RATIONAL SELECTION OF PROTON PUMP INHIBITORS (PPIs) THROUGH AN OBJECTIVE SCORING SYSTEM FOR EFFECTIVE FORMULARY MANAGEMENT

by

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LIST OF ABBREVIATIONS

PPI	Proton Pump Inhibitor
GERD	Gastroesophageal Reflux Disease
P&T	Pharmacy and Therapeutic
MOH	Ministry of Health
WHO	World Health Organization
NICE	National Institute of Clinical Excellence
H.pylori	Helicobacter pylori
NSAID	Non – steroidal anti inflammatory drugs
THIS	Total Hospital Information System
ARB	Angiotensin receptor blocker
ACE	Angiotensin converting enzyme
MREC	Medical Registration Ethical Committee
CRC	Clinical Research Centre
HOD	Head of Department
FDA	Food Drug Authority
UMMC	University Malaya Medical Centre
IJN	Institute Jantung Negara (National Heart Centre)
HKL	Hospital Kuala Lumpur
HTAR	Hospital Tengku Ampuan Rahimah
MO	Medical officer
od	once daily
LES	lower esophageal sphincter

LIST OF ABBREVIATIONS

SOJA	System of Objectified Judgement Analysis
CURE	Comparative Utilisation of Resource Evaluation Model
PPDEM	Pharmaceutical Product Drug Differential Evaluation
DESS	Drug Evaluation Scoring System

PEMILIHAN SECARA RASIONAL PENGHALANG PAM PROTON MELALUI SISTEM PENSKORAN OBJEKTIF UNTUK PENGURUSAN FORMULARI BERKESAN

ABSTRAK

Pemilihan ubat secara rasional adalah penting dalam pengurusan formulari yang berkesan. Tujuan utama mewujudkan sistem penskoran objektif adalah untuk memberi garis panduan kepada doktor dalam penggunaan ubat yang telah dibuktikan oleh kajian klinikal dari segi keberkesanan, keselamatan dengan kos yang paling murah tanpa mempengaruhi tahap penjagaan pesakit. Dalam bahagian pertama, objektif utama kajian ini adalah mewujudkan satu sistem penskoran objektif untuk 5 jenis penghalang pam proton iaitu esomeprazol, lansoprazol, omeprazol, pantoprazol dan rabeprazol dengan menentukan kriteria-kriteria yang sesuai dipertimbangkan serta diberi skor yang bersesuaian mengikut kepentingan kriteria tersebut dalam proses pemilihan penghalang pam proton dalam rawatan refluks gastroesofagus. Objektif bahagian kedua merupakan satu kajian kes untuk menganalisis penggunaan dan perbelanjaan penghalang pam proton di Hospital Serdang serta membuat perbandingan dengan keputusan yang diperolehi oleh sistem penskoran objektif. Bahagian ini juga menentukan langkah untuk menjimatkan kos penggunaan penghalang pam proton. Untuk bahagian pertama, kriteria yang dianggap tinggi kepentingannya akan diberi skor yang tinggi: 200 skor untuk dokumentasi, 300 skor untuk keberkesanan, 200 skor untuk keselamatan dan 300 skor untuk harga. Jumlah skor bagi sistem penskoran ini adalah 1000. Kaedah persampelan mudah telah digunakan untuk mendapatkan saiz sampel responden bagi kajian ini. Borang soal jawab telah diagihkan kepada 165 pakar perubatan dan pegawai perubatan klinik pakar di 6 hospital di Selangor dan Kuala Lumpur. Untuk bahagian kedua, satu

kajian restrospektif telah dijalankan. Semua preskripsi yang mengandungi ubat penghalang pam proton dari klinik pakar telah diperolehi dari Sistem Informasi Hospital Keseluruhan (THIS) . Bilangan preskripsi, penggunaan dan perbelanjaan penghalang pam proton juga dianalisis. Analisis lanjut telah dijalankan untuk menentukan potensi penjimatan kos dengan menggantikan esomeprazol, lansoprazol, pantoprazol and rabeprazol dengan omeprazol. Keputusan dari sistem penskoran objektif pada bahagian pertama dibandingkan dengan penggunaan penghalang pam proton di Hospital Serdang sama ada ia memenuhi jangkaan pengamalan klinikal di hospital. Untuk bahagian pertama, hanya 73 (44.2%) borang soal jawab dipulangkan lengkap. Pakar perubatan serta pegawai perubatan dikehendaki memberi skor mengikut pandangan dan pengalaman mereka terhadap kepentingan kriteria – kriteria tersebut. Keputusan menunjukkan omeprazol merupakan penghalang pam proton yang mendapat skor tertinggi, diikuti oleh lansoprazol dan pantoprazol. Bahagian 2 mendapati penggunaan omeprazol adalah tertinggi (70.41%), diikuti oleh pantoprazol (13.49%) dan esomeprazol (12.78%). Dari segi perbelanjaan, pembelian omeprazol adalah sebanyak 39.14% daripada perbelanjaan keseluruhan penghalang pam proton, diikuti oleh pantoprazol (29.24%) dan esomeprazol (27.54%). Sebanyak RM 330,000.00 telah dibelanjakan untuk membeli penghalang pam proton di Hospital Serdang pada tahun 2009. Penjimatan kos sebanyak 44.4% dapat dilakukan jika semua ubat penghalang pam proton digantikan dengan ubat generik omeprazol. Sistem penskoran objektif terbukti dapat membantu dalam pemilihan ubat secara objektif, berkesan dan sistematik.

