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THE USE OF THE GENERAL MEDICAL SERVICES PRESCRIPTION DATABASE FOR PHARMACOEPIDEMIOLOGICAL STUDIES IN IRELAND

David Williams

A thesis submitted for the degree of doctor of philosophy

University of Dublin, Trinity College

2002

DECLARATION

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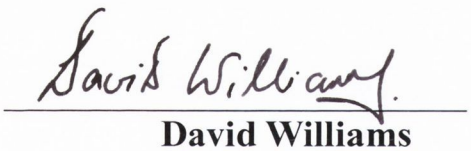

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Dedication

This thesis is dedicated to my wife Mary, who provided endless support and encouragement and to my daughters Lorna and Jennifer, who made it all worthwhile

Summary

Pharmacoepidemiology may be divided into three main subdivisions, namely pharmacovigilence, drug utilisation and prescribing quality. An aim of this thesis was to demonstrate the usefulness of the General Medical Services (GMS) prescription database to perform pharmacoepidemiological studies in Ireland. This database provides information on some 30% of the population who receive approximately 70% of prescriptions. In the field of pharmacovigilence I demonstrated the effect of external forces particularly the media and regulatory advice on prescribing patterns within the GMS which led to a marked decline in the use of third generation contraceptive steroids and cotrimoxazole. An attitudinal survey on adverse drug reaction(ADR) reporting by doctors confirmed the findings of other workers regarding the reasons for not reporting ADRs and highlighted the need to improve reporting rates.

Drug utilisation studies illustrated the extent of multiple drug use within the GMS and indicated that the elderly population were particularly likely to be exposed to major polypharmacy. A study of *Helicobacter Pylori* eradication demonstrated that over 50% of patients who receive such therapy will require subsequent anti-ulcer medications within six-months. Prescribing quality was studied by applying a number of recognised and newly developed prescribing indicators to prescription data which general practitioners felt were useful and could be used as a form of feedback on prescribing practice. An index of prescribing quality using the principle that avoidance of potential interactions e.g warfarin and H_2-antagonists could be used as a measure of prescribing quality was developed. Adherence to recognised prescribing guidelines was

also examined. There is evidence that women receive less secondary preventive therapies compared with men in the management of ischaemic heart disease. Adherence to prescribing guidelines for sildenafil indicated that prescribers exercised caution and avoid potential drug interactions. Nonetheless drugs associated with the development of impotence were prescribed to a significant degree indicating a possible cause of the underlying condition or that sildenafil is being prescribed to counteract such side-effects. Furthermore the initial fears regarding the economic impact of the prescription of sildenafil within the GMS were unfounded.

The second aim of the thesis was to determine whether material deprivation influenced prescribing patterns. It was possible to demonstrate that even within the materially deprived GMS population, that different levels of deprivation influenced prescribing patterns. In particular the prescribing of symptomatic centrally active agents e.g benzodiazepines increased with increasing deprivation, whereas the prescription of disease specific centrally active drugs such as antidepressant and antiparkinsonian therapies fell with increasing deprivation.

The GMS prescription database provided an important resource for performing studies of pharmacovigilence, drug utilisation and prescribing quality. By identifying a particular treatment and an outcome which can be measured in terms of drug therapy, it is possible to use the GMS prescription database for hypothesis testing even if one is constrained by a lack of diagnosis. Finally the reasons for the apparent inequalities in drug prescribing with respect to material deprivation will require further study. The GMS prescription database provides an important source of prescription data for

epidemiologic studies. It provides reliable data to expand the knowledge about the use and effects of drugs in the general population and could with the appropriate safeguards and consent be used to examine individual doctor or individual patient prescribing in Ireland and will have an important role to play in the continued development of pharmacoepidemiology in Ireland.

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LIST OF ABBREVIATIONS USED IN THIS THESIS

ADR: Adverse Drug Reaction

BNF: British National Formulary

CSM: Committee for Safety of Medicines

DURG: Drug Utilisation Research group

GMS: General Medical Services

EHB: Eastern Health Board

ERHA: Eastern Regional Health Authority

MIMS: Monthly Index of Medical Specialties

PPA: Prescription Pricing Authority

SAHRU : Small Area Health Research Unit

SPR: Standardised Prescribing Ratio

Chapter 1 - Introduction

1.1 Pharmacoepidemiology

Epidemiology is the study of the distribution and determinants of health and disease within populations. The term pharmacoepidemiology first appeared in the medical literature in a British Medical Journal editorial by Lawson [1]. This name was needed for a proper definition of the two essential disciplines- pharmacological, defining both beneficial as well as adverse drug effects, and epidemiological, studying the response of the population to these effects. While the discipline is relatively new, the use of medicines in the fight against illnesses captured the interest of epidemiologists at least as long ago as the turn of this century. Therefore, although it may not have been fully recognised as a distinct discipline until the 1980's, the practice of pharmacoepidemiology is not new [2].

Pharmacoepidemiology is the application of epidemiological reasoning, methods and knowledge to the study of the uses and effects (be they beneficial or not) of drugs in human populations. Pharmacoepidemiology has been described as a crossing of scientific paths between epidemiology, which studies disease occurrence, and pharmacology, which aims to reduce disease incidence and prevalence through interventions with drugs. Pharmacoepidemiology lies at the intersection of two such paths: clinical pharmacology and clinical epidemiology. It examines the population and the diseases that medications are used to treat, along with the benefits and problems associated with their use. Pharmacoepidemiological studies may examine a single individual (e.g. a case report of a rare drug reaction), or larger groups of individuals who are followed for many years. Information is

gathered and analysed to identify possible causation and related factors that can be applied in clinical practice to groups of people and also to individuals undergoing treatment.

1.2 Origins and evolution of pharmacoepidemiology

Current pharmacotherapy has developed largely during the 20th century. However, as modern effective drugs became increasingly available and used in large populations, appreciation of their potential for producing adverse drug reactions (ADRs) emerged, as well as other therapeutic problems including drug resistance, abuse and unexplained variations in rates of clinical effectiveness.

The awareness of the potential for drugs to cause adverse effects became evident to the general population in 1961 when case reports in the literature associated the maternal use of thalidomide with foetal malformations [3]. Although not the first drug to produce serious ADRs, the nature of the effect was so dramatic that much attention became focussed on the detection, prevention, and management of ADRs. It was the stimulus for the formation of many drug regulatory authorities. It also began the era of pharmacoepidemiology. Subsequently subdivisions have emerged where there was a focus on drug safety (pharmacovigilance), the quantity of drug use (drug utilisation) and quality prescribing.

1.3 Pharmacovigilance

Pharmacovigilance is the process of identifying and then responding to safety issues about marketed drugs and is the foundation upon which pharmacoepidemiology has developed. In the wake of the thalidomide disaster[3] a system for reporting adverse drug reactions was developed. This

system now operates in some 30 countries. Whilst the adverse drug reaction (ADR) reporting system can identify potential problems with drugs, determination of causation requires population-based studies of adverse events, which attempt to link unequivocally the adverse outcome to the drug in question. Examples of ADRs detected using these surveillance systems include the association of grey baby syndrome with chloramphenicol and of vaginal cancer in adolescent offspring of women who took diethylstilbestrol in pregnancy [4;5]. More recent concerns include associations of birth defects with isotretinoin [6], central nervous system (CNS) disturbances with triazolam [7] and venous thromboembolism with oral contraceptives [8-10]. Not all of these associations have been substantiated and by their nature often receive intense media attention [11;12]. In some instances drugs which had previously been withdrawn as a result of an adverse drug event have been reintroduced in special instances. Examples include thalidomide for the treatment of leprosy and clozapine for the treatment of schizophrenia.

The thalidomide disaster had profound effects on the development of new drugs, the pharmaceutical industry, and professional and public attitudes to drug safety. Despite attempts to improve the pre-marketing evaluation of new drugs, issues of safety continue to result in drug withdrawal. As a result pharmacovigilance is closely linked to post marketing surveillance, a term which refers to a specific period in the life of drug when it enters the general market. Post marketing surveillance is important because at the time a drug is approved for marketing, answers to important questions are only partially known. Such questions include:

- The long-term effects of drugs (e.g. in the prevention of chronic diseases or their complications, effects that manifest after long periods of use or after a long latency period).
- Low frequency effects, whose magnitude can only be established in large populations
- The effectiveness of drugs for their licensed indications or in new indications.
- Other factors that modify the efficacy, effectiveness and efficiency of drugs (lifestyle, co-morbidity, concurrent medications and socio-cultural factors).

Answers to questions on the safety and efficacy of drugs cannot always be provided even by the most valid, complex and lengthy pre-marketing studies and it is often more reasonable to expect that such answers be obtained by post marketing/phase IV epidemiological studies, be they observational or experimental. In addition it may well be ethically and scientifically sound to allow a drug to be marketed if well-designed epidemiological studies are initiated at the very moment of marketing approval.

The spontaneous reporting of adverse drug reactions (ADRs) is thus a fundamental safety net to limit the toxicity of marketed medicines. However a difficulty with this reporting system is the low level of reporting of adverse drug reactions by physicians world-wide [13] with less than 10% of all serious and 2-4% of non-serious adverse reactions being reported [14]. In 1997 the regulatory authority in Ireland, the Irish Medicines Board, received only 1,775 reports (35% from general practitioners, 12% from hospital doctors)[15] and yet some 20 million prescription items are dispensed each year in the General

Medical Services (GMS) scheme (which excludes hospital and private practice). In a previous study spontaneous adverse drug reactions were reported in less than 1 in 500 hospitalised patients whilst more intensive monitoring revealed a 10% occurrence [16]. One would thus expect a higher rate of reporting. As a result there is a need to determine the attitudes of Irish prescribers to adverse drug reactions.

1.4 Drug utilisation

The related field of drug utilisation developed in parallel with the study of adverse drug reactions. It began in the early 1960s both in North America and Europe [17]. Previously, drug utilisation studies had been conducted mostly for marketing purposes and data were not available for use by academic researchers or health authorities. The increased interest was in recognition of the dramatic increase in the marketing of new drugs, the wide variations in the patterns and extent of drug prescribing, the growing concern about ADRs and the increasing costs of drugs.

The World Health Organisation (WHO) defines drug utilisation as the 'marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences' [18]. In Europe, drug utilisation research developed at a national and international level with a common methodology for comparative drug utilisation studies, exploiting relatively inexpensive and readily available sources of drug statistics[17].

1.4.1 Units of measurements in drug utilisation studies

A number of different measures of drug utilisation are available and have been applied in different situations[17].

1.4.1.1 Monetary units

Drug use has been measured in monetary units to quantify the amounts being consumed by populations. It can be used to indicate the burden on a society from drug use. Monetary units (e.g. dollars, pounds etc.) are convenient and can be converted to a common unit such as the EURO which then allows for international comparisons. However there are a number of disadvantages in that the quantities of drugs actually consumed are not known and prices may vary widely, especially for different strengths and pack sizes of drugs.

In the UK, cost per item and cost per patient have been conventionally presented as prescribing statistics. Cost generally indicates net ingredient cost (NIC). This does not include additional fees to pharmacists, which in the UK add a further one-third to the total cost of the national drug bill [19]. In Ireland additional fees to pharmacist add up to 50% to the cost of a dispensed prescription

1.4.1.2 Numbers of prescriptions

Numbers of prescriptions have been used in research due to the availability and ease of use of this method. The difficulty with this method is that the quantities dispensed vary greatly, as does the duration of treatment. Without a diagnosis and other demographic data, the use of prescription numbers is at best a rough estimate of drug use. However for short-term treatments like antibiotics, the number of prescriptions may, however, provide a fairly good estimate of the number of people exposed and the number of treatment episodes.

1.4.1.3 Units of drug dispensed

Like the prescription unit, units of drug dispensed (e.g. packs, tablets) is easy to obtain and can be used to compare usage trends within countries. However, as with all sources on drug use, no information is available on the quantity of drug actually taken by the patient (e.g. one or four tablets may be taken daily). Thus it is difficult to determine the actual number of patients exposed to the drug. Patterns can however, be compared and hypotheses generated about excessive use or under use in some areas.

1.4.1.4 Defined Daily Doses (DDDs)

The concept of daily defined doses (DDDs) was originally developed in Scandinavia and is now promoted under the auspices of the WHO in an effort to produce a standard measure of drug utilisation. The DDD is a standardised unit of volume for use in drug utilisation studies. It is defined as the estimated average maintenance daily dose of a drug when used for its major indication in adults [20] and is a notional unit which does not necessarily reflect the dose in which the drug in question might be used. For example the daily defined dose of the lipid lowering agent pravastatin is 20mg whereas the standard daily dose used in the international clinical trials was 40mg [21]. Utilisation is normally expressed as DDDs/1000 inhabitants/day, which allows for comparisons between countries or regions. A variation adapted for use in hospitals is the DDD/100 bed-days, adjusted for occupancy [22].

This method has been useful in describing and comparing patterns of drug utilisation, and provides denominator data for estimation of adverse reaction rates, performing epidemiological screening for problems in drug utilisation, and monitoring the effects of informational and regulatory activities. The

advantages of this method is its usefulness for working with readily available drug statistics at various levels of the health chain. As a standardised unit of measurement, it allows comparisons between drugs in the same class, between different healthcare settings or geographic areas, and evaluations of trends over time. For chronic diseases such as diabetes and Parkinson's disease, the concept of DDD/1000 inhabitants/day also provides a rough estimate of the prevalence of the drug-treated population [23].

As mentioned above the DDD methodology also has some significant limitations. The DDD is not a recommended dose, but rather a technical unit of comparison. Many drugs have not yet being assigned DDDs, but guidelines have been published by the WHO Collaborating Centre For Drug Statistics Methodology in Oslo [24] for defining DDDs under these circumstances. Paediatric uses are usually not considered in any calculations. In this situation local paediatric formularies are often referred to. There are also no DDDs available for dermatological preparation. Problems can also arise when doses vary widely, such as with antibiotics or where there is more than one indication for a drug. One example is aspirin, which may be used in low doses in the prevention of ischaemic heart disease, moderate doses for pain, and high doses for inflammatory conditions.

1.4.1.5 Prescribed daily doses (PDD)

Because the DDD does not always reflect actual clinical practice, another unit- the prescribed daily dose (PDD)- is sometimes used. This is based on the average daily dose actually prescribed in a representative sample of prescriptions. The PDD may be a better measure for comparison within countries, because it reflects the actual prescribing practice in that country.

However dosage regimens vary considerably between countries; for example that higher PDDs for drugs such as hydrochlorothiazide, diazepam, and oxazepam have been noted in the USA relative to Sweden [17].

1.4.2 Limitations of drug utilisation data

It is important to realise the comparative limitations of drug utilisation data. The main deficiency is that it is usually impossible to determine the appropriateness of a particular prescription for an individual patient. For example, the consumption of H_2-receptor antagonists might be similar in two separate practices. However it is theoretically possible that all the prescriptions issued by doctors in one practice are 'appropriate'-i.e. all are for the recognised indications of H_2-receptor antagonists such as the treatment of peptic ulcer- and all the prescriptions issued by doctors in the second practice are 'inappropriate', with none of those who should receive H_2-receptor antagonists actually receiving them. The development of record-linkage where a patient's diagnosis is 'linked' to prescription data will help to determine the appropriateness of a particular prescription. By linking all the medical information about individuals in a population, even where this information originates in different data sources, all medical events can be considered together.

1.4.3 The importance of record-linkage for prescription databases

There are a large number of international prescription databases used for pharmacoepidemiological studies, some of which are linked to diagnosis (Table 1.1). The term record-linkage was coined by Dunn [25] in 1946 who used it to designate the linking of various records of a person's life with the following analogy:

Not Diagnosis -linked	Diagnosis-linked
North America	National disease and Therapeutic Index
National Prescription audit	Kaiser Permanente Medical Plan
US Pharmaceutical Market-Drug stores	Group Health Cooperative of Puget Sound
US Pharmaceutical market-Hospitals	DURbase®
Medicaid Management Information systems	
Saskatchewan Health Plan	Sweden's Diagnosis and Therapy
Europe	Sweden's Community of Tierp
Swedish National Corporation of Survey Pharmacies Project	
Sweden's Prescription Survey	
Sweden's County of Jutland Project	
Norwegian Medicinal Depot	
United Kingdom's Prescription Pricing Authority	
Spain's Drug Data Bank (National Institute of Health)	
Denmark's Odense Pharmacoepidemiologic Database	
Denmark's Pharmacoepidemiologic prescription Database of the	
County of North Jutland	
COMPASS®	
GMS(Payments) Scheme	

Table 1.1 Examples if international prescription databases some of which are linked to diagnosis, which are used for drug utilisation studies.
(Adopted from pharmacoepidemiology, 2nd edition)

'Each person in the world creates a book of Life. This book starts with birth and ends with death. Its pages are made of records of the principal events in life. Record linkage is the name given to the process of assembling the pages of this book into a volume'.

Thus record-linkage is the systematic bringing together of the records of individuals in a large population. This is particularly important for medical records, as medical data arising from different health care contacts are usually stored separately. By linking all the medical information about individuals in a population, even where this information originates in different data sources, all medical events can be considered together. Record-linkage has been facilitated in recent years by advances in computerisation.

There are two methods by which the linkage of records, belonging to the same individual but stored separately, can be achieved. Deterministic linkage refers to linkage that is based on the use of defined identifiers for each individual. These are usually assigned centrally and used in any records that are kept for that individual. Alternatively, probabilistic linkage is based on combinations of non-unique characteristics of each individual, such as name, date of birth or gender. These standard identifying items are prone to discrepancies due to error or changes in status. Therefore patterns of agreement and disagreement between identifying items are translated into quantitative scores, which are then used to predict whether the two records should be linked.

1.5 Prescribing quality

Drug utilisation studies have tended to concentrate more on the quantity than on the quality of prescribing. However prescribing has become an important issue in the provision of health-related services. Drug prescribing is an integral part of the health care service and represents a relatively safe, effective and inexpensive mode of treatment. There are a number of indicators available, which assume that a consensus has been reached regarding good quality prescribing. An indicator has been defined as a measurable amount of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality of care provided [26]. Inherent in this definition is the concept of medical audit. Audit may be defined in drug use terms as ' a searching examination of the way in which drugs are used in clinical practice carried out at intervals frequent enough to maintain a generally accepted standard of prescribing[27]. Audit focuses on medical practitioners with the aim of improving the rational use of medicines as therapeutic agents. Indeed medical audit and drug utilisation review concepts are essentially the same as both rely on the use of criteria for the evaluation of drug use and tend to be situation specific, with feedback for improvement.

In 1994 the Audit Commission recognised that general practitioner prescribing could not be considered in isolation from other general practitioner activities and services [28]. It proposed that more rational prescribing by general practitioners would lead to better quality care for patients and to major economies in drug expenditure. Prescribing indicators can be seen as part of a number of measures of indicators of quality care which also include measures

such as access to health care and the effective delivery of appropriate health care to patients. Prescribing indicators should not be viewed in isolation from these other measures of health care. The National Primary Care Research and Development Centre in the United Kingdom advocates a wide range of measures for assessing quality in general practice. Campbell *et al.* has assessed the validity of quality indicators (which include prescribing indicators) for use in general practice by health authorities [29].

Generic prescribing is one example of an indicator of prescribing quality which has been applied to Irish prescription data in the past [30]. However little is known regarding the quality of prescribing among general practitioners who are working within the General Medical Services scheme (GMS) in Ireland. Furthermore we have little information on the opinions of Irish general practitioners regarding recognised prescribing indicators.

1.5.1 Medical practice variation

At every level, from the comparison of the prescribing of individual doctors or medical practices, through the comparison of regions to the comparison of countries, large differences in prescribing rates, whether by volume, cost, therapeutic group or individual drug, are characteristic of prescribing practice[19]. At the level of individual practices and even within the same practice there can be large variation in prescribing habits, suggesting that it is the habits and attitudes of prescribers which are also important in addition to patient characteristics. One of the reasons for this variation is that most prescribing is elective and discretionary, with few instances where a medicine is absolutely essential (e.g. insulin).

The age-sex profile alone often cannot explain inter-practice variation in prescribing patterns [31]. In a study of fund-holding practices, Healy showed that 97% of the variation in practice prescribing costs could be explained by differences in practice list size, the proportion of patients aged 65 yrs and over, the proportion of patients living in 'deprived areas' and whether or not the practice qualified for inducement payments [32]. However at a higher level of prescription data, Family Health Services Authorities (FHSAs) in England and Wales, Forster and Frost in 1991 found that 51% of the prescription rates and 44% of the variation in prescribing costs could be explained by variation in the age-sex structure of the authorities [33]. The standardised mortality ratio and the number of general practitioners per head of population significantly improved the predictive power of their statistical model.

There are already well-established links between high mortality and low socio-economic status [34]. Prescribing in urban areas of northern England has been characterised by high volume and low cost per item, whereas prescribing in the more prosperous southern semi-rural areas are characterised by a low volume but high cost per item. Unemployment rates were the most robust determinant of this inverse trend of number of items and cost per item[35]. In a recent study it has been shown that the prescribing of statins in one primary care region increased four fold with the greatest increase occurring in the most deprived areas [36]. Higher levels of antibiotic prescribing have been found in practices serving more deprived communities, in single-handed practices, and in non-training practices [37]. Thus both patient and prescriber characteristics may account for variations in prescribing.

1.6 The use of prescription databases for pharmacoepidemiological studies

In 1992 Bergman summarised the perspectives of pharmacoepidemiology from a European point of view [38]. He emphasised the increasing development, refinement and use of large databases and record linkage systems in North America. He considered that these would provide good quality data for pharmacoepidemiological cohort and case-control studies, as well as for drug evaluation. However he viewed the European scene less optimistically. Despite some pioneering initiatives and innovative developments, such as the Prescription Event Monitoring (PEM) system in England, Bergman believed that Europe needed to develop its own strategy to respond to drug safety issues. The European Medicines Evaluation Agency (EMEA) was set up in January 1995. Its main role is to harmonise the licensing procedures through the European Union (EU). It also has a decisive role to play in the harmonisation of post marketing drug surveillance and pharmacovigilance across European countries.

The last decades have seen a rapid increase in the use of computerised health care data in observational drug epidemiology. A number of databases have been used extensively, primarily in North American countries. Pioneers of such databases include the databases of Group Health Cooperative of Puget Sound, a health maintenance organisation in Washington State, and Saskatchewan Health of the government of the province of Saskatchewan in Canada[4]. Both databases have been used for multiple pharmacoepidemiological studies since that late 1970s. Databases offer many advantages to undertake pharmacoepidemiological studies, including the

ability to recruit a large cohort in a short time and economy of the studies as the data are usually collected for other purposes. Other databases used in pharmacoepidemiology are Medicaid and Kaiser Permanente in the US.

Prescribing databases in addition to describing patterns of drug use within the community can also be used to estimate the burden of disease of those attending a general practitioner by estimating the number of different classes of drugs prescribed per patient. In addition the prevalence of a particular disease in a population can be estimated by determining the use of a drug used specifically for the treatment of the particular disease. For example the prevalence of insulin dependent diabetes mellitus may be estimated by determining the use of insulin in a population. Similarly the use of nitrate therapy (used in the symptomatic treatment of ischaemic heart disease) may be used as a surrogate for estimating the prevalence of ischaemic heart disease in a population.

In Europe, most countries have their populations covered through universal health care systems, which facilitates the generation of complete health care databases of all individuals in these systems. Studies routinely based on European health computerised databases have become available only in the last decade with resources in the UK, Netherlands, Italy and the Nordic Countries. Of all the European databases, the General Practice Research Database in the UK, has been the most widely used for pharmacoepidemiological research.

1.6.1 The United Kingdom General Practice Research Database (GPRD)

Since 1994, this database has belonged to the UK Department of Health, and is maintained by the Office of National Statistics (ONS). Currently around 1500 general practitioners with a population coverage in excess of 3 million, systematically provide their computerised medical data anonymously to ONS. Validation studies of the GPRD have documented the recording of medical data into general practitioners' computers to be near to complete. The GPRD collects population-based data, has a size that makes it possible to follow up large cohorts of users of specific drugs, and includes both outpatient and inpatient clinical information. Most published studies to date have been in the area of drug safety [39].

1.6.2 Prescribing Analysis and Cost (PACT) data

This comprehensive database came as a by-product of the need for the National Health Service in the United Kingdom to price every dispensed prescription to pharmacists through the Prescription Pricing Authority (PPA) and its equivalent in Scotland. The PPA collects information on all prescriptions issued by general practitioners that are dispensed by general practitioners, dispensing general practitioners, or appliance contractors. The information collected includes the name and cost of the drug and the number of items dispensed (an item is defined as each preparation on the prescription). The drugs dispensed are then used to calculate the cost of each item, and the information is entered onto computer by the PPA. Drugs are categorised by the section of the British National Formulary that they fall into. Hence, information is available for individual drugs (such as salbutamol), for categories of drugs (such as bronchodilators), or for therapeutic areas (such as

respiratory drugs). This information is available at individual practice level, health authority level, and national level, allowing different analyses to be performed. Following this analysis, the data are fed back to both health authorities and general practitioners who receive a printed version of the analysis. This information (the standard PACT report) contains information on the practice's rates and costs of prescribing along with comparative information. Traditionally, PACT has been mainly used as a financial tool to help health authorities set and monitor general practice prescribing budgets. However, PACT is now increasingly used for other purposes, including audit and research, improved methods of funding high cost drugs, and the development of practice formularies.

Since prescribing is heavily influenced by general practices' demography, weightings for age and sex have been developed so that rates and costs of prescribing in different practices or health authorities can be compared. Although comprehensive in its coverage of the whole country, and informative in its ability to identify time trends and inter-regional variations, this large database however was not designed for drug utilisation studies. Its main deficiencies are that it contains only prescription data, with no indication of diagnosis. It cannot distinguish acute from repeat prescriptions and individual prescriptions cannot be reliably assigned to individual doctors making inter-doctor comparison difficult. In addition the data cannot be linked to demographic data on patients. Hence, they cannot be used to calculate age and sex-specific prescribing rates or to look at prescribing for specific conditions. In addition as PACT data is based on dispensed NHS prescriptions, they do not include private prescriptions or prescriptions that a patient does not have

dispensed. It has been shown that up to 15% of patients over a three-month period do not redeem their prescriptions, with the highest non-redemption rate occurring at weekends indicating that observational studies of drug exposure may be more accurately estimated from dispensing rather than prescribing data [40]. The number of items prescribed is not always an accurate measure of the amount of a drug actually prescribed. Daily-defined doses (which can be calculated from PACT data) can be used to overcome this problem and provide a more accurate measure of the amount of a drug prescribed than the number of items. Finally, PACT tells us only about the prescribing carried out in general practice and does not contain any information on prescribing in hospitals [41].

1.6.3 The Medicines Monitoring Unit (MEMO)

MEMO is a university-based research organisation that record-links data for the population of the Tayside region of Scotland. This is enabled by the widespread use of the Community Health Index Number (CHNo) in Tayside which is a 10-digit number allocated to all patients when they register with a general practitioner in Scotland. The number is unique and specific to each patient, with the first six digits representing date of birth, then a three-digit serial number, the last digit of which indicates sex, and finally a check sum digit to ensure the validity of the CHNo. If a patient is assigned more than one CHNo in error, these can be linked together. The Community Health Index is a computerised list of the CHNo's of all GP-registered patients, containing names and addresses and up-to-date demographic details.

MEMO's role in pharmacovigilance is the post marketing surveillance (PMS) of drugs and it was for this purpose that the record-linkage database was

originally constructed at MEMO. The pivotal datasets are an 'exposure' database of dispensed prescriptions, and an 'outcome' database of hospital admissions. The exposure database is compiled from copies of all prescriptions that have been dispensed in community pharmacies in Tayside, and includes drug and patient details recorded on the form. In the past number of years, a number of studies have linked outcome databases to the dispensed prescribing database in MEMO to quantify the risks associated with prescribed drugs and MEMO's role has mainly been in hypothesis-testing, that is investigating drug hazards identified by other PMS, such as spontaneous reporting. MEMO also has a role in the auditing of general practitioner prescribing and in the construction of disease registers such as the Diabetes Audit and Research in Tayside Scotland (DARTS) which is a collaboration between MEMO, all GP practices in Tayside and the Diabetes Units in three Health Care Trusts [42].

1.7 The Irish healthcare system

The Irish Healthcare system is a combination of free, state-supported services and private medicine. Everybody is entitled to free hospital services. As outlined earlier just over 30% of the Irish population are entitled to free community healthcare on the basis of 'means' testing of individual income. The remainder of the population is required to pay for both ingredient costs and pharmacy dispensing fees. This system does however receive partial funding from the state. On approval by the individual health Board, individuals who suffer from one or more of a schedule of long-term illnesses such as diabetes or epilepsy are entitled to obtain, without charge, irrespective of income, the necessary drugs under the Long Term Illness (LTI) scheme.

The GMS (Payments) Board makes payments on behalf of health boards for LTI claims submitted by pharmacies. The Drug Cost Subsidisation (DCS) scheme covers persons who do not have a medical card and who are certified by a doctor as having a regular and on-going requirement for prescribed medicines not covered by the LTI scheme and which cost greater than IR£32 per month prior to July 1999. Such persons do not have to pay more than the specified amount in their pharmacy in a month and the balance is claimed by the pharmacy and is paid by the GMS (Payments) Board. Since July 1999, this limit has been increased to £42 per month but has been extended to other family members who may avail of the same subsidy. One can apply for a Drugs Payment scheme card on an individual or on a family unit basis. By December 2000 just over 1 million people (27% of the Irish population) availed of either the DCS or LTI schemes [43].

Drug costs in Ireland are particularly high when compared to other European countries. This may be due to Ireland's long-standing involvement in the European Union and the traditional linkage of our prices to the United Kingdom [44]. Ireland spends a relatively smaller percentage of its gross domestic product on medicines compared with its equally poor neighbours due to a lower overall consumption of medicines.

1.7.1 The General Medical Services scheme

The Irish General Medical Services (Payments) Board was set up in 1970 by order of the Minister for Health under section 11 of the Health Act, 1970. The functions of the board are to provide on behalf of the eight health boards, services by general practitioners, pharmacists and dentists to eligible persons. Eligibility is means-tested, and is confined to persons who are unable without

undue hardship to arrange general practitioner services for themselves or their dependants. An eligible person registers with the doctor of his/her choice, from among the list of named doctors who have entered into agreements with health boards. Drugs, medicines and appliances supplied under the scheme are provided through community pharmacies. GMS prescription forms may be dispensed in any pharmacy that has an agreement with a health board to dispense GMS prescriptions. In rural areas, where a doctor has a centre of practice three miles or more from the nearest retail pharmacy participating in the scheme, the doctor dispenses for those persons served from the centre who opt to have their medicines dispensed by him/her. The number of eligible persons by December 2000 was 1.16 million people making up approximately 30% of the general population [43]. Single persons aged up to 65yrs and earning less than IR£100 per week are eligible. The equivalent amount for a married couple is IR£144.5. A full list of eligibility criteria is given in Table 1.2 and a diagrammatic representation of the distribution of the GMS is shown in Figure 1.1. The GMS population cannot be regarded as being representative of the general Irish population because socially disadvantaged persons, children and the elderly are over-represented: however it comprises just over a third of the entire Irish population who receive some 70% of all medicines prescribed in general practice[45] and thus represents a valuable resource for epidemiological purposes.

Ireland is divided into eight regions known as health boards for the administration of health services. Prescriptions are dispensed through community pharmacists operating within the scheme and a computer system is used for processing pharmacists' claims, which in addition to providing details

Single person living alone

- Aged up to 65yrs.....£100
- Aged between 66-69yrs.....£109
- Aged between 70-79yrs.....£216
- Aged 80yrs and over.....£228

Single Person living with Family

- Aged up to 65yrs.....£89
- Aged between 66-69yrs.....£94
- Aged between 70-79yrs.....£187
- Aged 80yrs and over.....£195

Married Couple

- Aged up to 65yrs.....£144.5
- Aged between 66-69yrs.....£162.0
- Aged between 70-79yrs.....£324.0
- Aged 80yrs and over.....£340.5

Allowances

For Child under 16 yrs.....£18

For Child over 16yrs with no income maintained by applicant.....£19

For outgoings on house (rent etc) in excess of.....£18

Reasonable expenses necessarily incurred in travelling to work in excess of £16

- Persons aged 16-25 (including students) who are financially dependent on their parents will be entitled to a medical card if their parents are medical card holders. Those who are financially independent of their parents will have their income assessed in their own right.
- Persons with no income other than

a) Old Age non-contribritory pension (maximum)
b) Deserted Wife's allowance
c) Infectious diseases (Maintenance) allowance
d) Disability allowance
e) Lone Parent's Allowance (Maximum)
f) Single Woman's Allowance(Maximum)
g) Widow's (Non-Contributory) Allowance(Maximum)
h) Orphan's (Non-Contribrutory) Allowance(Maximum)
i) Blind (Non-Contributory) Allowance(Maximum)
j) Supplementary Welfare Allowance

- All persons aged over 70yrs and over will be entitled to a medical Card irrespective of income with effect from 1st July 2000

Number of Persons Eligible under the GMS scheme by Health Board as at December 2000

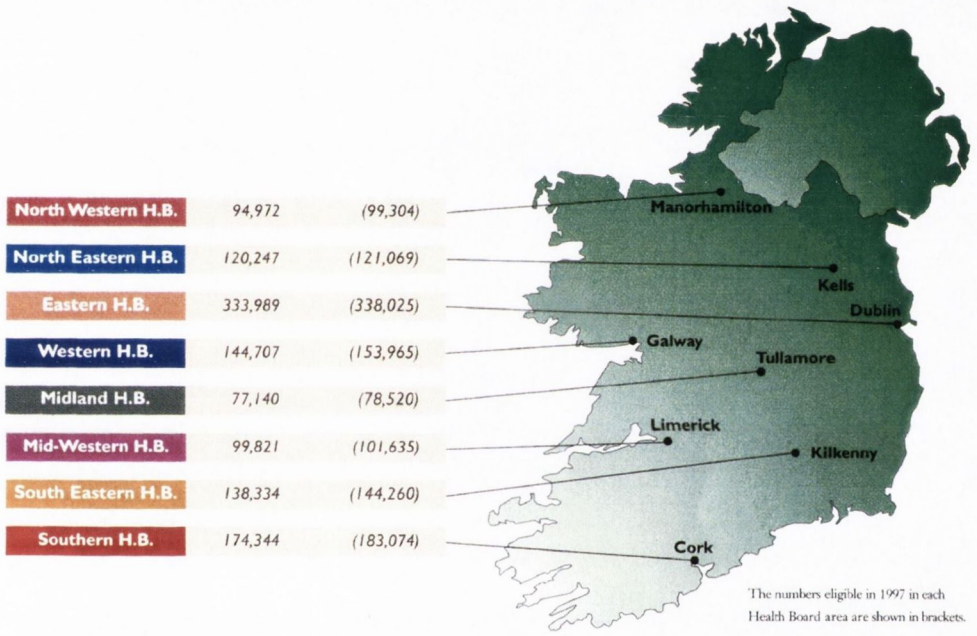


Figure 1.1 Number of persons eligible under the GMS scheme as at December 2000

on prescription claims also contains, unlike PACT data, demographic data on patients such as age and sex. Each patient record is uniquely identified by an eight-character alpha-numeric key. In addition individual prescribers have a unique identifying number. When a doctor prescribes a medication for a patient he writes the medical card number on the prescription. The patient then takes the prescription to the pharmacist of his/her choice (so long as the pharmacist is operating within the GMS scheme) who then dispenses the medication. The pharmacist then claims for re-imbursement from the General Medical Services (Payments) Board. Medications are coded according to the Anatomical Therapeutic Classification system by a five digit alpha-numeric figure. In addition the GMS has a separate code for each prescription item which identifies a particular product. An example of a typical report from the Eastern Health Board region of the GMS is shown in Table 1.3.

The region with the largest population is the Eastern Health Board (EHB or Eastern Regional Health Authority (EHRA) since March 2000) region, which includes the counties of Dublin, Wicklow and Kildare. The number of eligible persons within this health board was 333,390 for the year ending 2000. The total number of eligible persons within all the health Board regions at the end of 2000 was 1.15M and the total cost of prescriptions for the entire GMS scheme in 2000 amounted to £266.9M [43].

The GMS (Payments) Board in addition to demographic details on patients and prescription details also provides details with respect to the number of patients attached to a particular general practitioner, whether a practice nurse is attached to a particular practice and the number of doctors attached to a

GMS	NAME	Pack	Form	Strength		DDD	DNUM	PNUM	ATC	Sex	Age	Claim	Qnty	Fee	Cost
10391	ADALAT RETARD	56	TABS	10	MG	30	60212	0088743A	C08CA05	M	I	48002175	60	1.6931	9.6
10723	ATECOR	30	TABS	100	MG	75	64904	0090961A	C07AB03	M	H	47858745	30	2.289	5.45
10723	ATECOR	30	TABS	100	MG	75	64904	0090961A	C07AB03	M	H	47859436	30	2.289	5.45
11450	ALPROX	30	TABS	0.5	MG	1	64904	0089132A	N05BA12	F	H	48089138	30	1.6931	2.81
11533	ALUPENT EXPECT	300	MIXTURE				65501	0085228A	R03CB53	F	H	47781664	600	1.6931	8
11770	AUGMENTIN DISP	21	TABS	375	MG	1000	61204	0100054A	J01CR02	M	J	47744340	18	1.6931	8.32
11908	ATENOMEL	28	TABS	50	MG	75	65501	0087919A	C07AB03	M	H	47786128	28	2.289	3.88
11908	ATENOMEL	28	TABS	50	MG	75	65501	0091379A	C07AB03	F	D	47781704	28	1.6931	3.88
11916	ATENOMEL	28	TABS	100	MG	75	65501	0086911A	C07AB03	M	I	47786371	28	2.289	5.34
12475	ANGISED	100	TABS	0.5	MG	2.5	64904	0086700A	C01DA02	M	I	47895673	50	1.6931	3.15
13072	ASACOLON	100	TABS			1500	65501	0100151A	A07EC02	M	H	47528057	180	1.6931	45.52
13392	AULIN	30	TABS	100	MG		64904	0086673A	M01AX17	M	H	47868929	40	1.6931	13
13392	AULIN	30	TABS	100	MG		61107	0100259B	M01AX17	F	F	47683352	30	1.6931	9.75
13420	AUGMENTIN	100	TABS	375	MG	1000	62332	0087950A	J01CR02	M	H	48000962	15	1.6931	6.24
13420	AUGMENTIN	100	TABS	375	MG	1000	64904	0090805A	J01CR02	M	D	47874683	15	1.6931	6.24
13420	AUGMENTIN	100	TABS	375	MG	1000	62804	0090893C	J01CR02	F	C	47783958	15	1.6931	6.24
13420	AUGMENTIN	100	TABS	375	MG	1000	65501	0091379A	J01CR02	F	D	47788560	21	1.6931	8.74
13420	AUGMENTIN	100	TABS	375	MG	1000	65501	0091780A	J01CR02	F	D	47782098	21	1.6931	8.74
13420	AUGMENTIN	100	TABS	375	MG	1000	62804	0092254A	J01CR02	M	D	47781114	15	1.6931	6.24
13420	AUGMENTIN	100	TABS	375	MG	1000	81582	0100031A	J01CR02	F	G	47855217	30	1.6931	12.48
13420	AUGMENTIN	100	TABS	375	MG	1000	65544	0100223A	J01CR02	F	F	47693657	15	1.6931	6.24
13420	AUGMENTIN	100	TABS	375	MG	1000	66915	0100276A	J01CR02	M	H	47568332	20	1.6931	8.32
13501	BECONASE AQUEOUS	1	NASAL SPRAY			0.4	65501	0089883C	R01AD01	M	B	47785082	1	1.6931	5.52
13617	BECOTIDE 100	1	INHALER			0.8	65501	0085228A	R03BA01	F	H	47781664	1	1.6931	11.61

Table 1.3 Format of typical prescription report received from the Eastern Health Board region of the GMS

Key:GMS=GMS code for preparation, Pack=Pack size of preparation, Form=Form of medication, Strength=Strength of preparation, DDD=Daily defined dose of preparation, Age=Age group of patients.DNUM=Doctor number, PNUM= Medical card number of patient, ATC=Anatomical Therapeutic Classification of preparation, Claim=Prescription number, Qnty=Quantity of medication dispensed, Fee=Prescription fee, Cost= Cost of medication (excluding VAT for topical and Non-oral preparations).

particular practice. Hence this database may be used to examine both patient and prescriber characteristics which may influence prescribing patterns. A GMS person who is provided with a properly completed prescription form by his/her GP can choose to have such prescription forms dispensed in any of the pharmacies who have entered into agreements with health boards for the provision of services under section 59 of the Health Act 1970. In 2000 there were 9.74m such prescription forms containing 22.88m prescription items dispensed at a cost of over IR£258.6m i.e. an average cost of £11.3 per dispensed item. More than 88% of all eligible persons were prescribed for in that year. In 2000 approximately 45% of prescription forms contained a single item; almost 23% contained 2 items with an average number of items per form of 2.35. The average cost of medicines per GMS person in 2000 was IR£230.45 [43]. Payments made to pharmacies under the GMS scheme are inclusive of the ingredient cost of medicines, dispensing fees and VAT. Under the DP, LTI and European Economic Area(EEA) schemes the ingredient cost of items dispensed are also reimbursed. In addition to dispensing fees and VAT, a mark-up of 50% on the ingredient cost of items dispensed is also paid.

