whether a drug is likely to cause an adverse reaction and if it is dangerous enough to be withheld from normal usage or if there is a necessity to perform further risk assessment on its potential can be acquired.

   An online version of this combined scoring and assessment system has also been developed. Features which will increase its user-friendliness have also been incorporated into this online edition.

8.2 Contributions

The motivation of the current thesis resulted from wanting to identify and assess the most exact state of DRPs and ADRs in Singapore. With the knowledge of a more exact representation of the situation locally, it will then be possible to develop and implement strategies which will help in detecting, assessing and managing the situation of DRPs locally.

This thesis has indeed achieved the above purpose. A formal study on the prevalence of DRPs in Singapore was done and baseline results with regards to the exact state of DRPs and ADRs were obtained. With these results, a further study to assess whether having a pharmacist on a primary patient care review team on a regular basis will help to improve the situation of in-patients developing DRPs was performed. At the same time, the authors were interested in finding out if having a pharmacist permanently on such review teams will be a cost-effective measure. Both objectives were accomplished and the results suggest that it is indeed cost-effective to have pharmacists on board such teams. The cost-benefit ratio of such pharmacists' services, in addition to a possible improvement in in-patients' health related quality of life with the presence of pharmaceutical care (because of the detection and elimination of existing or potential DRPs) can help the pharmacy department in the hospital put forth proposals for the hospital administrators to increase their budget for the implementation of such clinical pharmacy services.

Emerging from the baseline study of the exact state of DRPs and ADRs in a local acute hospital also highlighted the large number of ADRs in Singapore. Since ADRs have the propensity to bring about dire consequences where mortality, health-

care resources and health-care costs are concerned, a method to detect these ADRs and consequently bring about management of such drug risks is required. The novel combined ADR causality and severity assessment system which was developed in the course of this study is intended for indicating ADR alerts. However, other than the initial target audience – the clinicians, this combined scoring system, ABACUS (**A**lerts **B**ased on **A**DRs' **C**a**u**sality and **S**everity), can also help investigators in clinical trials and regulatory authorities to determine the course of action to be taken following a particular ADR detection. ABACUS can be utilized to facilitate signal generation of drugs on the whole or for targeted drugs that the clinicians or authorities have interest in. The quantitative nature of ABACUS can also help clinicians, investigators and the authorities in case management when they are faced with limited time and resources. This scoring system will also be a useful tool for pharmacists in patient care review team for the purpose of detecting ADRs in the in-patients. An online version of ABACUS, equipped with its user-friendly interface and automatic calculation of scores was furthermore developed. This was done to allow convenience and ease of use of this scoring system.

In view of the results obtained from these studies, it could be inferred that with a change in the workflow of the current healthcare system in Singapore and by equipping the pharmacists with user-friendlier and simple tools (e.g. the algorithm developed in this thesis), it would be possible to allow the pharmacists to play a much bigger role in contributing to clinical risk management.

8.3 Limitations

The researchers acknowledge that the baseline study for the prevalence of DRPs was a retrospective one and the study was only performed in patients on polypharmacy. The retrospective nature was because by the time the study was embarked on, the acute hospital which was collaborating in the study already had pharmacists going around the wards monitoring patients' medication therapy. Hence, a prospective study will not be able to give a clean baseline where there is no intervention performed as it is unethical to prevent the pharmacists from carrying out their intervention work, though not on a regular basis. Due to the retrospective nature, requests for case-notes of patients from the medical record office to extract the relevant data had to be done. This meant that any information which was not provided or not clearly provided in the case-notes could not be used nor be reflected in the study. The retrospective nature of the study also brought about a limit to the number of cases that could be requested from the medical record office during the study period. Hence, only patients on polypharmacy were included in the study. However, prior to deciding on whether to include only patients on polypharmacy, a literature search was performed and it was confirmed that in the past two decades, most of the drug related problems encountered came from patients who were on polypharmacy. Hence, the results that were obtained should not be too skewed as a result of this limitation.

The study that was carried out on pharmacists' involvement in physician-pharmacist review teams was performed in only one acute hospital. However, all the six restructured, acute hospitals in Singapore are managed in a similar manner and the results from one hospital should be able to be extrapolated to another with minor

variations. Also, due to severe manpower shortage on the side of the hospital, the study could only be run for 4 months and only in the medical discipline. Nonetheless, the medical discipline was chosen because of the high turn-over rate of patients and also based on previous experience, patients in this discipline are exposed to the highest risk of drug related problems due to the large number of medications they are on to manage their conditions.

Due to limited time, after the development of ABACUS, the final version of the new algorithm, only retrospective data were used for testing the new assessment system. There was no opportunity to use newly collected ADR reports or reports emerging from clinical trials to test ABACUS.

8.4 Recommendations for future studies

After having established the cost-effectiveness of having a pharmacist to perform pharmaceutical care role on a regular basis, it will be interesting to follow on with a study to verify the impact of such clinical pharmacy services on the health-related quality of life (HRQoL) of the in-patients. The researchers postulate that there will be a positive impact on the HRQoL of the patients but a future study with proper results will provide auxiliary information to convince the hospital administrators that clinical pharmacy services are of great importance and should be considered seriously.

The newly developed ABACUS should be used in clinical trials, prospectively collected spontaneous ADR reports and also on targeted drugs, where risk assessments are to be established, to validate the consistency and ability of this assessment system in generating drug alert signals.