RATIONAL SELECTION OF PROTON PUMP INHIBITORS (PPIs) THROUGH AN OBJECTIVE SCORING SYSTEM FOR EFFECTIVE FORMULARY MANAGEMENT

ABSTRACT

Rational drug selection is fundamental for effective formulary management. The rationale of an objective scoring system is to establish and make available drugs which are proven to be the most efficacious, safe and cost-effective without compromising the quality of patient care. The aims of Part 1 of the study were to develop an objective scoring system by determining the criteria for 5 available PPIs i.e. esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole as well as to assign scores according to the importance in the evaluation process for the inclusion and exclusion of PPIs for the indication of GERD. Part 2 of the study was a case study aim to review and compare the usage and expenditure of PPI drugs used in Serdang Hospital with the most preferred PPI obtained in Part 1 of the study. This study also aims to determine appropriate cost saving measure in the treatment of acid related disease requiring PPIs. In the first part of the study, the higher the assigned score, the higher importance the criterion is. Two hundred were assigned to documentation, 300 points for efficacy, 200 points for safety and 300 points for cost. Total points were 1000. A convenience sampling method was used to generate the sample size of the participants in this survey. Self-administered questionnaire was distributed to 165 specialists / lecturers and medical officers in various out-patient clinics in 6 selected hospitals in Selangor and Kuala Lumpur. In the second part of the study, a retrospective study was carried out to review all prescriptions containing PPI drugs prescribed by the medical, gastroenterology, surgical, nephrology and cardiology out-patient clinics in Serdang Hospital. The number of prescriptions,

usage and expenditure of PPI drugs were analyzed. Further analysis were undertaken to estimate the potential savings that could be achieved by replacing esomeprazole, lansoprazole, pantoprazole and rabeprazole with the generic brand omeprazole. Out of 165 questionnaires distributed, only 73 questionnaires were successfully completed and returned (response rate = 44.2%). The scoring system showed that omeprazole was the most preferred PPI, followed by lansoprazole, pantoprazole, esomeprazole and rabeprazole. The expenditure of all PPIs available in Serdang Hospital in 2009 was RM 330,000.00. Omeprazole (70.41%) was the most commonly used, followed by pantoprazole (13.49%) and esomeprazole (12.78%). Omeprazole contributed 39.14% of the total spending of all PPIs, followed by pantoprazole (29.24%), esomeprazole (27.54%). It was found that 44.4% of the PPI expenditure could be saved when all PPIs were substituted with the generic brand omeprazole. The scoring system allows drug selection to be done in a more objective, transparent and systematic way.

CHAPTER ONE

INTRODUCTION

1.1 Introduction

The cost of healthcare budget in developed countries is increasing at an alarming rate (Heginbotham, 1992). The total value of drugs procured for the use in all hospitals and health clinics in Malaysia for 2008 was RM 1,510 million, an increase of 397% compared to RM303.8 million in 1998 (MOH, 2008). Cost containment measures have to be considered to overcome the high drug procurement cost. Having a reliable yet comprehensive drug formulary is one way to promote rational prescribing and to limit costs (Schwartz & Aeron, 1984).

The need of a National Drug Formulary is crucial for promoting rational and cost-effective use of medicines in hospital as the formulary will usually cover 80% of all prescribing decisions (Karr, 2000). It also helps in solving pharmaceutical problems recognized in most pharmaceutical system such as limited drug budgets, increasing number of therapeutic alternatives, improper use of medications in prescribing and high cost of handling large number of drugs of questionable quality in the market (Savelli et al., 1996).

The National Drug Formulary in Malaysia clearly defined the type and choice of drugs approved for use in all hospitals under the umbrella of the Ministry of Health to ensure uniformity and equity across all hospitals in Malaysia.

In most countries like the UK and The Netherlands, drugs selected in the National Drug Formulary were based on evidence-based clinical effectiveness, safety, tolerability and the selection of the minimum number of drugs needed to treat the prevalent disease. Selection of drugs were also based on clinical practice guidelines (CPG) of the disease. The inclusion of new drugs are only considered if they were found to have distinct advantages over drugs currently in use or at a lower cost (LeRoy & Morse, 1983).

In Malaysia, the Ministry of Health Drug List Review Panel consists of pharmacists and senior consultants and assisted by 17 Technical Drug Working Committees from various specialized disciplines. These panels will meet, review and update the drugs listed in the formulary two to three times a year and at the same time evaluate the proposals for additions or deletions of drugs in the drug formulary upon application from the state drug commitee. The applicants are required to put forward the application for i) Proforma A which is a proposal to delete any of the drug / dosage form / formulation in the MOH Drug Formulary, or ii) Proforma B which is a proposal to alter / add formulation / dosage form / category of the prescriber / indication in the MOH Drug Formulary or iii) Proforma D which is a proposal to introduce new drugs into the MOH Drug Formulary. The state drug commitee meeting will first review and recommends these proforma by forwarding the application to the Secretariat of the Ministry of Health Drug List Review Panel. The applicant would have to provide a comparative study between the new drugs and drugs which are already available in the MOH Formulary based on its efficacy, safety, tolerability and cost – effectiveness criteria. Applicants were also required to provide studies / trials with respect to the above criteria. This is to ensure all drugs

available in the National Drug Formulary were comprehensive and evidence-based. The proforma will then be reviewed by the Ministry of Health Drug List Review Panel. To further enhance a more objective and transparent drug selection process, an analytical scoring system should be developed to assist the process of drug evaluation and selection of drugs.