1.7.2 Data protection

The Data Protection Act, 1988 [46] came into force in April 1989 in Ireland. Its purpose was to give effect to the Council of Europe Data Protection Convention and for that purpose to regulate the collection, processing, keeping, use and disclosure of personal information that is processed automatically. The Act gives a right to every individual, irrespective of nationality or residence, to establish the existence of personal data, to have

access to any such data relating to him/her, and to have inaccurate data rectified or erased. The right of access to medical records is subject to a limited exemption where allowing access would be likely to damage the physical, mental or emotional well-being of the individual. The Act requires those who control the contents and use of personal data to ensure that the data they keep are collected fairly, are accurate and up to date, are kept for lawful purposes, and are not disclosed in any manner incompatible with those purposes. The Act also requires that the data is protected adequately and also imposes a special duty of care in relation to individuals to which the data relates. The Act allows one to pass on anonomysed or aggregate data, from which individuals cannot be identified to health boards or other bodies for administrative purposes. Such data can also be used or passed on for research or statistical purposes. If one wishes to use data which includes identifying details of the patient, one would need to obtain patient consent in advance. Cancer research and screening is an exception to this rule. Under the Health (Provision of Information) Act,1997, any person may provide personal information to the National Cancer Registry Board for the purpose of any of its functions, or to the Minister for Health, or any body or agency for the purpose of compiling a list of people who may be invited to participate in a cancer screening which is authorised by the minister. This Act does not extend to personal information kept on manual files. However the European Community Directive 95/46/EC, 'On the protection of individuals with regard to the processing of personal data and on the free movement of such data' [47], which was expected to be implemented in 2001 as an amendment to the 1988 Act, is expected to extend the scope of data protection by applying its

requirements to manual paper based files. It aims to create uniform legislative data protection provision throughout the EU. Under existing data protection law, there is no specific requirement to obtain a person's consent before using their personal data. The processing of data will be subject to the data subject's 'unambiguous consent'. In addition the rights of the data subject to access may be restricted in the case of data which is used for statistical analysis and data which is used for scientific research. In addition exceptions to this directive may be possible where studies are performed in the interests of public health.

The Data Protection Commissioner maintains a register of those individuals/institutions controlling the dataset. Those registering with the data controller must include the purpose and purposes for which he/she keeps or uses the personal data and a description of the data. The GMS is required to register under the terms of the Act. In addition pharmacies and general practitioners who hold patient information on computer are also required to register.

1.7.3 Method of payments to doctors operating within the GMS scheme

Prior to 1971 a dispensary system operated whereby patients were placed, based on their geographical location, on a panel or list of a specific doctor who was appointed to that location and paid a fixed salary. Medicines required by patients were supplied free to 30% of the population covered by this scheme. In 1971 this system was changed to a fee-per-item scheme, whereby patients were allowed to choose their own doctor, and each participating doctor received a fee each time he or she provided an item of service such as a prescription.

With the change to this method of payment, both the prescription rate and drug costs rose by 331% over the subsequent 5 years[48] whereas the Consumer Price Index rose by approximately 140% and the total cost of prescriptions in the United Kingdom rose by 160% during this period. Attempts were made to alter this perceived high rate of prescribing by changing to a capitation fee in 1989 which provided for an annual fixed fee ranging from £12.5 to £70.5 (depending on the age of the patient and distance from the practice) with some additional payment for emergency and night services.

A further attempt to reduce drug costs was the introduction of indicative financial targets for individual prescribers, which were set by the GMS (Payments) Board and the introduction of an Irish National Formulary. The introduction of such indicative prescribing budgets for general practice coincided with a renegotiation of the conditions of pay and service for general practitioners.

Payments to general practitioners for services provided to GMS persons under agreements with health boards are categorised as fees or allowances. For the majority of GPs who operate under the 1989 agreement the principal fee item is the capitation per person weighted for gender, age and distance from the doctor's centre of practice. Such capitation fees totalled IR£61,103,328 in 2000[43]. Fees totalling IR£1,384,100 were paid to 29 GPs who continue to provide services to their registered GMS patients under the fee per item of service agreements. Apart from 'out of hours' fees and fees for a range of special services the cost of services provided in normal hours by GPs for GMS persons, including the prescribing of necessary medicines, is encompassed by the capitation fee. All GMS persons can avail of full GP services and in many

cases they can benefit from specialist clinics provided by GPs for issues such as women's health, family planning and asthma.

1.8 The Anatomical Chemical Therapeutic (ATC) classification system

In the ATC classification system, drugs are first divided into different groups according to the organ or system on which they act and their pharmacological and therapeutic properties, and finally their approved chemical names. Drugs are classified in groups at five levels. The drugs are divided into fourteen main groups (1st level), with two therapeutic/pharmacological subgroups (2nd and 3rd levels). The 4th level is a therapeutic/pharmacological/chemical subgroup and the 5th group is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. The complete classification of amlodipine illustrates the structure of the code

C	Cardiac Therapy (1st level, anatomical main group)
C08	Calcium Channel Blockers (2nd level, therapeutic main group)
C08C	Selective calcium channel blockers with mainly vascular effects (3rd level, therapeutic/pharmacological subgroup)
C08C A	Dihydropyridine derivatives (4th level, chemical/therapeutic/pharmacological subgroup)
C08C A01	Amlodipine (5th level, subgroup for chemical substance)

Thus, in the ATC system, all plain amlodipine preparations are given the code C08C A01.A medicinal product can however be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses. Two examples are as follows

- Sex hormones in certain dosage forms or strengths are only used in the treatment of cancer and are thus classified under L02-Endocrine therapy. Remaining dosage forms/ strengths are classified under G03-Sex hormones and modulators of the genital system.

-Clonidine is available in two different strengths. One strength, which is used mainly in the treatment of hypertension, is classified under C02-antihypertensives. Another strength is mainly used in the treatment of migraine and classified under N02C-Antimigraine preparations.

Different formulations for topical and systemic use are also given separate ATC codes. An example includes prednisolone which appears under the following categories

A07E A01	Intestinal anti-inflammatory agents
C05A A04	Anti-haemorrhoidals for topical use
D07A A03	Dermatological preparations
H02A B06	Corticosteroids for systemic use
R01A D02	Nasal decongestants
S01B A04	Ophthalmologicals
S02B A03	Otologicals

The ATC system is therefore not strictly a therapeutic classification system. At all ATC levels, ATC codes can be assigned according to the pharmacology of the product. Subdivision on the mechanism of action will, however, often

be rather broad, since a too detailed classification according to the mode of action will often result in having one substance per subgroup which as far as possible is avoided (e.g. antidepressants). Some ATC groups are subdivided in both chemical and pharmacological groups (e.g. ATC group J05A-agents affecting the virus directly). If a new substance fits in both a chemical and pharmacological 4th level, the pharmacological group should normally be chosen. Substances classified in the same ATC 4th level cannot necessarily be considered pharmaco-therapeutically equivalent since their mode of action, therapeutic effect, drug interactions and adverse drug reaction profile may differ.

1.9 Material deprivation and prescribing

The impact of social disadvantage on morbidity and mortality is well established [49-51]. Patient morbidity, workload on general practitioners, and the costs of drug treatment have been shown to increase with decreasing social advantage [52-54]. Health policy now addresses the increasing inequalities arising within many countries [55]. Furthermore the content and derivation of measures of deprivation have been the subject of much discussion and contention, with researchers tending to develop their own combinations of variables and to combine them in different ways into an overall index with critics accusing them of poor conceptualisation, and arbitrary and pragmatic selection of indicators [56]. Ecological data (i.e. data aggregated at small area) can be particularly useful when examining trends in prescribing, as the increased number of observations reduces the variability in the data, allowing a more accurate estimate of actual prescribing rates. Social deprivation has been shown to be an important factor associated with the variation in the volume of

antibiotics prescribed by general practitioners [37]. Increased prescribing rates may be due to an excess of morbidity within a deprived community or increased consultation rates. Indeed demographic and socio-economic factors have been shown to act as powerful predictors of consultation patterns [54]. However, relatively little information is available on the effect of different levels of material deprivation on prescribing patterns in primary care in Ireland.

2.0 Aims and objectives of this thesis

The aims of this thesis are

1. To demonstrate the usefulness of the General Medical Services (GMS) prescription database for performing pharmacoepidemiological studies.
2. To examine the influence of material deprivation on prescribing patterns within the GMS.

The objectives will then be

1. To perform pharmacovigilance studies, drug utilisation studies and studies of prescribing quality using the prescription database of the GMS.
2. To examine the influence of different levels of material deprivation on prescribing trends using a locally derived material deprivation index.

Chapter 2-Pharmacovigilance Studies

2.1 Attitudinal survey of Irish doctors to adverse drug reactions (ADRs)

2.1.1 Introduction

The World Health Organisation (WHO) defines an adverse drug reaction (ADR) as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' [57]. A meta-analysis of 39 prospective studies from US hospitals suggested that 6.7 percent of in-patients suffer serious adverse drug reactions and 0.32 percent die as a result, a total of 100,000 deaths per year. This would make adverse drug reactions among the six leading causes of death in US hospitals [58]. While this study was criticised for extrapolating from heterogeneous studies it provides some indication of the potential magnitude of the problem concerning adverse drug reactions. Adverse drug reactions also lead to prolonged hospital stays and increased expenditure at an estimated cost of $4685 per preventable adverse drug event [59]. Clinical trials, case reports, spontaneous reporting systems and formal epidemiological studies can all detect adverse drug reactions. Pre-marketing trials frequently do not have sufficient power to detect important ADRs reliably, especially reactions which occur at rates of 1 in 10,000 or fewer exposures. For example, at least 30,000 people need to be treated with a drug to be 95% certain of observing at least one patient with an adverse reaction that has an incidence of 1 in 10,000 [14], thereby illustrating the importance of post marketing surveillance in the detection of less common adverse events. Despite attempts to improve the pre-marketing evaluation of

new drugs, issues of safety continue to result in drug withdrawal. Whilst there may be confidence in the efficacy of the new drug at the time of its introduction, conclusions about its safety must remain provisional. With wider clinical experience it is possible to identify less common adverse drug reactions in different patient populations or during long-term exposure. Post-marketing surveillance methods for ADRs include anecdotal reporting and voluntary organised reporting (including the WHO's monitoring programme and the Committee on Safety of Medicines (CSM) yellow card system and intensive event monitoring). Spontaneous reporting systems often identify 'signals' that stimulate further research into possible adverse drug reactions and are likely to remain the most efficient way to detect rare events that occur with long-term use.

The forerunner of a spontaneous reporting system was set up by the Lancet in 1893 to investigate anaesthesia-related deaths[60]. The thalidomide disaster had profound effects on the development of new drugs, the pharmaceutical industry, and professional and public attitudes to drug safety. This stimulated the development of spontaneous reporting pharmacovigilance systems and legislation in Europe, such as the UK's 'Yellow Card' system (1964) and legislation to regulate medicines in the UK (Medicines Act 1968) and Europe (EC Directive 65/65). The spontaneous reporting of adverse drug reactions (ADRs) is thus a fundamental safety net to limit toxicity of marketed medicines.

2.1.2 National and international pharmacovigilance systems

There are now two international systems, one under the auspices of WHO in which data on all suspected ADRs are pooled and co-ordinated by the Uppsala Monitoring Centre in Sweden, and the European Union (EU) pharmacovigilance system. In the latter, all member states and the European Medicines Evaluation Agency (EMEA) are connected via secure intranet for the exchange of pharmacovigilance information. A database known as Eudrawatch, for the collation and analysis of reports of serious ADRs associated with products authorised through the EU centralised procedure, is also under development. Most of the national systems are centralised, but an increasing number are decentralised with the monitoring centre being part of the drug regulatory authority in most countries.

In Europe, under the EC directive 75/319/EEC as amended [(iv) Va Articles 29a to 29i] each member state must establish a national pharmacovigilance system for the collection and evaluation of information on medicinal products with particular reference to adverse reactions [61]. Furthermore, member states should take all appropriate measures to

1. encourage physicians and other healthcare professionals to report suspected adverse reactions to the competent authorities and
2. oblige marketing authorisation holders to systematically collect information on risks related to their medicinal products and to transmit those to the competent authorities.

The national pharmacovigilance centre must be in a position to handle these pharmacovigilance data in a way which is compatible with the procedures undertaken in the other member states and the European Agency for the

Evaluation of Medicinal Products in order that pertinent data may be transferred between the member states and the agency. All member states should co-operate with the WHO collaborating centre for International Drug Monitoring through their national pharmacovigilance centre[61].

For most of the national systems the reporting of ADRs is voluntary, but for some, including France, Norway, and Sweden, it is mandatory by law for physicians and dentists to report cases of suspected serious adverse reactions to the regulatory authority. In addition it is obligatory for all pharmaceutical companies working in the EU to report suspected ADRs that have become known to them. The majority of countries emphasise the need to report even trivial reactions to newly marketed drugs, while for established medicines only serious reactions should be reported. Some countries clearly identify new drugs, which they wish to be monitored closely, such as in the UK where new drugs are marked with a black triangle.

Most centres review each report on an individual basis using a clinical pharmacology approach, often making judgements about cases as to how likely it is that the drug caused the adverse event. Others use mainly an aggregate or epidemiological approach to the analysis of the reports. Finally, the national centres differ dramatically in how they interact with reporters. Some treat their reporters anonymously, providing feedback only in the form of regulatory action. Others provide very direct feedback to maximise the dialogue between the reporters and the centre.

Since its inception in 1964, more than 400,000 reports of suspected ADRs have been submitted to the Committee on Safety of Medicines (CSM)/Medicines Control Agency (MCA) on a voluntary basis by doctors,

dentists, pharmacists, and coroners, and by pharmaceutical companies under statutory obligations. There are four regional monitoring centres in the UK who have a special responsibility for stimulating ADR reporting in their particular areas. In France a new drug control agency was formed in 1994, the French Medicines Agency, which has taken up the duties formerly undertaken by the Ministry of Health. It also serves as a coordinating and executive body for a network of 31 regional centres that are connected to major university centres. Each centre is responsible for ADR monitoring in its region and the evaluated reports are fed into a central database.

Regional systems have the advantage of establishing good communication between the staff of the monitoring centre and the reporting professionals. They are, however demanding in the number of staff needed and, unless the reports are fed directly into a central database, result in delays in the flow of information. The regional centres in France and Sweden also have responsibility for the provision of drug information, which may add further to the value of a centre, as the local physicians feel that not only do they contribute reports of ADRs, but in return they receive clinically relevant information.

National surveillance centres send information regarding adverse drug reactions to the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre) for analysis. The rationale for setting up the WHO International Programme for Adverse Reaction Monitoring, over 30 years ago was to make it possible to identify rare adverse drug reactions (ADRs) that could not be identified through clinical trial programmes. The only regular budgetary contribution to the centre is provided by the Swedish

government. In each country participating in the WHO programme (currently 58 full members and 6 associate members) there is a national centre which is responsible for collecting spontaneously reported suspicions of ADRs originating from health professionals. At the Uppsala monitoring centre, reports are checked for technical accuracy and are then entered into the WHO database. The centre has also set up an international panel of approximately 30 expert consultants who assist it in identifying new and clinically important adverse reaction signals within their own specific area of expertise. The present system of signal identification is by no means perfect, as indicated by the recent association between heart valve disorders and the administration of the appetite suppressants fenfluramine/dexfenfluramine and phentermine which was first reported to the WHO between 1989 and 1996, but which was only identified as a signal in the US in mid-1997 [62]. Difficulties associated with the database include: incompleteness of the database; delays in reporting of ADRs; the vast numbers of potential signals, many of which may be insignificant drug reaction associations; a lack of patient details, which makes causality assessment difficult; and limited resources for medical assessment of potential signals [63]. The role of the international system is to concentrate on the rare but clinically significant reactions where pooling of international data is most likely to increase the chance of detection.

In a number of European countries, all healthcare professionals are allowed to report adverse drug reactions. In the United States, patients can report through the MED Watch scheme [64]. However, a problem is that less than 10% of all serious and 2-4% of non-serious adverse reactions are reported [14;65]. In 1997 the regulatory authority, the Irish Medicines Board, received only 1,175

reports (35% from general practitioners, 12% from hospital doctors) [15] and yet some 20 million prescription items are dispensed each year in the General Medical Services which excludes hospital and private practice[66]. One would expect a higher rate of reporting. In a previous study we found that spontaneous ADRs were reported in less than 1 in 500 in hospitalised patients whilst more intensive monitoring involving review of patient records and collection of reports from both doctors and nurses revealed a 10% occurrence[16].

To further enhance our understanding of doctors' knowledge of the current ADR reporting scheme and whether there was any difference between doctors in hospital practice or general practice, we carried out an attitudinal survey and also recorded doctors' responses to hypothetical ADR situations.

2.1.3 Methods

The questionnaire (Appendix A) was posted to 400 doctors drawn at random from the 1997 Irish Register of Medical Practitioners with a stamped, addressed envelope to facilitate reply. The questionnaire included information on whether the respondent ever previously diagnosed or reported an ADR. Factors discouraging reporting were also sought, as were responses to 'hypothetical' ADR situations. We also quantified doctors' perceptions of ADR incidence terminology. The questionnaire was designed in such a way that respondents should have answered each part of each question. However, where respondents had answered individual questions incompletely they were removed from the analysis of that question only. A paired Chi-squared statistic was determined for a number of questions to quantify a difference in the responses between general practitioners and hospital doctors.

2.1.4 Results

A total of 158 doctors (39.5%) responded of which 106 were in general practice and 23 were in hospital practice. The majority of doctors (87%) were aged between thirty and sixty years of age.

Some 70% of doctors had ever reported an ADR some time in their professional lifetime. This was higher amongst general practitioners (74%) than amongst hospital doctors (50%)($p < 0.001$). Of interest in the last five years almost an equal number of doctors had reported ADRs to the pharmaceutical manufacturer (47/33%) as to the national reporting agency (56/37%). Some 90% of doctors had encountered adverse drug reactions (ever diagnosed an ADR) but had not reported them. The principal reasons that discouraged ADR reporting are shown in Table 2.1. Some 23% of doctors did not know how to report an ADR and many felt that the system was too bureaucratic or that they were too busy to report the reaction (Table 2.1).

The question regarding adverse drug reactions as too trivial or already well known was tested by a series of hypothetical adverse drug reaction situations. Relatively few practitioners would report weight loss in a 44-yr old patient eight weeks after starting a selective serotonin re-uptake inhibitor antidepressant (12%), a morbilliform rash with amoxycillin (21%), hypoglycaemic coma requiring hospitalisation in a well controlled insulin dependent diabetic (18%) or swollen ankles associated with a calcium channel blocker (10%). On the other hand more serious adverse drug reactions would be reported including deep venous thrombosis in a patient on the contraceptive pill (73%), agranulocytosis in a patient taking spironolactone (70%), angiodema one day after starting an ACE inhibitor (74%), or sudden

Reason for not reporting adverse drug reaction	% of respondents		
	% of Total	% of GPs	% of Hospital Doctors
Uncertain that the reaction is definitely caused by the drug	72.9	72.8	73.9
Adverse Drug Reaction considered too trivial to report	69.7	71.3	61.9
Adverse Drug Reaction considered too well known to report	85	84.6	95.2
Unaware of the existence of a national ADR reporting scheme	10.9	7.1*	22.7*
Unaware of the need to report an ADR	13.9	11.9	27.3
Lack of knowledge on how to report an ADR	22.7	22.5	22.7
Reporting an ADR too bureaucratic a process	43	46.3	36.8
Too busy to report an ADR	34.7	31.3	47.6
Concern that ADR reports may be used in a legal case for damages by the patient	5.7	7.22	0

Table 2.1. Percentage of respondents to attitudinal survey of adverse drug reactions (ADRs) who indicated a particular reason for not reporting an ADR(Statistically different replies between hospital doctors and general practitioners*$p<0.05$)

unexpected death in a patient 10 days after starting a new antipsychotic drug (88%).

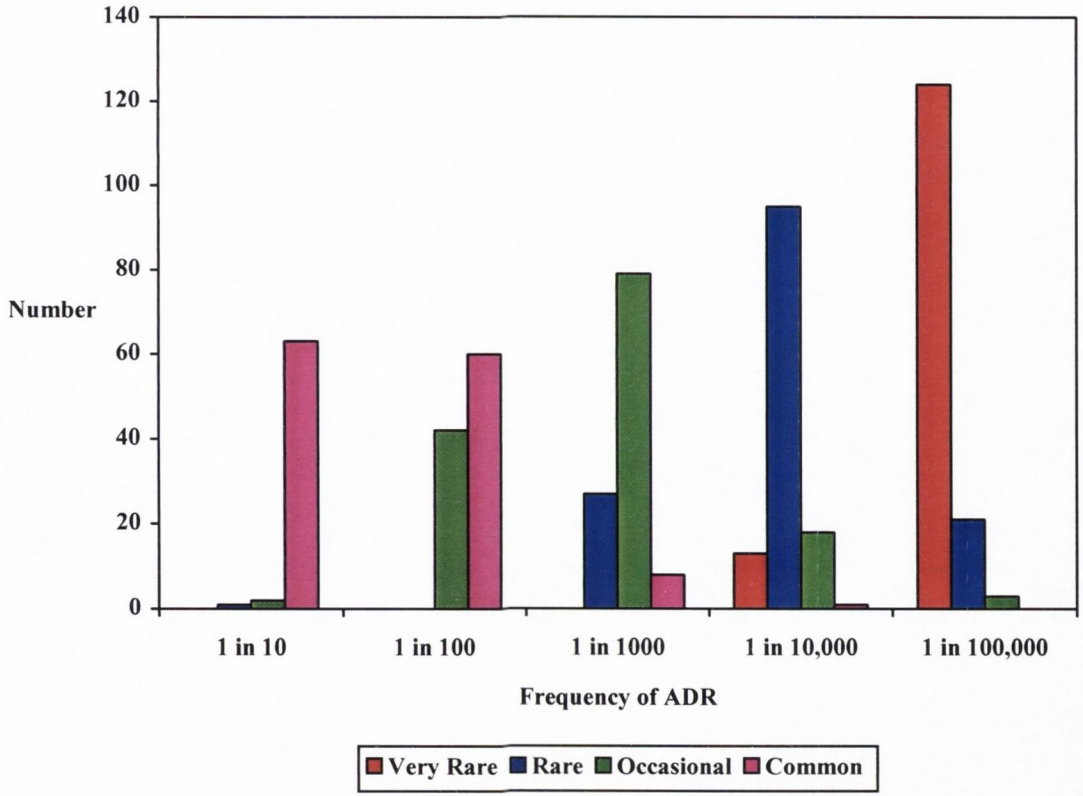
Doctors were asked if they were aware of the criteria of the National Drug Regulatory Agency specifying which adverse drug reactions should be reported and only 16 % were aware of these criteria. The majority (77%) of doctors would be willing to report an ADR for a medicine prescribed for their patient by another physician and a similar number if the patient had purchased the medicine without prescription themselves.

Figure 2.1 shows doctors' understanding of expressions used to describe the frequency of adverse drug reactions. There is considerable overlap in doctors' perceptions of occasional, rare, common or very rare adverse drug reactions. For example 1 in 1000 was considered occasional by 56%, rare by 19% and common by 6%.

2.1.5 Discussion

Our finding that 70% of doctors had ever reported an ADR is similar to the reporting rate in many other EU member states including the United Kingdom[13]. It is clear that the majority of doctors encounter ADRs but only one third have reported such to the regulatory agency in the last 5 years. The extent of underreporting is difficult to quantify but must be considerable as there is less than one ADR report per 36,000 GMS prescriptions and one per 3000 prescriptions in a general hospital (given that most hospitalised patients receive on average 6 medications and ADRs are reported in less than 1 in 500 patients[16]).We found little difference between general practitioners and hospital based doctors apart from more general practitioners reporting an ADR but this

Figure 2.1.Number of doctors who ascribed qualitative expressions used to describe the frequency of Adverse Drug Reactions (ADRs) to quantitative measures of ADR frequency.



is in part explained by the greater experience and mean age of the general practitioners. This is in keeping with a previous survey carried out in Ireland[67]. In common with many such surveys the response rate (40%) raises the question as to the validity of our sampling. Previous surveys have identified difficulties in locating younger doctors particularly when using the Medical Register allied to the fact that over a quarter of doctors registered are not in practice in Ireland. Also because of the temporary nature of positions a poorer response from non-consultant hospital doctors is not unexpected. It was surprising to note that whilst more general practitioners have reported an ADR, they were less aware (10% versus 24%) of any criteria from the National Regulatory Agency (The National Drugs Advisory Board/NDAB became the Irish Medicines Board/IMB on 1st January 1996) for reporting ADRs as compared with their hospital colleagues. This may in part be due to the greater experience of general practitioners for reporting adverse drug reactions compared to more recent graduates from medical school who would be more likely to work as hospital doctors.

We were somewhat surprised at the extent to which doctors were reporting ADRs to pharmaceutical manufacturers. As the regulatory authority advises sending such reports directly to them it is possible that some of this reporting is by way of mention to a pharmaceutical representative which may not indicate a formal report.

Table 2.1 lists the main issues that discourage reporting. Uncertainty that the reaction was definitely caused by the medicine was a common view and appears to be the case internationally[13]. There was no significant difference between hospital doctors and general practitioners in this regard. Also of note,

adverse drug reactions considered too trivial to report and adverse reactions too well known to report are common reasons for not reporting. In the hypothetical ADRs that we put by way of example to the doctors it was clear that this differentiation was present. This runs contrary to the requirements of the Irish Medicines Board who request reports on all ADRs [68]. It appears that the response of Irish doctors is more in keeping with the requirements of the UK Committee for Safety of Medicines, which does not encourage the reporting of trivial or well-known ADRs.

The single most important reason for reporting an ADR appears to be the seriousness of the reaction and this appears to be the case internationally [13;16]. Too busy to report an ADR, lack of knowledge on how to report an ADR (two of the 'seven deadly sins' discouraging reporting as described by Inman[69]) and a reporting process that is too bureaucratic were other reasons advanced for not reporting adverse drug reactions. Of some concern is that some 23% of doctors do not know how to report an ADR and taken in conjunction with the finding that some 84% are unaware of the reporting criteria of the National Drug Regulatory Agency it does suggest that additional information and education is required in this regard. The regulatory authority needs to be more explicit in its requirements and increase knowledge of the adverse drug reaction reporting system in order to stimulate a 'reporting culture'.

Recently, fenfluramine and dexfenfluramine were withdrawn from the market following concerns of a possible association between the occurrence of valvular heart disease with the use of these anorectic agents[70]. In addition other new drugs associated with unexpected major adverse effects have included Mibefradil and Terfenadine. Mebefradil, a calcium-channel

antagonist that is metabolised by the hepatic enzyme CYPA4, proved toxic in patients prescribed other drugs that are metabolised by CYPA4, such as the macrolide antibiotic erythromycin, prompting its removal from the market. Serious toxic effects - torsade de points and ventricular tachycardia-were found to be associated with terfenadine, an antihistamine which is also metabolised by CYPA4. However this problem was not recognised until terfenadine had been on the market for five years and had been taken by a significant number of patients.

It may be a poor reflection on society's attitude to preventative measures that drug safety only became a priority following thalidomide and in Ireland is foremost following the recent hepatitis C contamination of blood products. No independent agency as such exists with the responsibility to monitor and investigate adverse events due to drugs and to provide recommendations to prevent them. A recent proposal has suggested that responsibility for drug safety should be vested in an independent authority[71]. Such independence would help to ensure objectivity and avoid conflicts of interest.

Unfortunately, previous interventions to improve reporting rates (including verbal reminders, using a fee and increasing the availability of yellow cards) are only short-lived [16;72]. Approximately 1 year after the introduction of MED Watch, the number and quality of ADR reports to the FDA increased. However this increase was attributed to improved reporting by pharmacists. Physician reports declined slightly during this period [73]. It would appear that the present reporting system is inadequate. The present reporting system could be improved by using telephone/electronic-mail facilities. The use of the internet in the domain of drug safety is spreading rapidly. The US Food and

Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and other agencies have developed sites which contain information on pharmacovigilance in general and on specific drugs[74]. The electronic transmission of safety information, using the standards developed by the International Conference on Harmonisation, has been tested for the transmission of individual patient adverse event information between companies and governments. In addition, the FDA has begun to accept adverse events reports from healthcare providers and consumers directly on-line using an electronic version of its MED Watch form. Such developments will change the way that pharmacovigilance is carried out. With the advent of pharmacovigilance nurses in haematology, it may well be appropriate to appoint personnel with expertise in pharmacovigilance to hospitals. Extending the range of personnel who may report ADRs by including nursing staff may also improve reporting rates. We have previously shown that nurses reported more ADRs compared with doctors over a similar time-period [75]. Given their unique position in drug administration and recording observations on patients, nurses could contribute significantly to the reporting of adverse drug reactions. Doctors understanding of expressions used to describe the frequency of ADRs are of interest. Commonly textbooks and data sheets, MIMS, BNF and the Specifics of Product Characteristics (SPC or data sheet) use expressions like occasional, common or rare. Clearly this has a different meaning to different people and as shown in Figure 2.1 there is considerable overlap. Indeed an occurrence of 1 in 1,000 is regarded by some 6% as common, by 56% as occasional and another 19% as rare. There is clearly need for an agreed definition of the meaning of these words, not alone if we are to interpret the

literature in a meaningful way but also to express to patients the relative risk of adverse drug reactions. A European Union (EU)[76] directive stipulates that every medicinal drug supplied should be accompanied by a leaflet that has comprehensive information for patients, including all side-effects listed in the summary of the product's characteristics (or datasheet). An EU guideline, published after the directive, recommends that frequency of side-effects should now be described with one of five qualitative descriptions [very rare (<0.01%), rare (0.01-0.1%), uncommon (0.1-1%), common (1-10%) or very common (>10%)][77]. It is therefore important that doctors understand the meaning of such terms when explaining side effects to patients. A recent study has suggested that such qualitative descriptions may lead to a gross overestimation of risk when such terms are provided to patients[78].

Wood [71] describes the true safety profile of a drug as being dependent on the 'experiment' that necessarily follows a drug's release into the marketplace. This experiment requires adequate funding and monitoring to ensure that the relevant data is collected and analysed and the conclusions rapidly disseminated.

2.2 The effect of the British warning on oral contraceptive use in the General Medical Service scheme

2.2.1 Introduction

The introduction of combined oral contraceptives (commonly known as the 'pill') in the early 1960s made reliable contraception available for the first time. It is estimated that over 100 million women have taken the oral contraceptive pill since 1956, when the first clinical trials were undertaken. Unlike other forms of drugs which have primarily been formulated to prevent

or cure disease, the oral contraceptive pill was designed to be given to healthy women over long periods of time, making the necessity for regulation and medical monitoring that much more pertinent. Indeed oral contraceptives have been studied more intensively than any other medication in history [79]. However the use of the oral contraceptive pill has not been without controversy regarding its safety. Over the past three decades [80-83] there have been a number of concerns regarding the safety of the contraceptive pill, most recently in 1995 regarding the newer third generation contraceptive pill. On 18 October 1995 the Committee on Safety of Medicines (CSM) issued a warning on the risk of thrombo-embolism associated with combined oral contraceptives containing desorgestrel or gestodene [84]. It advised that third-generation oral contraceptives should be used only by women intolerant of other combined oral contraceptives and prepared to accept an increased risk of thrombo-embolism. This increased risk was based on the results of three studies which were submitted to the Medicines Control Agency (MCA) and a subcommittee of the Committee on Safety of Medicines, indicating that combined oral contraceptives containing desorgestrel and gestodene were likely to be associated with approximately a twofold increase in the risk of thrombo-embolism when compared with those containing other progestogens. Norgestimate-containing preparations were not included in this warning [9;10]. The statement was supplemented by another statement to the press and broadcast media which explained that doctors and pharmacists were 'being informed of important new information', explaining that:

'It is well known that the pill may rarely produce thrombosis (blood clots) involving veins of the legs. New evidence has become available indicating that

the chance of a thrombosis occurring in a vein increase around two-fold for some types of pill compared with others'.

It went on to list the brands of pills associated with the increased risk and concluded with the advice:

'For the vast majority of women, the pill is a safe and highly effective form of contraception. Women taking one of the relevant pills should, if possible, see their doctor before their current cycle ends. No one need stop the pill before obtaining medical advice.'

The specific advice given to general practitioners was as follows:

- that women who are taking combined pills containing the newer progestogens should be advised of the increased risk of venous thrombo-embolism;
- that in general women taking a pill containing gestodene or desorgestrel should be advised to change to another brand, unless they cannot tolerate other formulations; and
- that women who wish to continue to take the 'listed pills' should be advised of, and be prepared to accept, the relatively increased risk of thrombosis, and have no other factors which might predispose them to an increased risk (for example they should not be overweight, have a history of thrombosis or have varicose veins).

However as much of this data had not at the time been subject to peer review or published and the potential benefits of these products had not been fully elucidated, many were of the opinion that the warning was premature. The announcement by the CSM and the Department of Health was strongly criticised by Professor Walter Spitzer (a principal investigator in one of the

studies) who was so alarmed by the interpretation of his research that he flew to London to address a press conference at which he argued that the CSM had acted prematurely and misinterpreted his study. Dr Susan Jick whose data was also cited by the CSM as the basis for its warning was also critical. She believed that the CSM warning was 'premature and based on insufficient information' and added that 'we are quite distressed that our results are being used in this way' [85].

Two other national authorities adopted positions similar to that taken by the UK CSM. The German Federal Institute for Drugs and Medicinal Products (BFARM) issued a press statement on 20th October 1995, two days after the CSM announcement. This indicated that BFARM was taking the danger of increased risk of venous thrombo-embolism from oral contraceptives containing gestodene or desorgestrel very seriously and had requested comments on the results of the studies from the pharmaceutical companies responsible for the production of these products within four days. The statement indicated that if necessary BFARM 'intends to order the suspension of authorisation for these products' [86].

In a further press release issued on 6th November 1995, BFARM explained its intention to restrict 'the conditions for prescription and use of 'third generation' oral contraceptives'. It ordered that such pills should not be 'permitted for prescription to women below 30 years who wish to take an oral contraceptive for the first time'. In July 1996 BFARM reaffirmed its position and extended its restriction on the prescribing of third generation oral contraceptives.

A strongly restrictive position was also adopted by the regulatory authorities in Norway. Unlike the German authorities, the Norwegian Medicines Control Authority (NMCA) delayed for a number of months before reacting. On 20th December, the NMCA issued a statement, which restricted the prescribing of Marvelon®(a preparation containing desogestrel) to women for whom the second-generation pills was unsuitable.

The Committee for Proprietary Medical Products (CPMP) of the European Agency for the Evaluation of Medicinal Products which also had access to the same reports responded by seeking further information from, and holding discussions with the investigators involved in the studies and the pharmaceutical companies responsible for the development of the products[87]. It added 'in view of its benefit/risk re-assessment, the CPMP did not consider it appropriate to withdraw combined oral contraceptives containing gestodene or desorgestrel'.

In countries such as Ireland which is directly exposed to the British media, there was an urgent need to reassure public opinion. Having been informed of the British position at the CPMP meeting on 19th October 1995, the Irish Medicines Board (known at the time as the National Drugs Advisory Board/NDAB) issued a reassuring statement immediately which explained;

'The NDAB has always ensured that doctors are aware of the possibility of thrombo-embolism associated with the use of oral contraceptives and that the risk may be greater in some patients with predisposing factors. The prescribing data and package leaflets contain the appropriate precautions. The overall risk relating to oral contraceptive use is very small and it is not yet clear if in strictly comparable patients this risk is greater with gestodene and

desorgestrel. Any suggested increased risk with these agents would still be small in absolute terms and is smaller than the overall risk associated with pregnancy.'[88] This 'Dear Doctor' letter stressed that the CPMP meeting had decided that 'no regulatory action was necessary' and that it should be explained to women that the increased risk associated with the higher risk pills 'is small and amounts to approximately 2 extra cases per 10,000 women years'[89]. An NDAB press release[90] noted the UK response but went on to explain that as a member of the CPMP, Ireland would be following the advice of that body's special meeting at which it was decided that 'no regulatory action need be taken'. The Irish Medicines Board in a drug safety Newsletter in December 1995 reiterated it's previous advice and furthermore did not advise discontinuation of third-generation oral contraceptives but requested further study and analysis of the studies to evaluate the impact of biases and cofounders [91]. A subsequent 'update statement' issued on 19th April 1996 confirmed that this advice had not changed [92].