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SHORT REPORT

Therapy related hospital admission in patients on polypharmacy in Singapore: a pilot study

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Key words
Drug related problems
Geriatric patients
Polypharmacy
Singapore

Abstract
Objective: To estimate the incidence of drug-related problems (DRPs)-associated hospital admission, and its correlation to polypharmacy and age.
Method: A retrospective, cross-sectional study in in-patients on polypharmacy in Singapore. Significant differences ($P < 0.05$) between number of medications taken and age of patients were tested with the chi-square test.
Results: The study population consisted of 347 patients (aged 16–97) on a mean of 7.4 ± 2.1 medications. 10.8% of the study population had DRPs on admission: 71.9% of which were dominant reasons for admission, and DRPs contributed partly in the remaining cases. These DRPs were mostly avoidable, and can be broadly classified into non-compliance, adverse drug reactions, require synergistic therapy, inappropriate dose and untreated condition. 52% of these cases were made up of geriatric patients. No statistical difference was found between patients on polypharmacy and those on major polypharmacy (10 and more drugs) in having a DRP.
Conclusion: In this study, DRPs contributing to hospital admission appeared to be avoidable. Geriatrics were more susceptible to DRPs and future efforts are required in managing medications prescribed for these patients to reduce such incidences.

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Introduction

Drug-related problems (DRPs) have been shown to be a common reason for hospital admission[1,2]. Admittedly, many factors contribute to DRPs in patient management, However, among these factors, polypharmacy and older age have often been identified as important risk factors for patients suffering from DRPs[3–5].

Polypharmacy is the prescription, administration, or use of more medications than is clinically indicated in a given patient[3]. This use of multiple medications can easily predispose patients to drug-related problems (DRPs) like adverse drug reactions (ADRs), drug-drug interactions, and non-compliance[5].

Manifestation of ADRs incidences have been consistently shown to increase with the number of drugs taken[4,6]. It has been shown that significantly more patients for whom four or more drugs had been prescribed were admitted to hospitals because of ADRs than patients receiving up to three drugs (11.1% vs 3.6%)[1].

Besides the higher risk of experiencing ADRs, the use of multiple medications also makes compliance with medication regimens more difficult[5]. This is evident in a study which showed that medication errors, largely made up of non-compliance, increased from about 15% when only one drug was prescribed to 25% when two or three drugs were prescribed. When more than four drugs were taken, errors exceeded 35%[7].

Other than polypharmacy, advancing age has been shown to contribute to the substantial increase in risk of acquiring ADR, and hence increased risk of DRP-related hospital admission[4]. This is supported by data which showed a sevenfold increase in occurrence of ADRs from 3% of patients aged 20 to 30 years, to 21% in patients aged 60 to 70 years[8]. However, this propensity of older patients for ADR may be due to higher risk of inappropriate medication rather than just advancing age as a sole risk factor[9–11].

Hence, it can be seen from the above that polypharmacy can have adverse clinical consequences on the patients. In addition, the strain on health care cost is also substantial[12]. Nevertheless, although DRP-related hospital admission has been recognized as a healthcare problem, there has not been any formal research done in Singapore to study it systematically. As such, the correlations between DRPs with polypharmacy and age of patients have also not been examined and evaluated.

Objectives

We intended to estimate the incidence of drug-related admission to an acute care hospital in Singapore, and to evaluate its correlation to polypharmacy and age of the patients involved.

Methods

We carried out a retrospective, cross-sectional study at Alexandra Hospital, a 404-bed acute care hospital in Singapore. In-patient case notes and medication records were used for data collection. The patients were included in the study if they were in-patients on the four randomly selected days in November and December 2000, and had satisfied the criterion of being on polypharmacy.

In our study, we defined polypharmacy as the consumption of five or more medications. Different strengths of the same drug were counted as one item. However, formulations of the one drug that require different routes of administration were regarded as separate items. Combination drugs, that is drugs with more than one active ingredient, were regarded as a single item.

Each patient was characterised as having or not having a DRP on admission. Only definite cases of admission related to drug therapy were characterised as having a DRP. If there was any uncertainty because of lack of supporting documents, the case was then classified as not having a DRP. For problems like non-

compliance and lack of required drug therapy, we depended on documentation by the admitting doctor. Patients who required modifications to their drug therapy as a result of a newly diagnosed medical condition or worsening of an existing medical condition were not characterised as having a DRP on admission.

We used definitions from Hallas et al. to evaluate the identified DRPs on/coincidental to admission to evaluate for their contribution to hospital admission and their avoidability[13]. DRPs were classified as dominant reasons for hospitalisation if they were the main reason for admission. If there were other factors present, which contributed to admission, then the DRP was classified as partly contributing.

The DRPs were deemed as avoidable if (i) they were caused by drug treatments which were obviously inappropriate or contraindicated; (ii) no measures were taken to counteract known adverse effects of the drug (e.g., extrapyramidal side effects of anti-psychotic drugs); (iii) patients were not compliant or were insufficiently educated about their medication. The DRP was classified as possibly avoidable if the patient's disease state was considered to be potentially changing, thereby resulting in the need for altered drug therapy. Unavoidable DRPs would be those that were unpredictable.

For data analysis, the chi-square test was employed to test for significant differences between the age of patients and their risk of DRPs. This test was also used to compare the risk of DRPs between patients on minor (5–9 drugs) and major polypharmacy (10 and more drugs). The *a priori* level of significance for all comparisons was $P < 0.05$.