A scoring system is needed to enable the Pharmacy and Therapeutic (P&T) committee to objectively appraise and evaluate each drug when performing drug reviews such as in developing new drug monographs, re-evaluation of previous formulary decisions periodically or whenever there are changes in the clinical practice guidelines and therapeutic class review in a more reliable manner without any biasness or preferences. The P&T drug committee will then be able to make better and speedier decisions in the selection of all therapeutic class of drugs for the most efficacious, safe and cost effective drugs determined from an objective scoring system.

Many drugs selection tools have been developed and used for formulary purposes (Karr, 2000; Moore et al., 2002). Pharmaceutical Product Drug Differential Evaluation (PPDEM), Comparative Utilisation of Resource Evaluation Model (CURE), Formulary Analysis and System of Objectified Judgement Analysis (SOJA) are all drug selection tools in which drugs entity from the same therapeutic class are differentiated in terms of its efficacy, safety, side effects, patient compliance and price (Janknegt et al., 1997; Karr, 2000; Moore et al., 2002).

The methods from the above tools in particularly System of Objectified Judgement Analysis (SOJA) were adopted in the development of this scoring system. In this study, the criteria were adapted from various drug selection methods to develop a scoring system appropriate to evaluate the therapeutic group of Proton Pump Inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD). Prevalence rate of GERD in Malaysia has been estimated at 13.4% (Goh, 2004), while the prevalence of this disease in the UK and USA had been estimated to be about 29–44% (Dent, 2005). GERD is currently the most common among acid related disorders and an increased in prevalence is anticipated both locally in Malaysia and globally.

All PPIs that are available in Malaysia were included in the analysis i.e. esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. The PPI group of drugs were chosen because there has been a rapid increase in PPI drugs prescibing in Malaysia and therefore rational prescribing and cost containment measures are needed. Among the top 40 drugs utilised, omeprazole was ranked the fourth highest expenditure with RM33,056.4 million. Drugs for acid related disorders ranked 6th in the ranking of expenditure on therapeutic drug groups (Goh, 2004).

1.2 Problem Statement

There is no scoring system currently being used in Malaysia to evaluate drugs for the inclusion and exclusion in the drug formulary. Drug selection without a scoring system can lead to bias selection of drugs, influenced by the pharmaceutical company's advertisements and the preference of certain drugs by the drug commitee.

Another problem is that the prescribers were faced with difficult choices on the selection of PPI drugs made available to their patients. A scoring tool is necessary to help the drug committee make better decision on drugs selection in order for PPIs to be evaluated and reviewed in a more consistent and systematic approach (Janknegt et al., 1997). The scoring system can play its role as a check-list for the drug committee to review and update drugs in the Drug Formulary.

With a scoring system developed and available for every therapeutic drug class ready in hand, new information on drugs can be easily updated. Therefore, DESS is a flexible model that can compare and update current drugs updates for each therapeutic class of drugs easily and rapidly in order to keep the evaluation process 'live' (Karr, 1994).

The cost of health care budget in developed countries is increasing at an alarming rate. Pharmaceuticals comprise of up to RM 1,510 millon yearly in Malaysia, (MOH, 2008) and it is projected to increase 13% - 15% annually. Overcoming these cost is becoming more difficult and many cost containment measures are being considered. One of the measures that can overcome the high expenditure of drugs is to restrict the number of drugs within the same therapeutic class (Kessler, 1994). The selection of drugs can be done in a more objective and systematic approach by using an objective scoring system which is able to differenciate and to compare important criteria such as clinical documentation, clinical efficacy, clinical safety and acquisition cost for each drugs belonging to the same therapeuctic class as well as for any new inclusion of drugs in the formulary. As in this case, the scoring system was use to evaluate all the available PPI drugs and to select the most preferred PPI which was proven to

have the highest clinical effectiveness with the least safety issues and lowest cost to be included in the Drug Formulary.

Irrational prescribing of drugs is a common occurrence in clinical practice. It was shown that the average number of occurrence for poly-pharmacy was 3.8 per case per episode for both population of children and adult group (Laing, 1990). Irrational drug prescribing will cause failure in achieving therapeutic goals and hence contribute to higher drug expenditure. Rational prescribing of PPIs is defined as receiving medications appropriate to the patient's clinical needs, in doses that meet individual requirements for an adequate period of time, and at the lowest cost (Dott & Johnson, 1999). The Drug Formulary is one measure to encourage appropriate prescribing as all drugs selected to be in the formulary are clinically proven and carefully selected to be the most cost-effective drugs. Prescribers are strictly encouraged to adhere and to prescribe only from the selection of drugs available in the drug formulary.