Most national regulatory bodies that issued statements adopted a position that was broadly in agreement with that of the CPMP. In countries like Australia, Bulgaria, Ireland, Greece and Denmark, the regulatory authorities argued that there was no need to change the prescribing habits concerning oral contraceptives [86].

This was also the approach taken by the Food and Drug Administration (FDA) of the United States which issued a requirement that the association of desogestrel with an increased rate of deep vein thrombosis be included in package inserts, but that it did not intend additional action until more evidence was available [86].

The situation was further confused by a statement from the World Health Organisation (WHO) which seemed to fall between the advice given by the UK CSM and the CPMP. The WHO noted that the risks were 'very low and that the risks associated with pregnancy were greater, but concluded that 'until further information becomes available, low oestrogen dose oral contraceptives containing progestogens other than desorgestrel and gestodene may be preferred'. There was, however, no directive that a change in prescribing/issuing practice was required [93].

Finally on 8th April 1999 the Medicines Commission gave further advice regarding the third generation combined oral contraceptives. It had reviewed the relevant data which indicated a small excess risk of venous thrombo-embolism of about 10 cases per 100,000 woman years for women using combined oral contraceptives containing desorgestrel or gestodene which had not been satisfactorily explained by bias or confounding. However the Commission went on to state that 'the absolute risk of venous thrombembolism in women taking combined oral contraceptives containing desorgestrel or gestodene is very small and is much less than the risk of venous thromboembolism in pregnancy.....provided that women are fully informed of these very small risks and do not have medical contraindications, it should be a matter of clinical judgement and personal choice which type of oral contraceptive should be prescribed' [94]. Such advice which explained the risks of venous thrombo-embolism now appears in the summary of product characteristics for combined oral contraceptives containing desorgestrel and gestodene.

Headlines such as 'Blood clot risk for women on the Pill' and 'Scare centres on pill designed to be the safest of all' appeared in the British media. In the Irish Media similar concerns were expressed[95] whilst caution regarding the scare was expressed by one author[12].

This pill scare led in the UK and other countries where such a warning was not issued, to some users stopping oral contraceptives mid-cycle and a rise was subsequently noted in abortions and pregnancies[96-99]. Therefore, we studied the impact of the UK warning, on the prescribing of the oral contraceptive steroids in the General Medical Scheme (GMS) in Ireland to determine whether Irish prescribers were influenced more by local regulatory advice or by that provided by the CSM in the UK.

2.2.2 Methods

We obtained details of all prescriptions dispensed in the Eastern Health Board area (representing some 40% of the total GMS) for contraceptive steroids for a series of months between January 1995 and November 1996. The contraceptive steroids were divided into the following groupings; first generation oral contraceptives (norethisterone-containing), second-generation contraceptives (levonorgestrel-containing), third generation contraceptives (desorgestrel- and gestodene-containing), progesterone only pill and depot contraceptive. The contraceptive steroids were identified according to the Anatomical Therapeutic Classification system and the frequency of prescribing of the individual contraceptive items and the age characteristics of users of the contraceptive steroids over the period between January 1995 and November 1996 were determined. Furthermore in an effort to determine which class of contraceptive steroid that individuals may have switched from

following the CSM warning, a cohort was identified in September 1995 (i.e. preceding the warning). The prescribing characteristics of these individuals were determined in January 1996 (i.e. following the CSM warning). All statistical analyses were performed using JMP® version 3.

2.2.3 Results

Figure 2.2 describes the age frequency of users of contraceptive steroids prior to the CSM warning. Users of the third generation oral contraceptives were mainly from the younger age groups of women, whilst women of 35yrs plus used the progesterone only pill. This is in keeping with present prescribing guidelines which recommends that progesterone only pills may be more suitable for older women, in particular those who smoke. Table 2.2 and Figure 2.3 show the total number and frequency of contraceptive steroids dispensed from between January 1995 and November 1996 in the Eastern Health Board. The use of the third generation oral contraceptives fell from 53% of total contraceptive use to 30% of total contraceptive use over the time period studied. This fall was paralleled by a rise of 12% in the use of the second-generation oral contraceptives and a rise of 9% in the use of norgestimate containing contraceptives. The use of the first generation oral contraceptive, the depot contraceptive and the progesterone only pill changed little over the time period studied.

Figure 2.3 shows a steady linear decline in the number of contraceptive items dispensed between May 1995 and November 1996, which was estimated at 89 per month ($r^2 = 0.8$. $p < 0.01$). Figure 2.4 illustrates the percentage of

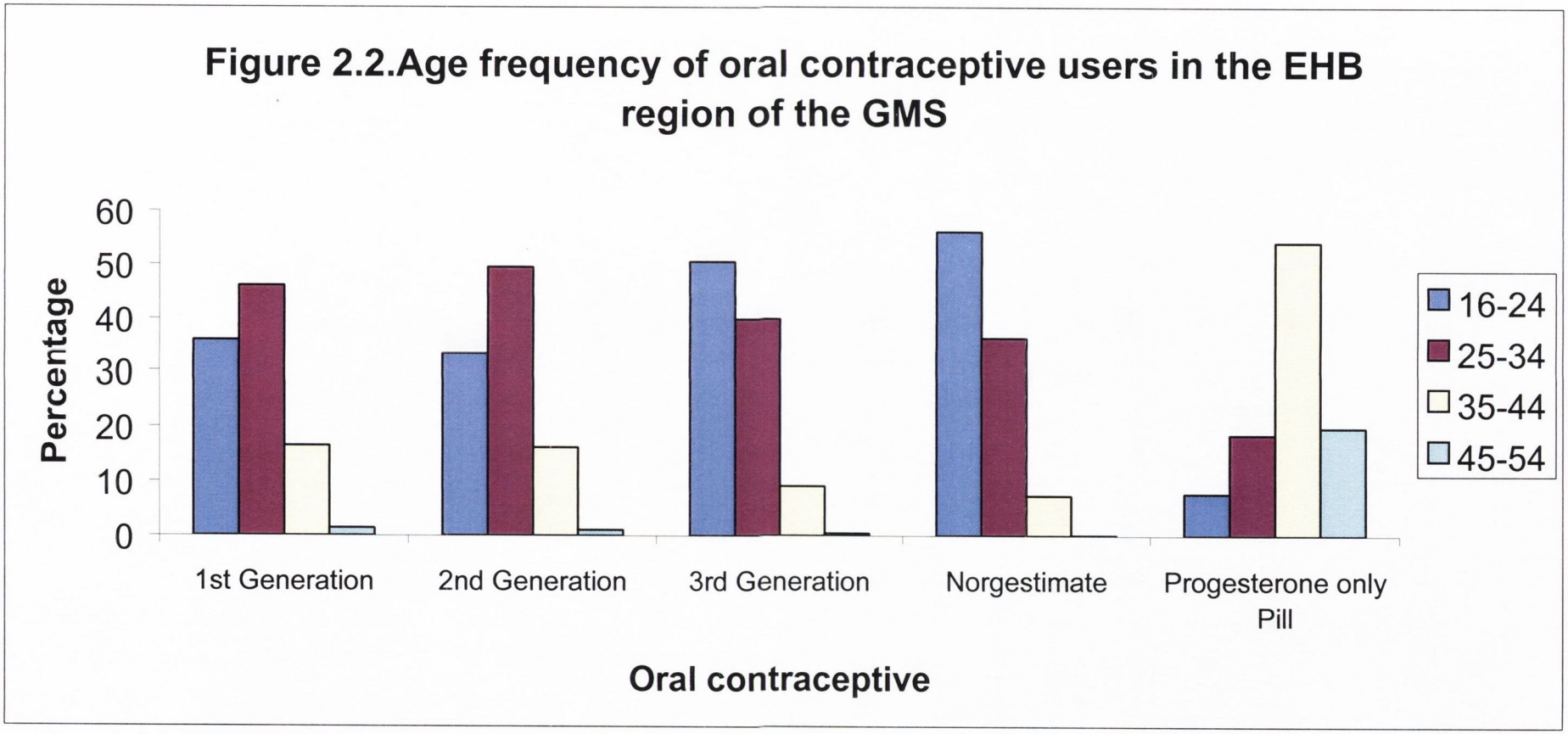


Figure 2.2.Age frequency of oral contraceptive users in the EHB region of the GMS
Percentage
60
50
40
30
20
10
0
1st Generation
2nd Generation
3rd Generation
Norgestimate
Progesterone only Pill
Oral contraceptive
16-24
25-34
35-44
45-54

Figure 2.3. Decline in Number of Contraceptive Steroids in the Eastern Health Board region of the GMS between January 1995 and November 1996 (CSM warning on third generation contraceptive steroids was issued in October 1995)

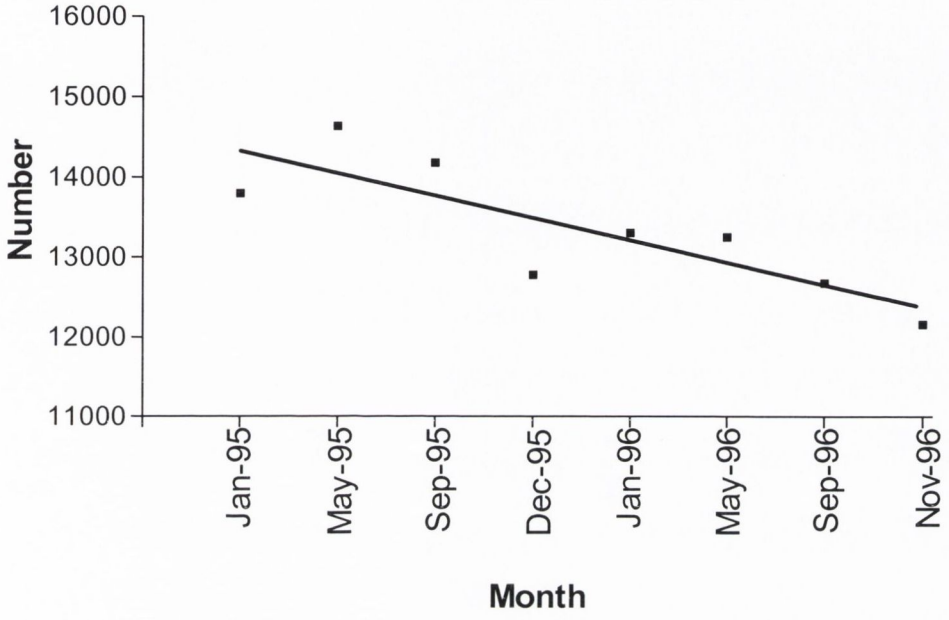
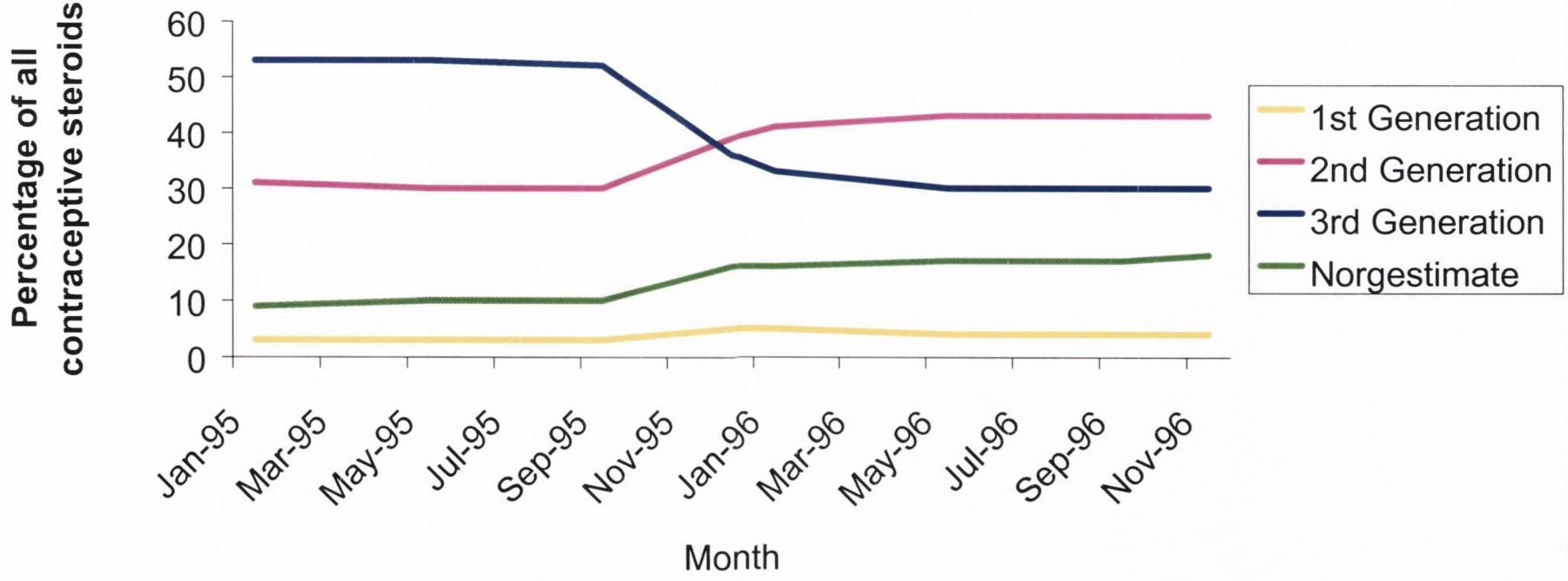


Figure 2.4.Percentage uptake of oral contraceptives by generation in the EHB region of the GMS between January 1995 and November 1996 (CSM warning on third generation contraceptive steroids was issued in October 1995)



Year	Month	Total Number	Total Number per 1000 eligible patients	Generation			Norgestimate
				1st %	2nd %	3rd %	%
1995	Jan	13,793	100.4	3	31	53	9
	May	14,631	106.4	3	30	53	10
	Sep	14,179	103.2	3	30	52	10
	Dec	12,778	92.9	5	39	36	16
1996	Jan	13,303	99.5	5	41	33	16
	May	13,249	99.2	4	43	30	17
	Sep	12,679	94.9	4	43	30	17
	Nov	12,159	91.0	4	43	30	18

Table 2.2: Total number and frequency distribution of contraceptive steroids dispensed within the EHB region of the GMS between January 1995 and November 1996.(progesterone only pill (4%) and depot (medroxyprogesterone-containing) preparations (<1%) did not alter).

prescriptions of the different generations of contraceptive steroids as a proportion of all the prescribed contraceptive steroids.

In an effort to determine which class of contraceptive steroid patients switched to, a total of 8072 patients were identified as receiving a prescription for a contraceptive steroid both in September 1995 and January 1996 (i.e. before and after the CSM warning). Of the 4129 patients who received a prescription for a third generation contraceptive steroid in September 1995 prior to the CSM warning, 2843 patients (68%) had remained on a third generation contraceptive steroid, with 739 (18%) moving to the older 2nd generation contraceptive steroid and 431 (10%) moving to the norgestimate-containing contraceptive steroids which were not included in the CSM warning (Table 2.3).

2.2.4 Discussion

The results which I noted show a clear shift in use from the third generation oral contraceptives to the older second-generation oral contraceptives and norgestimate-containing oral contraceptives. A similar, though more dramatic shift was seen in the UK where the use of the third generation oral contraceptives fell from 55% of total use to 12% of total use [100]. There was a similar rise (30% to 62% of total use) in the use of the second-generation contraceptives and norgestimate-containing contraceptives (7.3% to 12.3% of total use).

A fall was noted in the use of all contraceptive steroids, a trend, which was not seen in the UK. It is evident that Irish prescribers and pill users were more influenced by the UK advice than by the advice given by the Irish Regulatory

September 1995	January 1996						
Contraceptive steroid	**Contraceptive steroid**						
	1st Gen	**2nd Gen**	**3rd Gen**	**Depot**	**Norgestimate**	**POP**	**Total**
1st Gen	262	14	5	0	4	0	285
2nd Gen	16	2419	38	0	24	7	2504
3rd Gen	90	739	2843	5	431	21	4129
Depot	0	0	0	0	0	1	1
Norgestimate	0	43	14	0	774	2	842
POP	0	8	7	1	3	292	311
Total	377	3223	2907	6	1236	323	8072

Table 2.3. Number of patients who were prescribed a particular contraceptive steroid in September 1995 and who remained on them in January 1996 (CSM warning on third generation contraceptive steroids was issued in October 1995).
Key:Gen=Generation, Depot=Depot contraceptive, POP=Progesterone only Pill.

Authority. It illustrates how a regulatory decision taken in one member state of the EU which runs contrary to advice in another member state can influence prescribing. Furthermore the influence of the British media cannot be underestimated. Evidence exists that alarming medical news and warnings to the general public can influence medication use significantly, either positively as in the response to reports on the safety of anorectic agents [101] or negatively as in the case with the third generation oral contraceptive steroids. Media reports concerning the safety of the calcium channel antagonists also led to a decline in their use[102].

Pharmacovigilance involves the process of identifying and responding to risk-benefit issues arising with marketed medicines. Information should then be provided to prescribers and users to optimise the safe and effective use of medicines. Any remedial action should be based on sound scientific data. The manner in which this is done and its potential to influence drug use in other countries requires careful evaluation. In the case of the CSM's warning, which was leaked to the media, clinics were inundated by calls from worried women about their medication. Pharmaceutical companies felt the alert to be premature and speculated that behind the alert lay a government aim to save money on the expensive third generation contraceptives. Spitzer, an author of the original articles, admitted that there was still uncertainty as to whether the modest association found for venous thrombo-embolism was causal or due to bias. He regretted that preliminary findings showing a cardio-protective effect of the third generation oral contraceptives might never be confirmed if women stopped taking these preparations after the alert.

In the absence of authoritative unambiguous advice, misleading information may also prevent women taking up new methods of contraception. Women may also experience a reduction in choice in real terms by moving away from more effective methods of contraception to those methods with fewer perceived side effects but less contraceptive efficacy and a resultant rise in unwanted pregnancies.

Recent studies have suggested that second and third generation oral contraceptives are associated with identical risks of venous thrombo-embolism and that the results of previous studies implicating the third generation oral contraceptive with increased risk of thromboembolism were subject to confounding variables [103;104]. The focus of pharmacoepidemiology should be to reach the most appropriate decision based on the best evidence available. There should be a systematic and united approach to urgent issues in drug safety involving the regulatory body, the Department of Health and the Public Health agencies, the pharmaceutical industry together with prescribers in a co-ordinated manner. Clear unambiguous advice regarding risk needs to be disseminated to those concerned as clearly as possible. The risk of venous thromboembolism could also have been expressed as follows;

- Healthy women not taking contraceptive hormones 5/100,000 women years
- Pregnancy 60/100,000 women years
- Women taking third generation pills 30/100,000 women years
- Women taking second generation pills 15/100,000 women years
- Mortality of venous thromboembolic disease 2%

As the risk of venous thromboembolic disease has a low basal rate, a small increase in the incidence of a risk factor can also double, or increase by some

other multiple, the relative risk of occurrence. The presentation of such information in a relative format-such as three times as many will die- can increase perceptions of the danger. This was the procedure adopted by the United Kingdom Department of Health statement where it stated that 'New evidence has become available indicating that the chance of a thrombosis occurring in the vein is increased around two-fold for some types of pill compared with others'. Such a presentation of risk necessarily creates a greater impression of risks than if it had indicated the actual numbers of women at risk. If the desire to reassure had been uppermost in communicating the relevant information, the data could have been presented in a form showing the excess risks of death from venous thromboembolism with the combined pill as being 1.3 per million[105]. A correspondent to the *British Medical Journal* argued that 'the public relations disaster... might have been avoided if the data had been presented in a form shown below, which emphasises the difference in the percentage of event free women'[95].

	Third generation oral contraceptives	Other combined oral contraceptives
% of women free of thrombosis	99.985	99.993

The Chief Medical Officer in the United Kingdom, Kenneth Calman devoted a section of his annual report[106], *On the State of the Public Health* to the communication of risk, using the October pill scare as an example of the problems faced by the medical profession involving risk communication. In a

carefully worded statement, which implicitly recognised that the announcement had an unintended and unwanted outcome, Calman observed:

' It is true that the relative risk of venous thrombosis (defined as venous thromboembolic episodes) is doubled by the combined oral contraceptives containing gestodene or desorgestrel compared with the second-generation combined oral contraceptives. However, the absolute risk is very small in all types of oral contraceptives, and much smaller than the risk of pregnancy. The public presentation of these figures caused great anxiety; although the increased risk was small, women did need to be informed that there was a difference in risk between the oral contraceptives available to them. The message to continue to take the oral contraceptive pill seemed to be ignored in the pressure for action.'

The majority of health scares tend to be transitory. However there may be longer-term outcomes following the pill panic. Even if people have forgotten the specifics of the CSM warning, the international pill scare will contribute to the perceived problems associated with oral contraception. Questions over the safety of oral contraceptive pills in the past have re-emerged through the 1995 panic. The cumulative impact of such events is to strengthen public concern regarding the risks associated with oral contraception. The very questioning of the safety of particular types of oral contraceptive pills has the effect of consolidating public concern about their side effects. Even in instances where the pill is declared to be safe, the association of oral contraception with a variety of risks remains in the public imagination. This may have contributed to the overall fall in the use of oral contraceptives within the GMS population. In addition, doctors may be more reluctant to prescribe combined pills than

previously. Even those who are enthusiastic about the value of the third generation pills may think twice about prescribing a drug about which respectable authorities have issued a warning.

There is now a centralised European mechanism to licence drugs in the European Union. As the decisions of one regulatory agency may have implications for drug use extending well beyond its geographical boundaries, we need to develop a European perspective on these issues of drug safety, in order to present a more standardised approach to pharmacovigilance. Our data show that decisions taken in one country may have major consequences, which may run contrary to the stated public health policy of that country. With regard to such decisions no EU member state should act in isolation.

2.3 Influence of media and regulatory changes on prescribing of trimethoprim and cotrimoxazole

2.3.1 Introduction

Cotrimoxazole, the fixed-dose preparation of trimethoprim (80mg) plus sulphamethoxazole (400mg) first became available in 1969 [107]. Trimethoprim was combined with sulphamethoxazole to provide a wider spectrum of bactericidal activity and to delay the emergence of resistance to trimethoprim. Trimethoprim was known to inhibit bacterial dihydrofolate reductase, one of the enzymes responsible for bacterial folate synthesis; it was thought that by combining trimethoprim with a sulphonamide, which blocks an earlier step of folate synthesis, synergy might result. Synergy was demonstrated in vitro at low concentrations of both drugs and, whilst individually trimethoprim and sulphamethoxazole were bacteriostatic, used in combination their effects were bactericidal. In 1980 when trimethoprim became available alone it was recommended that it should replace co-trimoxazole for uncomplicated

infection of the urinary tract [108]. Indeed the clinical value of the synergy between sulphamethoxazole and trimethoprim was questioned as clinical trials found that , for acute urinary tract infections, trimethoprim by itself was as effective as the combination [109]. In experimental models of such infections, using therapeutic concentrations of trimethoprim, sulphamethoxazole or cotrimoxazole, the effect of trimethoprim by itself was found to be so dominant that sulphamethoxazole contributed little to the antibacterial effect and any weak bactericidal effects demonstrated were probably due to trimethoprim whether present alone or in combination [110]. In 1985 the Committee on Safety of Medicines warned that cotrimoxazole was particularly likely to cause adverse effects, particularly bone marrow suppression, generalised skin reactions and death in patients over 65years [111]. By March 1986 the British National Formulary advised that cotrimoxazole be prescribed in older patients only if there was no acceptable alternative. By mid-1995, the CSM had received reports of 127 deaths (71% in patients over 60 years old) associated with Co-trimoxazole and 15 deaths (87% in patients over 60 yrs old) associated with trimethoprim. Concerns regarding the safety of cotrimoxazole received media attention in 1994 [112] and subsequently in 1995 the licensed indications for cotrimoxazole were limited to the treatment of urinary tract infections and acute exacerbations of chronic bronchitis where there was bacterial evidence of sensitivity to cotrimoxazole and good reason to prefer the combination to a single antibiotic. Similarly the combination was licensed for the treatment of acute otitis media in children where there was good reason to prefer co-trimoxazole to a single antibiotic [113]. Of interest the CSM did not explain in detail how and why the decision to change the licence

of cotrimoxazole. The CSM said that 'there is no new safety data, but in the light of changing clinical practice, the indications for co-trimoxazole should be limited to specific illnesses'. The committee also cited a large post-marketing study which confirmed that the most serious adverse drug reactions were very rare and failed to demonstrate any significant difference in the frequency with which serious hepatic, renal, blood and skin disorders were associated with the combination products and trimethoprim alone [114]. Only in the treatment and prevention of pneumocystis carinii is co-trimoxazole established as first-line treatment [115]. Cotrimoxazole may also be used in the treatment of toxoplasmosis and nocardiasis. The change in the licensed indications for co-trimoxazole meant that, in practice there were few occasions, apart from pneumocystis carinii pneumonia, in which co-trimoxazole should be prescribed in preference to a single antibiotic. To document the influence of media and regulatory advice on prescribing patterns within the General Medical Services (GMS) scheme, we studied the prescribing patterns of cotrimoxazole and trimethoprim.

2.3.2 Methods

National prescribing data for cotrimoxazole and trimethoprim between the years 1990 and 1998 were obtained from the GMS Board. This data was adjusted for the number of persons eligible and the prescription rate was expressed as the number of prescriptions per 1000 eligible persons. In addition prescribing data for cotrimoxazole and trimethoprim from the Eastern Health Board region (representing 32% of the total GMS/333,989 eligible persons) for the year 1998 [66] were analysed in more detail to determine the most common length of therapy prescribed to individual patients. Duration of

therapy in adults was estimated by determining the number of daily-defined doses prescribed to each patient. The daily defined dose is the assumed average daily maintenance dose for a drug when used for its main indication in adults [20]. As the quantity and strength of medication dispensed to a patient along with the daily-defined dose is available in the prescription details provided by the GMS, the number of daily-defined doses dispensed to a patient may be estimated from the following formula;

Number of Daily Defined Doses (DDDs) =

$$\frac{\text{Strength of Medication (mg)}}{\text{DDD (mg)}} \times \text{Quantity}$$

For comparison purposes prescribing information was obtained from the United Kingdom Prescription Pricing Authority (PPA) regarding the prescribing trends of cotrimoxazole and trimethoprim over a similar period of time.

2.3.3 Results

The national GMS prescribing frequency for cotrimoxazole and trimethoprim between 1990 and 1998 is illustrated in Figure 2.5. It illustrates that the decline in the prescribing of cotrimoxazole preceded the change in its licensed indication in July 1995, and had largely occurred in 1994 at the time of media reports concerning the safety of cotrimoxazole. A similar decline was noted in England and Wales where the prescribing of trimethoprim was at a higher level in comparison with cotrimoxazole (Figure 2.6).

Figure 2.5 National prescribing Frequency for Cotrimoxazole and Trimethoprim in the GMS(Licensed indications for cotrimoxazole were changed in July 1995)

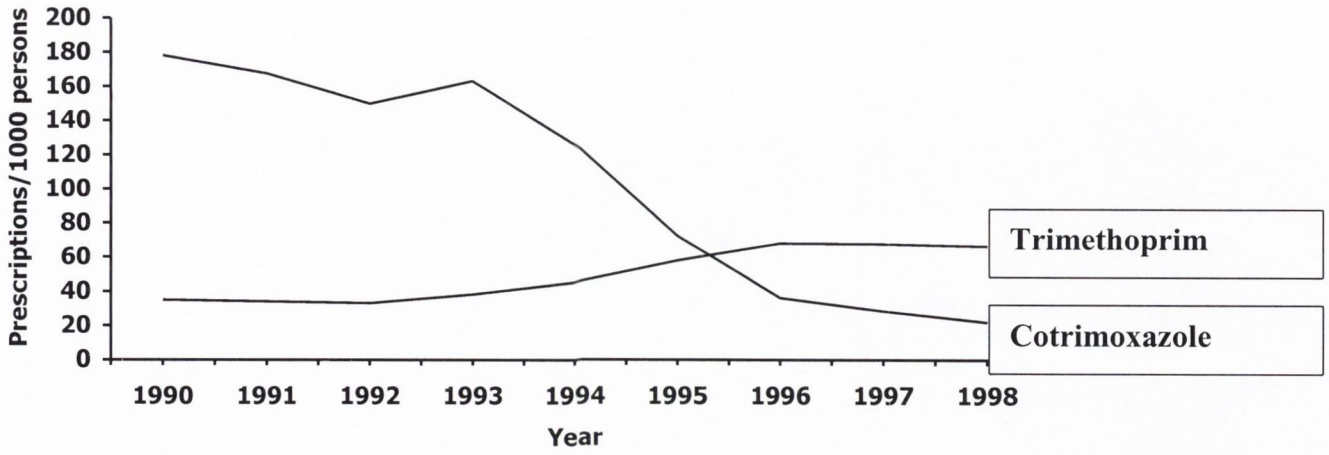
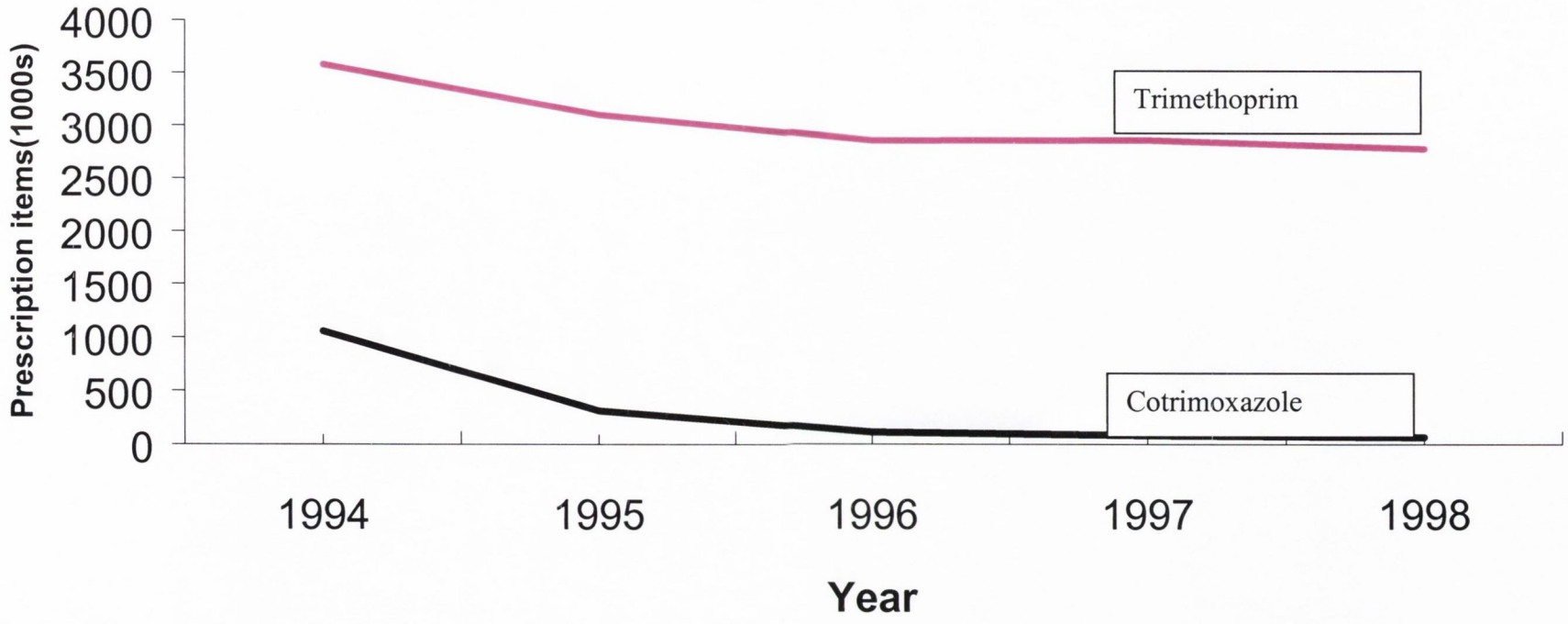


Figure 2.6.Prescribing Frequency of Trimethoprim and Cotrimoxazole in England and Wales between 1994 and 1998 (Licensed indications for cotrimoxazole were changed in July 1995)



The prescribing frequency for cotrimoxazole and trimethoprim by age and sex in the Eastern Health Board (EHB) region of the GMS in 1998 is illustrated in Figure 2.7. Whilst the prescribing rate of cotrimoxazole was similar among children (18/1000 patients) and the elderly (15/1000 patients) there was a significant difference in prescribing rates for trimethoprim between children (17/1000 patients) and the elderly (101/1000 patients).

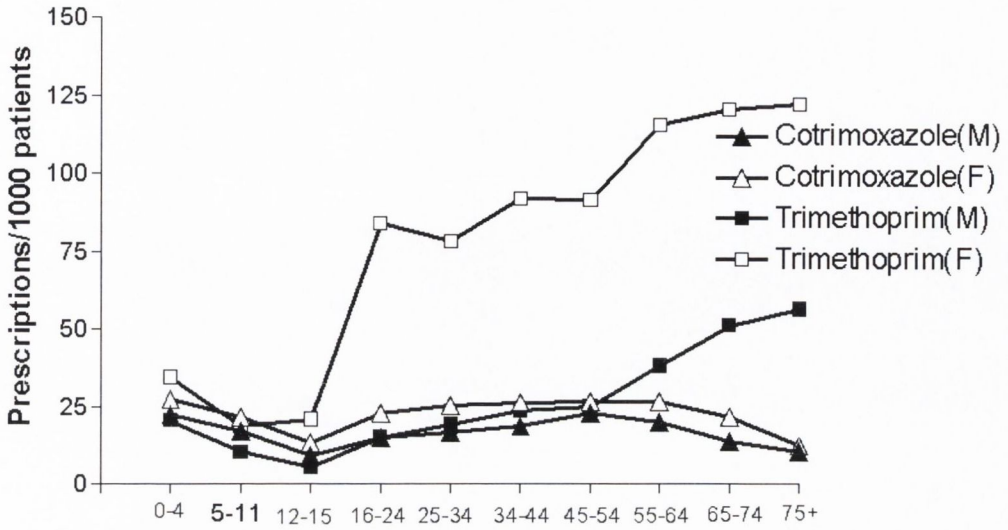
Prescription details for trimethoprim and cotrimoxazole within the EHB are shown in Table 2.4. 80% of patients received a single prescription for these antimicrobial agents over the study period while the remaining 20% received more than one prescription.

2.3.4 Discussion

Adverse drug reactions are an important cause of morbidity and mortality. It has been estimated that approximately 100,000 people die annually in the United States of adverse drug reactions, making them one of the most common causes of death [58]. In addition such adverse drug reactions can also have a significant economic impact [59]. By and large patients may be informed of the potential risk of drug toxicity individually by their physicians, by pharmacists, by patient information/product inserts or, as a group, by the media.

Evidence exists that alarming medical news and warnings to the general public can influence medication use significantly, either positively (such as the response to reports on the safety of anorectic agents [101]) or negatively (such as reports on the third generation oral contraceptive agents, leading to immediate cessation and a subsequent increase in abortions[96]).

Figure 2.7. Prescribing frequency for Cotrimoxazole and Trimethoprim in the EHB by age and sex in 1998.



Antibiotic	Number of patients		Number of prescriptions		Mean Number of Daily Defined Doses	
Sex	M	F	M	F	M	F
Trimethoprim	2574	11271	3754	16122	7.9	6.9
Cotrimoxazole*	1507	2894	2324	4115	8.3	7

Table 2.4. The number of individuals by gender receiving trimethoprim and cotrimoxazole in the Eastern Health Board region of the GMS and mean number of defined daily doses for these antibiotics. (*The daily-defined dose of Cotrimoxazole was estimated using the standard dose of 960mg twice daily)

Media reports regarding the safety of the calcium channel antagonist group of antihypertensive agents also led to a decline in their use [102]. The recent controversy concerning an alternative anticancer treatment developed by DiBella illustrated how an emotional media campaign promoting this unproven therapy could influence patient behaviour. Despite the advice of oncologists and the Minister of Health in Italy, most patients tended to interpret the message optimistically [116 117].

We have previously reported the dominant influence of the media in contrast to regulatory advice on the prescribing patterns of the third generation oral contraceptive agents in Ireland [118]. Advice regarding the prescribing of cotrimoxazole was sent to Irish general practitioners in December 1995 [119]. By then the decline in the prescribing of cotrimoxazole had already occurred indicating that media influences had affected prescribing patterns before regulatory advice. However our results also indicate that cotrimoxazole is still being prescribed to a significant degree (20 per 1000 patient) across all age groups despite its revised indications. We are unaware of further advice on the prescribing of cotrimoxazole being circulated to Irish general practitioners.

These results also show that recommended changes to long established practices of drug dosage are slow to be adopted. In addition despite evidence that a 3-day course of trimethoprim is suitable for the treatment of uncomplicated urinary tract infections [120], our results suggest that the most common length of therapy is seven days. This is in keeping with a previous study, which found that educational newsletters sent to general practitioners had no impact on their prescribing patterns [121]. In addition we found a female predominance in the use of these antimicrobial agents. This was more marked

with respect to trimethoprim. This may be explained by the increased incidence of urinary tract infections in women [120;122] for which trimethoprim is often used as first line therapy [123].

Pharmacovigilance involves the process of identifying and responding to safety issues regarding marketed medicines. Relevant drug safety information should be provided to prescribers to optimise the safe and effective use of medicines. Any regulatory actions should be based on sound, peer-reviewed scientific data. Communicating information regarding drug safety can be quite complex and is fraught with vested interests such as the pharmaceutical industry, government legislators, health care professionals and consumer groups. A systematic and united approach to urgent issues regarding drug safety is required to ensure that prescribers can advise patients appropriately. In addition such information should be communicated in a systematic fashion to avoid undue public concern. Regulatory advice may need to be continuous to produce an effective and sustained response. Despite criticism by the profession of the presentation of such issues by the general media, in many cases it appears to have a greater effect than information provided by regulatory authorities. The manner of presentation of important information by regulatory agencies requires reconsideration.

2.4 Conclusions of pharmacovigilance studies

Given the level of underreporting noted in the attitudinal survey of voluntary reporting of adverse drug reactions, there is a need for the regulatory authority to be more explicit in its requirements for reporting and to increase the range of knowledge regarding adverse drug reaction reporting in order to create a 'reporting culture' among health professionals. Indeed it may be more

appropriate to transfer responsibility for drug safety to an independent authority in order to ensure objectivity and avoid possible conflicts of interest. The appointment of personnel with an expertise in pharmacovigilance will help to improve reporting rates. However this will require adequate funding and monitoring to ensure that the relevant data is collected and analysed and the conclusions rapidly disseminated.

Furthermore doctors' understanding of the frequency of the occurrence of adverse drug reactions needs to be improved. This lack of knowledge may be one of the reasons why patients may overestimate the perceived risk of an adverse drug reaction [78].

The pharmacovigilance studies on contraceptive use and on the prescription of trimethoprim and cotrimoxazole illustrate the influence of external forces such as the media and regulatory advice outside the particular country in relation to prescribing patterns. In many cases the media has a greater effect on prescribing practice. It is important that any regulatory action taken should be based on sound, peer-reviewed scientific data and that such information is communicated to prescribers and the public in a systematic fashion to avoid undue public concern. Furthermore the GMS prescription database has been shown to be a sensitive indicator of prescribing practice in relation to issues on drug safety.