Results

There were 640 in-patients during the study period. Of these, 347 patients (54.2%) satisfied our criterion of being on polypharmacy. Their ages ranged from 16 to 97 years (mean ± SD: 66 ± 18 years), and 43% of the study subjects were female. The number of medications per patients ranged from 5 to 14 (mean ± SD: 7.4 ± 2.1). Geriatric patients (that is patients over the age of 65) made up 58.2% of our study population.

There were 32 cases (10.8% of study population) of DRPs which resulted in or were coincidental to admission. In 71.9% of these cases, DRPs were the dominant reasons for hospital admission, and contributing factors for the remainder. Based on the criteria by Hallas et al.[13], these DRPs were all avoidable and can be broadly classified into non-compliance (28.1%), adverse drug reactions (25%), require synergistic therapy (25%), dose too low (12.5%), untreated condition (6.3%) and dose too high (3.1%) (Figure 1).

Among these DRPs, 52% were found in elderly patients (more than 65 years old). However, statistical analysis showed that when corrected for the number of drugs used by the patients, the geriatrics did not appear to have a higher risk of acquiring DRP-related hospital admission when compared to the younger patients ($P = 0.574$).

Further analysis showed that there is a higher trend of DRP-related admission in patients on major polypharmacy in comparison to those on minor polypharmacy (12.1% vs 8.7%). In spite of this trend, there was no statistically significant difference between these two groups ($P = 0.454$).

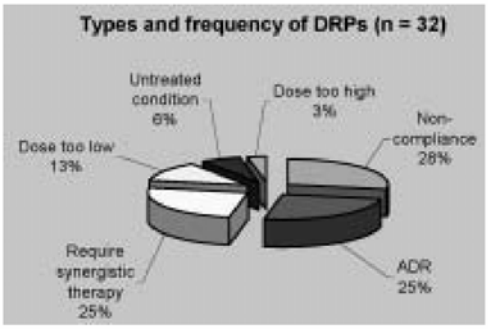

Figure 1 *Types and frequency of DRPs.*

Discussion

From our results, 10.8% of our study population had DRPs, which resulted in, or were detected on admission. This figure is lower than the 41% previously reported in Canada[14]. However, in the Canadian study, DRPs were reported for all elderly patients aged 65 and above, and the number of medications per patient ranged from 0 to 17 (average 5.7). In our case, we recruited only patients with five drugs or more. Hence, we may have missed out on DRPs present in patients consuming less than five drugs. Moreover, our incidence of 10.8% was likely to be an underestimate, due to the lack of comprehensive charting of medical and medication history upon patient admission.

Due to the retrospective nature of the study design, incomplete charting of history was a major limitation in our study. It hindered our ability to judge if a fall experienced by a patient was due to an accident, secondary to a medical condition, or secondary to an ADR. Moreover, information regarding chronic disease states, drug prescribing and compliance was not routinely gathered from the patient or recorded by the admitting doctor. Hence, the ability of the present study to identify of inappropriate drug therapy, lack of therapy and non-compliance was limited. This may further contribute to the relatively low cases of admission related to drug therapy. Nevertheless, even an incidence rate of 10% for patients on polypharmacy to have DRP-associated hospital admission would be a case of concern for any health care system.

Considering the major causes of drug-related hospital admissions, non-compliance was the most common cause of DRP, contributing to 28% of such hospital admission. Eight patients were either non-compliant to their medications or diet, and one patient was not using his metered-dose inhaler properly. This would not be surprising, as non-compliance had been strongly correlated with the number of medications given. It had been reported as the main reason for most out-patient treatment failure, and a cause of serious medical complications.

Following non-compliance, adverse drug reactions also played an important role, as one of the causes of

drug-related hospital admissions (25%) in our study. All the identified ADRs were found to be avoidable if the patients were monitored closely to ensure they were getting the optimum dosage of medication based on the status of their conditions, and if plasma drug concentration was monitored. Thus, this is an area that needs to be looked into, as ADRs are known to complicate existing disease, affect quality of life and may delay the cure of the original disease[4]. Furthermore, ADRs may result in inappropriate treatment of unrecognized drug-induced problems.

Although our results did not demonstrate any statistically significant difference in DRP-associated hospital admission between geriatrics and younger patients, the clinical importance of the higher trend observed in geriatric patients may not be totally discounted. This could probably be due to the small sample size of this current study.

In conclusion, this baseline study suggests that the incidence of drug therapy-related admission to hospital in Singapore would be comparable to that occurring in other developed countries. In addition, the finding that the DRPs were avoidable gives us a basis to derive suitable strategies to lower the incidence of drug therapy-related hospital admission. Effective management of medications taken by patients, with special emphasis on the geriatrics, should be incorporated into our future efforts.

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Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender

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Background: Drug-related problems (DRPs) have been shown to prevail in hospitalized patients, and polypharmacy and increasing age have been identified as two important risk factors.

Objective: 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.

Method: A retrospective cross-sectional study was performed in an acute-care hospital in Singapore. Only patients prescribed polypharmacy were included. Mann-Whitney test was used to test for significant difference between the age and gender of patients and their risk of acquiring DRPs. The relative risks of developing DRP and ADR for geriatric patients and female patients were estimated.

Results: Of 347 patients prescribed polypharmacy (43% female and 58.2% geriatrics), no statistical correlations were observed between age and gender with developing DRPs. An increased number of medications was associated with higher risk for patients with DRPs on admission ($p = 0.001$), but not for inpatients with DRPs ($p = 0.119$). Results from patients with ADRs showed that the relative risk (RR) of geriatrics prescribed polypharmacy and major polypharmacy (10 and more drugs) were 1.01 and 1.23, respectively. Female patients had a RR of 0.79 compared with male patients in developing ADRs.