1.3 Study Justification

This study focused on developing a scoring system which consists of a list of criteria and assigning weightage to each criterion and sub-criterion for the rational selection of PPIs. A scoring system is required to assist the drug committee in the inclusion and exclusion of drugs in the drug formulary so that drugs can be selected in a more consistent and objective approach. PPIs were used as a platform to assess the Drug Evaluation Scoring System (DESS). The PPIs group was chosen as it has been proven to be more superior to H_2 - receptor blockers (H_2RAs) in the treatment of

GERD (Chiba, 1997) and the usage of PPI drugs in the government hospital has recorded an upwards trend with the PPI drug class ranked 9th with a total spending of RM 18,413,000.00 in 2006 and ranked 8th with a total spending of RM 29, 434,000.00 in 2007 in the top 10 therapeutic group by expenditure (Malaysian Statistics on Medicine, 2007). The scoring system can be used to re-evaluate the same therapeutic group of drugs when new data or new drugs emerge or it can be extended to other group of drugs with the appropriate criteria selected in the near future.

The scoring system can also be used to evaluate newly marketed drugs, where comparison can be easily made in terms of its experience with the drugs, clinical efficacy, safety and cost. This is to evaluate if a drug is good enough or better than the available drugs already listed in the national drug formulary. There is no need to include a newly marketed drug from the same therapeutic class if the drug was found to be of equivalent in clinical efficacy and safety which usually comes at a higher price. Restricting the number of drugs in the same group class in the drug formulary can prevent poly-pharmacy which can lead to irrational prescribing. This study is important as limiting the number of drugs for the same indication in the Drug Formulary will help to reduce the government's expenditure on drugs.

An objective scoring system would be able to help the drug committee and physicians to make better, unbias and reliable choice of drugs for their patients, and hence promote rational use of drugs. This is vital to ensure quality, efficacy and safe drugs to be used on patients at the most affordable cost.

1.4 Objectives

Based on the problem statement and study justification mentioned previously, this study was conducted with the general aims of developing and initiating an objective and transparent scoring system intended for promoting rational selection of all therapeutic class of drugs in the Ministry of Health.

The specific objectives of the study were:

1) To determine the list of criteria that can be used as a scoring system for the inclusion and exclusion of Proton Pump Inhibitors (PPIs) in the Drug Formulary for Gastroesophageal Reflux Disease (GERD).
2) To determine the weightage for the selected criteria and sub-criteria of Proton Pump Inhibitors (PPIs) to be used as a scoring system.
3) To determine the scores obtained for each PPI drugs and to rank these PPIs from the most preferred to the least preferred sequence.
4) To reduce the number of Proton Pump Inhibitors (PPIs) in the Drug Formulary using the ranking of the scoring system.
5) To evaluate and compare the usage and expenditure of all PPI drugs prescribed in Serdang Hospital with the array of the most preferred Proton Pump Inhibitor (PPIs) based on the scores obtained from the scoring system.
6) To propose cost saving measures in the treatment of patients requiring Proton Pump Inhibitor (PPIs) therapy.

1.5 Contribution of the Study Findings

Developing an objective scoring system is very important for rational selection of drugs. The study finding is crucial for the prospect of drug expenditure in the government sector, it also provides an objective system to evaluate the characteristics of drugs as well as provide useful drug information for healthcare providers and the patients. Physicians always believe they are prevented from prescribing the medications which their patient needs while patients believe they are being denied access to the drugs they deserve. A sound and reliable Drug Formulary is the solution to put an end to this dispute and prevent against unnecessary purchase of drugs in hospitals under the MOH.

The P&T drug committee will benefit, as having an objective yet transparent scoring system will prevent the committee from making any unbiased drug selection to be listed in the Drug Formulary. There will be less scrutiny from doctors as the criteria in the decision making process can be revealed specifically if required. Selecting the right choice of drugs to be included into the Drug Formulary will help in reducing the drugs inventory and subsequently help to better manage stocks and drugs procurement for the purchasing pharmacists in the government hospitals. Well-managed drug procurement should contain only restricted number of drugs for the same indication. Drugs having only marginal difference or equivalent in clinical effectiveness and safety profile from the same therapeutic class should not be selected and should be excluded, an approach which can help the Malaysian government to save on drugs expenditure, as the government is finding it hard to cope with the escalating drug cost. With the development of a scoring system, the drug committee can continuously evaluate and update drugs already in the formulary,

whenever there is any update in clinical practice guidelines (CPG) which can bring to a change in the prescribing pattern. Drugs which are no longer in use in the clinical practice guidelines should be reviewed and removed from the Drug Formulary. This will promote rational prescribing among physicians. By having only limited number of drugs from the same therapeutic class in the Drug Formulary, this will contribute to lesser irrational prescribing such as poly-pharmacy, hence achieving higher pharmacotherapeutic success for patients. The Drug Formulary generally provides useful comprehensive information for all drugs made available in the MOH, as a reference to all healthcare providers. A drug formulary also allows the doctors to develop better knowledge of a limited range of drugs which may lead to increase monitoring of drug therapy and improved patient care. It is hoped that the scoring system would be able to help to optimize PPI prescribing with the most economical agent.

CHAPTER TWO

LITERATURE REVIEW:
DEVELOPING A RATIONAL DRUG SELECTION TOOLS
FOR FORMULARY MANAGEMENT

The main goals of developing a Drug Formulary are to develop and implement policies on drug selection, evaluation, procurement, use of safe drugs and to disseminate reliable drug information to optimize patient care through rational selection and use of drugs. A drug formulary is used to ensure quality drug use and cost effective prescribing among physicians (Savelli et al., 1996).