Chapter 3 Drug utilisation studies

3.1 Features of multiple drug use (polypharmacy) within the General Medical Services scheme

3.1.1 Introduction

The simultaneous use of multiple drugs (polypharmacy) is associated with adverse drug reactions, medication errors, poor compliance with medications, increased costs and increased hospitalisation from drug-related morbidity[124;125]. Studies have shown that when the number of co-administered drugs exceeds four, the risk associated with such use for the patient increases [126;127]. However clinical situations may exist where the use of multiple medications is justified in order to produce effective pharmacotherapy.

As older patients may respond differently to both pharmacokinetic and pharmacodynamic changes with age, they as a group are particularly vulnerable to the adverse effects associated with polypharmacy. As a result there has been a greater awareness of the problems associated with drug therapy, particularly polypharmacy in the elderly. In the 1960s a number of reports were published which showed an increase in the incidence of adverse drug reactions with advancing years [128]. Such adverse events have economic implications as in certain circumstances they may lead to hospitalisation. It has been estimated that the cost of an adverse event is $4700[59]. Previous studies of polypharmacy have focussed principally on hospital departments, nursing homes and single practices all of which may not be representative of the general population [129;130]. The emergence of large prescription databases allows population-based analysis of individuals exposed to multiple drugs [131].

The prevalence of polypharmacy within the general population in Ireland, as well as the characteristics of those exposed to polypharmacy have been studied only to a limited extent. The General Medical Services (GMS) prescription database provides a unique opportunity to study multiple drug use within primary care. Whilst the GMS population only make up approximately 30% of the general population, they consume over 70% of drugs prescribed in Ireland [44] and thus provide a valuable data source to examine multiple drug use within primary care in Ireland. While diagnosis should be the ultimate determinant of drug prescription, there may not always be a clear link between treatment and diagnosis and differences in drug treatment may relate to differences such as age and sex. The purpose of this study was to determine the prevalence of polypharmacy among the population of patients receiving medications on a chronic basis within the Eastern Health Board region of the GMS and furthermore to determine whether certain patient characteristics and/or drug class contributed to polypharmacy.

3.1.2 Methods

We studied the number of prescription items dispensed for a series of months (March to May 1998) in the Eastern Health Board region of the GMS. Patients who received prescriptions continuously over a three-month period were defined as receiving chronic medication. Polypharmacy was defined as the concurrent use of two or more drugs in the particular month in question. The concurrent use of two to four drugs within a particular month was classified as minor polypharmacy and five or more drugs as major polypharmacy. Patients who remained stable within a particular polypharmacy grouping were studied further regarding the contribution of age, sex and Anatomical Therapeutic

Classification (ATC) grouping to each polypharmacy class. When necessary, adjustments were made for the number of eligible persons within each age group when estimating rates.

The contribution of the different ATC groups to major as opposed to mono-pharmacy can be analysed by determining an odds ratio (OR) which compares the number of patients who receive a prescription for a particular ATC in both the major and mono- polypharmacy groupings. An example of how such an OR was determined is shown below.

Example of derivation of OR for cardiovascular group of drugs

Total number of persons exposed to Major Polypharmacy: 12616

Total number of persons exposed to Monopharmacy: 4727

Total number of persons exposed to Major Polypharmacy and cardiovascular drug therapy: 9746

Total number of persons exposed to Monopharmacy and cardiovascular drug therapy: 891

This allows the setting up of a 2 by 2 table, which allows the derivation of an odds ratio with the outcome measure being major polypharmacy.

Cardiovascular Medication	**Major Polypharmacy**		**Total**
	Yes	**No**	
Yes	9746	891	10637
No	2870	3836	6706
Total	12616	4727	17343

$$\text{Odds Ratio} = \frac{9746/891}{2870/3836} = \frac{10.9}{0.74} = 14.6$$

Similarly odds ratios to estimate the risk of exposure to major polypharmacy versus mono-pharmacy according to the different age bands within the GMS were also determined.

3.1.3 Results

A total of 66, 346 patients were identified from a total of 199,112 as receiving prescriptions for medications continuously over the three-month period. The median number of prescriptions consumed by these patients over the 3-month period was 10 (interquartile range,6-16). Whilst a number of patients moved from the different polypharmacy groupings, some 31,777 patients (M:F 36%:64%) were identified as remaining constant within their grouping over this time period. Table 3.1 shows the numbers and age groups of those patients (n=31,777) exposed to no, minor and major polypharmacy. The male/female distribution of the different polypharmacy types are shown in Figure 3.1.

The trends in polypharmacy by age and sex (adjusted for the number of eligible persons in each age group and the relative contribution which each type of polypharmacy makes to each age group are shown in Figures 3.2 and 3.3 respectively.

In patients over 65yrs of age only 1110(6.8%) were on monotherapy. Overall 56% of chronic polypharmacy (minor and major) occurs in this group which constitutes only 24% of the total GMS population. The prevalence of chronic polypharmacy in this age group was 23/100 eligible patients.

ble 3.1. Numbers (%) and contribution of age groups of patients exposed to ,Minor(2-4 drugs) and Major(>4 drugs) Polypharmacy as defined by the number of scription items received per month) within the EHB region of the GMS.

Age(yrs)	No Polypharmacy(%)	Minor Polypharmacy(%)	Major Polypharmacy(%)
0-4	131(2.77)	109(0.75)	11(0.08)
5-11	96(2.07)	137(0.94)	25(0.19)
12-15	62(1.31)	84(0.6)	11(0.08)
16-24	796(16.83)	650(4.5)	178(1.4)
25-34	894(18.9)	946(6.55)	383(3.0)
35-44	510(10.8)	1141(7.9)	613(4.85)
45-54	586(12.4)	1918(13.2)	1214(9.62)
55-64	542(11.5)	2505(17.35)	2105(16.68)
65-74	623(13.2)	3574(24.76)	3773(29.90)
75+	487(10.3)	3370(23.34)	4303(34.1)
Total	4727 (100)	14434(100)	12616(100)
ımber/100 eligible patients	1.4	4.4	3.8

Figure 3.1. Male/Female distribution of polypharmacy(PP) types(No,Minor and Major PP) as defined by the number of medications prescribed per patient per month

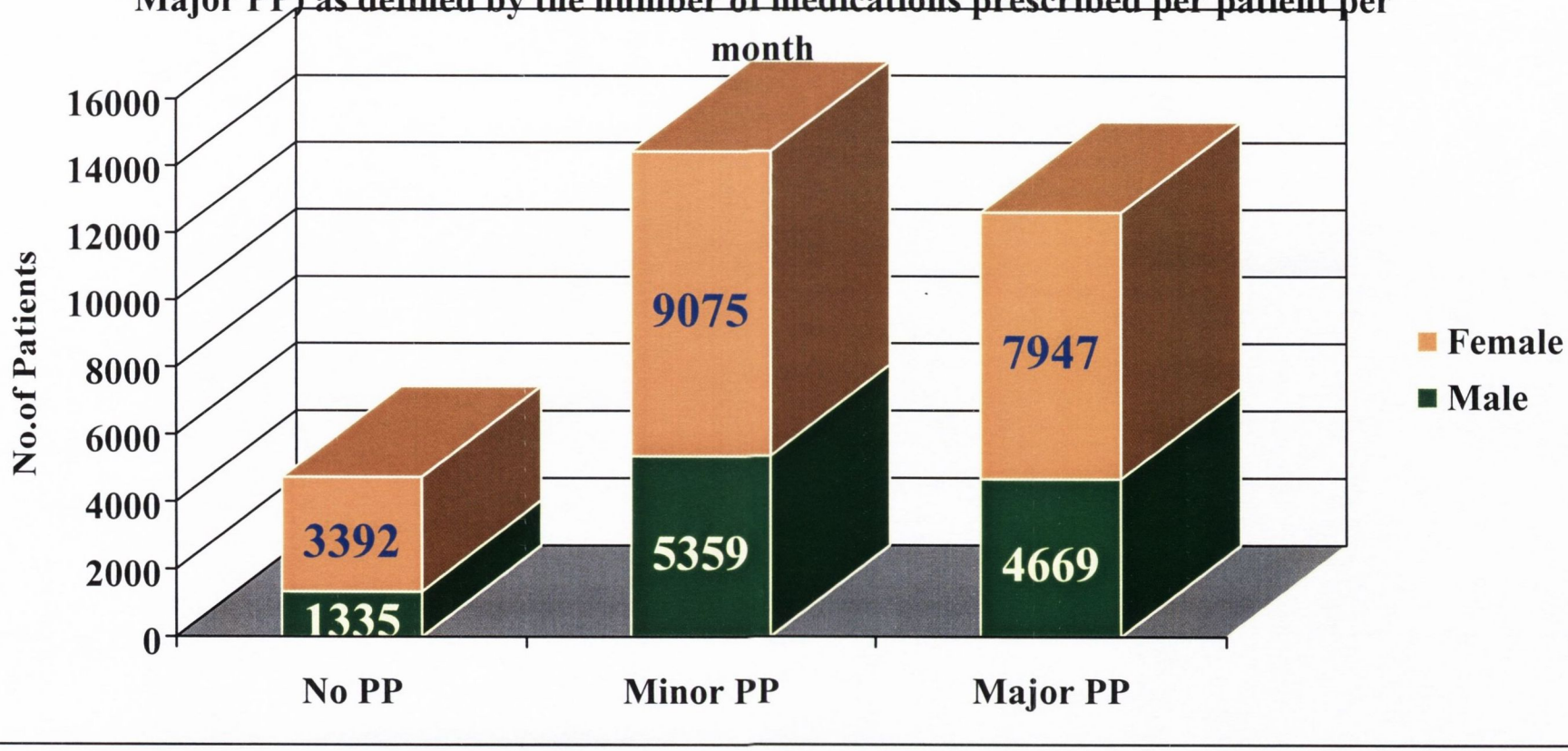


Figure 3.2. Trends in Polypharmacy (No, Minor and Major polypharmacy) by Age and Sex

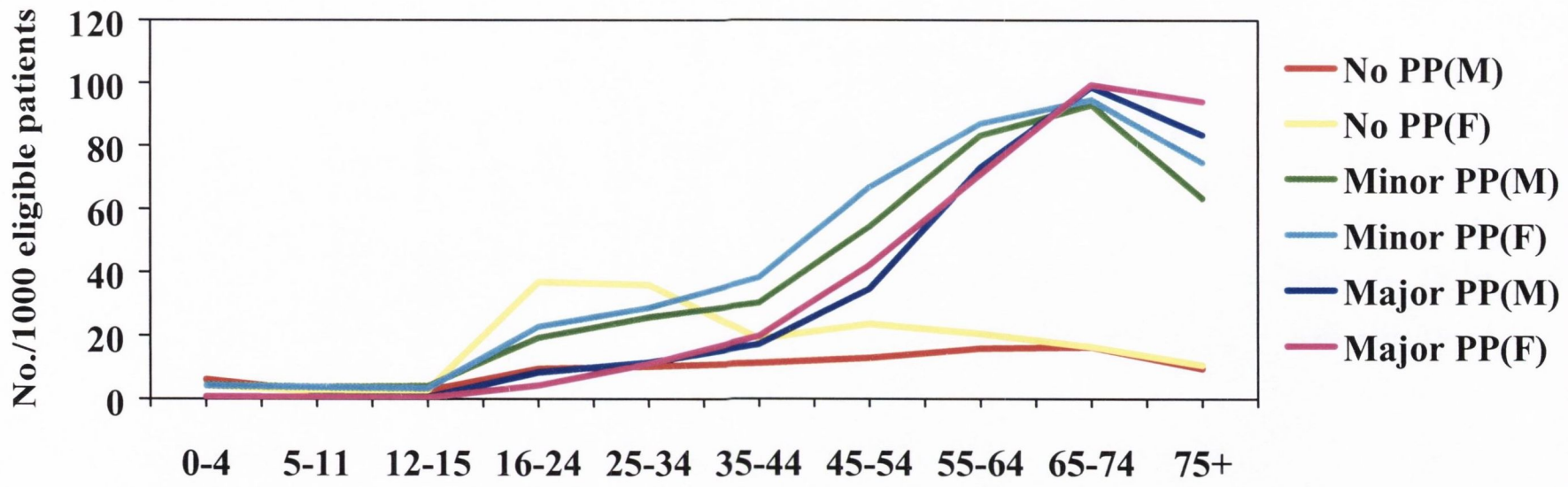


Figure 3.3 Relative contribution of polypharmacy type (No, Minor and Major as defined by the number of medications prescribed per patient each month) to each age group

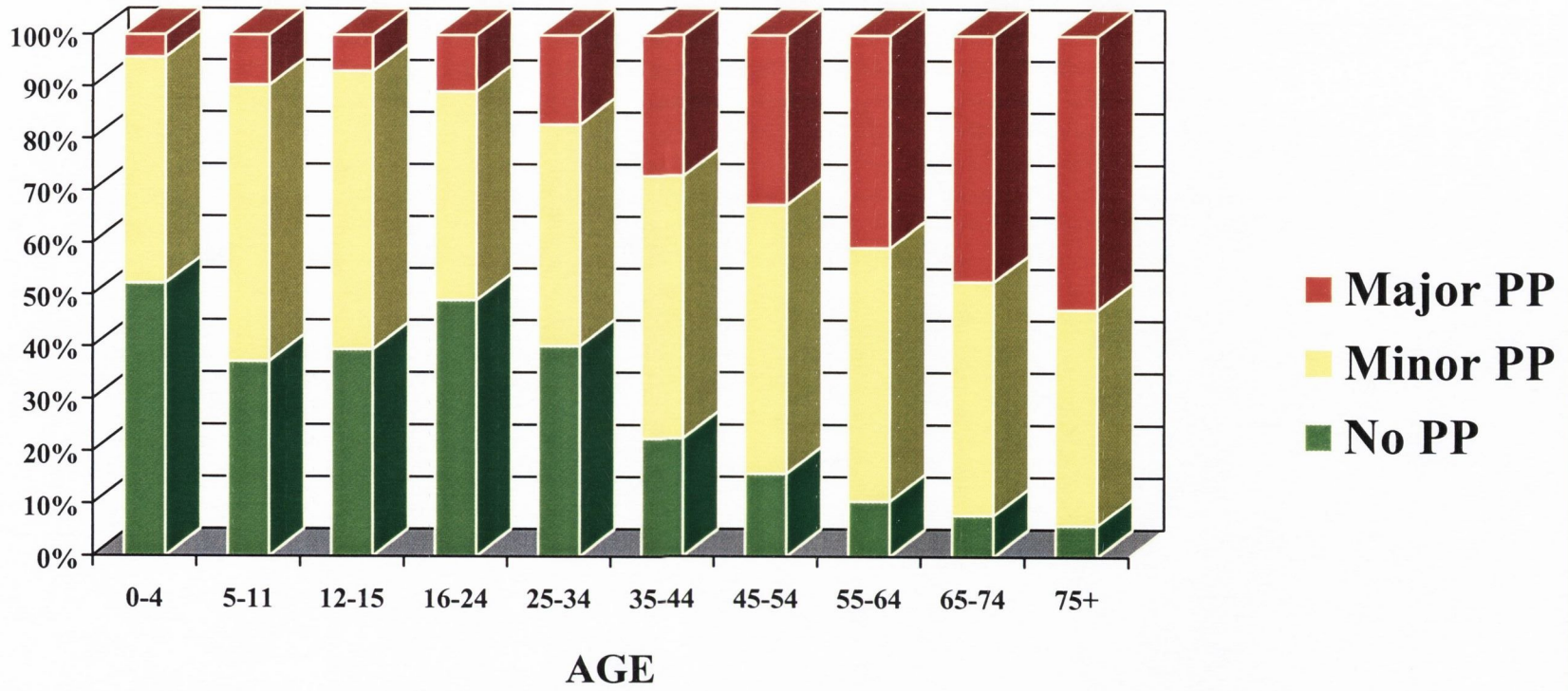


Figure 3.4. Number of indivuduals by age and sex exposed to monopharmacy as defined by the number of medications prescribed per patient each month

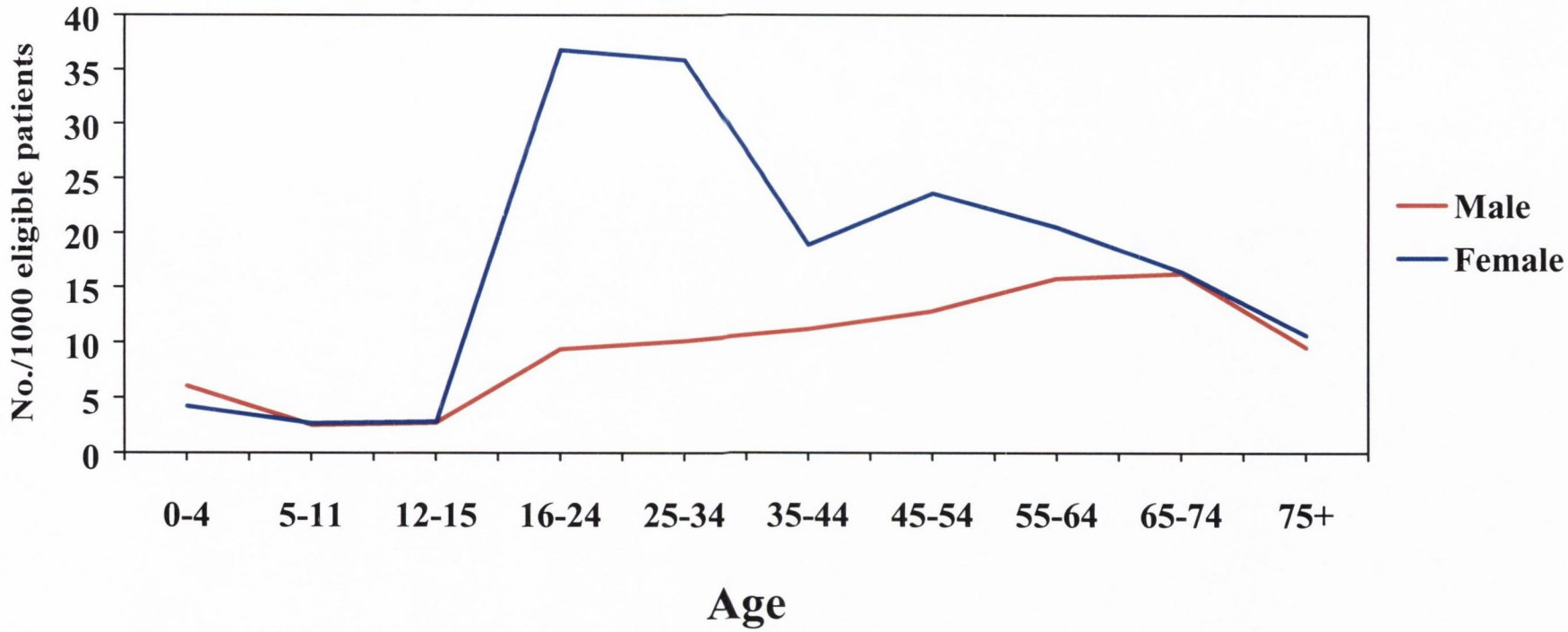


Figure 3.4 demonstrates the major contribution which younger women (predominantly the oral contraceptive pill) make to monopharmacy.

To further explore the relationship between age and the number of prescriptions dispensed per person over this three month period, we plotted these variables against each other for both male and female (Figure 3.5). The data was normalised for the number of persons eligible in each particular age group. There is almost a linear relationship between the volume of prescriptions prescribed and the age groups for both males and females (correlation coefficients of 0.86 and 0.92 respectively)

Figures 3.6 and 3.7 show the contributions which the different ATC groupings make to mono-pharmacy and major polypharmacy. Of the patients on monotherapy, 82% remained on the same medication (as defined by the ATC code) over the three-month period.

The odds ratios (adjusted for age and sex) estimating the risk of being exposed to major polypharmacy according to each ATC group are illustrated in Table 3.2 which shows that all the major ATC groupings are strongly associated with major polypharmacy apart from the genitourinary class of drugs which is more strongly associated with mono-pharmacy.

Figure 3.5. Relationship between age and prescribing rate within the EHB region of the GMS.

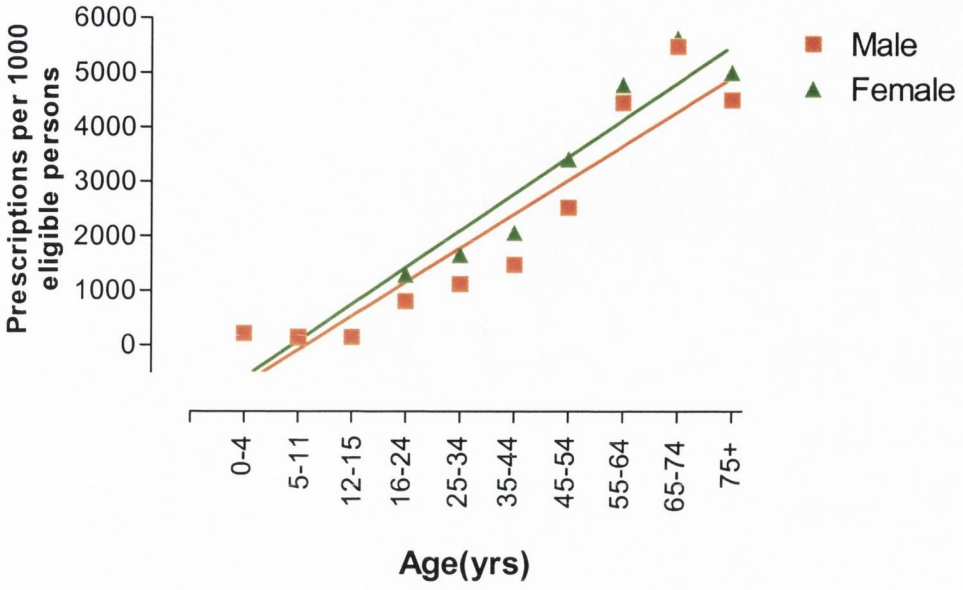


Figure 3.6 Contributions of the principal Anatomical Therapeutic Chemical (ATC) groups to Monopharmacy(as defined by the number of medications prescribed per patient per month).The contributions of each ATC subgroup are shown.

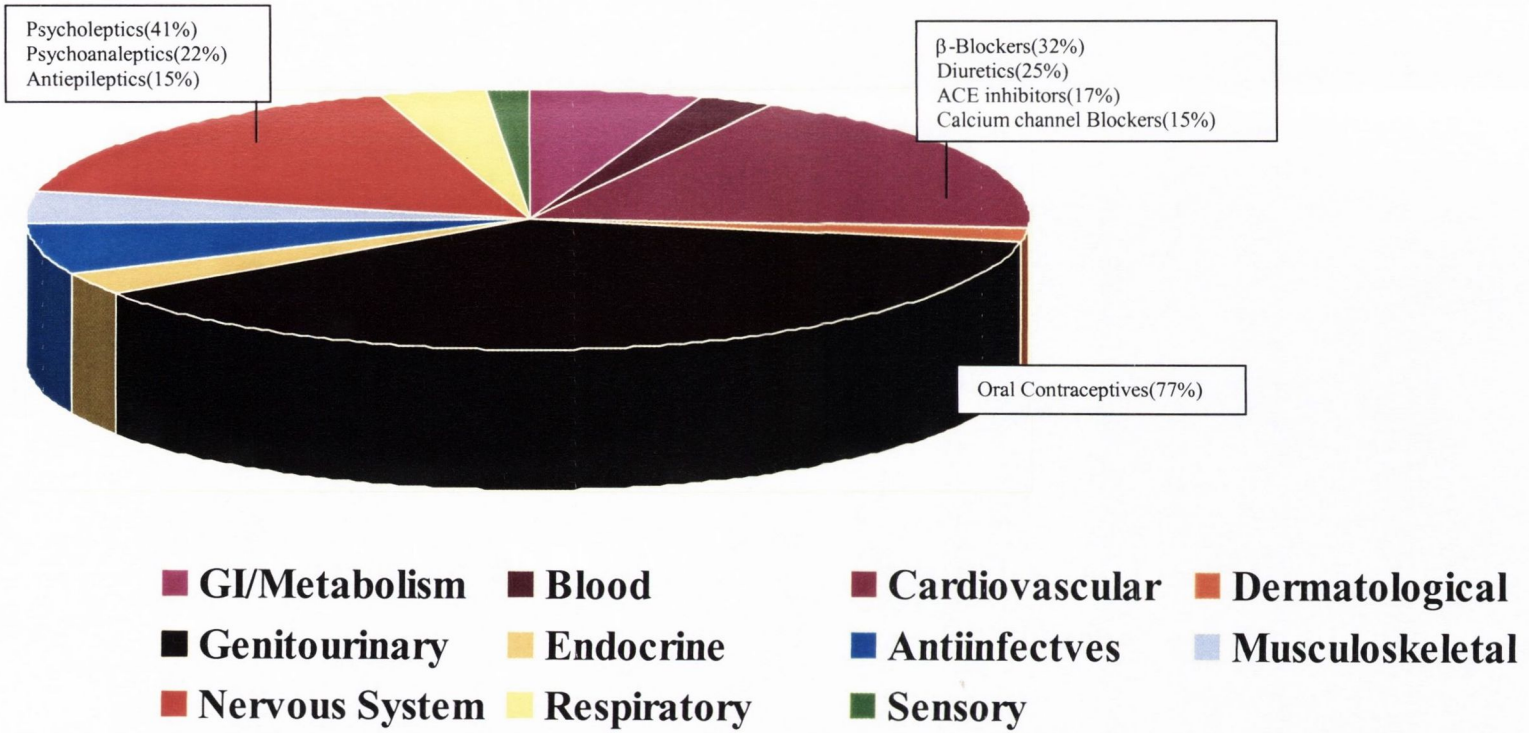
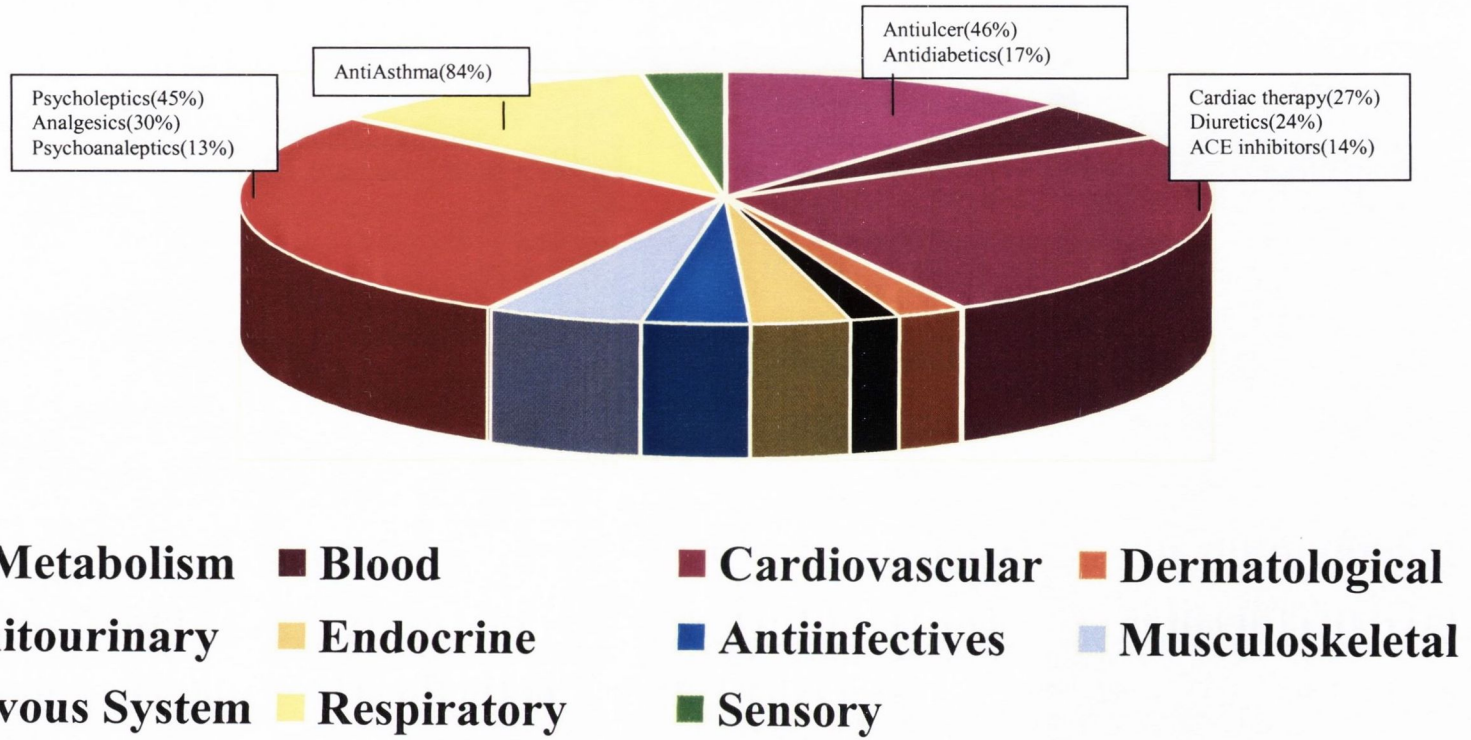


Figure 3.7. Relative contributions of the principal Anatomical Therapeutic Chemical(ATC) groups to Major Polypharmacy(defined by the number of medications prescribed per patient each month. The contributions of each ATC subgroup are shown.



ATC Class	Odds Ratio (95% Confidence interval)	P value
GI/Metabolism	18.6(16.5-21)	<0.001
Blood	10.5(8.9-12.5)	<0.001
Cardiovascular	7.3(6.6-8)	<0.001
Dermatological	13.9(11.6-16.7)	<0.001
Endocrine	9.7(8.2-11.7)	<0.001
Antiinfectives	11.5(10.1-13)	<0.001
Musculoskeletal	11.4(10-13)	<0.001
Sensory	7.9(6.4-9.8)	<0.001
Genitourinary	0.72(0.65-0.8)	<0.001
Nervous system	21.1(19.1-23.3)	<0.001
Respiratory	21.9(18.6-25.9)	<0.001

Table 3.2. Adjusted (For age and sex) odds ratios for major polypharmacy compared with monopharmacy according to the principal Anatomical Chemical Therapeutic (ATC) class

The odds ratios for major polypharmacy with regard to the different age bands within the GMS are shown in Table 3.3 and Figure 3.8. They indicate that as one gets older the odds of being exposed to major polypharmacy increases. Additionally despite the fact that females have a greater representation within the study group, males are more likely to be exposed to major polypharmacy (Age-adjusted OR=1.48, 95% Confidence interval, 1.36-1.60).

Unfortunately, no indication of the date of a particular prescription is provided in the monthly report provided by the GMS. Hence a patient who receives two prescriptions (each of which may contain more than one prescription item) may have received one prescription at the beginning and end of the month without any overlap between the prescriptions. On average patients exposed to major polypharmacy on a chronic basis received more prescriptions which contained more prescription items over the study period (Table 3.4). In addition the interquartile range of prescription items was wider for the major polypharmacy grouping.

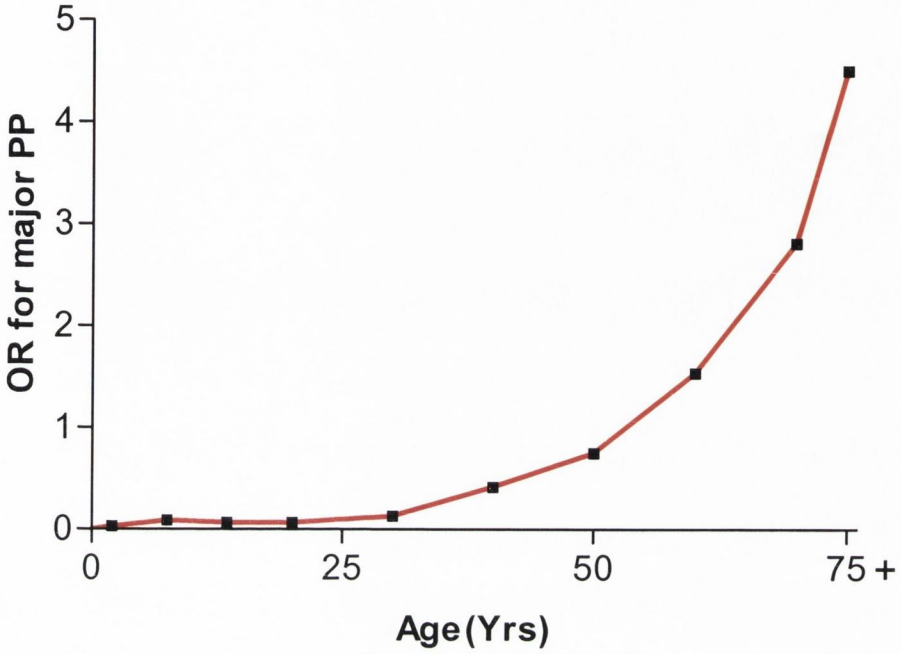
Age(yrs)	Odds Ratio	95% Confidence interval	P value
0-4	0.03	0.01-0.05	<0.001
5-11	0.09	0.06-0.15	<0.001
12-15	0.07	0.03-0.11	<0.001
16-24	0.07	0.06-0.08	<0.001
25-34	0.13	0.11-0.15	<0.001
35-44	0.42	0.37-0.47	<0.001
45-54	0.75	0.67-0.84	<0.001
55-64	1.54	1.39-1.71	<0.001
65-74	2.81	2.56-3.08	<0.001
75+	4.5	4.07-4.98	<0.001

Table 3.3. Odds ratios for major polypharmacy(> 4 drugs) compared with monotherapy as a function of age.

Polypharmacy Type	**Mean number of prescriptions per month (Median and interquartile range of, number of prescription items per prescription)**		
	March	April	May
Minor	1.33 (2, 1-3)	1.31 (2,1-3)	1.31 (2,1-3)
Major	2.37 (3,1-5)	2.36 (3,1-5)	2.34 (3,1-5)

Table 3.4. Mean number of prescriptions (and median and interquartile range of prescription items per prescription) received by those patients exposed to Minor (2-4) and Major (>4) polypharmacy.

Figure 3.8. Odds ratios for the development of major(>4 drugs) polypharmacy(as defined by the number of medications prescribed per patient each month) by age



3.1.4 Analysis of multiple drug use using prescription claims data

As mentioned earlier the definition of polypharmacy according to the number of prescription items prescribed per month may have led to an overestimation of the degree of polypharmacy and differing patterns of polypharmacy. To further investigate this issue we examined individual prescriptions over the identical three-month period and defined multiple drug use as the prescription of more than one drug on an individual prescription. As individual prescriptions have a unique prescription number which is not re-used, each prescription needs to be linked back to the individual patient who can then be followed over the 3-month study period.

3.1.4.1 Methods

Multiple drug use was again defined according to whether a patient received 1(no polypharmacy), 2-4 (minor polypharmacy) or greater than 4 (major polypharmacy). For each month prescriptions were divided into these three sub-groupings. The prescriptions were then linked back to the patient numbers and only patients who remained within the same polypharmacy grouping over the three-month period were analysed. Similarly the contribution of the ATC groupings to the different polypharmacy subgroups was analysed for the three-month period. Again the prescription claims were linked to patients who remained in the same polypharmacy subgroup over the three-month period.

3.1.4.2 Results

The results of a similar analysis to that performed previously are summarised in Figures 3.9-3.13 and in Table 3.5. 53,281 patients remained within the same polypharmacy grouping over the three-month period. Similarly 56% of chronic polypharmacy was accounted for by the 65+ age group. Similar trends in polypharmacy were demonstrated when polypharmacy was defined by prescription data (Figures 3.10-11). Similar contributions of the major ATC groupings were also demonstrated (Figures 3.12-13). Thus similar results were obtained whether polypharmacy was defined by monthly or individual prescription data.

Figure 3.9. Male/Female distribution of polypharmacy(PP) types(No, Minor and Major)as defined by the number of prescription items per prescription within the EHB region of the GMS .

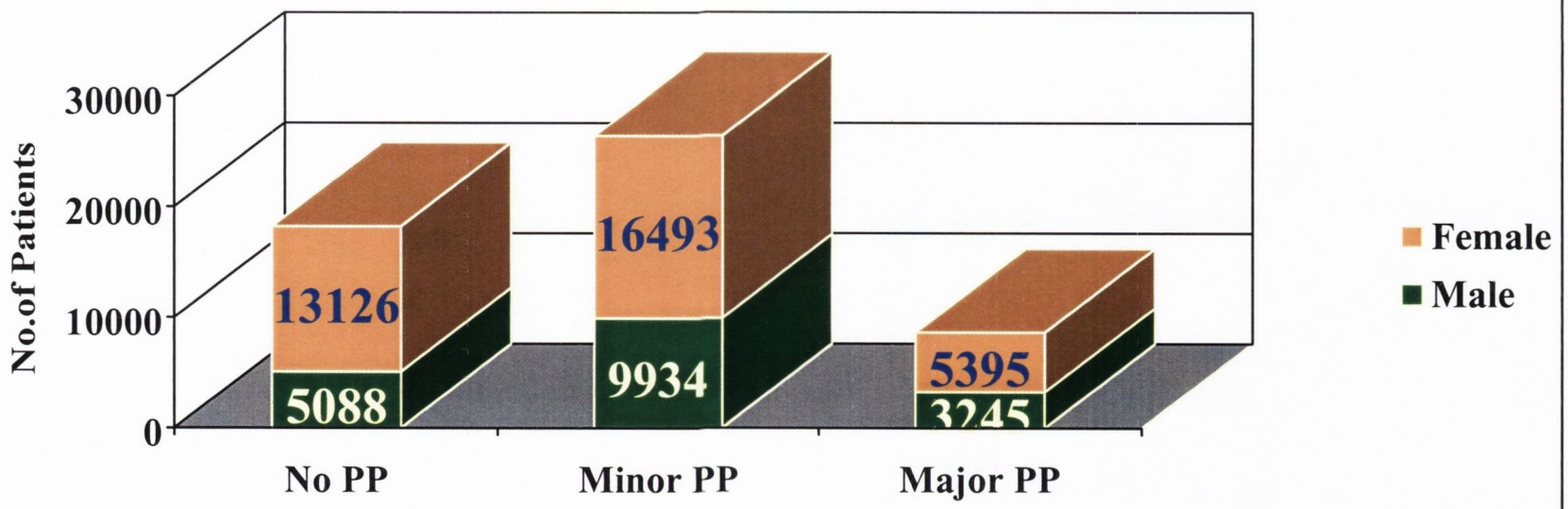


Figure 3.10. Trends in Polypharmacy(No,Minor and Major) as defined by the number of prescription items per prescription by age and sex, within the EHB region of the GMS.