Conclusion: Results showed that among patients with polypharmacy, age and gender may not be as important as number of drugs prescribed as predictors of experiencing a DRP. A similar trend was observed in the development of ADRs.

Keywords: polypharmacy, drug-related problems, adverse drug reactions, geriatrics

Introduction

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% (Steel et al 1981; Stewart and Cooper 1994). Undeniably, many factors can contribute to the high prevalence rate, but polypharmacy and older age have often been identified as important risk factors (Nolan and O'Malley 1988; Montamat and Cusack 1992; Stewart and Cooper 1994).

Polypharmacy is defined as the use of multiple medications by a single patient and is commonly observed among geriatric patients (Stewart and Cooper 1994). The use of multiple medications has been shown to predispose patients to ADRs (Williamson and Chopin 1980; Inman 1985; Nolan and O'Malley 1988; Hoigné et al 1990; Chrischilles et al 1992), drug–drug interactions (McInnes and Brodie 1988; Beers and Ouslander 1989; Stewart and Cooper 1994), and medication noncompliance

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(Bergman and Wiholm 1981a; Ramsay and Tucker 1981; Gillum and Barsky 1984), particularly in the geriatric population.

Among the potential contributing factors of DRPs, the association between polypharmacy and the incidence of ADRs has been most widely studied and documented. Incidences of ADR have been consistently shown to increase in an exponential rather than a linear manner with the number of drugs taken (Hurwitz and Wade 1969; Morgan et al 1988; Nolan and O'Malley 1988; Cadieux 1989). 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%) (Bergman and Wiholm 1981b). 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 (Hurwitz and Wade 1969). Besides the undesirable clinical consequences for the patients, ADRs also pose a significant financial burden to the healthcare system (Beers et al 1992). In a US study performed in 1992–1994, the estimated cost of treating reported adverse drug events among inpatients was US$1.5 million per year at a university-affiliated hospital (Schneider et al 1995). Another more recent French study conducted in 1996–1997 showed the annual cost of drug-related hospital admission to a university hospital as €3.85 million per year (Lagnaoui et al 2000). Thus, reducing the use of unnecessary medicines and avoiding polypharmacy would be beneficial in aiding the reduction of healthcare cost beyond the confines of reduction in drug costs alone.

Of the risk factors, advanced age has been associated with substantial increased risk of acquiring ADR (Gurwitz et al 1990). 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 (Hurwitz 1969). 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 (Grymonpre et al 1988; Colt and Shapiro 1989; Scheneider et al 1992; Stuck et al 1994; Hanlon et al 1997). 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 (Hanlon et al 1997).

However, other researchers had argued that this propensity of older patients experiencing ADRs was not being well substantiated by epidemiological data (Hoigné et al 1990). 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 (Gurwitz and Avorn 1991). 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 (Lindley et al 1992). 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.

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 (Bergman and Wiholm 1981a; Bero et al 1991; Hallas et al 1992; Prince et al 1992; Courtman and Stallings 1995; Fattinger et al 2000), or focused only on ADRs among hospitalized patients (Hurwitz and Wade 1969; Brennan et al 1991; Classen et al 1997). A more comprehensive study of DRPs in hospitalized patients would provide valuable insights for the healthcare professionals trying to reduce the incidence of DRPs.

Finally, 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 (Bergman and Wiholm 1981b; Nolan and O'Malley 1988; Hallas et al 1992; Lindley et al 1992; Green et al 2000), 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 (Hurwitz and Wade 1969; Williamson and Chopin 1980; McMillan et al 1986; Beijer and De Blaey 2002), 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 (Bergman and Wiholm 1981b; Veehof et al 1999; Fattinger et al 2000). 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.

Methods

Study population

We conducted a retrospective, cross-sectional study in a 404-bed acute-care hospital in Singapore. 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 November and December 2000, and who satisfied the criteria of being prescribed polypharmacy (see definition below). 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.

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 (Hepler and Strand 1990).

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 (WHO 1972).

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.

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 (Cockcroft and Gault 1976). 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 (YK), and any need for confirmation of the decision was resolved with the other investigators.

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 (BNF Joint Formulary Committee 2002).

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".

In assessing the appropriateness in the choice of drugs, Beer's explicit criteria (Beers 1997) were used to identify medications that were deemed unsuitable for use in elderly patients more than 65 years old.

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

Characteristics of study population

There were 640 inpatients during the study period. Data were collected for 347 patients (54.2%) prescribed polypharmacy. Their age ranged from 16 to 97 years (mean 65.9 ± 17.7 years). Of the subjects recruited, 43% were female. Geriatric patients (patients more than 65 years old) made up 58.2% of our study population.

Medication profile

The number of medications per patient ranged from 5 to 14 (mean 7.4 ± 2.1). Paracetamol was the most commonly used drug (33.4%) followed by two laxatives, senna and lactulose (prescribed in 30.3% and 29.7%, respectively). A total of 181 patients (52.2% of our study population) were taking laxatives; of which, 13 patients (3.7%) were on 3 laxatives and 80 patients (23.1%) were on 2 laxatives simultaneously. The ten most commonly prescribed medicines are shown in Table 1.