The rapidly rising cost of drug therapy is a concern to healthcare provider in developing countries such as Malaysia. At least RM 1,510 million was spent annually in the procurement of drugs alone for the public hospitals throughout Malaysia (MOH, 2008). The government is finding it hard to subsidize this large spending. The introduction of new drugs which frequently offer only marginal improvements over existing therapies but at substantially increased cost does contribute to the heavy spending on drugs (Kessler et al., 1994). One means of controlling the overall drug expenditure is through the development of drug formulary. Rational selection of drugs through a structured and stringent selection process will only allow medications which are listed to be prescribed. Reducing the number of drug entities of the same therapeutic class with only slight differences in terms of clinical effectiveness and adverse effect can further help in containing cost (WHO, 2003).

2.1 Therapeutic substitution

A study on preferential listing of a single drug within a drug class was done in the Canada Forces (CF) in 2003 to control drug procurement cost. An observational cohort study was performed using the database in the Canadian Forces Pharmacy and a total number of 4738 PPI users who receive more than 1 PPIs between 1 January 2004 – 31 December 2004 were evaluated to explain the usage pattern of PPIs. The study selected pantoprazole as the most preferred agent in the PPI class based on clinical evidence, availability of dosage forms and costs while removing esomeprazole, lansoprazole, omeprazole and rabeprazole from the CF Drug Benefit List. Studies showed that very marginal difference in efficacy exist between PPIs when prescribed at equivalent doses (Amidon et al., 2000; Gearson et al., 2000). In the study, 87% (n=4112) were prescribed pantoprazole while 13.2% (n=626) received other PPIs. The reasons for those prescribed with other PPI drugs other than pantoprazole were 'failure to respond', and side effects with pantoprazole. The CF Pharmacy spent Can$ 214,451.98 for the year from 2003 to 2004 for pantoprazole alone, taking over 50% of cost associated with the PPI class of Can$431,504.42 which includes PPI drugs other than pantoprazole and the stocking up of intravenous pantoprazole in standardized military medical kits for use during deployment (Ma et al., 2008). Therefore, cost savings with therapeutic substitution will only be achieved with stringent policies and full compliance from physicians.

2.2 Drug Formulary

The conventional way of developing a formulary system usually involve a process whereby the medical staff of an institution, working through a Formulary and Therapeutics Committee, manages, evaluates and selects from the numerous

available drug products that are considered most efficacious, safe, and cost effective. It is a mechanism to streamline procurement activities, minimize costs and optimize patient care (Savelli et al., 1996).

The MOH Drug Formulary is one example of drug formulary developed using the conventional method. The MOH Drug Review Panel which comprise of the Director General of Health Malaysia (chairman), the Deputy Director General of Health (Medical Services), the Director of Pharmaceutical Services, 8 Consultants in Public Service, 2 Pharmacists in Public Service and a Senior Pharmacist in Public Service (secretary) will review and update the drugs listed in the formulary from time to time to ensure that a comprehensive, evidence-based and dynamic list of drugs is available for prevention and treatment of patients. The MOH Drug List Review Panel will meet two to three times per year to consider proposals received from the State / Institution Drug committees. The panel is assisted by 17 Technical Drug Working Committees from various specialised disciplines (MOH Drug Formulary Manual, 2008). The existing formulary system employs a disadvantageously very time consuming and not so transparent procedure to complete an approval and / or disapproval application.

In order to make the existing process to be more objective and transparent, a flexible and rational tool that exclude emotional factors, advertising influence or even cost interest can be develop. This tool can be used for any evaluation that requires re-assessment with time or provides ease of updating to accommodate changes in the context in which selection decisions are being made. This tool will be of great help to

the Formulary and Therapeutics Committee especially in drugs decision process as it becomes clear on which criteria the decisions are based on.

2.3 Drug selection system

Many drugs selection tools such as the Pharmaceutical Product Drug Differential Evaluation (PPDEM), Comparative Utilization of Resource Evaluation Model (CURE), System of Objectified Judgement Analysis (SOJA) and Formulary Analysis have been developed and used for formulary purposes worldwide (Janknegt et al., 1997; Karr, 2000; Moore et al., 2002).

Drug selection methods should be able to aid in providing optimal drug therapy to all patients through the development of standard treatment guidelines, to objectively evaluate clinical data of new drugs proposed for use in hospitals, to prevent unnecessary duplication of drugs, to develop list of drugs accepted for procurement and use in the hospital, to recommend and approve additions and deletions from the formulary and to conduct ongoing drug use evaluation programs (Savelli et al., 1996).

PPDEM is an analytical tool to support evaluations on drugs selection. PPDEM is usually used to distinguish selection criteria of drugs belonging to the same therapeutic class of drugs which were used to treat a particular prevalent disease (Karr, 1994; Rawlins, 1999).

CURE is a similar flexible model for drugs evaluation and selection that can differentiate drugs within the same therapeutic class which includes criteria such as efficacy, safety, side effects and cost. The advantage of CURE over PPDEM is the inclusion of an additional criterion called climate for change. Climate for change includes the experience factor of the prescriber, hospital readiness to change to a new drug, patient acceptability of changing to new drugs when the current drugs works well on them, resource benefit where by changing to a new drug with only marginal cost savings is gained and frequency of review especially when new drugs are launched at a fast pace, the susceptibility of the prescriber and patient to alter the prescribing practice. CURE model provides decision makers with an analytical tool to support evaluations on drug selections and also intended to stimulate discussion or debate by decision makers and may assist in providing a suitable mechanism for producing the decision itself. CURE model is auditable, flexible and it accommodates changes.