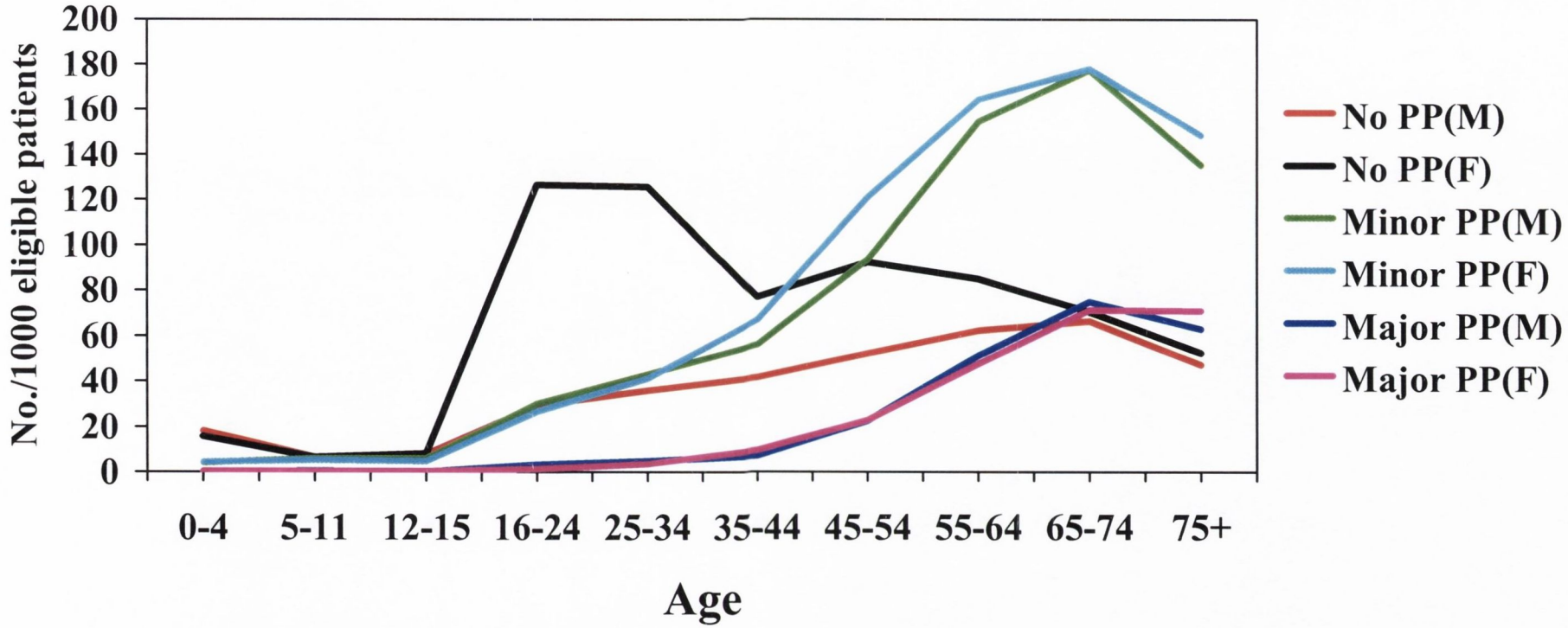


Figure 3.11.Trends in monopharmacy (as defined by the number of prescription items per prescription) by age and sex within the EHB region of the GMS.

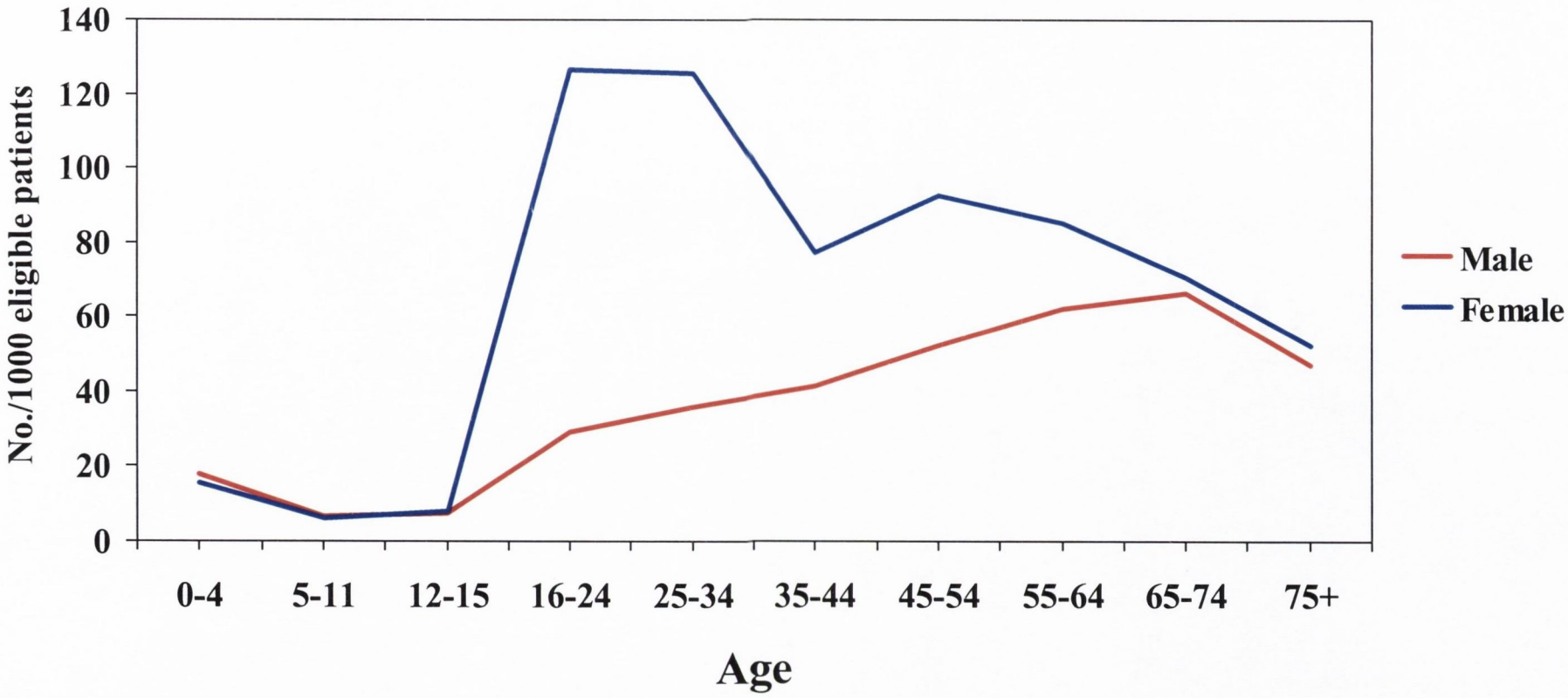


Figure 3.12. Contributions of the principal Anatomical Therapeutic Chemical(ATC)groups to Monopharmacy (as defined by the number of prescription items per prescription) within the EHB region of the GMS.The contributions of each ATC subgroup are shown.

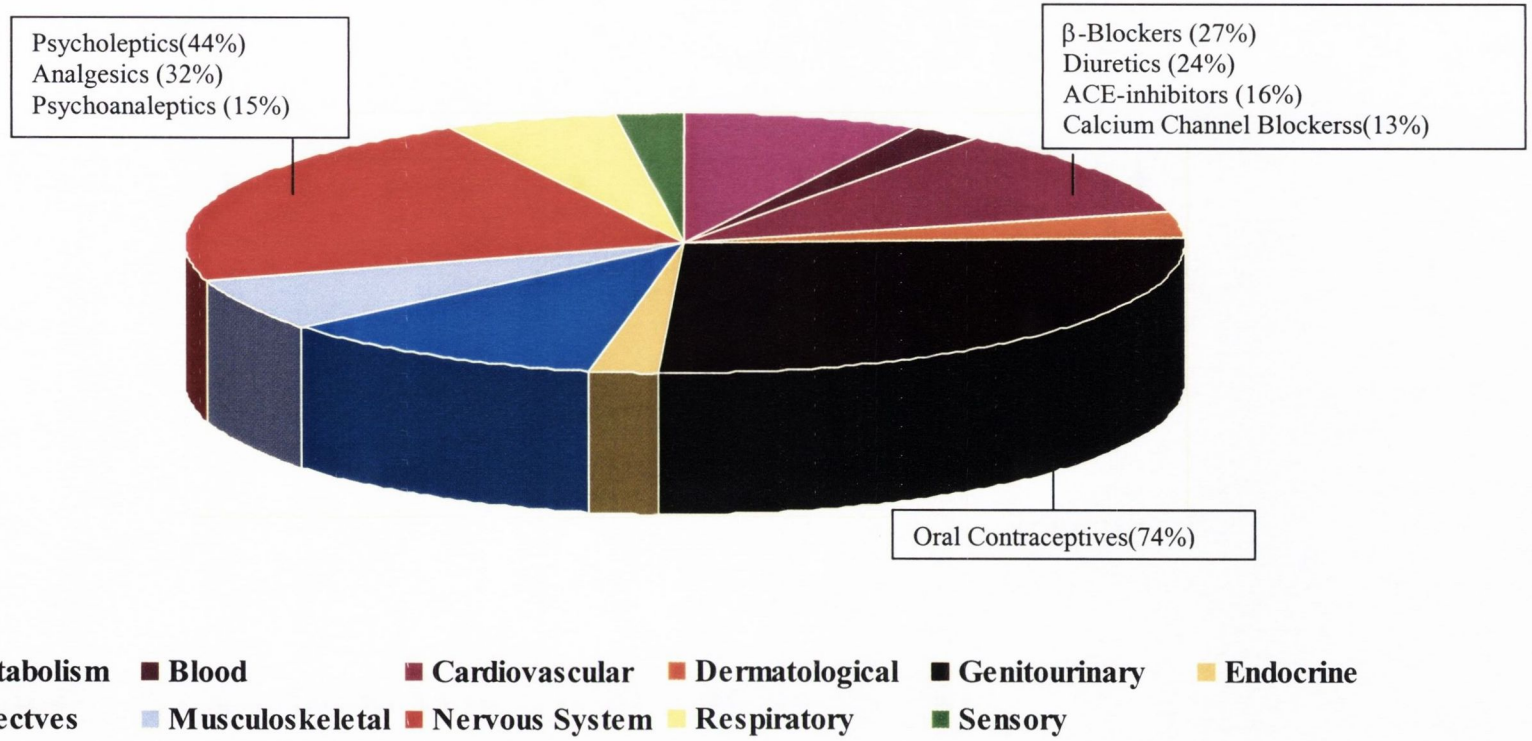
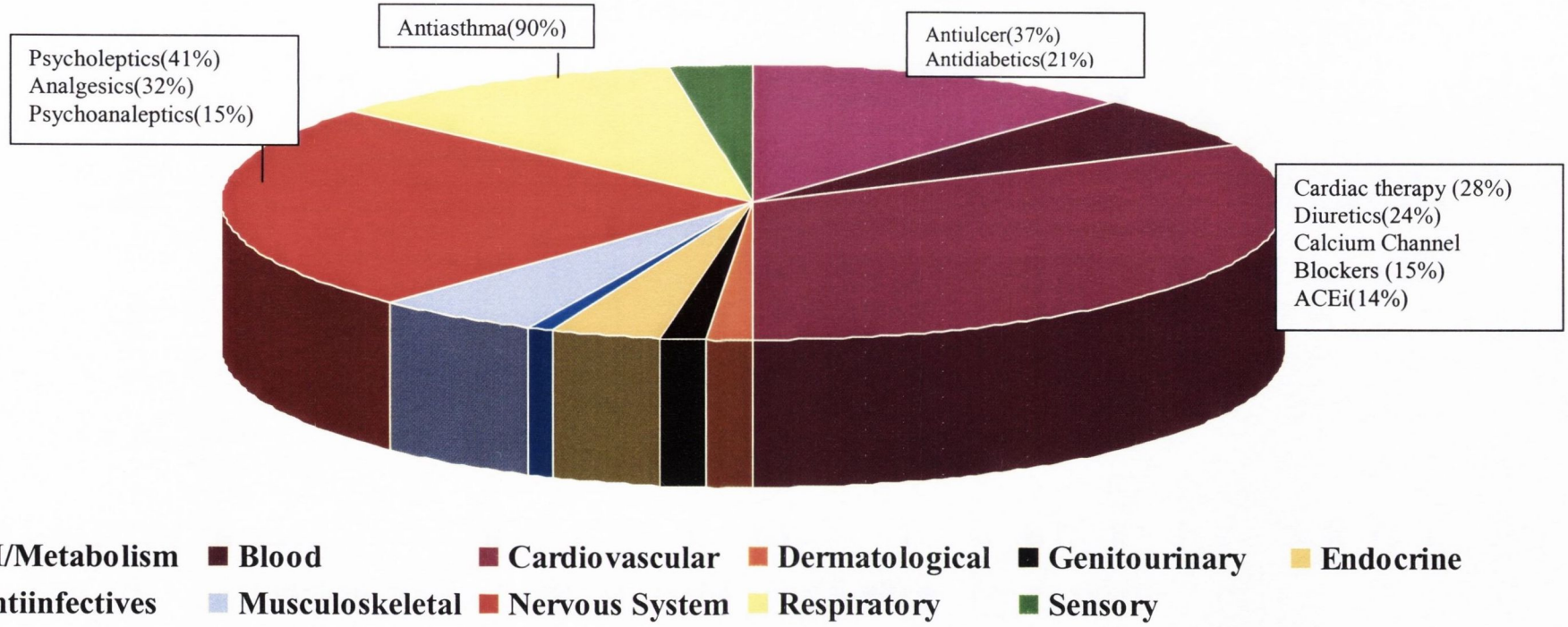


Figure 3.13. Contributions of the principal ATC groups to Major(>4 drugs) polypharmacy as defined by the number of prescription items per prescription within the EHB region of the GMS. The contributions of each ATC subgroup are shown.



Age(yrs)	No Polypharmacy(%)	Minor Polypharmacy(%)	Major Polypharmacy(%)
0-4	430(2.36)	106(0.4)	4(0.04)
5-11	234(1.28)	200(0.8)	11(0.12)
12-15	175 (0.96)	117(0.4)	3(0.04)
16-24	2694(14.8)	845(3.2)	58(0.7)
25-34	3132(17.2)	1435(5.4)	136(1.6)
35-44	2081 (11.1)	2041(7.7)	275(3.2)
45-54	2317 (12.7)	3400 (12.8)	711 (8.3)
55-64	2197 (12.1)	4686 (17.7)	1436 (16.6)
65-74	2617 (14.4)	6762 (25.5)	2677 (32)
75+	2400 (13.2)	6835 (25.9)	3240 (37.5)
Total	18214 (100)	26427(100)	8640(100)

Table 3.5. Numbers (%) and age groups of patients exposed to No, Minor(2-4 drugs) and Major(>4 drugs) Polypharmacy(as defined by the number of prescription items per prescription).

3.1.5 Discussion

Previous methods for estimating the occurrence of polypharmacy by means of a prescription database have included an estimation based on the number of simultaneously used drugs (calculated from the date of purchase and the number of daily defined doses (DDDs)), the number of drugs purchased in 3 months and the mean number of drugs used in one year [131]. A previous study by Bjerrum et al has shown that 80% of individuals who had purchased five or more drugs over a three-month period were subject to an episode of major polypharmacy (as estimated by calculating the number of DDDs) at least once during the year [131]. As the GMS prescription database provides no information on the date of purchase of medications we studied drug usage per month and only studied patients who received medications continuously over a three-month period to identify chronic users of medication.

There are a number of factors which contribute to polypharmacy. These include increasing age, multiple medical conditions, multiple symptomatology, increasing prescribing rates by practitioners, lack of coordination of drug therapy (for example between hospital and primary care), drug regimen changes and self-medication.

Independent of the age of the patient, multiple symptoms and diseases can result in polypharmacy. As the number of somatic complaints and diseases increases, so do the indications for pharmacotherapy. Even when no organic cause for disease is determined, symptoms can be multiple, and somatisation can contribute to unnecessary prescribing in an attempt to address these complaints.

In addition to patient factors, prescribers also have a significant impact on polypharmacy. In the United States, over 75% of physician visits terminate in a prescription [132]. General practitioners describe themselves as being under considerable pressure to prescribe, even when this is against their better judgment. In a study of prescribing decisions with which the doctor admitted some discomfort, doctors describe feeling pressurised into prescribing by a variety of influences, including the expectations of the patient, precedents set by colleagues prescribing, and concerns about the possible effect of not prescribing on the doctor-patient relationship [133]. These pressures to prescribe can, therefore, be identified as coming from three main sources: patients, doctors, and the pharmaceutical industry. The prescription can be seen as a tangible end to a consultation, and may be perceived by the patient as having greater value than education or reassurance. It may also be easier for the busy practitioner to provide the former than the latter two, which may take considerably more time. More recently, a countermanding pressure to avoid prescribing wherever possible has come from those responsible for the funding of health care.

Multiple drug use is widespread within the GMS population. In 1998 over 95% of the population received at least one prescription. This compares with a 1-year prevalence of drug use of 57% reported in a previous study of polypharmacy using the Odense Pharmacoepidemiological Database (OPED)[134]. Our study may have underestimated the degree of polypharmacy as we have no estimate of the use of over-the-counter (OTC) or non-subsidised medications. Hence drug regimens classified as mono-pharmacy may in fact be polypharmacy and drug use classified as minor polypharmacy may have

involved five or more drugs. This bias however may be counter-balanced to a certain degree by the fact that poor-compliance with medications is widespread [40;135]. In addition a number of medications such as analgesics or anxiolytics may have been used on a 'PRN' or as required basis and not chronically as indicated in this study. Multiple drug use is particularly common among the elderly population with 58% of chronic polypharmacy occurring in the 65+ age group which constitute only 24% of the total GMS. In this group of patients the average number of drugs prescribed per patient over the 3-month study period was 14.62+/- 8.83. This compares with a previous study by Nolan who examined repeat prescriptions for patients on 'long-term' drugs in general practice and found that the mean number of drugs prescribed per elderly patient was 2.6 [136]. It is widely recognised that elderly people consume relatively more medication than younger people [136]. Whilst a higher level of drug use is related to the increased prevalence of chronic disease among this population, there is a concern that part of the increase in medication use may be as a result of excessive or inappropriate prescribing [137]. Elderly patients are extremely susceptible to the side-effects of drugs, particularly those that effect the cardiovascular and central nervous systems, and have degenerative disorders affecting several systems and have impaired homeostatic mechanisms. Elderly patients' comprehension is often poor, leading to increasing difficulties when taking several drugs [124].

Our estimate of the incidence of chronic polypharmacy in this elderly (>65yrs) age group of 23% compares with a figure of 10% as reported by Bjerrum in Denmark[131]. In previous studies 20 to 30% of the elderly were taking three or more drugs [130;138;139]. In one of the few studies performed in general practice

in Ireland, Nolan et al examined all the drugs dispensed during a one-week period in a sample of community pharmacies in Dublin which included both GMS and Non-GMS patients. They found that the number of drugs per prescriptions increased linearly from 1.5 in children aged 0-9 years to 2.8 in patients 80yrs and over. They noted the lack of a denominator was a limiting factor as they could not estimate the absolute prescribing rates for different age groups over a one-week period in 1985 [140]. One of the advantages of the GMS data is that it allows one to determine exact prescribing rates as the number of patients in each age group is available. A previous study performed in an elderly population in Belfast found that the number of drugs received by patients was not predicted by age or sex, but by institutional or hospital placement. Placement was also found to be the most significant predictor of drug class [141].

In this study, polypharmacy has been used simply to mean multiple drug use. However our prescription data do not allow us to draw any conclusions about the justification for polypharmacy. For many patients, treatment with two to four drugs may be appropriate. Indeed a patient who has suffered a myocardial infarct might well be expected to receive aspirin, nitrate therapy, a β-blocker and a statin or ACE-inhibitor depending on whether the patient had hypercholesterolaemia or heart failure. However when the number of number of simultaneously used drugs increases to five or more, there is an increased risk of medication errors, especially when the drugs need to be taken at different times of the day [142]. Furthermore, polypharmacy poses a potential hazard to any patient through adverse drug reactions, drug-disease interactions and drug-drug interactions.

3.2 Utilisation of Helicobacter pylori eradication therapy in the General Medical Services scheme.

3.2.1 Introduction

Dyspepsia is a common symptom affecting some 30-40% of adults over a 6-month period [143], and accounts for 2-3% of consultations in primary care [144]. In 1991 peptic ulcer disease was estimated to account for over one-third of all national health (NHS) expenditure on gastrointestinal diseases and by March 1999, 2.9% of prescriptions written in England were for ulcer healing drugs accounting for 10% of all drug costs or £110 million per quarter [145]. Within the General Medical Services (GMS) scheme in Ireland, anti-secretory agents contributed to 4% of the total drug expenditure [66]. Symptomatic peptic ulcer disease, affecting 5 to 10% of the population, is associated with *H.pylori* infection which has emerged as an important aetiological agent [146]. Cross-sectional studies have shown an association between *H.pylori* and dyspepsia[147;148]. Guidelines recommending eradication of *H.pylori* using various regimens incorporating antimicrobials and anti-secretory therapy have reported success rates of over 90%[149] and recurrence rates as low as 1% per year [150;151]. In addition to providing clinical benefits to patients, the diagnosis and treatment of *H.pylori* infection has proved to be cost-effective[152-154]. However most research into *H.pylori* has taken place in highly selected hospital populations who have a precise diagnosis and where compliance may be higher. Most patients are treated empirically by primary care physicians unless there are features such as bleeding and weight loss[155]. Little is known of the efficacy of *H.pylori* eradication regimens in reducing the consumption of acid-lowering drugs or improving dyspeptic symptoms in

the setting of undiagnosed dyspepsia in primary care [156] although a recent study demonstrated that only 15% of infected patients with dyspepsia could be cured by eradication therapy [157]. We wished to test the success of eradication therapy as used in general practice, using a large prescription database which identified those patients who received eradication therapy, to determine whether such patients subsequently received further anti-secretory therapy.

3.2.2 Methods

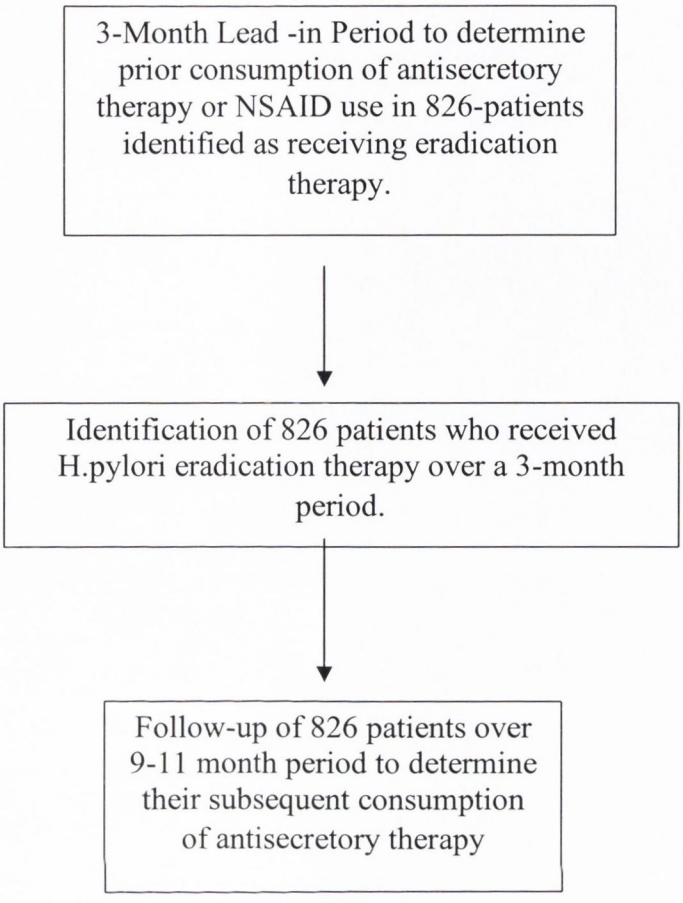
We identified a total of 50,398 (M: F 21,520:28,878) patients from the Eastern Health Board Region of the GMS prescription database who received prescriptions for drugs used in the treatment of peptic ulcer disease, as defined under the WHO Anatomical Therapeutic Chemical (ATC) classification system. From this group we identified a total of 3847 patients (M: F, 1813:2034, median age 49 years) who received 3851 prescriptions for one of the standard *H.pylori* eradication regimens. Only patients who received a prescription for an antiulcer drug and antibiotic on the same prescription were included. In addition, regarding patients who received dual therapy, only those who received at least 2 weeks therapy with an antibiotic in addition to a proton pump inhibitor were included to minimise confounding by indication. Patients who received eradication therapy were then followed to estimate the success or failure of such therapy in reducing the subsequent prescription of antiulcer medications. Failure of therapy was defined as the subsequent receipt of a prescription for an antiulcer drug such as a proton pump inhibitor or H_2-antagonist, but not including antacids.

As the entire group of 3847 patients had a variable follow-up period ranging from 0-14 months (median follow up of 8 months), which may have led to an underestimation of failure, we identified a subgroup of 826 patients who received eradication therapy over a 3 month period (February 1998-April 1998) and followed these over a period of 9-11 months (Figure 3.14). This definition of failure of eradication therapy was chosen as practitioners might reasonably expect that if they are treating patients with a high index of suspicion for eradicating *H.pylori* infection, that further anti-ulcer medications would be unnecessary as continued anti-secretory therapy following eradication therapy is now considered unnecessary in peptic ulcer disease [158]. Univariate analysis, followed by cox proportional hazards modelling, was undertaken to identify variables thought to contribute to the failure of eradication therapy. Kaplan-Meier failure curves were developed for such variables. Statistical modelling was performed using Stata® (Version 6,1999).

3.2.3 Results

From the entire group of 3847 patients who received eradication therapy proton pump inhibitors were used in the majority of regimens while bismuth-containing preparations contributed to less than 2% of the eradication therapies (Table 3.6). The overall failure rate for this group of patients receiving eradication therapy was 49%. However these results may have underestimated the overall failure rate of eradication therapy as patients receiving eradication therapy towards the end of the study period would have had a shorter potential time to fail. Hence in addition we identified a cohort of 826 patients (M:F 373:453 median age 49 years) who received 828 prescriptions for eradication therapy over a three-month period (February to

Figure 3.14. Outline of study design to determine success of H.pylori eradication therapy within the EHB region of the GMS



		Overall Group (n=3851) with 0-14 month follow-up.		3-month group (n=826) with 9-11 month follow-up	
Therapy	Number (% of H.pylori therapy)*	Failure rate (%)	Number (% of H.pylori therapy)	Failure rate(%)	Time of median failure (months)**
PPI+Amoxycillin+ Clarithromycin	2353(61)	49%	490(60%)	57%	6
PPI+Clarithromycin+ metronidazole	880(23)	48%	201(24%)	56%	7
PPI+Amoxycillin+ Metronidazole	270(7)	44%	61(7%)	44%	Not available as less than 50% fail
PPI+clarithromycin	153(4)	59%	34(4%)	62%	2
PPI+Amoxycillin	87(2.2)	51%	19(2%)	53%	8
H_2-antagonist+ Amoxycillin+ Metronidazole	36(0.9)	47%			
H_2-antagonist +Clarithromycin+ Metronidazole/ Amoxycillin	29(0.8)	38%			
Bismuth-containing regimens	43(1.1)	67%			

Table 3.6 Failure rates (defined as the prescription of acid suppressant therapy subsequent to receiving eradication therapy) for eradication therapies for the overall group of 3847 patients(n=3851 prescriptions) followed for 0-14 months and failure rates and median time to failure for the group of 826 patients (n=828 prescriptions) for which co-prescribing information was available and who were followed for 9-11 months. Eradication regimens with less than 10 patients were omitted.

April 1998) and followed these patients for 11, 10 and 9 months respectively. Kaplan-Meier failure estimates were determined for this group of patients (Figures 3.15–3.18). Because of the variable follow-up period, some outcomes are effectively censored. The results are shown in Table 3.6. A total of 464 (56%) patients, with a time of median failure of only 6 months, subsequently received a prescription for antiulcer therapy and were deemed failures of eradication therapy. The failure rate varied from 44% to 62% but was not significantly different between treatment combinations. Patients who failed from eradication therapy received on average 4 prescriptions for antiulcer medications following eradication therapy. A total of 93 patients were retreated with one further eradication therapy whilst 23, 9 and 6 patients were re-treated twice, three times or four times respectively without any particular pattern to their re-treatment regimens though patients initially treated with a proton pump inhibitor, clarithromycin and metronidazole tended to receive a different antibiotic subsequently.

A total of 415 patients out of 826 patients were naïve to antiulcer therapy (absence of antiulcer therapy for at least 3 months prior to eradication therapy) and had a failure rate of 44%. This compares with a failure rate of 69% (time of median failure = 2months) for patients labelled as chronic (i.e. receiving antiulcer therapy prior to eradication therapy, (Figure 3.16).

Of 232 patients who received a prescription for aspirin/non-steroidal anti-inflammatory agents for at least 3 months prior to their eradication therapy the failure rate was 66% with a time of median failure of 3 months (Figure 3.17). The failure rates of the differing strengths of aspirin varied little (63% for

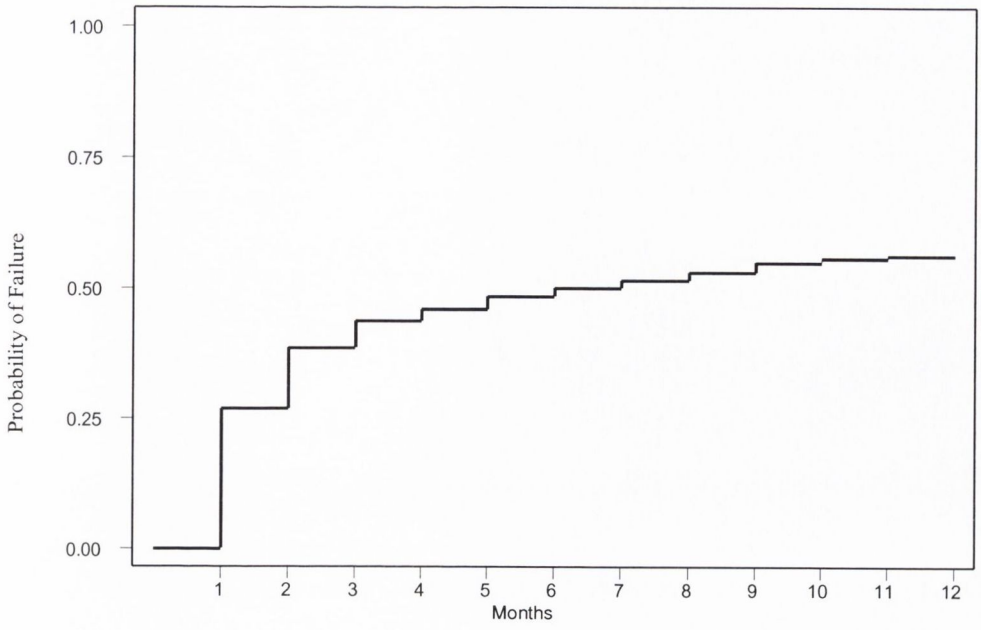


Figure 3.15. Kaplan-Meier failure estimate of *H.pylori* eradication therapy for overall group of patients who received eradication therapy within the EHB region of the GMS.

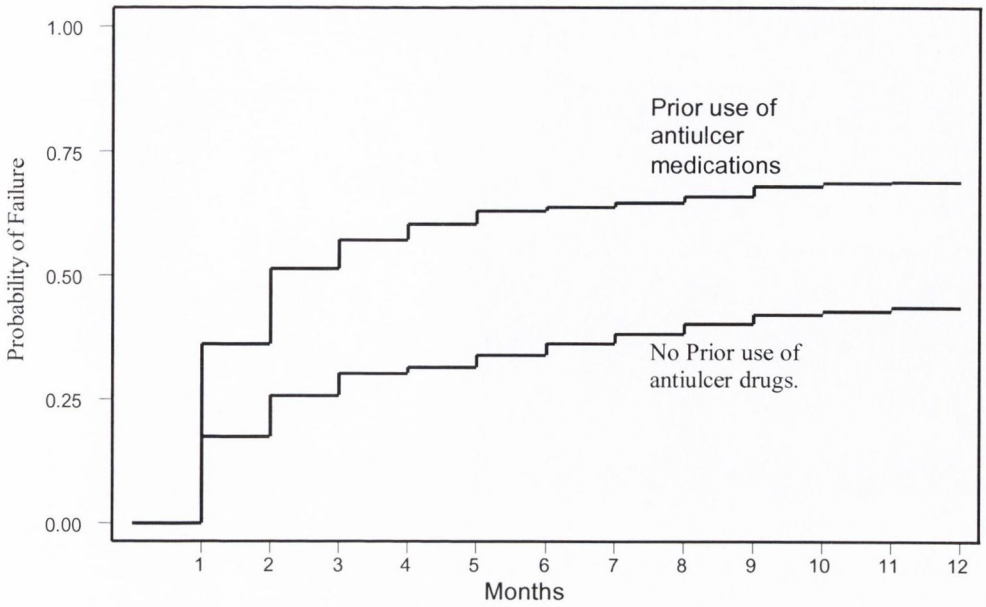


Figure 3.16. Kaplan-Meier failure estimates of *H.pylori* eradication therapy in patients with prior exposure to antiulcer therapy within the EHB region of the GMS.

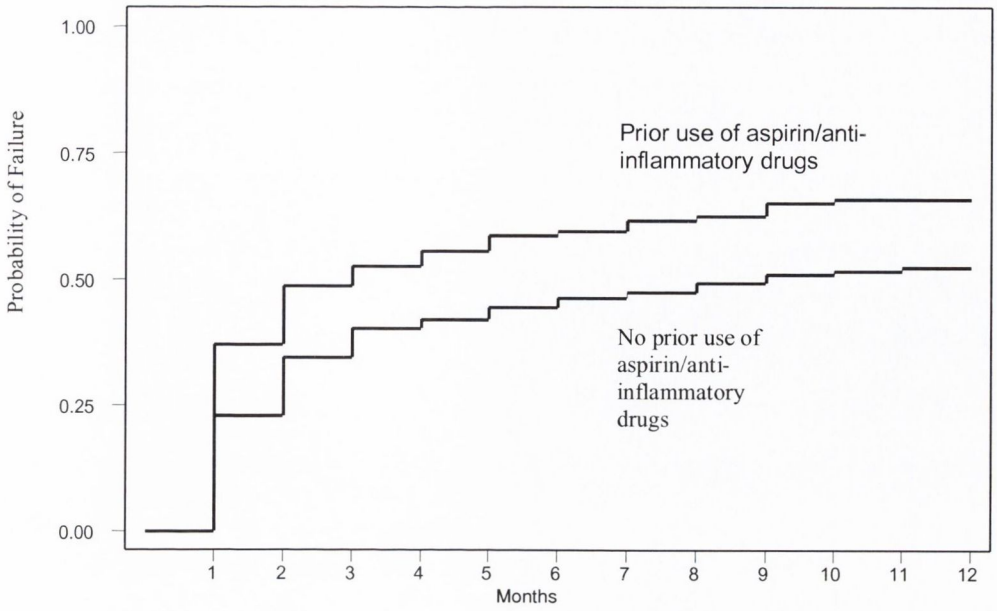


Figure 3.17. Kaplan Meier failure estimates of *H.pylori* eradication therapy by prior use of aspirin or non-steroidal anti-inflammatory agents within the EHB region of the GMS.

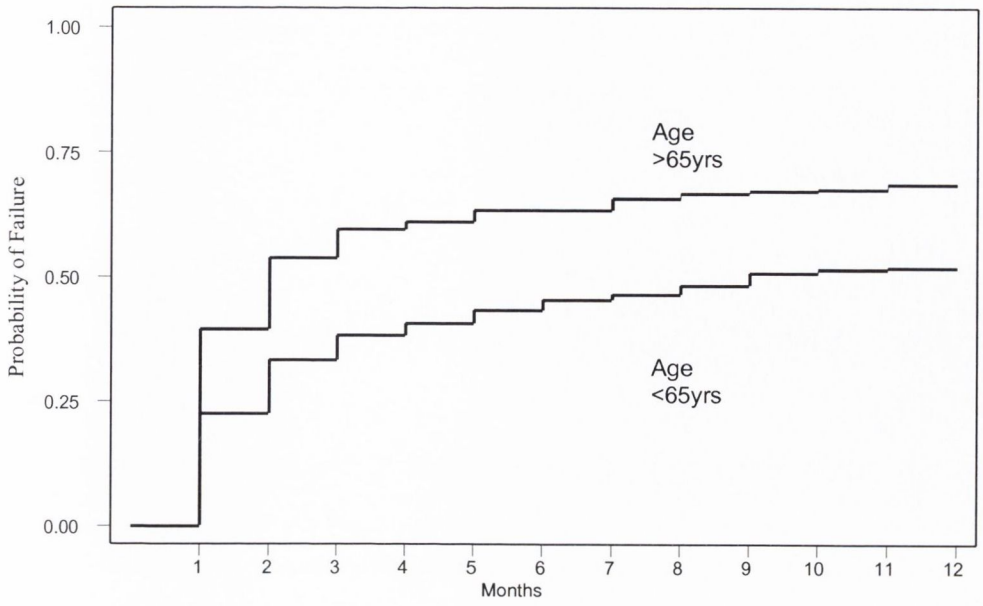


Figure 3.18. Kaplan Meier failure of *H.pylori* eradication therapy estimates by age within the EHB region of the GMS.

aspirin 75mg and 65% for aspirin 300mg/600mg). Forty six percent of those patients who failed eradication therapy received a prescription for either aspirin or NSAID. Patients not exposed to aspirin/NSAIDs prior to eradication therapy had a failure rate of 52% with a time of median failure of 9 months. Patients aged greater than 65 years of age were also more likely to fail (failure rate of 69%; time of median failure =2 months) when compared to those aged less than 65years (failure rate of 52%; time of median failure = 9 months (Figure 3.18).

A univariate analysis of those variables thought to contribute to the failure of eradication therapy showed that three variables: prior exposure to antiulcer therapy (Hazards Ratio [HR] = 1.97,95% CI =1.63-2.37, $p<0.001$), age >65 years (HR=1.57, 95% CI 1.29-1.91, $p<0.001$) and prior exposure to aspirin/non-steroidal anti-inflammatory agents (HR=1.43, 95% CI 1.18-1.73, $p<0.001$) were found to be statistically significant in predicting failure following eradication therapy. Gender or the particular form of eradication therapy were not shown to be associated with failure. A Cox proportional hazards model found that prior use of antiulcer medications (HR=1.92, 95% CI-1.59-2.32, $p<0.001$), age greater than 65years (HR = 1.44, 95%CI =1.18-1.77,$p<0.001$) and prior use of aspirin/non-steroidal anti-inflammatory agents (HR=1.27, 95% CI =1.04-1.55, p=0.02) predicted failure.