DRPs on admission

There were 32 cases of DRPs which resulted in, or were coincidental with admission. They could be classified into 4 broad categories: requiring additional therapy (31.3%), non-compliance (28.1%), adverse drug reactions (25%), and inappropriate dosing (dose too low 12.5%, dose too high 3.1%).

For the 10 patients who required additional therapy, the existing medical conditions of nine may have been better controlled if synergistic drugs were added onto their current medication. The tenth patient was admitted as a result of syncope secondary to chronic anemia which was not treated with medication.

Of the noncompliant patients, one of them had poor inhaler technique resulting in the exacerbation of his asthma problem. The remaining 8 patients were not compliant with their medication regime. Details of the DRPs during admission are published elsewhere (see Koh et al 2003).

Table 1 Ten most commonly prescribed drugs

Drug	Number of patients[a]	(%)[b]
Paracetamol	116	33.4
Senna	105	30.3
Lactulose	103	29.7
Sangobion	70	20.2
Aspirin	67	19.3
Isosorbide dinitrate	55	15.9
Potassium chloride	51	14.7
Amlodipine	50	14.4
Famotidine	50	14.4
Enalapril	42	12.1

[a] Those who are receiving the drug.
[b] The percentage of study population receiving the drug.

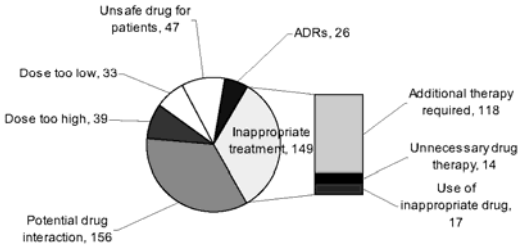

Figure 1 Drug-related problems and their number of incidences identified in patients during hospital stay. **Abbreviation:** ADRs, adverse drug reactions.

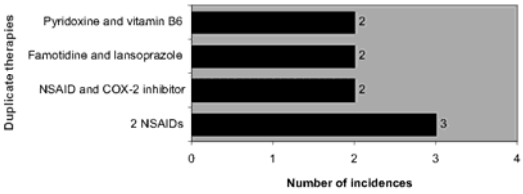

Figure 2 List of duplicate therapies. **Abbreviation:** NSAIDs, nonsteroidal antiinflammatory drugs.

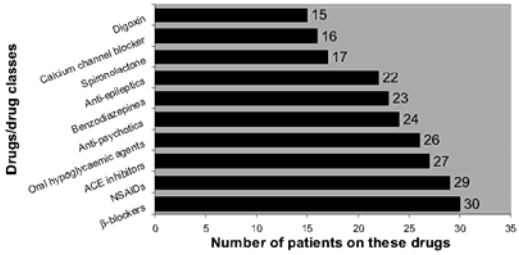

Figure 3 Ten drugs/drug classes that were most likely to be involved in causing drug–drug interactions.

DRPs during hospital stay

The types of DRPs identified during the study period included: (1) inappropriate treatment (comprises additional therapy, unnecessary drug therapy, and use of inappropriate drug); (2) potential drug interactions; (3) inappropriate dosages – dose too high or dose too low; (4) unsafe drug for patients; and (5) ADRs (Figure 1).

Of the 149 incidences of inappropriate treatment, 118 had an untreated condition that required additional therapy, with anemic patients (identified by their biochemistry results) making up 64.4% of this group. Another 9 patients would require additional drugs to improve the management of their existing medical conditions. For patients receiving unnecessary drug therapies, 5 had no recorded medical indication for their prescribed medications and the remaining patients were prescribed duplicate therapies (Figure 2). Patients taking drugs not recommended for their conditions made up the remaining 17 cases of inappropriate treatment. Of these, 82.4% was due to usage of a particular drug when contraindicated (eg, the use of propranolol in an asthmatic), and the rest was due to using a drug when the condition was already refractory to it (eg, using ciprofloxacin when culture and sensitivity results showed bacterial resistance) or when a particular drug was not even indicated for the condition (eg, prescribing paracetamol for giddiness).

For inappropriate dosages, the cases encountered were wrongly prescribed dosages, inappropriate administration frequencies, or the serum drug concentrations were higher or lower than recommended ranges during therapeutic drug monitoring. For some patients, the dosages of their medications were deemed as too high when we took into account their abnormal hepatic or renal function (Table 2).

Each combination of the drugs prescribed for the patients during their hospitalization were checked for potential interaction, and the top ten drugs/drug classes that were most likely to be involved in causing drug–drug interactions are listed in Figure 3. We only managed to identify cases of potential drug interactions during hospital stay as the documentation of drugs which the patients were on prior to admission was not comprehensive for all the patients.

The 47 cases of unsafe drug regimes during hospitalization were based on Beer's criteria, which identifies drugs unsuitable for use in patients more than 65 years old. Again, we could not identify unsafe drug usage for patients on admission due to limited documentation. Drug-pairs identified in our study that could give rise to potential severe interaction are shown in Table 3.