A Formulary Analysis on angiotensin receptor blockers (ARBs) was done in the Sheffield Teaching Hospital Trust, England. Six ARBs which consist of candersartan, eprosartan, irbersartan, losartan, telmisartan and valsartan were reviewed and evaluated by a panel of cardiologists, a physician and a pharmacist. Nine selection criteria were developed as a comparison framework between these drugs. A relative weight was assigned to each criterion by the panel. Each ARB was systematically evaluated against each criterion and scores were calculated. Results obtained were presented and recognized by the hospital's P&T committees. Losartan was ranked the highest (707), followed by valsartan (611) and candersartan (610) (Moore et al., 2002).

Another structured approach to the selection of drugs for formulary inclusion was of System of Objectified Judgement Analysis (SOJA) which was first developed in The Netherlands for the evaluation of hypnotics, NSAIDs and ARBs. The criteria included in the method for hypnotics drugs selection were clinical efficacy (300 points), adverse effects (250 points), clinical documentation (150 points), cost (120 points), pharmacokinetic properties (80 points), toxicity (50 points), drug interactions (30 points) and the number of tablet strengths available (20 points).

A slight modification of the SOJA system was then developed which was tested on the selection of ACE Inhibitors (ACEIs) in Northern Ireland. ACEIs included in the study were captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinalapril and trandolapril. The relative weighting for each drug were assigned to each criterion and were determined by a panel of expert which consisted of a consultant cardiologist, a general practitioner, two pharmacists, a regional pharmaceutical procurement manager, a hospital pharmaceutical services manager and a health economist. The selection criteria for ACEI were based on evidence based pharmacotherapeutic evaluation for all the ACEIs, safety and cost impact. Relative weightings were then assigned to the criteria by the expert panel. The resultant scoring system containing the selection criteria as well as the weighting scores was validated by 103 key decision makers and secondary care consultants in Northern Ireland, the association of British Pharmaceutical Industry, the British General Manufacturing Association and the Parallel Pharmaceutical Distribution Industry. These prescribers were asked to comment on the allocation of the scores and to change the scores and give importance to the criteria by adding and removing

criteria. The last step involved scoring of the individual ARBs by 33 expert panels (7 cardiologists, 6 nephrologists, 8 pharmacists 2 endocrinologists, 2 internal medicine consultants, 1 senior geriatrician and 7 decision makers) using published literature as well as from both proprietary and generic manufacturers within the class of ACEIs. Only 5 ACEIs i.e. trandolapril, lisinopril, ramipril, enalapril, fosinopril scored the highest and were included in the drug formulary. Modified SOJA allows drug selection within a drug class across a range of indications and confers clinical effectiveness primacy over cost (Alabbadi et al., 2006).

SOJA, modified SOJA, Formulary Analysis, PPDEM and CURE are scoring systems that can be used to evaluate and then re-evaluate drugs in the same therapeutic class whenever there is new update on the drugs (Karr, 1994; Rawlins, 1999; Janknegt et al., 1997). The summary of each tools were demonstrated in Tables 2.1, 2.2 and 2.3.

Table 2.1: Comparison between drug selection methods in terms of criteria

Drug Selection Method	Criteria
PPDEM	Efficacy, safety, cost
CURE	Efficacy, safety, cost, climate for changes
Formulary Analysis	Efficacy, safety, cost
SOJA	Documentation, efficacy, safety, cost
MOH Drug Formulary	Efficacy, safety, cost

Table 2.2: Comparison between drug selection methods in terms of evaluator

Drug Selection Method	Evaluator
PPDEM	Expert panel which consists of consultants and healthcare providers
CURE	Expert panel which consists of consultants and healthcare providers
Formulary Analysis	Expert panel which consists of consultants and healthcare providers
SOJA	Expert panel which consists of consultants and healthcare providers
MOH Drug Formulary	Expert panel which consists of consultants and healthcare providers

Table 2.3: Comparison between drug selection methods in terms of weightage

Drug Selection Method	Scores
PPDEM	Arbitrary; Depend on the degree of importance in the evaluation process. The more important criteria will assigned a higher score. Total score:100
CURE	Arbitrary; Depend on the degree of importance in the evaluation process. The more important criteria will assigned a higher score. Total score: 100
Formulary Analysis	Arbitrary; Depend on the degree of importance in the evaluation process. The more important criteria will assigned a higher score. Total score:1000
SOJA	Arbitrary; Depend on the degree of importance in the evaluation process. The more important criteria will assigned a higher score. Total score: 1000
MOH Drug Formulary	Highly dependent on panelists' experiences, evidence-based information No score points.

2.4 Gastroesophageal reflux disease (GERD)

GERD is the retrograde movements of gastric contents from the stomach into the esophagus which can cause inflame and damage to the lining of the esophagus. The regurgitate liquid usually contains acid and pepsin. GERD symptoms can vary from mild to severe; from typical symptoms include heartburn, belching, hypersalivation, and regurgitation without endoscopically demonstrated esophagitis, to severe esophageal mucosal damage such as peptic stricture and Barrett's metaplasia (Devault & Castell, 1999).

The normal function of lower esophagus sphincter (LES) is to produce contraction and closing of the passage from the esophagus into the stomach. This closing

prevents reflux. When food is swallowed, the LES relaxes for a few seconds to allow the food to pass from the esophagus into the stomach, and then contracts and closes again. Weak contraction of the LES and transient LES relaxation which caused abnormal relaxation of LES are dysfunctions of the LES that cause GERD. Other factors that may contribute to GERD are hiatal hernias, pregnancy and obesity (Devault & Castell, 2005).