3.2.4 Discussion

Our results suggest that more than half of those patients who received eradication therapy in general practice require further antiulcer medications. There may be a number of reasons for these apparent high failure rates of eradication therapy in reducing the subsequent use of antiulcer medications. Firstly, without knowledge of the underlying diagnosis in this population we have no information on the proportion of patients who tested positive for *H.pylori* and hence are more likely to benefit from eradication therapy. Indeed there is a lack of correlation between patients' self-reported symptoms of dyspepsia and infection with Helicobacter pylori[159]. In a previous study carried out in primary care, *H.pylori* status was known in only one-third of patients before eradication treatment and in only 15% following eradication therapy [160]. A recent survey of primary care practitioners suggested that up to 59% had at some point prescribed eradication therapy without knowledge of *H.pylori* status [161]. Consequently we have no information on the percentage of patients who may have had non-ulcer dyspepsia, reflux-oesophagitis or NSAID-induced peptic ulceration in which the role of eradication therapy is less clear [162-166]. Inclusion of such patients would be expected to reduce the overall success rate of therapy. It is however likely that some of these patients were diagnosed as *H.pylori* positive in hospital as in a previous study [45] we found that 33% of prescriptions for gastrointestinal drugs in general practice originated from recommendations of hospital clinics, hospital discharges or hospital-based doctors. In addition, even if some patients with NSAID-induced peptic ulceration were infected with *H.pylori* which was successfully eradicated, recurrent symptoms may occur with the future use of ulcerogenic

drugs. Secondly the higher failure rates associated with the elderly and with those patients with prior use of aspirin/NSAIDs drugs suggest that these drugs may play a key role in such failures. Within the entire group of patients who received antiulcer medications 68% of those patients aged greater than 65 years received a prescription at any time for aspirin/NSAID. Thirdly the high failure rates in those patients with prior exposure to antiulcer medications may indicate incorrect diagnosis or *H.pylori*-negative disease. Finally, a proportion of the high failure rates, particularly those associated with dual therapy, may be confounded by the coincidental use of amoxycillin or clarithromycin in patients already on antiulcer drugs (though we attempted to reduce this by including only patients receiving at least 14 days therapy of antibiotic) or by poor compliance with eradication therapy. Although recurrence or a new infection with *H.pylori* in these patients cannot be excluded, this is unlikely as the rate of acquiring a new or recurrent infection after 4-7 years is only 2-8%[151;167].

There was no suggestion that any one eradication therapy was associated with a greater likelihood of failure. Of interest, less than 2% of patients received a prescription for bismuth containing preparations, possibly indicating poor patient acceptability with these preparations despite their proven clinical effectiveness [168]. Indeed standard triple therapy-that is, the combination of bismuth plus metronidazole plus either amoxycillin or tetracycline was seldom used as eradication therapy. The extensive use of proton pump inhibitors confirms their popularity in primary care in part due to a perceived greater efficacy of these agents [169].

Of those patients who failed on eradication therapy, the majority (73%) were subsequently prescribed a proton-pump inhibitor. This may be explained by the observed greater efficacy of symptom relief obtained by proton pump inhibitors in functional dyspepsia [170;171]. Alternatively unmasking of oesophageal reflux disease following *H.pylori* eradication may explain the higher proportion of proton pump inhibitors in those patients who failed following eradication therapy [171] as patients with cured *H.pylori* infection appear to develop more reflux-like symptoms [172].

Concerns regarding escalating health care expenditure has led to an increased emphasis over both the clinical and economic impact of medical interventions. A number of studies have shown that treating *H.pylori*-positive patients with dyspepsia empirically without endoscopy can be cost-effective although the benefits may take several years to be realised [173;174]. If prompt endoscopy is not an option, the empirical treatment of *H.pylori* in selected patients using a reliable non-invasive screening test has been advocated [175]. Indeed there is evidence to suggest that primary care practitioners choose eradication therapy over endoscopy in such patients[176]. However the economic benefits of eradication therapy will only be realised if savings can be made on long-term anti-ulcer medications, specialist visits and hospitalisations. Time lost from work and interference with quality of life are more difficult to measure but are likely to be considerable. Our results suggest that the promised financial benefits from cessation of long-term anti-ulcer therapy are unlikely to be realised due to the high rate of recurrence of dyspeptic symptoms. The failure of complete resolution of dyspeptic symptoms as evidenced by the subsequent prescription of antiulcer medications may not be surprising as several studies

have shown that while eradication therapy is successful, dyspeptic symptoms may persist [177;178]. While our analysis was constrained by a lack of diagnosis, nevertheless these results do reflect the reality of clinical practice where a practitioner 'intends to eradicate' *Helicobacter pylori* infection in an effort to treat dyspepsia and suggest that the treatment of dyspepsia in primary care may be confounded by other variables not associated with *H.pylori* infection.

3.3 Conclusions of drug utilisation studies

The studies performed on drug utilisation illustrate that multiple drug use is widespread within the GMS. As noted earlier more than 90% of patients eligible to avail of the GMS services receive at least one prescription item over a 12-month period. Age, male gender, cardiovascular drugs, central nervous system drugs, gastrointestinal drugs and respiratory drugs all make a significant contribution to the consumption of more than 4 drugs per month (major polypharmacy). Furthermore the results were unaltered when drug usage was defined according to the number of prescription items dispensed per month or according to the number of prescription items dispensed on the one prescription.

The example of the treatment of *Helicobacter pylori* infection, illustrated the usefulness of the GMS prescription database for performing drug utilisation studies. It allows one to test the effectiveness of a particular treatment regimen by measuring the consumption of other medications used for the treatment of a particular condition. One of the advantages of the GMS prescription database is that it provides an insight into 'real-world' prescribing at the level of primary care where the majority of patients are treated. While the analysis

was constrained by a lack of diagnosis, nevertheless these results do reflect the reality of clinical practice where a practitioner 'intends to eradicate' *H.pylori* infection in an effort to treat dyspepsia and suggest that the treatment of dyspepsia in primary care may be confounded by other variables such as concurrent NSAID use and incorrect diagnosis, which are not associated with *H.pylori* infection. This has obvious clinical and economic implications for this form of treatment. Without clear information regarding the appropriateness of a particular prescription, such utilisation studies will be limited in the conclusions they can draw: however, they have an important role in deciding where further research should be directed and give accurate information regarding the prescription of particular drugs.

Chapter 4 -Studies of Prescribing Quality within the General Medical Services Scheme.

4.1 Development of an index of good prescribing practice

4.1.1 Introduction

Hitherto pharmacoepidemiology has concentrated more on the quantity than on the quality of prescribing. Prescribing quality has become an important issue in the provision of health-related services. Drug prescribing is an integral part of the health care service and represents a relatively safe, effective and inexpensive mode of treatment. Therefore some measure of the quality of drug prescribing is needed. The majority of indicators of prescribing quality assume that a consensus has been reached about evidence-based prescribing. An indicator has been defined as a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality of care provided [26]. Prescribing indicators can be used as objective measures of prescribing, allowing comparison between different prescribers. They may be used to improve the quality and effectiveness of prescribing in general practice and also to reduce prescribing costs.

While a broad range of measures to assess quality prescribing have been advocated such as the ratio of inhaled corticosteroid to bronchodilators, the percentage of drugs which are prescribed generically or the use of drugs of questionable therapeutic efficacy [179;180], recently it has been suggested [181] that potentially serious interactions might be included as an indication of prescribing appropriateness. Such interactions have both clinical and financial implications. The Adverse Drug Event prevention Study estimated an overall

event rate of 6.5 per 100 admissions in US hospitals, of which 28% were judged preventable [182]. In a recent hospital based study, drug interactions which were deemed preventable accounted for 4.6% of all adverse drug events[183]. In a related study [59] the cost of medical errors was estimated to be $4685 per preventable adverse drug event emphasising the financial impact of adverse drug events although the relative cost of interaction based events was not computed .

We therefore attempted to develop a quantifiable index of prescribing using a pharmacoepidemiological database based on the potential for interactions. A previous study had identified a significant level of potentially dangerous drug interactions with warfarin [184]. Evidence of good prescribing practice can be inferred where a prescriber chooses as co-therapy within a particular drug group (for example H_2-antagonists), a non-interacting rather than an interacting drug. For a sensitive index it is important that the drug(s) are in common use and for the interaction to be clinically relevant. Warfarin was chosen because of its potential for serious drug interactions.

Cimetidine, but not ranitidine, famotidine or nizatidine inhibits the metabolism of not alone warfarin, but also phenytoin and theophylline [185]. As a measure of good prescribing we examined the relative risk of being prescribed an interacting combination by determining an odds ratio comparing co-prescribing with cimetidine to that of other non-interacting H_2-antagonists.

4.1.2 Methods

The total number of patients who were prescribed H_2-receptor antagonists over a 12-month period (January-December 1998) in the Eastern Health Board (EHB) region of the GMS was determined. From this group the number of

patients who were co-prescribed the potentially interacting drugs warfarin, phenytoin and theophylline was determined.

An odds ratio was derived comparing the ratio of the use of the interacting drug cimetidine with that of the non-interacting H_2-antagonists in the population at risk and those not at risk of the potential drug interaction (users and non-users of warfarin, phenytoin and theophylline respectively).

Odds ratio =

$$\frac{\text{Interacting drug(s)/Non-interacting drug(s) in population at risk of drug interaction.}}{\text{Interacting drug(s)/Non-interacting drug(s) in population not at risk of drug interaction}}$$

An odds ratio of 0.5 indicates that the interacting drug cimetidine is half as likely to be co-prescribed compared with the non-interacting drugs. Odds ratios were determined for each month over the study period to determine if there was any seasonal variation.

4.1.3 Results

A total of 86,510 prescriptions were dispensed for the H_2-antagonists over a twelve-month period to 8188 patients in the EHB region of the GMS in 1998. This number represented 1.6% of all prescriptions dispensed in that particular year or 8.6% of those patients who received prescriptions in that year. Odds ratios for the prescription of the interacting drug cimetidine compared with the non-interacting H_2-antagonists in patients who are prescribed warfarin, phenytoin or theophylline are shown in Table 4.1. Prescribers were five

	H_2-antagonist				
	Cimetidine	Ranitidine/ Famotidine/ Nizatidine	Odds ratio	95% confidence interval	p Value
Warfarin	**443**	**2475**	0.20	**(0.17-0.21)**	**<0.001**
Not on Warfarin	**39865**	**43727**			
Phenytoin	**252**	**473**	0.60	**(0.52-0.70)**	**<0.001**
Not on Phenytoin	**40056**	**45729**			
Theophylline	**1595**	**2950**	0.60	**(0.57-0.64)**	**<0.001**
Not on Theophylline	**38713**	**43252**			

Table 4.1. Number of co-prescriptions with H_2-antagonists and odds ratios comparing the use of the interacting H_2-antagonist cimetidine with that of the non-interacting H_2-antagonists ranitidine, famotidine and nizatidine in users and non-users of warfarin, phenytoin and theophylline for 1998.

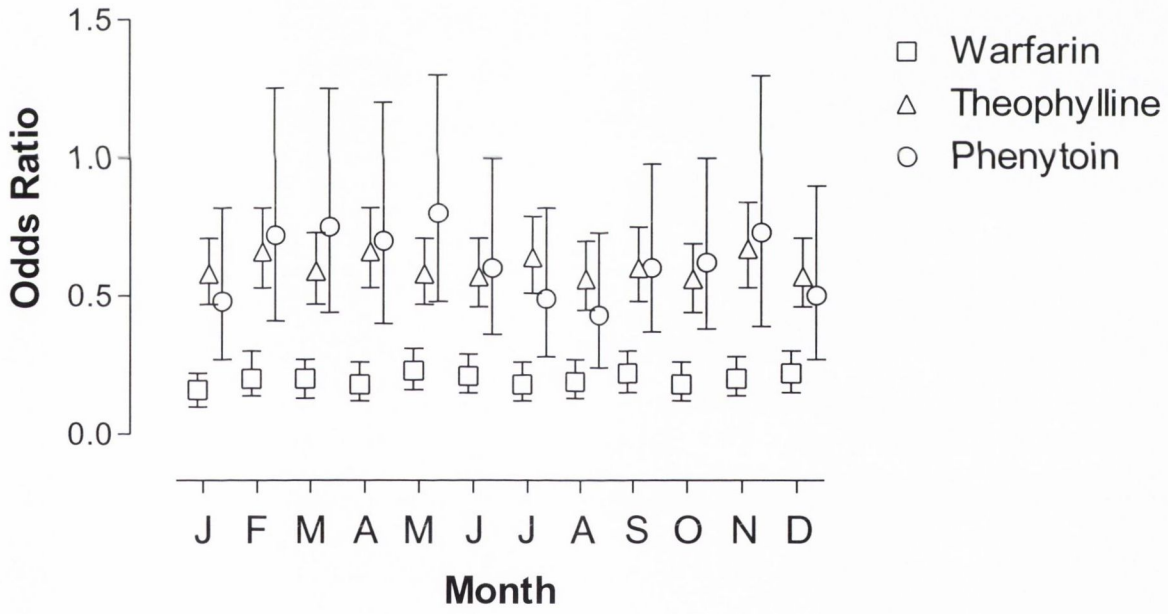
times less likely to prescribe cimetidine in users of warfarin and 1.7 times less likely in users of phenytoin and theophylline. Figure 4.1 demonstrates that there was little seasonal variation in the odds ratios over the entire year. While the values for users of warfarin and theophylline remained consistent, the odds ratios for users of phenytoin were variable largely due to the smaller number of patients on this combination.

4.1.4 Discussion

Prescriptions for medicines should be necessary, safe, efficacious and economical. However in practice there is considerable variation in prescribing standards. There is a need for agreed standards of prescribing performance, both to inform individual prescribers and to provide assurance that public expenditure is used efficiently.

In 1994 the Audit Commission recognised that general practitioner prescribing could not be considered in isolation from other general practitioner activities and services[28]. It proposed that more rational prescribing by general practitioners would lead to better quality care for patients and to major economies in drug expenditure. More recently performance indicators which include prescribing indicators for primary care groups, using an evidence-based approach have been described[186-188]. Such indicators cover not only measures of efficiency, but also measures of access to health care and effective delivery of appropriate health care to patients. Indeed the National Primary Care Research and Development Centre advocates a wide range of measures for assessing quality in general practice. It emphasises the need for Primary Care Groups (PCGs) to develop their own priorities for quality

Figure 4.1 Odds ratios for the prescription of interacting compared with non-interacting H_2-antagonists in patients prescribed warfarin, theophylline and phenytoin within the EHB region of the GMS.



improvement. In addition Campbell et al have assessed the validity of quality indicators being proposed for use in general practice by health authorities[29]. Indicators of prescribing quality are therefore of importance and may be divided broadly into three categories[189].

1. Indicators which assess the appropriateness of prescribing specific drugs or combinations in selected conditions where there is sound evidence base, e.g. ACE inhibitors for cardiac failure, anticoagulation with aspirin/warfarin for atrial fibrillation.
2. Descriptive prescribing indicators, which do not attempt to define optimal values, e.g. number of items prescribed per patient.
3. Indicators which are based on unnecessary or potentially harmful prescribing, e.g. duplication of medications, drug interactions.

The former however requires knowledge of individual patient diagnosis and only the latter two categories are amenable to study with currently available prescribing databases, which do not include diagnosis or indication for treatment. Since drug interactions may prove costly in financial terms, their avoidance indicates cost effective prescribing.

The prescribing index described is both qualitative and quantitative and suggests selective prescribing to avoid therapy-related toxicity. Furthermore it provided consistent results for warfarin and theophylline on a monthly basis albeit to a lesser extent with phenytoin due to the relative small number involved in such a short period. Recently Suissa has described a relative excess risk as an alternative measure of comparative risk which may be applied to pharmacoepidemiological studies [190].

The odd ratios, which we obtained, indicate that for patients receiving warfarin, phenytoin or theophylline, there was a significant shift to the use of the non-interacting ranitidine, famotidine or nizatidine compared to the use of cimetidine when the choice of an H_2-receptor antagonist was made. Furthermore the extent of this selective prescribing is in keeping with the rank order of severity of interaction with these drugs. While these drugs have a narrow therapeutic ratio and for warfarin, interactions have led to life-threatening haemorrhage, for phenytoin (gait disturbance) and theophylline (nausea and tachycardia), the interaction has less severe consequences [191-193].

The odds ratio developed in this study, although explored in one national database, may be applied, we believe, to other health care systems and drug groups where a physician has a choice between an interacting and non-interacting drug as a sensitive marker of good prescribing practice. This indicator should be applied to other prescription databases and incorporated into the range of quality indices used to audit prescribing in primary care.

4.2 Indicators of prescribing quality and their application to the GMS prescription database

4.2.1 Introduction

Of all the activities that take place in general practice, prescribing has the greatest potential to produce health benefits or to cause harm. Therefore, indicators of the appropriateness of prescribing should have a central place in evaluating the performance of general practitioners and encouraging improvements in the quality of care. It is surprising therefore, that little research has been done on the validity and reliability of indicators of

prescribing in general practice. There have been numerous attempts to develop and use indicators of appropriateness in general practice [28;179]. Indeed it has been suggested that up to 400 different prescribing indicators have been developed by the various health authorities in England and Wales [194]. An indicator has been defined by a European working party on quality in primary care as 'a measurable element of practice performance for which there is evidence or consensus that it can be used to assess quality, and hence change in the quality, of care provided' [26]. In many countries, interest in the quality of prescribing is increasing. In part, this is because of the rising costs of drugs, coupled with the desire to avoid adverse effects of drugs. This has led to research into key performance indicators in general practice [195]. Furthermore with the recent advent of clinical guidelines, one needs a clear view of the standards to be attained and valid methods for assessing progress [196].

There are a number of reasons for the increased use of performance indicators for general practice prescribing [197]. Firstly, recognising good prescribing is an important issue in terms of the quality of care provided to patients. Secondly, there are costs associated with poor prescribing. These include unwanted side effects and interactions, and financial costs from using drugs of limited clinical value and possibly inappropriate use of some expensive preparations. However good quality prescribing does not always lead to a reduction in costs as increased expenditure on drugs in some areas such as untreated hypertension or chronic asthma would probably bring disproportionate benefits. Thirdly, unless each doctor's prescribing is to be studied in great detail by reviewing each individual prescription, prescribing performance will need to be analysed by proxy measures.

Furthermore, most doctors appear to work with a limited list of medications which they find effective and relatively free from side effects. This can be viewed as a 'personal formulary', which is generally not written down, has developed as a matter of habit rather than rational thought, and has been shaped by colleagues, patients and experience. These are the drugs that are prescribed regularly and constitute the bulk of the prescribing undertaken by the doctor. The World Health Organisation (WHO) "Guide to Good Prescribing" refers to such drugs as P (personal) drugs. In the WHO model, the selection is evidence based [198]. A doctor's use of a limited number of agents within a particular class may be measurable from routinely collected prescribing data sources and has been suggested as a potentially useful indicator of the quality of prescribing. Such indicators are conceptually appealing as they are based on patterns of care (which is used for the majority of prescribing) and may therefore be examined using aggregate data rather than requiring a case-by –case assessment of practice, using individual patient-level data. In the United Kingdom, an important focus of such research has been on the cost savings that might be achieved by persuading doctors to work with a limited number of drugs in a class. In Sweden, the 'DU90%' (the number of drugs that account for 90% of drug use) has been proposed as a measure of prescribing, and a parameter that could be used to compare the performance of different health care facilities [199].

Prescribing indicators for general practice have been used in the National Health Service in the United Kingdom for the past two decades and are likely to have a central role in the clinical governance activities of many primary care groups as prescribing continues to rise at a rate of approximately 9% a

year and two-thirds of all general practice consultations generate a prescription[28]. The majority of prescribing indicators for United Kingdom general practice have been based on PACT (Prescribing Analysis and Cost) data, which provides detailed information on the drugs dispensed on behalf of general practitioners, but lack any link between the data and the reason for a particular prescribing decision. Therefore they cannot be used directly to assess the quality of an individual doctor's prescribing. Nonetheless, prescribing databases will continue to provide assessments of prescribing performance and hence it is justifiable to consider ways to use such databases. Furthermore it has been suggested that with the move towards a primary care National Health System, such performance indicators would become an important management tool. League tables of practice performance based on such indicators were suggested as a possibility [188]. It has been suggested that performance indicators could be used to identify and reward high performing practices with increased allocations for staff and premises. General practitioners can benefit from performance indicators by using them to identify how their practice deviates from the norm and where scope for further investigation and audit may exist. Performance indicators can be used to carry out descriptive research into variations in medical practice in primary care [188]. The most important limitation of performance indicators is that they measure only certain aspects of performance. For example, they can tell us what a practice's referral rate is but tell us nothing about the appropriateness of these referrals. More importantly, performance indicators tell us nothing about the clinical care of patients. Performance indicators could lead to general practitioners concentrating on improving the indicators rather than improving

the quality of their care. The doctor who spends more time with a patient in a consultation in order to identify for example underlying cardiac disease may not be rewarded by such a system [200].

To be useful, indicators of prescribing should possess several attributes. For example they should cover elements of practice that are acknowledged to be important and not simply record what is easy to measure. Ideally they should be devised with the help of general practitioners, and they should fairly reflect their efforts to prescribe appropriately. The data on which indicators are based should be valid and reliable, and the results should be presented in a user friendly way. It should be made clear that indicators should be used for guidance and should not on their own, provide definitive evidence of success or failure and should be used to raise questions and not provide answers[194]. The difficulty with the majority of indicators that have been developed for assessing prescribing by general practitioners is that they do not possess all of these attributes. Many indicators focus on cost while paying little attention to other areas of appropriateness [28]. In other cases, there is an emphasis on basing indicators on what is measured easily, rather than what is important.

In a number of cases general practitioners have been involved in the development of indicators. Bateman [179] describes how, by using prescribing and analysis and costs (PACT) data, a consensus group of eight general practitioners set standards for 13 aspects of prescribing. These indicators can give an impression of prescribing performance which are based on reliable data which are easily accessible in England and Wales. However, as there is no link between PACT data and the reason for individual prescribing decisions such data has its limitations. Whilst Avery et al[197] were able to demonstrate

correlations between different indicators, lending support to the idea that such indicators might act as proxies for more general prescribing patterns, nonetheless, most of the observed correlations were not strong. Cantrell et al in 1998 also evaluated the appropriateness of general practitioner's prescribing which was also based on a consensus of opinion leaders and prominent academics in the field of prescribing [196]. They rejected the approach of deriving quality indicators from clinical guidelines as these are necessarily focussed on specific conditions or drugs. They believed that clinical guidelines focus on disease management, not patient management, and so may neglect interactions between treatment regimens in patients with two or more chronic conditions. Hence they based their indicators on GP medical records, as opposed to other sources, as the medical record links prescribing with clinical information. It was thus capable of allowing reviews of medication or assessments of appropriateness of prescribing. In a recent study by Campbell et al, using a Delphi consultation method, of the 41 indicators tested, only seven were rated valid and reliable for cost minimisation and five for quality[195]. In addition the 12 indicators rated as valid by leading prescribing advisors had a narrow focus and would allow only a limited examination of prescribing at a general practice, primary care group, or health authority level[195].

Although many prescribing performance indicators have been suggested, few have been evaluated in detail. The Audit Commission suggested a number of potential indicators which included generic prescribing, drugs of limited clinical value, combination and modified release products, 'premium price preparations' and the range of drugs prescribed in different clinical areas [28].

They provided some descriptive data on variations between practices and suggested that if all practices in England and Wales were to prescribe like 50 selected practices, annual savings of $425 million would be made. The thrust of the Audit Commission's report was that good quality, inexpensive prescribing could be recognised from certain prescribing patterns. Bateman's[179] set of indicators developed by a consensus group of general practitioners included lists of lower cost drugs choices within particular therapeutic groups, generic prescribing and drugs of limited clinical value. An overall score was given to practices according to these indicators and there was a tendency for practices with lower prescribing costs to have more favourable scores.

Anecdotal evidence also suggests that prescribing indicators are more appropriately related to cost than quality, particularly at the practice level. Campbell's findings again suggested that prescribing indicators based on PACT at the population level are less valid for quality than for cost minimisation[195]. As a result there are few validated quality indicators which exist for prescribing in the public domain.

It is important to remember that without the ability to link prescribing to indication, it is usually only possible, from aggregate data, to infer appropriateness of a particular prescription. Thus we felt it important to obtain both a qualitative and quantitative view of prescribing from general practitioners before applying such indicators to our prescription dataset. We proposed to apply a number of these indicators to prescription data provided by the General Medical Service scheme. We decided to focus on a range of indicators which have been suggested in the literature. Much of the analysis was based on data from therapeutic areas where general practitioners are faced

with a large range of drug choices. However, as little information is available regarding general practitioner's attitudes to prescribing indicators, in order to generate these indicators we surveyed general practitioners working within the scheme regarding their applicability.

4.2.2 Methods

4.2.2.1 The Development of Prescribing Indicators

Sixteen prescribing indicators reflecting good prescribing practice were developed from the literature [29;179;180;189;195]. The indicators fell into three broad groups

1. Indicators which were purely descriptive with no attempt to define an optimal value such as the number of items prescribed per patient.
2. Indicators which reflected potentially harmful or ineffective prescribing such as the prescribing of long-acting sulphonylureas or agents of limited clinical value.
3. Indicators which assessed the appropriateness of prescribing of specific drugs such as the prescribing of aspirin in patients with ischaemic heart disease.

Some of the indicators show the proportion of total use of the drug class represented by a particular drug or group of drugs. Similar to ratio measures, these provide a means of examining the relative use of agents or groups of agents and focus on the choice of drugs being made by general practitioners within a particular therapeutic group. No optimal value was assigned to these indicators as some of the variation in prescribing is a result of practice demographics, data for which was not available at the time of analysis.

4.2.2.2 Application of prescribing indicators to prescription data

These indicators were then applied to the entire prescription dataset of the Eastern Health Board over a six-month period from July to December 1999. This period was chosen as it coincided closely with the time when the general practitioners were surveyed. During the survey the appetite suppressant phentermine was withdrawn as a result of safety concerns. However this agent was still available for prescription during the period of analysis.

4.2.2.3 Study of general practitioner prescribing variability

In an effort to estimate the variability of prescribing patterns among the general practitioners working within the Eastern Health Board, prescribing rates for each of the quality indicators were determined for each practitioner. As the data were quite skewed, median prescribing rates and interquartile ranges (25^{th}-75^{th} percentile) are quoted. The ratio between the 75^{th} and 25^{th} percentile was used to determine the variability of the prescribing rates among the practitioners as the conventional 90^{th} to 10^{th} percentile produced too many zero denominator ratios. Thus a ratio of 2 would indicate two fold variation between general practitioners. When determining the prescription rate of aspirin in patients receiving nitrate therapy, the number of patients receiving nitrate therapies were used as the denominator. Practitioners who did not prescribe the particular drug associated with the particular analysis were excluded from the analysis when calculating ratio indices. In an effort to reduce results due to random variability, practice lists of less than 100 were excluded from the analysis.

In order to adjust for the influence of age and practice list size on prescribing rates, standardised prescribing ratios (SPRs) based on the method devised by

Johnson et al [201] were calculated for a subset of 461 general practitioners on which complete data regarding the age-distribution of the practitioner's list were available. Age-specific prescribing rates were determined for the selected prescribing indicator for the entire Eastern Health Board region (reference population). For each GMS GP panel (study population), the number of patients in defined age groups was multiplied by the appropriate reference rate, yielding the number of persons in that age group expected to be receiving that particular drug if prescribing for the study population was that of the reference population. This expected number for each age group of the study population was summed, yielding the total number of patients expected to be on the selected drug. The SPR was calculated by dividing the actual (observed) number of patients in the study population by the expected number, and the result was multiplied by 100. Like the standardised mortality ratio (SMR), the SPR is the ratio of observed to expected prescriptions for each panel expressed as a percentage. It is a measure of the extent to which the number of patients receiving a particular drug is above the average or below the group norm, taking age into account. An SPR of 100 is average for the group of general practitioners being studied, an SPR of 200 is twice the average and an SPR of 50 is half the average.

4.2.2.4 Survey of general practitioners' attitudes to prescribing indicators

As mentioned earlier, without the ability to link prescribing to indication, it is usually only possible from aggregate data to infer appropriateness of prescribing. Thus it was felt important to survey the views of general practitioners working within the GMS scheme before applying such indicators to their prescription data. The survey also included General Practice Unit

doctors who work part-time for the health board and liase between general practice and the health boards. These practitioners were included for comparison and also to determine if health board policy influenced their opinions on prescribing. A postal survey of general practitioners (including General Practice Unit doctors) who were working within the GMS scheme regarding the applicability of prescribing indicators was carried out in April 2000. The GPs were selected randomly from a list provided by the GMS. They were asked to rate on a scale of one to five the applicability of 16 proposed indicators of prescribing quality which could be applied to the GMS prescription database. A score of 5 was rated as a good indicator of prescribing quality and 1 as a poor indicator of prescribing quality. A copy of this questionnaire along with a copy of the accompanying letter is shown in the appendix B. A section of the questionnaire also allowed the respondent to comment on the particular indicators used. A total of 145 general practitioners including 28 unit doctors were sent questionnaires. A repeat questionnaire was sent to the general practitioners 4 weeks later in an effort to improve the response rate. Incomplete questionnaires were not included. A Wilcoxon sign-rank test was performed for each indicator based on a mean score of 3. This non-parametric test is used to determine whether the responses in the various categories are different from what one would expect by chance and is used when one cannot assume normality in the data. In addition the chi-squared statistic was applied to determine if there was a statistical difference in the answers provided by unit and non-unit doctors.

4.2.3 Results

4.2.3.1 General practitioner survey

Completed questionnaire were received from a total of 69 (including 20 unit doctors) general practitioners giving a response rate of 48%. As the replies were anonomysed, there was no indication of the characteristics of the respondents. The results of the survey are shown in Table 4.2. There was no statistically significant difference between the unit and non-unit general practitioners in their replies. General practitioners felt that prescribing indicators based on agents of questionable efficacy/ poor quality prescribing would make suitable indicators. These included

- a low-rate of prescribing of cerebral and peripheral vasodilators,
- a low rate of prescribing of appetite suppressants,
- a low rate of prescribing of hypnosedatives and anxiolytics,
- a low rate of prescribing of hypnosedatives for more than four-weeks duration,
- a low rate of prescribing of quinolone antibiotics as a % of all antibiotics and
- a low rate of prescribing of aspirin in children (<12yrs).

Similarly there was broad agreement that indicators based on good prescribing practice could be used as prescribing indicators. Examples include

- high rate of prescribing of trimethoprim compared to cotrimoxazole,
- a high rate of generic prescribing,
- a high rate of prescribing of aspirin in patients who are receiving nitrate therapy and

No	Prescribing Indicator	% of respondants assigning a rank of 1 to 5 to each indicator					Wilcoxan Sign-rank test
		1	2	3	4	5	
1	Low-rate of prescribing of cerebral and peripheral vasodilators	11.5	4.3	14.5	23.2	46.4	<0.001
2	Low-rate of prescribing of appetite suppressants	10.1	2.9	0	5.8	81.2	<0.001
3	Low-rate of prescribing of topical non-steroidal anti-inflammatory drugs	8.7	14.5	21.7	27.5	27.5	<0.001
4	Low-rate of prescribing of long-acting compared to short-acting sulphonylureas.	8.7	15.9	34.7	23.2	17.4	<0.05
5	Low-rate of prescribing of amoxycillin + clavulanic acid compared to oral amoxycillin.	8.7	14.4	37.7	20.2	18.8	<0.05
6	High-rate of prescribing of trimethoprim compared to oral cotrimoxazole.	7.2	2.9	4.3	13	72.4	<0.001
7	High rate of prescribing of atenolol as a % of all beta-blockers.	4.3	5.8	24.6	40.5	24.6	<0.001
8	High rate of prescribing of diclofenac, ibuprofen, indomethacin and naproxen as a % of all NSAIDs.	8.7	13	39.1	31.8	7.2	N/S
9	High rate of generic prescribing.	8.7	4.3	17.4	37.7	31.8	<0.001
10	High rate of prescribing of aspirin in patients who are receiving nitrate therapy.	0	0	7.2	36.2	56.5	<0.001
11	Low rate of prescribing of hypnosedatives and anxiolytics.	0	15.9	8.7	33.3	42	<0.001
12	Low-rate of prescribing of hypnosedatives for more than four-weeks duration.	2.8	2	8.7	23.1	44.9	<0.001
13	High ratio of of prescribing of inhaled corticosteroids to inhaled bronchodilators in asthmatic patients.	1.4	1.4	8.7	24.6	63.7	<0.001
14	High rate of prescribing of hormone replacement in post menopausal women.	1.4	13.0	23.1	34.7	27.5	<0.001
15	Low rate of prescribing of quinolone antibiotics as a % of all antibiotics.	5.8	7.2	18.8	20.2	47.8	<0.001
16	Low rate of prescribing of aspirin in children (<12yrs)	10.1	1.4	5.8	7.2	75.4	<0.001

Table 4.2. Percentage of General Practitioners who ranked the indicators of prescribing quality from 1(poor indicator) to 5 (good indicator) in postal survey.

- a high ratio of prescribing of inhaled corticosteroids to inhaled bronchodilators in asthmatic patients.

Opinion was more divided on the following indicators

- Low rate of prescribing of topical non-steroidal anti-inflammatory drugs
- Low rate of prescribing of long-acting compared to short-acting sulphonylureas
- High rate of prescribing of diclofenac, ibuprofen, indomethacin and naproxen as a % of all NSAIDs.
- High rate of prescribing of Hormone replacement therapy (HRT) in post-menopausal women.

In their comments, practitioners appreciated the importance of the practice demography on prescribing patterns with one respondent suggesting that hospital prescribing was not addressed adequately in our indicators. It was recognised that some of the prescribing indicators are related to low-cost prescribing, but that low-cost prescribing does not necessarily indicate better prescribing. One practitioner suggested that appetite suppressants should be excluded from the General Medical Services scheme and that they should not be penalised against prescribing expensive medications such as hormone replacement therapy or inhaled corticosteroids. Other suggested indicators included the prescribing of cholesterol and lipid lowering agents in patients with coronary artery disease, the rate of prescribing of antibiotics for minor illness especially in childhood, prescribing of selective serotonin re-uptake inhibitors versus tricyclic antidepressants, prescribing of ACE-inhibitors or β-blockers in patients with ischaemic heart disease, prescribing of appropriate

antibiotics for lower respiratory tract infections, prescribing of narrow spectrum antibiotics as opposed to broad spectrum antibiotics, the prescription of gastro-protective agents in elderly patients receiving aspirin/non-steroidal anti-inflammatory agents, a comparison of the prescribing of paracetamol to NSAIDs and a high rate of prescribing of thyroxine. Whilst it was appreciated that there was little evidence for the benefit of some agents such as cerebral/peripheral vasodilators, practitioners would still prescribe such agents in patients for symptomatic relief. The importance of not considering these indicators as absolute evidence of good quality prescribing was emphasised by one practitioner. Feedback of their prescribing habits was mentioned by a number of practitioners as a way of improving prescribing quality.

4.2.3.2 Application of prescribing indicators to prescription data

A total of 2,896,461 prescription items were available for analysis. 60,373 prescriptions which were uncoded or which were coded with an ATC code V[24] (which includes allergens, diagnostic agents, general nutrients, non-therapeutic products, contrast media, diagnostic radiopharmaceuticals, therapeutic radiopharmaceuticals and surgical dressings)were excluded, leaving 2,836,088 for further analysis. The results are shown in Table 4.3. Relatively low rates of prescribing were noted for indicators based on drugs of limited efficacy whereas indicators based on good prescribing practice such as the prescription of aspirin in patients receiving nitrate therapy was associated with higher prescribing rates. Similarly where a choice between two drugs was available to prescribers, drugs associated with good prescribing practice were

Number	Prescribing indicator	Rate/1000 prescriptions
1	Rate of prescribing of cerebral and peripheral vasodilators	3.1
2	Rate of prescribing of appetite suppressants	0.3
3	Rate of prescribing of topical non-steroidal anti-inflammatory drugs	10.9
4	Rate of prescribing of short-acting compared sulphonylureas.	4.5
	Rate of prescribing of long-acting sulphonylureas.	1.8
5	Rate of prescribing of amoxycillin + clavulanic acid.	14.5
	Rate of prescription of amoxycillin.	20.3
6	Rate of prescribing of trimethoprim .	3.6
	Rate of prescription of cotrimoxazole.	0.8
7	Rate of prescribing of atenolol.	14.2
	Rate of prescription of all β-blockers	28.7
8	Rate of prescribing of diclofenac, ibuprofen, indomethacin and naproxen.	26.4
	Rate of prescription of all NSAIDs.	50.2
9	Rate of generic prescribing(% of all prescriptions).	49.9(4.9)
	Rate of prescribing of branded generics(% of all prescriptions).	168.5(16.8)
	Rate of prescribing of proprietary drugs which have a branded or generic equivalent(% of all Prescriptions).	181.4(18.1)
	Rate of prescribing of proprietary drugs which have no branded or generic equivalent(% of all prescriptions).	600.2(60)

Table 4.3. Unadjusted prescription rates of prescribing indicators (1-9) applied to prescription data of the EHB region of the GMS.

Number	Prescribing indicator	Rate/1000 prescriptions
10	Rate of prescribing of aspirin in patients who are receiving nitrate therapy.	71.3/100 patients (71.3%)
11	Rate of prescribing of hypnosedatives and anxiolytics.	78.2
12	Rate of prescribing of hypnosedatives for more than four-weeks duration.	5.2/100 patients
13	Ratio of prescribing of inhaled corticosteroids to inhaled bronchodilators in asthmatic patients(Number of Defined daily doses)	0.54(0.91)
14	Rate of prescribing of hormone replacement in post menopausal women(per 100 eligible patients). 35-44yrs 45-54yrs 55-64yrs 65-74yrs 75+	 4/100 patients 28.9/100 patients 22.2/100patients 3.6/100patients 0.7/100 patients
15	Rate of prescribing of quinolone antibiotics.	1.7
	Rate of prescribing of all antibiotics.	77.8
16	Rate of prescribing of aspirin in children (<12yrs)	0.7

Table 4.3. (contd) Unadjusted prescription rates of prescribing indicators (10-16) applied to prescription data of the EHB region of the GMS.

chosen. Examples include the higher prescribing rate of short-acting compared with longer acting sulphonylureas and a higher rate of prescribing of trimethoprim compared with cotrimoxazole.

There was also evidence that practitioners used 'personal formularies'-i.e. when given a choice of drug treatment from a particular drug class, prescribers would choose only a limited range of drugs. Thus atenolol accounted for approximately 50% of all the prescriptions for β-blockers and a small group of NSAIDs accounted for a similar percentage of all NSAIDs.

4.2.3.3 Estimate of general practitioner prescribing variability.

The median standardised prescribing ratios (SPRs) for the selected indicators are shown in table 4.4 together with the interquartile ranges and $75^{th}/25^{th}$ percentile which was used to assess prescribing variability. The $75^{th}/25^{th}$ percentiles for each indicator illustrates how prescribing rates vary for the individual indicators. For example the $75^{th}/25^{th}$ centile ranged from 1.2 for the prescribing of aspirin in patients receiving nitrate therapy to 66.6 for the prescribing of long-acting sulphonylureas. The largest variability in prescribing was seen with the prescribing of peripheral and cerebral vasodilators and the prescribing of long-acting sulphonylureas (Table 4.4).