With regards to the analysis of risk factors, there were no statistical correlations when age and gender were compared between patients with and without DRPs, both on admission and during hospital stay. However, based on Mann-Whitney test, the number of medications prescribed for patients was not a risk factor for the presence of DRPs

Table 2 Dose of medication too high for existing renal or hepatic function

Drug	Impaired function	Number of patients
Enalapril	Renal	4
Metronidazole	Hepatic	2
Allopurinol	Renal	1
Cefuroxime	Renal	1
Fluoxetine	Renal	1
Tolbutamide	Renal	1
Tramadol	Renal	1

Table 3 Significant potential drug interactions

Drug pair	Possible effects
Atenolol + nifedipine	Severe hypotension and heart failure occasionally
Phenytoin + folic acid	Decrease plasma level of phenytoin
Simvastatin + erythromycin	Increase risk of myopathy
Simvastatin + warfarin	Enhanced anticoagulant effect
SSRI + valproate	Convulsion threshold lowered
Theophylline + calcium channel blocker	Possibly enhanced theophylline effect

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

Table 4 Identified cases of adverse drug reactions

Drug class	Drugs	Manifestations of ADRs	Number of patients
NSAIDs	Aspirin	Coffee ground vomitus	4
		Bleeding GIT	2
		Epigastric pain with vomiting	1
		Gastric ulcer	1
ACE inhibitor	Enalapril	Declining renal function	1
		Chronic cough with wheezing	1
		Postural hypotension	1
Antiepileptics	Carbamazepine	Hyponatremia	1
		Thrombocytopenia	1
	Phenytoin	Giddiness	1
	Valproate	Tremors	1
SSRIs	Fluvoxamine	Hyponatremia	1
		Increased INR	1
		Increased liver function tests	1
	Fluoxetine	Hyponatremia	1
Loop diuretic	Frusemide	Dehydration	2
		Increased liver function tests	1
Calcium channel blocker	Amlodipine	Postural hypotension	2
Antiplatelet	Ticlopidine	Generalized rash	1
		Decreased hemoglobin	1
Analgesic/antipyretic	Paracetamol	Itch	1
Antiarrythmic	Procainamide	Antiphopholipid syndrome	1
Antibiotic	Ethambutol	Generalized rash	1
Antipsychotic	Sulpiride	Extrapyramidal side effects	1
Beta-blocker	Propranolol	Asthma exacerbation	1
Fibrinolytic	Streptokinase	Rigors and facial flushing	1
Statins	Simvastatin	Increased liver function tests	1
Sulfonylurea	Glipizide	Increased liver function tests	1

Abbreviations: ADRs, adverse drug reactions; NSAIDs, nonsteroidal antiinflammatory drugs; ACE, angiotensin converting enzyme; SSRIs, selective serotonin reuptake inhibitors; GIT, gastrointestinal tract; INR, international normalized ratio.

($p=0.119$) during hospital stay, but it was a risk factor for patients with DRPs on admission ($p=0.001$).

ADR analysis

There were 8 cases of identified ADRs on admission and 26 cases that occurred in 33 patients during hospital stay (one patient experienced two ADRs during the study period). Due to their small number of occurrence, we did an aggregated analysis of all the ADR cases (Table 4). Patients suspected of experiencing an ADR were taking a mean of 8.2 ($\pm$2.6) different medicines compared with those not having an ADR with a mean of 7.3 ($\pm$2.1) medicines ($p=0.015$). Of those who experienced ADRs, 60.6% were geriatrics. This formed about 10% of the geriatric patients in our study, and 36.4% of these geriatric patients were female.

Based on the results, the relative risk for geriatrics above 65 years in our study to develop ADRs was 1.01 (95% confidence interval (CI): 0.52, 1.85), and the relative risk for female patients in developing ADRs was 0.79 (95% CI: 0.40, 1.55). However, when we did the same analysis for patients on major polypharmacy (10 or more drugs) the relative risks for geriatrics and female patients developing ADRs were 1.23 (95% CI: 0.36, 4.25) and 0.66 (95% CI: 0.21, 2.02), respectively.

The prevalence rates of developing DRPs and ADRs for the various patient subgroups during the study period are summarized in Table 5.

Discussion

Polypharmacy is a ubiquitous problem plaguing nearly all healthcare systems. Here, we investigated the occurrence of not only ADRs, but all DRPs on admission and 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, nearly 10% of our study population had at least one DRP at admission. However, this might be an underestimate due to the lack of comprehensive

Table 5 Prevalence rates of developing DRPs and ADRs for the various patient subgroups

	Prevalence rate					
	Polypharmacy		Minor polypharmacy		Major polypharmacy	
Patients	**%**	**(n/N)[a]**	**%**	**(n/N)[a]**	**%**	**(n/N)[a]**
DRP						
All study patients	72.0	250/347	70.2	203/289	81.0	47/58
Less than 65 years old with DRP	72.9	102/140	74.2	89/120	65.0	13/20
65–74 years old with DRP	71.6	53/74	67.3	37/55	84.2	16/19
7–84 years old with DRP	69.0	58/84	64.3	45/70	92.9	13/14
85 years old and above with DRP	75.5	37/49	72.7	32/44	100	5/5
Female patients with DRP	41.2	103/250	37.4	76/203	57.4	27/47
Male patients with DRP	58.8	147/250	62.6	127/203	42.6	20/47
ADR						
All study patients	9.5	33/347	9.3	27/289	10.3	6/58
Less than 65 years old with ADR	15.7	22/140	16.7	20/120	10.0	2/20
65–74 years old with ADR	0	0/74	0	0/55	0	0/19
75–84 years old with ADR	6.0	5/84	2.9	2/70	21.4	3/14
85 years old and above with ADR	12.2	6/49	11.4	5/44	20.0	1/5
Female patients with ADR	27.3	9/33	29.6	8/27	16.7	1/6
Male patients with ADR	72.7	24/33	70.4	19/27	83.3	5/6

[a] n denotes number of patients experiencing the event, and N denotes the total number of subjects in the particular category.
Abbreviations: DRPs, drug-related problems; ADRs, adverse drug reactions.

documentation at the point of admission. 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.