The goals of treatment for GERD include:

i. relieving symptoms
ii. healing of esophagitis
iii. prevent further symptoms and complications.
iv. prevention and recurrence of the disease

There are two grading scheme that has been used in endoscopic assessment in comparative clinical studies. The Savary-Miller grading scale is the most commonly applied while the Los Angeles (LA) scale is the most often used grading scale for reflux esophagitis. Table 2.4 and Table 2.5 are the classifications of the grading scheme for the Savary-Miller grading scale and the LA scale:

Table 2.4: The Savary – Miller classification of reflux esophagitis

Grade	Descriptions
I	Single erosion above gastro-esophageal mucosal junction
II	Multiple, non- circumferential erosions above gastro-esophageal mucosal junction
III	Circumferential erosions above mucosal junction
IV	Chronic change with esophageal ulceration and associated stricture
V	Barett's esophagus with histologically confirmed intestinal differentiation with columnar epithelium

Table 2.5: The LA classification of reflux esophagitis

Grade	Descriptions
A	One or more mucosal break not longer than 5 mm, that does not extend between the tops of two mucosal folds
B	One or more mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
C	One or more mucosal break that is continuous between the tops of two or more mucosal folds but involves less than 75% of the circumference
D	One or more mucosal break which involves at least 75% of the circumference

(Gut. 1999; 45:172-180 Lundell et al., 1999)

2.5 Clinical Practice Guidelines

As stated in the 2004 Asia-Pacific Consensus on the management of GERD, lifestyle modifications are commonly used as first line of therapy in patients presenting with GERD-related symptoms. They include weight loss, smoking cessation, avoidance of postprandial recumbency for a period of at least 3 hours, elevation of the head of the bed, avoidance of tight-fitting garments, and avoidance of large heavy meals as well as food and drink that exacerbate GERD symptoms (e.g. spicy foods, fatty meals, peppermint, chocolate, onions, citrus juices, and carbonated beverages) (DeVault & Castell, 2005)

PPIs are the most efficacious medical intervention for GERD. Studies have shown repeatedly and consistently that PPIs are superior to H_2-receptor antagonists (H_2RAs) in healing the esophageal mucosa and relieving GERD related symptoms of patients with ERD (Caro et al., 2001). In a meta-analysis, the authors demonstrated that after

12 weeks of treatment, healing rates were 83.6% with PPIs, 51.9% with H_2RAs, 39.2% with sucralfate, and 28.2% with placebo (Chiba et al., 1997). In addition, treatment with PPIs resulted in healing rates of esophageal inflammation and relief of heartburn symptoms that were two-fold higher than what was observed in patients receiving H_2RAs. Similarly, PPIs demonstrate superiority in relieving heartburn symptoms in patients with NERD when compared to H_2RAs (Richter et al., 2000).

According to NICE guidance for dyspepsia (2004), patients who are present with typical GERD symptoms should be started on full dose PPI for 4 – 8 weeks. If patients have severe esophagitis and remain symptomatic, double-dose PPI for a further 4 weeks may increase the healing rate. PPIs appear more effective than H_2RAs in endoscopy-negative reflux disease. For recurring symptoms, a PPI at the lowest dose possible should be given to control symptoms, with a minimum number of repeat prescriptions. PPIs are more effective than H_2RAs at maintaining against relapse of esophagitis in trials of 6–12 months duration (NICE, 2004).

American Gastroenterology Association (AGA) drew the same guidelines and it was adopted by the National Guidelines Clearinghouse on GERD that lifestyle modifications should be recommended throughout the treatment of GERD. This is followed by pharmacological treatment such as H_2-receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), and prokinetics. For non-erosive reflux disease (NERD), step-up (H_2RAs followed by a PPI if no improvement) and step-down (PPI followed by the lowest dose of acid suppression) therapy are equally effective for both acute treatment and maintenance. On-demand (patient-directed) therapy is the most cost-effective strategy. For erosive esophagitis, initial PPI therapy is the

treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis. Antireflux surgery is an alternative modality in the treatment of GERD in patients who have documented chronic reflux with recalcitrant symptoms (DeVault & Castell, 2005).

2.6 Pharmacology of PPIs

All PPIs are substituted benzimidazoles that suppress the final step in gastric acid secretion by binding to the proton pump (H^+/K^+-ATPase enzyme system) on the gastric parietal cell. The proton pump inhibitors are given in an inactive form. In an acidic environment, the inactive drug is protonated and rearranges into its active form. The active form will covalently and irreversibly bind to the gastric proton pump, deactivating it. Minor differences exist among PPIs with respect to the mechanism of action within the parietal cell (Vanderhoff & Tahboub, 2002). Rabeprazole forms a partially reversible bond with the proton pump (Vanderhoff & Tahboub, 2002). Pantoprazole preferentially binds avidly to an additional acid inhibiting cycteine residue located deep within the membrane which greatly impairs the reversibility of bindings and prolongs duration of action (Welage & Berardi, 2000). Once inhibition occurs, recovery can only occur with regeneration or resynthesis of new ATPase. Recovery is therefore generally a relatively slow process compared with the initial inactivation (Fock et al., 2008).