Number	Quality Indicator	SPR	Inter-quartile range	75TH/25th Centile
1	Rate of prescribing of cerebral and peripheral vasodilators	71.35	24.4-136.4	5.6
2	Rate of prescribing of appetite suppressants	0	0-49.5	N/A
3	Rate of prescribing of topical anti-inflammatory agents	81.9	48.9-125.5	2.56
4	Rate of prescribing of long-acting sulphonylureas	68.4	2.3-153.2	66.6
	Rate of prescribing of short-acting sulphonylureas	85.2	48.96-123.0	2.51
5	Rate of prescribing of amoxycillin	83.4	53.3-124.5	2.33
	Rate of prescribing of Coamoxyclav	80.6	57.5-120.4	2.10

Table 4.4 Median Standardised Prescribing Ratios(SPRs) and $75^{th}/25^{th}$ centiles for specified prescribing indicators(1-5)

Number	Quality Indicator	SPR	Inter-quartile range	75TH/25th Centile
1	Rate of prescribing of cerebral and peripheral vasodilators	71.35	24.4-136.4	5.6
2	Rate of prescribing of appetite suppressants	0	0-49.5	N/A
3	Rate of prescribing of topical anti-inflammatory agents	81.9	48.9-125.5	2.56
4	Rate of prescribing of long-acting sulphonylureas	68.4	2.3-153.2	66.6
	Rate of prescribing of short-acting sulphonylureas	85.2	48.96-123.0	2.51
5	Rate of prescribing of amoxycillin	83.4	53.3-124.5	2.33
	Rate of prescribing of Coamoxyclav	80.6	57.5-120.4	2.10

Table 4.4 Median Standardised Prescribing Ratios(SPRs) and $75^{th}/25^{th}$ centiles for specified prescribing indicators(1-5)

Number	Quality Indicator	SPR	Inter-quartile range	75TH/25th Centile
6	Rate of prescribing of trimethoprim	83.4	51.1-123.4	2.41
	Rate of prescribing of cotrimoxazole	25.6	0-100	N/A
7	Rate of prescribing of atenolol	89.2	58.2-125.2	2.15
	Rate of prescribing of all β-blockers	95.5	72.4-118.1	1.63
8	Rate of Prescribing of diclofenac, ibuprofen, indomethacin and naproxen	83.4	58.6-111.28	1.90
	Rate of prescribing of all NSAIDs	90.65	71.1-113.7	1.60
9	Rate of Generic Prescribing	87.4	61.4-116.2	1.89
	Rate of prescribing of branded generics	86.1	64.6-112.5	1.74
	Rate of prescribing of proprietary drugs which have a branded or generic equivalent	94.0	73.0-117.9	1.62
	Rate of prescribing of proprietary drugs which have no branded or generic equivalent	95.0	80.8-114.7	1.42

Table 4.4 (contd). Median Standardised Prescribing Ratios(SPRs) and $75^{th}/25^{th}$ centiles for specified prescribing indicators(6-9)

Number	Quality Indicator	SPR	Inter-quartile range	75TH/25th Centile
10	Rate of prescribing of aspirin in patients receiving nitrate therapy.	102.0	92.2-113.8	1.23
11	Rate of prescribing of anxiolytics and hypnosedatives	90.1	61.9-116.3	1.88
12	Rate of prescribing of Hypnosedatives for more than 4 weeks duration	92.6	67.2-120.0	1.79
13	Rate of prescription of Inhaled corticosteroids	94.5	68.8-119.4	1.74
	Rate of prescription of inhaled beta-agonists	94.3	70.2-116.3	1.66
14	Rate of prescrption of HRT	93.2	67.5-126.8	1.88
15	Rate of prescribing of Quinolone antibiotics	69.1	35.3-120.8	3.42
	Rate of prescribing of all anti-bacterial agents	90.6	72.5-110.4	1.52

Table 4.4 (contd). Median Standardised Prescribing Ratios(SPRs) and $75^{th}/25^{th}$ centiles for specified prescribing indicators(10-15)

4.2.4 Discussion

The majority of general practitioners felt that these prescribing indicators could be used as an indication of prescribing quality. No numeric quality standards were applied in this study which was not designed to define an acceptable, or appropriate standard of care and little discrimination was made between the appropriateness of the individual indicators. Application of these indicators to the GMS prescription data provided information on the overall prescribing patterns of general practitioners working within the general medical services scheme.

In general where practitioners agreed on the usefulness of a particular indicator, this was mirrored by the particular prescribing patterns of the appropriate indicators. Thus indicators based on agents of questionable efficacy/poor quality prescribing and which were felt by practitioners to be good indicators of prescribing quality were associated with relatively low prescribing rates. The principal exceptions were the prescribing rates of hypnosedatives and anxiolytics and the prescribing of hypnosedatives for more than 4 weeks duration with 5% of patients receiving these drugs for more than 4 weeks (Table 4.3). Similarly indicators based on good prescribing practice and which were also thought to be good indicators of prescribing quality were associated with higher prescribing rates. The principal exception to this was the rate of generic prescribing which was relatively low at 4.9% of all prescriptions (Table 4.3). The low overall rate of generic prescribing of 21.4% (if one included branded generics in addition to pure generics) is disappointingly low given the clear advantages associated with generic prescribing [202;203]. Indeed the level of generic prescribing

(including pure generic and branded generics together) has changed little since 1993 where it comprised 17.4% of total dispensing within the General Medical Services [30]. This has obvious implications on the overall cost of medicines within the GMS.

The results were variable for indicators where there was no general agreement among practitioners on the usefulness of the chosen indicators. Thus the prescription of topical non-steroidal anti-inflammatory agents was significant (approximately 20% of overall NSAID prescriptions) despite their doubtful efficacy [204] whilst the prescription of long-acting compared with short acting sulphonylureas was relatively low (Table 4.3).

There is also evidence that practitioners use 'personal formularies' (also referred to P/personal drugs in the WHO guide to good prescribing [198]) when prescribing certain agents such as β-blockers and non-steroidal anti-inflammatory agents with more than 50% of prescriptions being accounted for by either atenolol in the case of β-blockers and a small group of specific NSAIDs in the case of all NSAIDs. For the non-selective NSAIDs, epidemiological data on the variation in the risk of serious gastrointestinal complications suggest that most prescribing should come from agents associated with lower risk [205;206]. Furthermore concerns regarding the emergence of resistant strains of bacteria with the excessive use of antibacterial agents in general, and broad spectrum agents in particular, provide a rationale for the limited use of these agents in clinical practice [207;208]. While the prescribing of quinolone antibiotics was found to be low in this study, it is important to monitor the patterns of prescribing of these agents so

as to ensure that the excessive use of such expensive agents does not encourage the development of resistant strains of organisms.

The majority of prescribing indicators are based on rates of prescribing of key drugs[195]. The numbers of prescriptions written by a doctor are related to the number of consultations to derive an index, which may be adjusted for the case-mix of the population. However such prescribing rates may be difficult to interpret in the absence of clinical information on the indications for prescribing, which generally cannot be derived from routinely collected data. Indicators based on a doctor's personal preference for certain drugs which was demonstrated by the prescription of β-blockers and selected NSAIDs may have a number of advantages[209]. It has been suggested that doctors who familiarise themselves with a relatively small number of drugs are likely to make better use of them and may be less likely to make frequent changes to their prescribing repertoire in response to industry promotional activities, an approach which is central to the WHO guide to good prescribing [198]. Furthermore it has been suggested that a pattern of prescribing in one therapeutic area may be indicative of overall prescribing practice [197]. Such a practice which focuses the bulk of their prescribing on a relatively narrow range of drugs within each therapeutic group tend to have lower overall prescribing costs, whereas those prescribing a relatively large number of drugs tend to have higher costs [197].

Prescribing is a controversial area of assessing health care quality. Previous research has highlighted the importance of critical approaches to prescribing[29;210], defining and measuring the appropriateness of prescribing, variations in prescribing across general practices, adherence to standards, and

the role of prescribing analysis and cost (PACT) data in general practice [197]. As a result there is considerable interest in the use of routinely collected data to derive measures of prescribing quality. The indicators chosen in this study can be used in feedback programmes to general practitioners, such as those conducted using PACT (Prescribing Analysis and Cost) data in the UK and by the National Prescribing service in Australia. Although such feedback on its own may have little impact on prescribing, it is an important adjunct to educational programmes and academic detailing, particularly if it is timed close to the act of prescribing.[121;211]. Computerised feedback of prescribing information has been shown to increase the prescription of generic formulations and to reduce prescription costs[212;213]. We also noted some variability among general practitioners regarding a number of indicators (Table 4.4). The largest variability was noted with the prescribing of cerebral and peripheral vasodilators and the prescribing of long-acting sulphonylureas. Reducing the extent of this variation will be a challenge to general practitioner prescribing. Feedback of such prescribing indicators will allow practitioners to examine their own prescribing practice against that of their colleagues. When general practitioners are given regular information regarding their prescribing habits over a two-year period, they write fewer prescriptions and prescribe less expensive medications, but this altered behaviour is not sustained once feedback ceases [214].

Prescription databases are a valuable tool for examining and improving some aspects of general practice prescribing. While we were able to adjust for the case-mix of the practitioners patient population by using the standardised prescribing ratio, a significant limitation of these data is their inability to link a

prescription to a diagnosis. This becomes particularly relevant when a drug is indicated for more than one condition. For example, the ratio of inhaled steroids to bronchodilators has been used as an indicator of performance in general practice that is available to health authorities in the United Kingdom[188]. Although this indicator is arguably of value for judging the quality of care for asthma, it is inappropriate for chronic bronchitis, another prevalent disease in general practice. Bronchodilators are of symptomatic benefit for many patients with chronic bronchitis, but inhaled steroids are rarely of value [215]. Thus it can be argued that a high steroid:bronchodilator ratio represents poor prescribing in the context of non-asthmatic respiratory disease. The chosen indicators may thus need further refinement in their applicability to general practice. Further discussion among clinical pharmacologists, general practitioners and community pharmacists may be appropriate in order to obtain further consensus on the applicability of these indicators.

The overall aim of clinical governance is to safeguard and improve the health of patients. It performs this task by keeping a constant check on performance, improving standards of care and minimising risks[216]. With the development of clinical governance in general practice, prescribing indicators such as those described in this study may be used as a quality assurance measure with respect to prescribing in general practice within the EHB.

In summary, prescribing criteria based on specified drugs provide more rigorous prescribing standards, but may give a misleading picture of prescribing quality in the absence of information on patients and their indications for treatment. Further development of prescribing indicators along

with other initiatives such as the provision of therapeutic guidelines should be undertaken with close involvement of general practitioners.

4.3 Adherence to established guidelines for the secondary prevention of ischaemic heart disease-evidence for differential prescribing patterns in the General Medical Services scheme.

4.3.1 Introduction

Adherence to established prescribing guidelines can be used as a measure of prescribing practice[189]. Furthermore such guidelines may be applied universally to all patient populations. The Cardiovascular Health Strategy Group was established in 1998 in Ireland to develop a strategic approach to reduce avoidable death and illness caused by cardiovascular disease[217]. It set out the blueprint for treating heart disease in Ireland which has the third and sixth highest mortality rates worldwide for ischaemic heart disease for men and women respectively [218]. Furthermore the decline in ischaemic heart disease in Ireland has been slower in women compared with men [219]. The prescribing of aspirin [220], β-blockers [221], statins [222] and more recently ACE-inhibitors [223] have been shown to be effective in the secondary prevention of coronary artery disease whilst the evidence regarding the benefits of calcium channel antagonists is equivocal [221]. However there is evidence to suggest that a gender [224] and age [225] bias exists in the management of coronary heart disease. Little information is available regarding the existence of this gender bias in primary care where the majority of patients with coronary heart disease are cared for [226]. Nitrate prescribing has been shown to be a useful surrogate marker for coronary heart disease with a sensitivity (i.e. the % of patients with ischaemic heart disease who are prescribed nitrates) of approximately 73%

and specificity (% of patients identified by nitrate therapy who actually have ischaemic heart disease) of 96% [227]. We wished to determine the adherence to established guidelines and whether there exists a gender or age bias in the prescription of secondary preventive therapies in primary care.

4.3.2 Methods

We examined the prescription database of the GMS from the largest region, the Eastern Health Board (population of 334,031 or 28% of the total GMS, which includes the counties of Dublin, Wicklow and Kildare) over a twelve-month period (September 1999-August 2000) and identified those patients who received a prescription for a nitrate (ATC code C01DA). We then examined the number of nitrate patients who received a prescription for a β-blocker, calcium channel antagonist, statin, aspirin, or ACE-inhibitor over the study period. Logistic regression analysis was used to determine the odds ratios for these medications for females compared to males. The odds ratios were adjusted for the effect of age >65yrs. As depression and anxiety are associated with ischaemic heart disease [228;229] and for comparison purposes we also determined odds ratios for non-cardiovascular drugs including antidepressants, anxiolytic benzodiazepines (as defined in the British National Formulary [230]), antiulcer medications, non-steroidal anti-inflammatory drugs, insulin and antiepileptic medications in this group of patients. One would not expect a gender difference in the prescription of insulin or antiepileptic medications where prescribing is not discretionary.

4.3.3 Results

We identified a total of 15,590 patients (M: F, 7751:7839, Mean age M: F, 65.5 +/-10.8yrs: 67.7 +/-10.9yrs) who received at least one prescription for a nitrate preparation over this period of time. A total of 113,770 prescriptions were dispensed for nitrates of which the majority were for isosorbide mononitrate(56.2%) followed by glyceryl trinitrate(38.5%) and isosorbide dinitrate(5.3%). The one year prevalence of nitrate prescribing rose from 11.6%(Male: Female, 15.1%:9.6%) in those aged >55yrs, to 12.3%(Male:Female,16.1%:10.3%) in those aged >65yrs.

The number (and percentages) of patients who received a prescription for a β-blocker, calcium channel antagonist, statin, aspirin or ACE inhibitor are shown in Table 4.5. Using the chi-squared statistic, the gender difference was statistically significant ($p<0.001$) for all of these medications. These differences remained statistically significant when patients who received only 2 monthly prescriptions for nitrates over the study period were excluded from the analysis. Odds ratios and 95% confidence intervals for women receiving these medications were determined and are shown in Table 4.6. The results of a similar analysis for non-cardiovascular drugs are shown in Tables 4.7 and 4.8. Women receiving nitrates had higher odds of receiving an anxiolytic benzodiazepine(OR=1.68,95%CI,1.56-1.82,$p<0.001$) which was also to a much greater extent ($p<0.001$) than in women who did not receive any cardiovascular drug over the study period (OR=1.27,95%CI, 1.23-1.30, $p<0.001$). In contrast there was no difference in the prescription of antidepressants in women receiving nitrates (OR=1.55, 95% CI, 1.43-1.69,

p<0.001) and those not receiving cardiovascular drugs (OR=1.56, 95%CI=1.52-1.61, p<0.001).

	β-blocker (%)	Calcium Channel antagonist(%)	Statin(%)	Aspirin(%)	ACE-Inhibitor (%)
All	6243 (40)	6034 (38.7)	4699 (30.1)	11425 (73.3)	5131 (32.9)
Male	3346 (43.2)	3112 (40)	2490 (32.1)	5952 (76.8)	2674 (34.5)
Female	2897 (37)*	2924 (37.3)*	2209 (28.2)*	5473 (69.8)*	2457 (31.3)*

Table 4.5. Number(%)of patients who received a prescription for nitrate therapy and were co-prescribed a β-blocker, calcium channel antagonist,statin, aspirin, or ACE-inhibitor(*statistically different from male, p<0.001).

Drug	Odds Ratio (95% Confidence interval)	Adjusted Odds ratio (95% confidence interval)
β-blocker	0.77*(0.72-0.82)	0.81*(0.75-0.86)
Calcium channel antagonist	0.89*(0.83-0.95)	0.87*(0.82-0.93)
Statin	0.83*(0.77-0.89)	0.89*(0.83-0.96)
Aspirin	0.7*(0.65-0.75)	0.71*(0.66-0.76)
ACE-inhibitor	0.87*(0.81-0.93)	0.83*(0.78-0.89)

Table 4.6. Unadjusted and adjusted (for age >65) Odds ratios and 95% Confidence intervals for the co-prescription of β-blockers, calcium channel antagonists, statins, aspirin or ACE-inhibitors in women who received a prescription for nitrate therapy.(*$p<0.001$)

	Antidepressants	Benzodiazepines	NSAIDs	Antiulcer Drugs	Anti-epileptics	Insulin
ALL	2858(18.3)	3578(22.4)	6199 (39.8)	6648 (42.6)	649 (4.2)	317(2)
Male	1179(15.1)	1447(18.6)	2889 (37.3)	3265 (42.1)	321 (4.1)	157(2)
Female	1679(21.4)*	2131(27.1)*	3310(42.2)*	3383(43.2)	328(4.2)	160(2)

Table 4.7. Number (%) of patients who received a prescription for a nitrate and who were co-prescribed an antidepressant, benzodiazepine, insulin, antiepileptic,antiulcer drugs or NSAID(*$p<0.001$).

Drug	Unadjusted Odds Ratio (95% Confidence interval)	Adjusted Odds ratio (95% Confidence Interval)
Antidepressants	1.51*(1.4-1.65)	1.55*(1.43-1.69)
Benzodiazepines	1.63*(1.51-1.75)	1.68*(1.56-1.82)
NSAIDs	1.23*(1.15-1.31)	1.25*(1.2-1.33)
Antiepileptics	1.0(0.86-1.18)	1.1(0.89-1.23)
Antiulcer drugs	1.0(0.99-1.1)	1.0(0.97-1.1)
Insulin	1.0(0.81-1.26)	1.0(0.83-1.3)

Table 4.8. Unadjusted and adjusted (for age >65yrs) Odds ratios and 95% Confidence intervals for the co-prescription of antidepressants, benzodiazepines, insulin, antiepileptics, antiulcer drugs and NSAIDs in women who received a prescription for nitrate therapy(*$p<0.001$).

In a separate analysis we found that patients aged >65yrs who were prescribed nitrate therapy were less likely to be prescribed a β-blocker (OR=0.66, 95% CI =0.62-0.71)), statin (OR=0.5, 95% CI=0.46-0.53) or aspirin (OR=0.92, 95% CI=0.85-0.99) and were more likely to receive a prescription for a calcium channel antagonist (OR=1.14, 95% CI=1.1-1.20) or an ACE-inhibitor (OR=1.51, 95% CI=1.41-1.63).

4.3.4 Discussion

Our results suggest that there is a gender and age bias in the prescription of secondary preventive therapies. Differential prescribing patterns for women compared with men have been described for a number of diseases [231-234]. Whilst coronary artery disease is the leading cause of death in women with a mortality rate exceeding that for all neoplastic diseases combined [224] in addition women do not usually list heart disease among the health problems they consider important [235]. A lesser degree of adherence to acute myocardial infarction guidelines has also been shown in women [236]. Fewer women are referred for non-invasive tests for coronary artery disease and even if the non-invasive evaluation indicates a high likelihood of coronary artery disease, fewer women are referred for coronary arteriography and coronary artery bypass surgery- a difference which could not be explained by the sex-related differences in the prevalence of cardiovascular disease [237;238]. Women are also referred later in the course of their disease, are less likely to receive secondary prophylaxis with β-blockers or aspirin following a myocardial infarct[239]and have a higher risk of re-infarction [240] and unstable angina [241] following a myocardial infarct. As a result women with ischaemic heart disease are often older, have concomitant diseases, require acute re-vascularisation and are

often admitted with unstable angina leading to an increased mortality and morbidity.

Research performed in primary care has shown that doctors' interpretation of patients' symptoms and conversational styles are different for men and women[242;243]. Furthermore women express a greater willingness than men to accept a physician's recommendation of cardiac catheterisation, coronary angioplasty or coronary artery bypass graft surgery indicating that patient preferences are unlikely to explain gender disparities in the use of such invasive cardiac procedures[244]. In the absence of evidence that patient choice accounts for gender differences in therapy [245] any differences in the treatment between men and women at the level of primary care provides one with a valuable source of epidemiological information. Despite the fact that women use more health care services than men [246;247] our results suggest that women with ischaemic heart disease may receive significantly less secondary preventive therapies as compared with their male counterparts thus exposing them to a higher risk of myocardial infarction and death.

One of the limitations of this study is the unavailability of a specific diagnosis of ischaemic heart disease in our population. However whilst nitrate prescribing alone may be less sensitive than other methods of estimating the prevalence of ischaemic heart disease, its relatively high specificity means that the majority of patients who are prescribed nitrate therapy do indeed have established ischaemic heart disease. In addition the prevalence of ischaemic heart disease in our population as estimated by nitrate prescriptions closely matches that reported in a recent epidemiological survey which reported a prevalence of angina of 13% in men and 9% in women aged over 55yrs of

age[217]. Our results were unaltered when patients receiving only 1 or 2 prescriptions for nitrates were excluded from our study confirming the validity of our results in patients receiving chronic nitrate therapy. While accepting that a diagnosis of ischaemic heart disease, based on the use of nitrates may not be 100 per cent accurate in this population, nonetheless the prescribers treating these patients believe their patients have ischaemic heart disease and should therefore prescribe appropriate secondary preventive therapy. Our data therefore reflects the reality of prescribing practice. Finally the accuracy of our data was confirmed by the finding that no gender bias exists in the prescription of drugs which are not discretionary such as insulin or antiepileptic therapy.

A number of theories have been put forward to explain this differential care in women. As chest pain is more often associated with normal epicardial arteries in women than in men, physicians may believe that angina in women is less likely to be followed by serious cardiovascular events[248] and this may explain why physicians are more likely to attribute anginal symptoms in women to non-cardiac causes [237]. It has been suggested that the favourable prognosis noted for women with angina in the Framingham study most likely reflected a high prevalence of women with chest pain originating from disease other than that affecting the coronary arteries, creating the impression that women tolerated angina better with the result that angina in women received less attention than their male counter-parts [240;249]. Thus physicians may believe that angina is a benign symptom in women, as many women with chest pain do not have coronary artery disease. However this conclusion was based on studies in younger women and is not necessarily valid in older women.

Women are less likely to attend cardiac rehabilitation following a myocardial infarct which further reduces the opportunity to implement adequate secondary preventive measures that may have not have been performed in hospital [250]. Anxiety is common in patients with acute coronary syndromes, and may influence outcome including sudden death in ischaemic heart disease[251]. Whilst anxiety is more commonly diagnosed in women [228], our results adjusted for this gender difference show a significantly greater use of anxiolytic benzodiazepines in women with established coronary heart disease. While the prescription of antidepressants is greater in women than in men, this is not affected by the presence of ischaemic heart disease. Our results may represent a gender bias in the perceived value of treating men and women with ischaemic heart disease, the former being given secondary prevention therapy and the latter offered symptomatic therapy. Irrespective of the reason for these inequalities, a significant number of women need to have their therapy reviewed. Since 1985 the mortality from ischaemic heart disease in Ireland has declined by 37% in men and by 30% in women. Similarly the mortality from acute myocardial infarction has declined by 50% in men and 39% in women [219]. Lack of secondary preventive measures in women may be one reason for the slower decline in mortality seen in women. Increased prevention, diagnosis, and treatment efforts should be directed toward women in primary care.

Research on health issues that are common to both sexes must include both men and women as there is evidence that women are under-represented in clinical trials [252]. In the CARE study, lowering cholesterol after myocardial infarction in patients with average cholesterol values reduced death or

subsequent infarction by 46% in women and 26% in men [253]. The results of studies performed exclusively on men cannot be generalised to apply to women without evidence that the results can be used safely and effectively on both sexes. This issue has been recently addressed in the Heart Protection Study which demonstrated reductions of at least one-third in major vascular events, such as myocardial infarction or stroke in both women and people aged over 70 years [254].

We found that patients aged greater than 65 years were less likely to receive a statin, β-blocker or aspirin, suggesting that as previously noted[225], ageism also exists in our study population. This effect was even more significant in patients aged greater than 75 years. However as older patients are more likely to have more severe disease and be treated medically rather than surgically, they would be expected to benefit more from important secondary preventive treatments. Pooled data from several large placebo controlled trials have demonstrated that the absolute reduction in mortality following treatment for myocardial infarction is at least as great in older as in younger patients [255]. Statin therapy has been shown to reduce coronary events and mortality in patients up to 75 years of age with average cholesterol [256]. One reason for this under-treatment may lie in the fact that older patients are largely excluded from major clinical trials [257] and as such will be under-represented in the evidence base used to determine clinical effectiveness. It has also been suggested that implicit age-based prioritisation policies are operating in health care [225]. As a result physicians may exhibit caution when treating the elderly.

The overall prescribing of aspirin and β-blockers of 70% and 37% respectively compares with figures of over 90% and 60% in a recent study of

US patients with a diagnosis of acute myocardial infarction and who were eligible to receive such treatment [258]. However we have no information on whether the patients in our study had contraindications to such therapy. Another study reported that when relative medical contraindications were dropped as reasons for ineligibility for treatment 96% of patients with acute myocardial infarction were eligible to receive aspirin and 24% were eligible to receive β-blockers [236]. The recent EUROASPIRE II survey reported that the use of aspirin was 86%, β-blockers 63%, ACE inhibitors 38% and lipid lowering drugs 61%, in patients with established coronary heart disease [259]. Indeed it has been demonstrated that a lower mortality among patients with acute myocardial infarction was associated with higher rates of aspirin and β-blockers rather than to rates of thrombolytic therapy or primary angioplasty emphasising the importance of appropriate secondary preventive measures [258]. The use of these medications can reduce the risk of cardiovascular death and non-fatal reinfarction, respectively by 22% and 27% for β-blockers [260;261], 13% and 31% for aspirin [262], 14% and 25% for all lipid-lowering medications combined [263] and 25% and 20% for ACE-Inhibitors [223]. However it has been suggested recently that there has been a collective failure of medical practice in Europe to achieve the substantial potential among patients with coronary heart disease to reduce the risk of recurrent disease and death [264]. There is a need to improve the transfer of evidence gained from clinical trials to prescribers in an effective manner as there is evidence to suggest that the effectiveness of interventions aimed at improving drug-prescribing behaviours may be sub-optimal [121;236].

4.4 Adherence to prescribing guidelines following the introduction of sildenafil in Ireland.

4.4.1 Introduction

Erectile dysfunction is now recognised as a common problem with its prevalence increasing with age. Sildenafil, an oral preparation for the management of erectile dysfunction, although licensed in Ireland in September 1998, was not initially freely available. There had been extensive debate about the socio-economic aspect of this treatment for erectile dysfunction with governments being concerned about the affordability of sildenafil [265;266]. The use of sildenafil was restricted in the United Kingdom to those patients who had undergone prostatectomy or radical pelvic surgery, or have a spinal cord injury, diabetes, multiple sclerosis, or single gene neurological disease[267]. In July 1999 Ireland became the only country in Europe, apart from Sweden where sildenafil was free under its health service. The Minister for Health, following the advice from an expert panel however imposed a limit of four tablets per month per patient, to 'reduce the possibility of inappropriate usage'[268].

As little information was available on the prescription of sildenafil in primary care, we examined the GMS prescription database to document the initial uptake of sildenafil within the Irish Health service.

4.4.2 Methods

We examined the prescription database of the GMS from the largest region, the Eastern Health Board (population of 334,031/ 28% of the total GMS which includes the counties of Dublin, Wicklow and Kildare) over a six-month period (July 1999-December 1999) for prescriptions for sildenafil. In addition for each month we determined the number of patients who were co-prescribed nitrate therapy, inhibitors of cytochrome P450 3A4 (ketoconazole, itraconazole, fluconazole, cimetidine, erythromycin, clarithromycin) and drugs associated with impotence (thiazide diuretics, spironolactone, β-Blockers, methyldopa, verapamil, tricyclic antidepressants, antipsychotics, antiepileptic drugs, oestrogens and corticosteroids)[269] with sildenafil. For comparison, we also determined the rate of co-prescribing of nitrates in patients receiving alprostadil which is also licensed for impotence.

As hypercholesterolaemia and diabetes are also risk factors thought to be associated with sildenafil-associated deaths [270] we determined the number of patients receiving lipid-lowering therapy and anti-diabetic medications. To assess adherence to therapy we determined the mean number of patients who received at least one prescription per month for sildenafil over the study period. As a number of patients received more than one prescription for sildenafil per month, we also computed the average number of prescriptions per patient over the study period.

4.4.3 Results

We identified a total number of 1422 patients, representing some 1.4% of the eligible adult male population who received 3740 prescriptions for sildenafil between July 1999 and December 1999. 66% of these prescriptions were for

the 50mg strength of sildenafil with 22% for the 100mg strength and 11% for the 25mg strength. The total number of prescriptions dispensed and patients receiving sildenafil over this period of time are shown in Figure 4.2.

The total cost of these prescriptions (including ingredient cost and dispensing fee) amounted to £92,814 over this period representing 0.14% of the Eastern Health Board's total budget for 1999. In addition 78 patients received 174 prescriptions for alprostadil which is also licensed for impotence.

The age characteristics of these patients are shown in Figure 4.3. The prevalence of use of sildenafil rose from 0.3% in the 16-24yr old age category to 3.5% in the 55-64 year old age category. The results of the co-prescribing study are shown in Table 4.9.

Up to 2.5% of patients receiving sildenafil and up to 23% of patients receiving alprostadil was co-prescribed nitrate therapy within a given month. The most commonly prescribed medications associated with impotence were antidepressants (38%), β-blockers (24%), antipsychotics (10%), corticosteroids (9%) and thiazide diuretics (8%). Glyceryl trinitrate was the most frequently prescribed nitrate (54% of all nitrate prescriptions followed by isosorbide mononitrate (44%) and isosorbide dinitrate (2%). In patients receiving potentially interacting drugs there was no significant difference in the use of the differing strengths of sildenafil. Up to 7% of patients were co-prescribed lipid-lowering therapy each month while up to 9% of patients received a prescription for drugs used in the treatment of diabetes (i.e. insulin/oral hypoglycaemics).

Figure 4.2.Number of prescriptions for and patients recieving sildenafil between June 1999 and December 1999 in the EHB region of the GMS

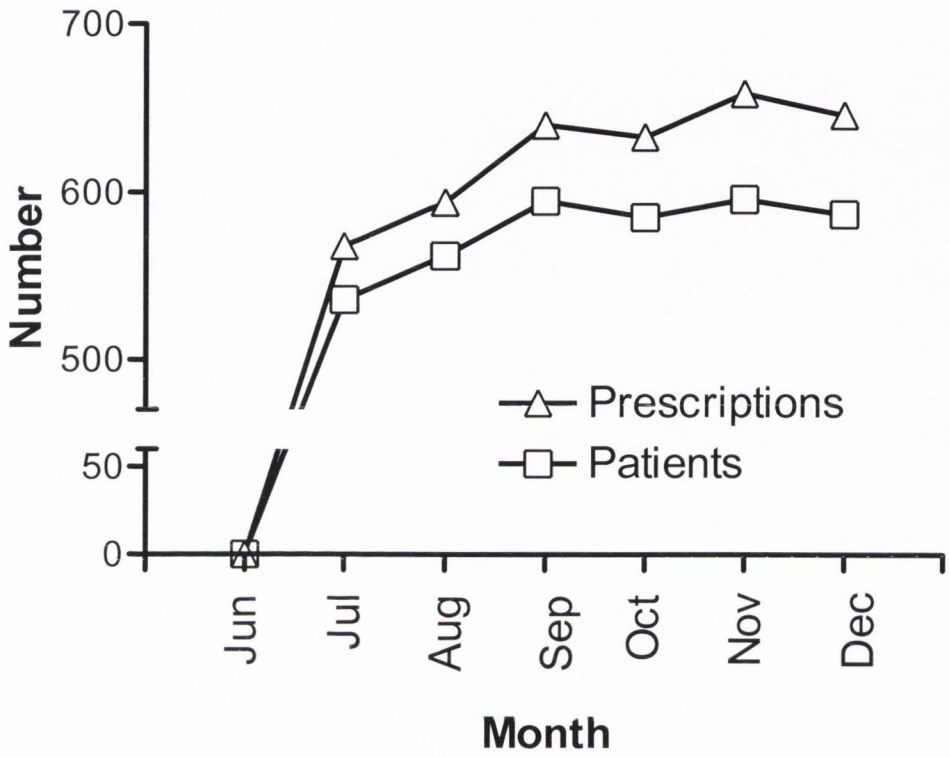
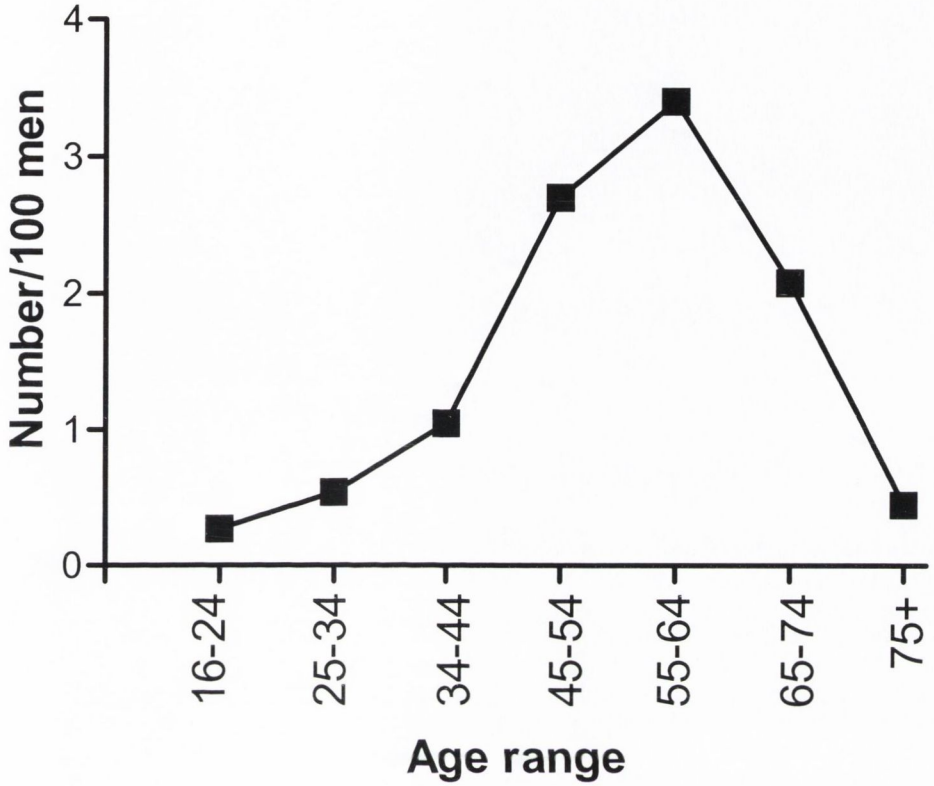


Figure 4.3. Number of men by age recieving Sildenafil in the EHB region of the GMS between June 1999 and December 1999.



Month	Number	Patients Receiving Nitrate Therapy	Patients receiving potentially interacting drugs	Patients receiving drugs associated with impotence
July 1999	536	6(1.1%)	29(5.4%)	117(22%)
August 1999	562	13(2.3%)	22(3.9%)	131(23.3%)
September 1999	595	14(2.4%)	28(4.7%)	137(23%)
October 1999	585	14(2.4%)	30(5.1%)	133(22.7%)
November 1999	596	15(2.5%)	25(4.1%)	148(24.8%)
December 1999	587	12(2%)	35(6%)	146(25%)

Table 4.9. Number of patients receiving sildenafil and co-administered medications between July 1999 and December 1999 in the Eastern Health board region of the GMS.

The mean number of months for which a patient received a prescription for sildenafil was 2.43+/-1.59(range 1-6). 42% of patients received at least one monthly prescription for sildenafil, 18% at least two monthly prescriptions and 13% at least three monthly prescriptions. Only 5% of patients received at least one prescription every month over the six-month period. The average number of prescriptions per patient as 2.63+/- 1.84(range 1-10) over this six-month period.

4.4.4 Discussion

Since its launch in the United States in March 1998, sildenafil has become the fastest selling drug ever [271]. This demand was predictable given a prevalence of erectile dysfunction of over 50% in men aged 50-70, and the unacceptability, poor effectiveness or unavailability of other treatments such as implants, intracavernosal injection and vacuum devices [272]. Its efficacy has been reported in a wide range of patient groups including those with depression, hypertension, and diabetes mellitus and in those following radical prostatectomy [273]. There is thus an accumulating body of evidence that nearly all men with erectile dysfunction, regardless of cause, can potentially respond to the drug and may warrant a therapeutic trial in the absence of a contraindication. An overall prevalence of erectile dysfunction of 10% has been reported which would equate to 98,740 men within the Eastern Health Board region of the (GMS) in Ireland. The low prevalence (1.4%) of use of sildenafil, which we found, may reflect either under-diagnosis or under treatment of this condition in primary care. Erectile dysfunction is often a hidden condition, which is seldom enquired about as part of a routine consultation and patients rarely volunteer this information because of

embarrassment and a feeling that little can be done [274]. Hackett reported that only 10% of a group of non-diabetic patients with erectile dysfunction had consulted their general practitioners, although 80% said that they would like to discuss it if an effective treatment existed [275].

The additional fears regarding the excessive costs associated with the prescription of sildenafil appear to date to be unfounded. The Department of Health estimated that it would cost IR2.3 million a year to supply the drug[268], which is approximately 3.5 times the cost to date. There are a number of reasons for the low uptake of sildenafil. Firstly, fewer patients than anticipated presented for treatment. Secondly, we have shown that the majority of patients do not receive repeat monthly prescriptions. The original limit of 4 tablets per month in this light appears to strike a balance between having the medicine available to all and limiting the total population costs if maximum uptake occurred. Using cost utility analysis, the treatment of erectile dysfunction with sildenafil compared favourably with papaverine-phentolamine injections. However the cost-effectiveness of sildenafil fell with increasing frequency of use and as a result it has been suggested that reimbursement should not be unconditional [276]. Indeed the validity of these findings have been questioned[277]. Using an accepted Markov decision model to estimate the incremental cost-effectiveness of sildenafil, treatment costs compared favourably with accepted interventions for other medical conditions such as renal dialysis, cholesterol-lowering medication and coronary bypass grafting, even though the authors systematically biased the analysis against sildenafil use. The authors concluded that other factors may over-ride cost-effectiveness in making sildenafil available under medical insurance schemes such as the

adverse effects of sildenafil, the cost of supplying a potentially large group of patients or the political pressure to make sildenafil available [278].