Although we separated those DRPs present on admission and those discovered while hospitalized, they will be discussed as a whole with emphasis on potential drug–drug interaction, appropriate dosages, and ADRs, as these DRPs might have been preventable if proper checks were carried out by physicians and pharmacists.

Our analysis on DRPs showed that potential drug–drug interactions accounted for a substantial amount of potential drug toxicity (34.8%). Numerous drug combinations that resulted in modification of pharmacological action or in drug toxicity have been documented (D'Arcy and Griffen 1986). In the present study, 59% of possible drug–drug interaction occurred in geriatric patients. The drugs most implicated were β-blockers (namely, atenolol and propranolol), nonsteroidal antiinflammatory agents (NSAIDs) (including aspirin, ketoprofen, diclofenac, and mefenamic acid), and angiotensin converting enzyme (ACE) inhibitors. This is consistent with published data citing that the average number of drug–drug interactions involving anticoagulants and antihypertensives were significantly higher than other drug groups (May et al 1977).

In addition, we also identified drug-pairs in our study that could give rise to potential severe interaction (Table 3). 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 drug interactions can affect patient's clinical outcome, quality of life, as well as contribute to unnecessary healthcare cost, the high prevalence rate (~30%) in this study would make this an important area requiring further investigation. 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.

Another common aspect of DRPs is inappropriate dosages of medicines. Medication dosages were not adjusted for 11 patients with either renal or hepatic impairment. This made up 15.3% of all the patients receiving inappropriate drug dosages, and 2.4% of the entire DRPs in this study. Again, this might be an underestimate as the documentation in the patient's case notes was not very comprehensive and

our judgment was based on available biochemistry reports. Moreover, there might be further cases of renal and hepatic impairment that were missed during analysis. With proper monitoring, it is possible to substantially reduce such incidences.

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 (Lazarou et al 1998). 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 (Brennan et al 1991). 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 4), NSAIDs and ACE inhibitors were ranked the highest, closely followed by antiepileptics and serotonin-selective reuptake inhibitors (SSRIs). The drugs implicated in the present study are again similar to what has been reported (Courtman and Stallings 1995; Green et al 2000). This congruency highlights that there is a rationale to focus more attention on patients prescribed certain drugs or drug classes.

In the attempt to identify risk factors, our results supported published findings that the number of drugs taken by a patient is an important risk factor for ADRs. Definitely, the use of polypharmacy in patients is sometimes necessary to control or manage medical conditions. However, a patient may often be taking a multitude of medications because medications were used as substitutes for careful diagnostic maneuvres or effective nonpharmacologic therapies (Gurwitz et al 1990). Therefore, before prescribing a medication, it is important to determine if the patient's condition is caused by a current medication. It defeats the purpose if additional agents are prescribed to deal with the symptoms of adverse drug effects and this in turn potentiates the problem of polypharmacy.

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 (see McMillan et al 1986). 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 1.23 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. This finding is contrary to those reported from Denmark (Hallas et al 1992) and the Netherlands (Veehof et al 1999) where the relative risk in developing ADRs for female patients was 1.57 (95% CI: 1.15, 2.14) and 1.46 (95% CI: 1.09, 1.75), respectively. However, there were some differences in patient characteristics between the studies. In the Danish study, a total of 1999 patients of all ages, regardless of whether they were receiving polypharmacy or not were recruited (Hallas et al 1992). 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

In summary, 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 Singapore 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, but this may be confounded by our inclusion criteria. 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.

Based on these findings, we would advocate applying the 20/80 principle in business management into clinical risk management here. 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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CORRESPONDENCE

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A New Algorithm to Identify the Causality of Adverse Drug Reactions

Adverse drug reactions (ADRs) are recognised as a major contributor in iatrogenic illness. They are known to complicate existing disease, affect quality of life and may delay cure of the original disease.[1] The clinical, legal and financial consequences of ADRs have made reporting a major initiative for healthcare organisations,[2] and pharmacovigilance has become an integral part of governmental drug regulation.[3] However, for the regulatory authorities, assessing causality of a reported ADR unambiguously remains a major challenge. To assess causality, differential diagnosis of ADRs can usually be achieved with the use of clinical judgements and/or algorithms.[4] Algorithms are either flowcharts or questionnaires that attempt to determine drug causation in the occurrence of an ADR. They are preferred over clinical judgment for assigning ADR causalities because of their systematic approach to information acquisition, which helps to improve the reliability of assessments, as well as intra- and inter-rater agreement.[5,6] However, the problem of uncertainties pertaining to the causal involvement of the suspected drugs still remains because of the structure or data requirement of several commonly used algorithms. Therefore, a new or improved algorithm that can provide more consistent risk probability and differential diagnosis assessment of a plausible adverse drug event, but without the disadvantages of the existing algorithms, would be beneficial.

In developing the new algorithm, we used the information commonly gathered in ADR reporting forms as a platform to formulate the necessary questions. This was to ensure that the questions for our algorithm could be answered from routinely collected information. With this approach we hoped that the resulting algorithm would be of practical use and impose minimal extra burden on information collection. The preliminary questions derived were matched and modified against the 56 questions in Kramer's algorithm,[7] which was used as the 'gold' standard for comparison in the evaluation because of its comprehensive nature. Those questions from Kramer's algorithm that cannot be answered using information available on the ADR reporting form were eliminated. The remaining questions in Kramer's algorithm were then summarised to form main questions and reconciled with the preliminary questions we developed to arrive at the final questions for the new algorithm.