2.7 Pharmacokinetics of PPIs

Table 2.6 showed the pharmacokinetics of the five PPI drugs. The absolute bioavailability ranges from 35% for a single dose of omeprazole to 90% with repeat administration of esomeprazole. Unlike other PPIs, the bioavailability of rabeprazole

remains unchanged with repeated dosing. On the whole, the time to reach the peak plasma concentration (t_{max}) is about 2 hours. After absorption into the circulation, PPIs are taken up preferentially by gastric parietal cells, especially when they are actively secreting acid. Once inhibition occurs, recovery can only occur with regeneration or resynthesis of new ATPase. These mechanisms suggest that despite the short elimination half-lives, the biological effect persists for much longer (Fock et al., 2008).

All PPIs are extensively protein bound and undergo hepatic metabolism via the cytochrome CYP-450 pathways and the isoforms CYP2C19 and CYP3A4. Esomeprazole is the S-isomer of omeprazole, which is a racemic mixture of two optical isomers, the R- and S-isomers. However, esomeprazole and the omeprazole differ in the ratios in which they are metabolised by CYP2C19 and CYP3A4. Esomeprazole is metabolised to a greater extent by CYP3A4 than omeprazole and to a lesser extent by CYP2C19 (Abelo et al., 2000). The metabolism of rabeprazole does not appear to be significantly affected by CYP2C19 where in one particular study on rabeprazole showed similar healing rates at 4 and 8 weeks were obtained in extensive metabolisers (EMs), intermediate metabolisers (IMs) and poor metabolisers (PMs) (Ariizumi et al., 2004), whereas for omeprazole, lansoprazole and pantoprazole, a marked difference in metabolism exists between EMs and PMs (Ishizaki & Horai, 1999). At 4 weeks, the healing rates were 57.1%, 69.2% and 72.7% in EM, IM and PM, respectively, while the healing rates at 8 weeks were 77.4%, 95.0% and 100%, respectively (Kawamura et al., 2003). These differences in polymorphisms affect the metabolic and pharmacokinetic profiles of PPIs and may influence the therapeutic effectiveness. Esomeprazole has a lower total intrinsic

clearance than omeprazole, and its first-pass metabolism is decreased compared with omeprazole. The advantageous metabolism of esomeprazole results in higher area under the plasma concentration-time curve (AUC) values than those for omeprazole at the same dose, and hence may achieve better acid suppression than omeprazole in clinical practice (Fock et al., 2008).

Rabeprazole, lansoprazole and pantoprazole have similar bioavailability on days 1 and 5. The bioavailability of omeprazole increases 1.5 to 2 fold at day 5, while that of esomeprazole increases 3 fold at day 5 (Hellstrom & Vitols, 2004).

The currently available PPIs have short elimination half-lives ranging from 1 to 1.5 hours. A PPI with a longer elimination half-life may produce more prolonged blockade of proton pumps with the potential for greater acid suppression and, hence, a greater clinical effect, particularly for patients with significant postprandial evening and/or nocturnal symptoms. Table 2.6 summarizes the pharmacokinetics of all PPI drugs (Fock et al, 2008).

Table 2.6: Pharmacokinetics of PPIs

Parameter	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Bioavailability	90%	80%-85%	30%-40%	77%	52%
Time to peak plasma concentration	1.5 hours	1.7 hours	0.5-3.5 hours	2.5 hours	2-5 hours
Half-life (plasma)	1.2-1.5 hours	1.5 hours	0.5-1 hour	1 hour	1-2 hours
Major cytochrome P450 pathway	CYP2C19	CYP3A, CYP2C19	CYP2C19	CYP2C19	CYP3A CYP2C19
Protein binding	97%	97%	95%	98%	96.3%

2.8 Clinical Efficacy of PPI drugs

All double blind randomized studies that were published comparing two or more PPIs or doses for the treatment of acute gastroesophageal disease (GERD) were obtained. The prospective evaluations of measurable clinical efficacy such as healing of esophagitis or symptoms resolution were summarized in Appendix A.

In one study comparing esomeprazole 40 mg, esomeprazole 20 mg and omeprazole 20 mg once daily, pH > 4 was maintained for 16.8 hours, 12.7 hours and 10.5 hours respectively (Lind et al., 2000). In another study involving 2425 patients with erosive esophagitis, esomeprazole 40 mg and omeprazole 20mg were compared at 4 and 8 weeks. At 4 weeks, 93.7% on those on esomeprazole and 84.3% of those on omeprazole were healed (Richter et al., 2001). One study with 1960 patients with erosive esophagitis, it was found that esomeprazole 40 mg, esomeprazole 20 mg and omeprazole 20 mg have healing rates of 94.1%, 89.9% and 86.9% respectively (Kahrilas et al., 2000). These studies were often cited as evidence of the superiority of esomeprazole in esophageal healing, but it should be noted that the dose is not comparable. A meta-analysis concluded that esomeprazole healed erosive esophagitis at significant higher rates than omeprazole (Edward et al., 2001). However, all the studies were funded by AstraZeneca and two out of the three authors are employed by AstraZeneca.

In the only study that use comparable dosages of esomepazole and omeprazole at 40 mg respectively, those taking esomeprazole maintained a gastric pH > 4 for a mean of 16.4 hours while those taking omeprazole maintained for 14.9 hours. However, its small sample size of 114 patients limits its validity (Rohss et al., 2002).