The scores for the final questions were developed based on their importance in determining the ADR causality of the suspected drug. The cut-off points for the various causality categories were determined by analysing the total number of theoretical 'unlikely', 'possible', 'probable' and 'definite' cases in Naranjo's and Kramer's algorithms. The new algorithm was then tested together with seven other algorithms (Kramer,[7] Naranjo,[6] Karch,[8] Jones,[9] Begaud,[10] Adverse Drug Reactions Advisory Committee [ADRAC] guidelines[11] and WHO Uppsala Monitoring Centre [WHO-UMC] causality assessment[12]) using ADR reports consolidated from hospitals and clinics in Singapore over an 8-month period. The results obtained from the various algorithms were translated into four categories of causality (unlikely, possible, probable and definite) and compared to Kramer's algorithm in terms of percentage congruency.

Our final proposed algorithm consists of eight questions with a scoring scale (table I). A total of 450 ADR reports were used for the congruency study. Results from this comparison are shown in table II (for absolute number of cases in the different causality categories) and table III (for percentage of congruency with Kramer's algorithm).

In this study, we used percentage of congruency, i.e. the percentage of cases that have exactly the

Table I. List of questions for a proposed adverse drug reaction algorithm[a]

Questions	Yes	No	Do not know	Not applicable
1. Is there a reasonable time interval between administration of the suspected drug and the adverse reaction?[b]	2	−4	0	–
2. Has the adverse reaction been associated with the suspected drug before?	2	−2	0	–
3. Could this adverse reaction be due to an existing clinical condition?	0	4	0	–
4. Is there any overdose of the suspected drug?	2	0	0	–
5. If the drug was discontinued, did the adverse reaction improve? (if the drug brought about irreversible changes, please classify as 'do not know')	1	−2	0	0
6. If the drug was NOT discontinued, did the reaction resolved on its own?	−2	0	0	0
7. Did the reaction improve when a specific antagonist/antidote was administered?	4	0	1	0
9. Did the adverse reaction recur when the suspected drug was discontinued and readministered again?	4	−2	0	0
Total score				

a Scores: ≥12 = definite, 8–11 = probable, 0–7 = possible, <0 = unlikely.

b Within 24–48 hours.

same causality assignments, to evaluate the comparative performance of all the algorithms against Kramer's algorithm. From the results obtained among the other six established algorithms, Naranjo's algorithm showed the best agreement with Kramer's, followed by the algorithms from ADRAC, Jones, Begaud, Karch and the WHO-UMC. On the other hand, our new algorithm managed to reach 98.44% congruency with Kramer's algorithm.

The relatively poor performance of several established algorithms such as those of Jones, Karch and the WHO-UMC was due to the presence of substantial unclassifiable cases, which ranged from 16.7% (WHO-UMC) to 40.2% (Jones). Hence, these three algorithms are not particularly suited for our use based on the type of information from our ADR reports.

In pharmacovigilance, the ability to identify 'definite' ADR cases is of paramount importance. These comparative results showed that our algorithm has a lower threshold than the other algorithms tested in triggering warning signals, i.e. in the assigning of 'definite' cases. The lower threshold represents a more conservative approach that would be acceptable in the context of public safety. Hence, with this short algorithm, we feel that it provides ease of use and requires less time to get a causality assignment for the suspected drug than Kramer's algorithm. Although patient-unrelated factors such as the quality-of-data documentation and the medical knowledge of the assessors are likely to influence the assessment outcomes, the presence of such an

Table II. A comparison of the different causality categories for the 450 adverse drug reaction reports

Algorithm	Definite	Probable	Possible	Unlikely	Unclassifiable
Kramer	12	370	64	4	0
Proposed algorithm	13	367	70	0	0
ADRAC	4	436	10	0	0
Jones	0	248	21	0	181
Karch	4	236	1	35	174
Naranjo	4	391	54	1	0
WHO-UMC	3	196	175	1	75
Begaud	4	226	165	55	0

ADRAC = Adverse Drug Reactions Advisory Committee; **WHO-UMC** = WHO Uppsala Monitoring Centre.

Table III. Results from a comparative study of the various algorithms against Kramer's algorithm

Algorithm	Congruency (%)	95% CI
Our new algorithm	98.44	96.82, 99.37
Naranjo	94.67	92.17, 96.55
ADRAC	84.44	80.76, 87.67
Jones	56.44	51.72, 61.08
Begaud	55.33	50.61, 59.99
Karch	52.22	47.49, 56.92
WHO-UMC	45.11	40.45, 49.84

ADRAC = Adverse Drug Reactions Advisory Committee; **WHO-UMC** = WHO Uppsala Monitoring Centre.

algorithm is nevertheless still valuable for improving the ADR reports by focusing on pertinent information, particularly the dates concerning drugs and events.

In conclusion, by evaluating the advantages and disadvantages of several established algorithms for assigning ADR causality, we have developed a simple algorithm that requires no extra data collection than those routinely collected in most ADR reporting forms. The algorithm also adopts an additional safety feature of using a lower threshold in assigning 'definite' ADR cases than most established algorithms, a feature that may be desirable in the context of public safety. However, the trade off for such a feature will be a possible increase in the number of false positive 'definite' ADR cases.

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