Safety continues to dominate discussions about sildenafil and has drawn considerable media attention. The most important drug interaction described is the potentially dangerous potentiation of the hypotensive effect of nitrates [279], a contraindication which is mentioned in the summary of product characteristics for sildenafil [280]. This particular contraindication is important, as erectile dysfunction is commonly associated with cardiovascular disease. Guidelines recently published by the American Heart Association and American College of Cardiologists advise caution in using sildenafil in men with congestive heart failure, men who are taking drugs that can raise serum levels of sildenafil, men with unstable angina, and in men taking several antihypertensives [281].

The co-prescription of nitrates (both short and long-acting in almost equal proportion) albeit at a low level (2% in contrast to16% of all patients receiving cardiovascular drugs within the GMS and 23% of patients receiving alprostadil) is of concern because of the seriousness of the potential interaction which may cause marked hypotension [281]. Whereas patients can temporarily avoid co-use with short-acting nitrates, this is not possible when on continuous long-acting nitrates. Such co-prescribing may have serious medico legal implications if a patient suffered a cardiac event. In addition the co-administration of drugs, which inhibit the metabolism of sildenafil, may lead to higher plasma levels and possibly a higher incidence of adverse effects. This is of lesser concern when 25mg and 50mg strengths of sildenafil are used

and also the adverse effects such as flushing and headache are not life threatening as they are directly related to sildenafil.

Up to 25% of patients receiving sildenafil also received drugs, which are associated with impotence. This may indicate that such drugs may be contributing to the patients' condition or that sildenafil is being used to counteract such side effects. While we are unable to determine the extent of iatrogenic erectile dysfunction, the data gives some indication of the upper limit of its potential to cause this problem.

4.5 Conclusions from studies of prescribing quality within the General Medical Services scheme

The indicator of prescribing quality based on drug interactions and developed using the GMS prescription database is both qualitative and quantitative and suggests selective prescribing to avoid therapy-related toxicity. Consistent results were provided for the particular drug interactions chosen. Furthermore this prescribing indicator has universal applicability in that it can be used to study other potential drug interactions within a prescription database and can be incorporated into the range of quality indices to audit prescribing quality in primary care.

The majority of general practitioners surveyed felt that the suggested prescribing indicators could be used to measure prescribing quality within the General Medical Services scheme. Indeed, the general practitioners felt that such indicators could be used as a form of feedback. The increasing computerisation of general practitioner surgeries will facilitate this feedback process. The level of prescribing of agents of doubtful efficiency was relatively low indicating good prescribing practice. However the prescription of topical non-steroidal anti-inflammatory agents was significant

(approximately 20% of overall NSAID prescriptions) despite their doubtful efficacy and there was a relatively low rate of generic prescribing, indicating poor prescribing quality. I also found evidence that general practitioners use 'personal formularies' in that they prescribe from a limited range of drugs within a particular therapeutic group (e.g. β-Blockers and NSAIDs). Doctors who familiarise themselves with a relatively small number of drugs are likely to make better use of them and may be less likely to make frequent changes to their prescribing repertoire in response to pharmaceutical industry promotional activities, an approach which is central to the WHO "Guide to Good Prescribing". Furthermore prescribing from a relatively narrow range of drugs within each therapeutic group leads to lower overall prescribing costs[194]. Prescribing indicators based on the prescription of key drugs may be difficult to interpret in the absence of clinical information on the indications for prescribing, which generally cannot be derived from routinely collected data. Lack of diagnosis is one of the limitations of the data provided by the GMS prescription database. We also demonstrated significant variability among general practitioners in prescribing for a number of drug classes. In an effort to reduce this variability, greater use of routinely available prescribing data linked to diagnosis should be made which can be fed back to prescribers to allow comparison with their peers. Further development of prescribing indicators should be undertaken with close involvement of general practitioners.

Adherence to established prescribing guidelines is another important measure of prescribing quality. Furthermore such guidelines should have universal applicability. The study of adherence to recognised guidelines for the

secondary prevention of ischaemic heart disease demonstrated a gender and age imbalance, in that women and the elderly were less likely to receive the best available secondary preventive therapy in primary care. Whilst I was limited by a lack of diagnosis, nitrate prescribing has been shown to be a useful surrogate for ischaemic heart disease in the community which allows the GMS prescription database to be used to audit prescribing practice. Increased prevention, diagnosis and treatment efforts should be directed toward women and the elderly in primary care. Furthermore the relatively low overall level of prescription of aspirin, β-blockers and statin therapy may represent missed opportunities to treat patients with ischaemic heart disease.

The introduction of sildenafil allowed the determination of adherence to newly established prescribing guidelines which are specified in the summary of product characteristics for sildenafil. In particular I found a relatively low level of prescribing of sildenafil with nitrates and interacting drugs indicating good prescribing practice. Furthermore, the co-prescribing of drugs associated with the development of impotence may indicate that such drugs are contributing to the patient's condition or that sildenafil is being prescribed in order to counteract these particular side effects. I was also able to confirm that initial fears regarding the potential economic effect of sildenafil on the GMS were unfounded.

Chapter 5 -Influence of material deprivation on prescribing patterns within a deprived population.

5.1 Introduction

The impact of social disadvantage on morbidity and mortality is well established[49-51]. Patient morbidity, workload on general practitioners, and the costs of drug treatment have been shown to increase with decreasing social advantage[52-54]. Health policy now addresses the increasing inequalities arising within many countries[55]. A recent approach to measuring deprivation has seen attempts to locate areas (and populations within them) on a level which reflects the access which people have to goods, services, resources, amenities and physical environment which are customary, or at least widely aspired to in society. Ecological data (i.e. data aggregated at small area level) can be particularly useful when examining trends in prescribing, as the increased number of observations reduces the variability in the data, allowing a more accurate estimate of the actual prescribing rates. This approach has lead to the compilation of 'material' deprivation indices, two of which have been developed in the UK, one for the North of England[282] and the other for Scotland[283]. Little information is available on the effect of different levels of material deprivation on prescribing patterns in primary care. This study examines the effect of material deprivation on the prescription rates of certain medications using a locally derived deprivation index similar to that of Carstairs[283] and Townsend[282], which may reflect better in the Irish setting.

5.1.1 Background to deprivation indices

Deprivation is a concept which has taken a variety of forms and has had many different meanings which have evolved over time. No single variable can be said to measure deprivation, but rather a number of variables must be combined in some way. Deprivation has been defined as a state of 'observable and demonstrable disadvantage relative to the local community to which an individual belongs'[284]. Since the early 1980s, a number of deprivation indices have been proposed[56]. A number of these indices have been defined specifically in relation to health while others, designed in a different context, have been brought into the field of health. Early attempts at deriving suitable deprivation indices exhibited many methodological differences and the number of indicators included were large. One criticism of these early indices was the tendency to include socio-demographic sub-groups of the population, like elderly living alone, population aged under 5, one parent families, or ethnic minorities, as part of the definition of deprivation[282]. While many people in these subgroups may be deprived, some are not, and the challenge is to find out how many are deprived rather than operate as if all were in that condition. Socio-demographic indicators should also reflect groups which 'may be at risk' of deprivation rather than those 'presently experiencing' deprivation.

A recent approach to measuring deprivation has seen attempts to locate areas (and populations within them) on a level which reflects the access which people have to goods, services, resources, amenities and physical environment which are customary, or at least widely aspired to in society. This approach has lead to the compilation of 'material' deprivation indices, two of which

have been developed in the UK, one for the North of England[282] and the other for Scotland[283].

The North of England index, developed by Townsend, is a composite of four census-based indicators which are widely believed to represent, or be a determinant of material disadvantage, namely:

- **Unemployment**-Proportion of economically active who are unemployed
- **No Car**- Proportion of private households who do not possess a car.
- **Home Ownership**-Proportion of private households which are not owner occupied.
- **Overcrowding**-Proportion of private households with more than one person per room.

Using a similar methodology Carstairs and Morris[283] developed a Scottish deprivation index which contained the following four census-based indicators;

- **Male unemployment**-Proportion of economically active males who are seeking work.
- **Low Social Class**-Proportion of all persons in private households with a head of household in social class 4 or 5.
- **No Car-**Proportion of all persons in private households with no car
- **Overcrowding**-Persons in private households living at a density of >1 person per room as a proportion of all persons in private households.

A number of differences exist between these two material deprivation indices. Townsend did not include social class in their material deprivation index on the basis that being in a low social class (i.e. in semi-skilled or unskilled occupations) did not necessarily mean being deprived. He maintained, as with

socio-demographic variables, that this was a category within the population that were especially prone to forms of deprivation. However, Carstairs and Morris argued the case for including low social class in their deprivation index on the basis that it indicated earnings at the lower end of the income scale. Reduced income, like unemployment, has important implications with regard to access to material resources and the ability to make choices in life.

Housing tenure did not appear in the Scottish material deprivation index on the grounds that a higher proportion of the country's housing stock was in the public sector and lesser variation existed between areas compared to the North of England. Another difference between the Townsend and Carstairs indices is that in the Carstairs index all four variables were calculated on the basis of individuals not households. While this was considered preferable for the purpose of the analysis of events which related to individuals it was felt that in practice any differences from using the two approaches were likely to be small.

Geographical measures of deprivation show wide variations in the socio-economic characteristics of populations who live in small areas. This variation has led governments in the past to target deprived areas within these small areas with the aim of improving the resident's circumstances. In Scotland, some health boards target resources towards areas at the most deprived extreme of the Carstairs deprivation scale, which ranges from –7.5 (most affluent) to +12.9 (most deprived)[283]. Townsend argued that an area based approach should not be central to improving the conditions of people in poverty, and concluded that the spatial concentration of aspects of deprivation could be low, a finding which was reaffirmed by McLoone [285]. On the basis

of Carstairs scores, more than 60% of the population in Scotland would need to be targeted to include 74% of low-income households. The poor sensitivity of an area based approach means that the group of people to whom resources are directed includes people who are not poor [285]. Thus deprived areas can include people who are not deprived and vice versa. This phenomenon has also been referred to as the 'ecological fallacy' (that is the extent to which associations between socio-economic characteristics of a small area and utilisation rates may not hold for individual patients). Debate continues about whether the health experience of poor people in deprived areas is worse than that encountered by other poor people [51].

5.1.2 Irish deprivation indices

Howell developed a deprivation index for each county of Ireland using eight equally weighted variables[286]. Four of the variables were similar to those used by Townsend, namely, the proportion of the labour force who were unemployed, the proportion of households not owning a car, the proportion of people living in overcrowded conditions, and the proportion of households not owner occupied. The remaining four variables were: the proportion of the population in either social class 5 or 6, the proportion of those completing formal education before 15 yrs of age, the proportion of those holding a GMS medical card, and the proportion of families in receipt of Family Income Support. The latter two variables were non-census variables and not available at a small area level and hence this approach was not suited as a basis for developing a national index.

Jackson and Haase reported a small area deprivation index for Ireland comprising 13 census based indicators[287]. The diverse range of indicators

included both socio-economic variables (age, dependency rate and lone parents) as well as traditional material deprivation indicators (unemployment, overcrowding, car ownership, housing tenure). This indicator may also be wrong in principal as it includes socio-demographic sub-groups of the population in a definition of deprivation. This index also mixes indicators of potential affluence (households with two or more cars, third level education, higher and professional classes) with indicators of deprivation, and includes a number of variables which are at opposite ends of the same spectrum such as local authority rented households and owner occupied households.

5.1.3 Development of a new material deprivation index - the Small Area Health Research Unit (SAHRU) deprivation index

In response to the need to provide an area based measure of deprivation, the Small Area Health Research Unit (SAHRU), developed a national material deprivation index which was used to investigate the effect of material deprivation on prescribing patterns [288]. This index is intended to provide a national overview of deprivation by small area and to serve for comparisons between health board regions. The final indicators chosen for the SAHRU index of deprivation which was used in this study were as follows:

- Proportion of the economically active population (15-64 yr) unemployed or seeking a first-time job (unemployed). Unemployment reflects a lack of access to earned income and the facilities of employment. Moreover it may impose other pressures on individuals through loss of self-esteem, and on families through problems and tensions generated.

- Proportion of the population (social class 1 to 6) only in social class 5 or 6 (Low social class). The Irish social class scale is an ordinal scale from 1 (higher professional) to 6 (unskilled manual). It is based on the concept of groups whose members possess capacities for the generation of income through their occupations, not the status/prestige associated with particular occupations. A social class code of 7 is assigned to people who cannot be assigned to any of the other six groups. Being in a low social class reflects earnings at the lower end of the income scale. Low income limits access to material resources and the ability to make choices in life.

- Proportion of permanent private households with no car (no car). Car ownership has been suggested as a surrogate for current disposable income. Apart from the cost of purchasing a car there are necessary licensing, insurance, maintenance and repair costs, as well as day-to-day running expenses. Car ownership also confers benefits in terms of access to other resources. It can be argued that in city areas, with good access to public transport, owning a car is not a necessity. Nevertheless despite the availability of public transport ownership of a car appears to be something that many households do wish to achieve. This may be a reflection of the inconvenience and/or limited scope of public transport as well as the prestige associated with owning a car. In rural areas car ownership is more of a necessity and its value as a discriminator between affluent and deprived areas may be diminished. However in rural Ireland there is considerable variability in car

ownership between areas (range:0% to 92%, median 23%) but the range is similar to that in urban areas (range:0% to 96%, median 43%).

- Proportion of permanent private households rented privately or from a local authority, or in the process of being acquired from a local authority (rented accommodation). Non-owner occupation has been suggested as a surrogate for income in the long-term. Taken together with car ownership, these two indicators are likely to provide a fairly good reflection of income levels in different areas.

- The average number of persons per room in permanent private housing units (overcrowding). Overcrowding reflects living circumstances and housing conditions. It may also reflect wealth as people in overcrowded circumstances are likely to wish to improve their circumstances provided financial resources are available.

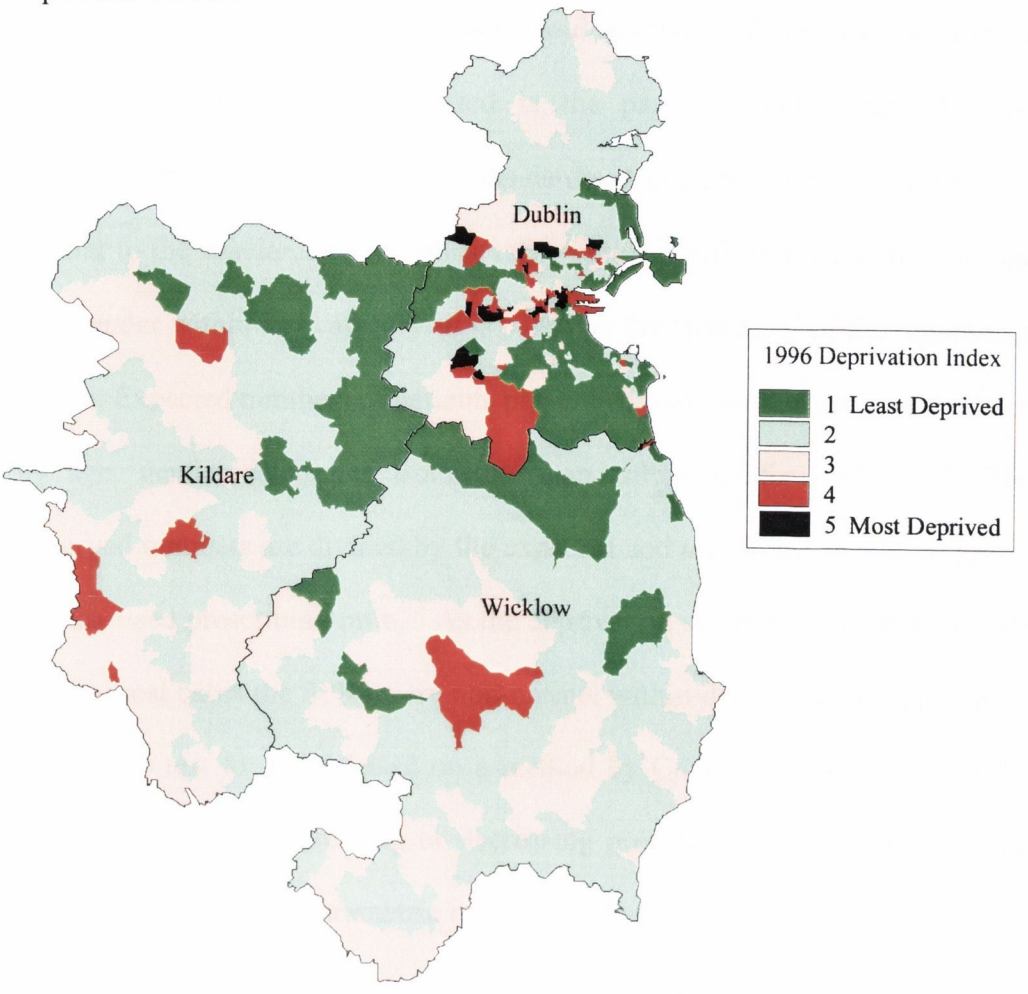
The deprivation score ranges from 1(least deprived) to 5 (most deprived) and patients are assigned a deprivation score according to the District Electoral District (DED) in which the patient lives. While this national deprivation index provides a unique ranking of the 3,444 DEDs for the entire country and serves to identify areas of extreme variation, this index is not optimal for the requirements of individual health boards where there is a need to identify the degree of relative deprivation within a region. The weight attached to each indicator may vary from region to region and thus separate indices have been calculated for each health board. A diagrammatic representation of the Eastern Health Board Region according to the level of deprivation is shown in

Figure 5.1. By linking areas of deprivation to prescription data it is possible to determine the influence of material deprivation on prescribing patterns within the Eastern Region of the GMS.

5.2 Methods

As discussed earlier, eligibility for free health care within the GMS population is means tested, and is confined to those who are unable without undue hardship to arrange general practitioner services for themselves and their dependants. Thus the GMS population represent an already 'materially-deprived' population. We examined the prescription database of the GMS from the largest region, the Eastern Health Board (population of 334,031 or 28% of the total GMS population), over a twelve-month period (September 1999-August 2000). It was possible to geo-code 234,441 (72%) of the eligible GMS patients, using the address of the patient, and thus assign a deprivation score based on the District Electoral District (DED or ward) in which the patient lived. Each DED has a census-derived material deprivation index, known as the SAHRU deprivation index which as discussed earlier is based on the deprivation indices of Townsend and Carstairs [289]. The deprivation score ranges from 1(least deprived) to 5 (most deprived). There are a total of 493 DEDs within the EHRA. 126 DEDs were assigned to deprivation level 1, 191 to deprivation level 2, 89 to deprivation level 3, 60 to deprivation level 4 and 27 to deprivation level 5. A total of 181,647 patients with deprivation scores assigned appeared in the 12-month prescription dataset. Age-sex standardised prescription ratios (SPRs) by DED were determined for each group of drugs as defined by the Anatomical Therapeutic Chemical (ATC) classification system[20]. Furthermore, SPRs were also

Figure 5.1. Representation of the Eastern Health Board Region according to Deprivation level.



determined for a number of specified drug classes which could be used to identify particular diseases such as thyroid disease, diabetes and depression. Nitrate prescribing has been used in the past to identify patients with ischaemic heart disease [227]. The standardised prescribing ratio (SPR) [201] is similar to the standardised mortality ratio, in that it effectively controls for age and gender within any category. It is based on the 'standard' of the region as a whole. Expected numbers of patients prescribed particular drugs are calculated by age, gender categories from the 'standard' rates for each DED. The observed numbers are divided by the expected and multiplied by 100 to give a standardised prescribing ratio. As the deprivation score is a nominal variable and in most cases the SPRs were non-normal within deprivation group, a non-parametric test for trend based on a method by Cuzick[290] was applied to the dataset to examine increasing or decreasing prescribing trends with material deprivation. This non-parametric test for trend statistic is based on ranking the data and calculating a weighted sum of ranks (weights according to the order 1,2,3 etc), This is compared with an expected value (assuming equal group status) divided by its standard error, and approximated to a standard normal distribution, using the z-score. A z-score greater than 1.96 indicates that there is a statistically significant trend at $p<0.05$. As the data were skewed median SPRs and interquartile ranges are also presented by deprivation group. Significance was at $p<0.05$.

5.3 Results

An example of the how the age-sex Standardised prescription ratios (SPRs) for the anti-infectives, anti-parasitic drugs, benzodiazepines and anti-depressive group of medications vary with material deprivation are shown in the form of box and whisker plots in Figures 5.2-5.5. A summary of the results of SPRs and non-paramedic tests for trend for all the ATC group of drugs and the specified drug classes are shown in Tables 5.1 and 5.2. The box and whisker plots for the entire analysis are shown in appendix C. Our results reveal a statistically significant increase in prescription rate with increasing material deprivation for ATC groups A (alimentary tract and metabolism), D (dermatological), J (anti-infective), M (musculoskeletal), P (anti-parasitic), R (respiratory) whilst prescription rates fell with increasing deprivation for ATC groups H (hormonal preparations) and L (anti-neoplastic and immunomodulating agents). For the more specific group of drugs which could be used as indicators of particular disease states, prescribing rates increased with increasing material deprivation for anti-asthma preparations, insulin, oral hypoglycaemic agents, anti- thyroid preparations, nitrate therapy, antiulcer preparations and benzodiazepines whilst prescribing rates fell with increasing material deprivation for antipsychotics agents, anti-parkinsonian drugs, antiepileptic agents, antidepressive agents and thyroid hormones.

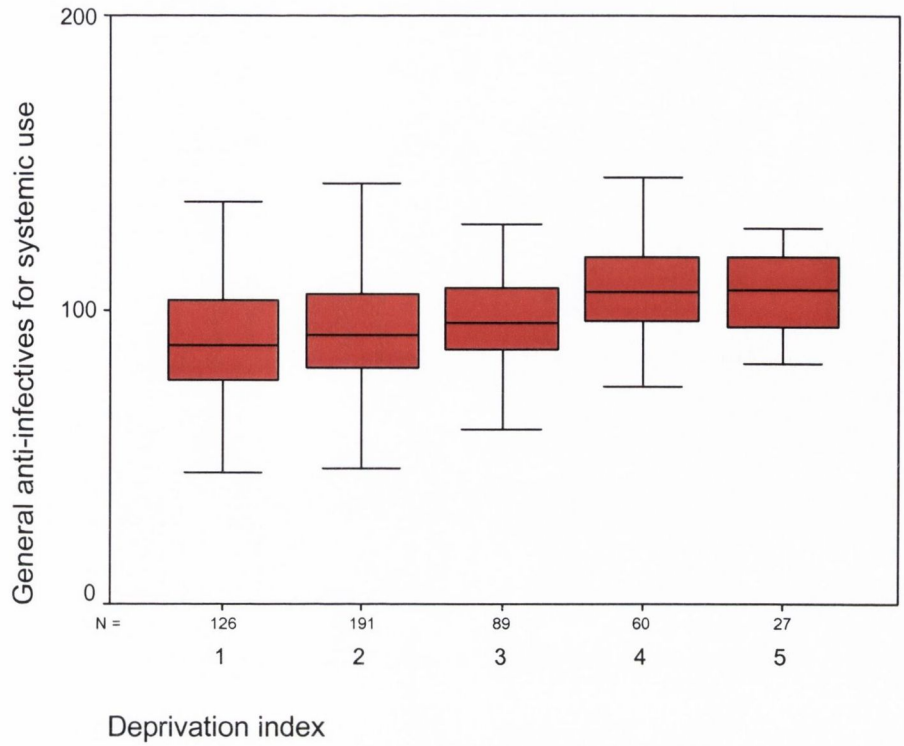


Figure.5.2 Relationship between the standardised prescribing ratio and deprivation score(1-5) for ATC group J(General antiinfectives for systemic use) within the EHB region of the GMS

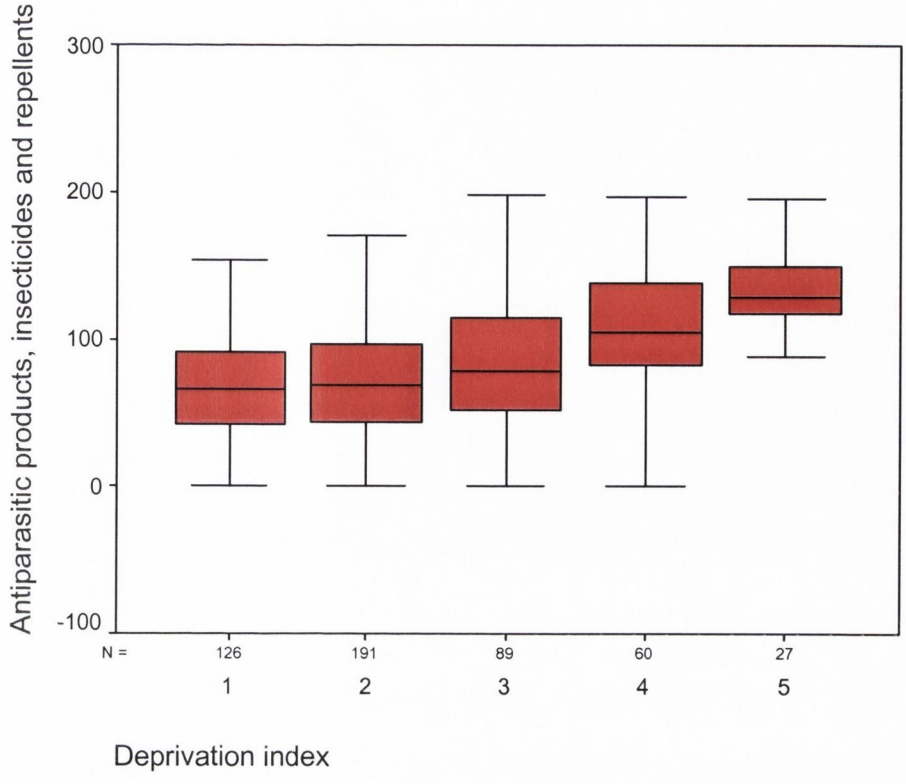


Figure.5.3 Relationship between the standardised prescribing ratio and deprivation score(1-5) for ATC group P (Antiparasitic products, insecticides and repellents) within the EHB region of the GMS

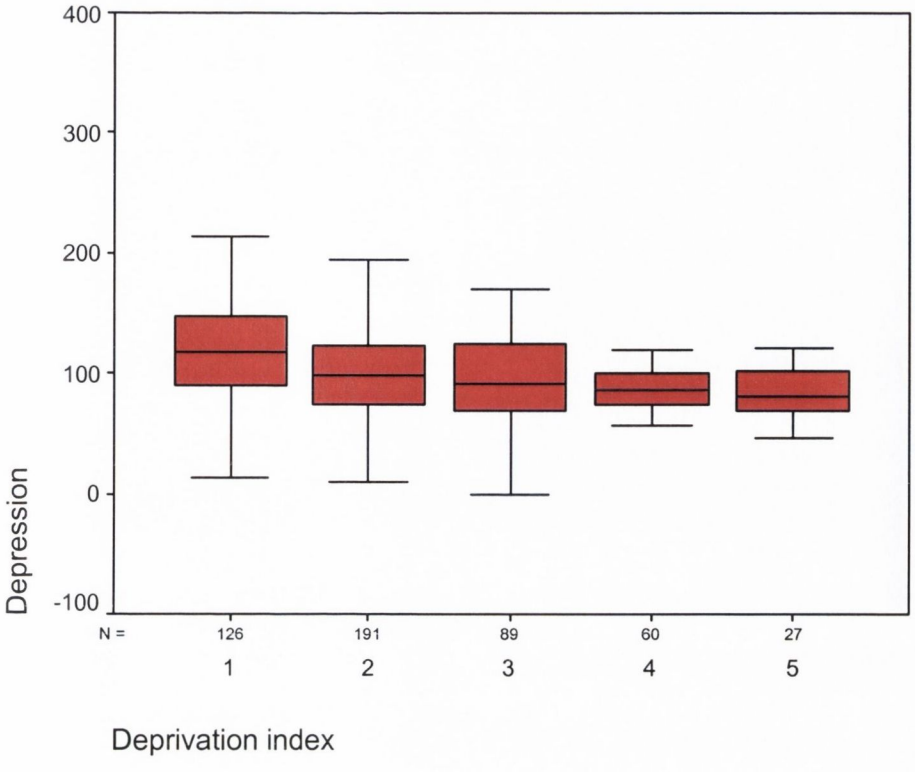


Figure.5.4 Relationship between the standardised prescribing ratio and deprivation score(1-5) for Anatomical Therapeutic Chemical (ATC) subgroup N06A (Anti-Depressive agents)

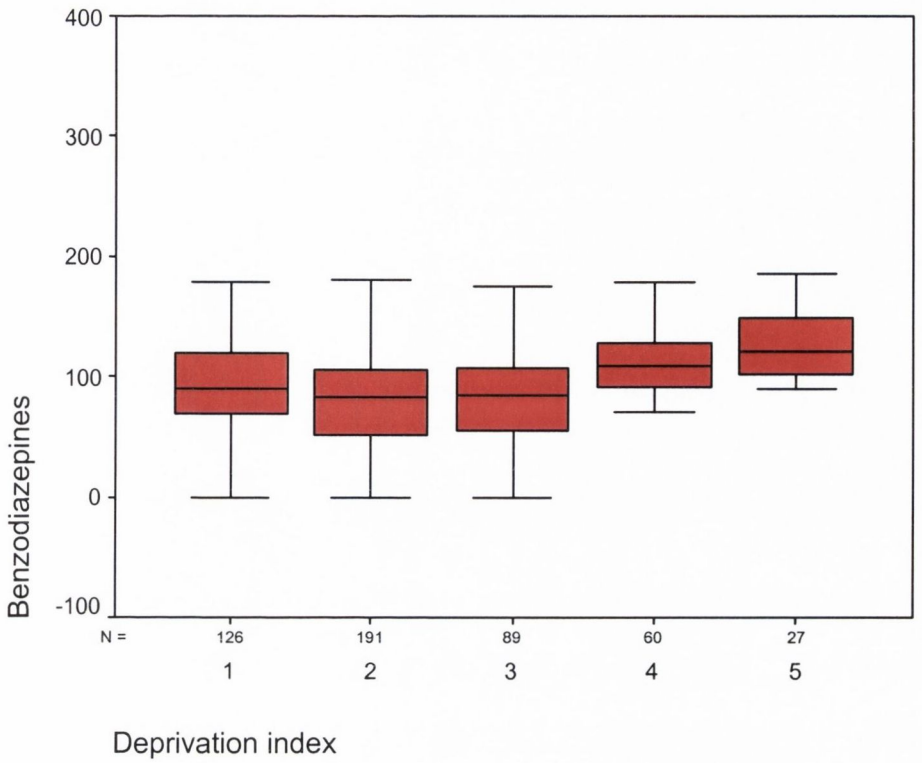


Figure 5.5 Relationship between standardised prescribing ratio and deprivation score(1-5) for Anatomical TherapeuticChemical (ATC) subgroup N05BA (Benzodiazepines)

ATC Class	Median SPR (95% Interquartile range) for Deprivation Level					Non-parametric trend test
	1(n=126 DEDs)	2(n=191 DEDs)	3 (N=89DEDs)	4 (n=60DEDs)	5 (n=27DEDs)	
A(Alimentary tract and metabolism)	96.7(82-113.5)	95.2(79.6-111.1)	96(83.4-111.1))	103.4(97.4-117))	102.2(95-110.6))	Z=2.52, p<0.01
B(Blood and Blood-forming organs)	95.5(77.1-110.8))	96.8(81.3-118.8))	94.3(69.7-111.8))	97.6(83.3-112.1))	101.1(81-113.3))	Z=0.26, p=0.79
C(Cardiovascular system)	100.2(84.8-115)	98.8(84-115)	105(89-120.6).	101.4(87.4-113.9))	93(84.6-108.4)	Z=-0.28,p=0.78
D(Dermatologicals)	92.4(76-112.4)	87.6(65-103.2)	91.6(70-110.1)	105.6(94.4-127.5)	109.5(95.4-117.4)	Z=4.3, p<0.01
G (Genito-urinary and sex hormones)	101.8(82.2-117.5)	96.1(74.3-110.8)	99.3(71-114.3)	97.9 (90.5-108.2)	99.5(93-107.8)	Z=-0.27, p=0.79
H (systemic Hormonal Preparations)	104.5(84.1-134.7)	96.3(73.8-120)	98.1(77.2-134.4)	90.1(77.5-102.9)	85.9(71.5-91.6)	Z=-3.8, p<0.01
J(General anti-infectives for systemic use)	88.1(75.8-102.9)	91.1(79.9-105.6)	95.6(86.1-107.6)	105.7(96-117.7)	106.5(92.5-117.9)	Z=6.13, p<0.01
L(Anti-neoplastic and immunomodulating agents)	106.5(47.2-170.1)	82.6(0-124))	70.8(2.3-120.2))	88.1(68.3-107.3)	81.2(52.6-90.1)	Z=-2.46, p<0.01
M(Musculoskeletal)	91.5(80.3-109.6)	94(78-109.5)	100.3(79.9-111.6)	104.1(93.6-112.8)	106.6(94.8-114.5)	Z=3.68, p<0.01
N(Nervous system)	106.4(92.4-123.3)	92.6 (74.1-109.2)	89.1 (73.4-107.9)	101.5(91.4-112.7)	98.8(94-115)	Z=-0.97,p=0.33
P(Anti-parasitic)	65.4(42.7-91)	69(43.8-96.1)	78.6(48.2-115.4)	105.2(82.2-139)	128.5(117.5-151)	Z=8.3, p<0.01
R (Respiratory system)	86.2(69.6-104.1)	90(68.7-105.3)	100.7(81.9-122.7)	108.2(96.6-121.3)	109.2(98.9-127)	Z=6.72, p<0.01
S(Sensory Organs)	100.3(79.6-134)	92.1(69-119)	83.9(53.4-108.6)	98.2(87.4-110.6)	92.7(71.7-110.4)	Z=-1.77, p=0.08

Table 5.1. Median Standardised Prescribing Rates (SPRs) for each deprivation level (1-5) and non-parametric tests for trend for the principle ATC drug groups
Key:DED=District Electoral Division

Drug class	Median SPR (interquartile range) for Deprivation Level					Non-parametric trend test
	1(n=126 DEDs)	2(n=191 DEDs)	3 (N=89DEDs)	4 (n=60DEDs)	5 (n=27DEDs)	
Anti-Asthmatics	88.7(63.7-106.8)	90(63.4-107.2)	98.1(74.5-130.8)	106.2(94-124.6)	114(101.2-122)	Z=6.13,p<0.01
Anti-psychotics	132.9(86.6-207)	87.7(58.8-128.6)	80.6(42.3-131.4)	72.9(63-101.2)	65(47.2-82.8)	Z=-6.78.p<0.01
Anti-Parkinsonian Medications	137.1(69.2-201.9))	94.2(32.4-148.7)	62.3(0-117)	66.2(31.4-110.5)	38.1(24-66.3)	Z=-5.58,p<0.01
Anti-epileptic medications	108.3(68.3-163.1)	96.5(48.5-143.2)	70(19.4-120.1)	88.4(68-117.8)	70.6(53.5-99.5)	Z=-3.15,p<0.01
Anti-depressive medications	117(89.3-149)	99.4(74.2-123.4)	92(66.8-126.1)	85.6(74-100)	81.4(68.2-102.7)	Z=5.8,p<0.01
IDDM	40.7(0-122.9)	53.9(0-141.3)	39.4(0-96.1)	93.2(54.1-146.7)	121.9(81-136)	Z=3.9,p<0.01
NIDDM	65.4(27.6-106.5)	98.1(66.9-137.2)	95.2(68.3-171.4)	108.1(74.6-134.4)	109.7(89.2-118.9)	Z=4.34,p<0.01
Anti-thyroid therapy	38.3(0-129.1)	49.1(0-140.4)	61.8(0-195.7)	106.2(49.3-137.2)	93.6(53.7-165.6)	Z=3.95,p<0.01
Thyroid medication	113(77.1-158.6)	92.7(49.4-120.9)	93.6(50.9-126.5)	86.1(68-104.1))	82.1(67.3-94.1)	Z=-3.65, p<0.01
Nitrate therapy	80.6(49.7-110.7)	91(63.2-120.5)	89.8(58.6-128.7)	113.8(88.8-133.3)	107.9(90.1-138)	Z=4.88, p<0.01
Anti-ulcer Disease	92.7(72.9-114.6)	94.2(76.5-115.4)	93.8(77.9-118.6)	107.6(96.9-120)	107.6(98.5-120.2)	Z=3.77, p<0.01
Benzodiazepine therapy	90.2(69.5-119.4)	82.1(51.3-105.6)	85.1(53.1-107.4)	108.5(90.9-128.2))	122(102.2-149.8)	Z=4.47, p<0.01

Table 5.2. Median Standardised Prescribing Rates (SPRs) and non-parametric tests for trend for specified drug groups which could be used to quantify a particular medical condition. Key:DED=District Electoral Division

5.4 Discussion

This study used specific census-based indicators to define levels of deprivation within specific DEDs. The concept of deprivation used here could be considered rather narrow by comparison with the popular concept of depressed inner city communities, with concomitant crime, traffic, pollution, etc. However, it is census-based indicators, along the lines of the index used here that are being used increasingly in the planning of policies and the allocation of resources. With the increasing popularity of deprivation indices for targeting health and social policy, care should be taken not to read too much into them as it has been shown that the deprivation effect may be due entirely to the concentration of disadvantaged people in the one area with some individuals living in deprived areas who were not disadvantaged not experiencing the excess risk [51].

However despite these limitations our results suggest that material deprivation even among the already 'materially deprived' GMS population has some effect on prescribing rates though the effect is variable. Our results suggest that nitrate prescribing, a marker for the presence of ischaemic heart disease[227] increases with increasing material deprivation. Socio-economic deprivation has been shown to have a profound effect on the risk of having a first myocardial infarction, the chance of reaching hospital alive, and the probability of surviving the first month [49]. Socio-economic group affects not only death rates from myocardial infarction but also event rates and chance of admission to hospital [291].

Social deprivation is an important factor associated with the variation in volume of prescribing of antibiotics among general practitioners[37], a finding

which was confirmed in this study where the rate of prescribing of anti-infective agents increases with increasing material deprivation. Antibiotic prescribing has come under increasing scrutiny as evidence of developing antibiotic-resistance accumulates. Infections are among the most frequent reasons for patients to consult a general practitioner and often result in the prescribing of an antibiotic [292]. Because of its effects on both morbidity and patient/doctor expectation, socio-economic deprivation is often considered to be a particular important factor encouraging the prescribing of antibiotics, although there is little firm evidence to support this. Similarly it is often said that single-handed GPs prescribe antibiotics more often than partnered GPs, and that training practices prescribe antibiotics less often than non-training [37]. Some of this increased prescribing may be due to an excess of morbidity within a deprived community. Some is probably also due to the increased number of patient/doctor consultations among more deprived communities [52] which in turn leads to increased prescribing [293]. Indeed demographic and socio-economic factors can act as powerful predictors of consultation patterns[54].

The prescription item has been criticised as a poor measure of prescribing volume, but for antibiotics which are prescribed acutely and not generally as repeats, the prescription item may be more appropriate than volume measures such as the defined daily dose, since our interest is in the influences on the decision to issue a prescription and less on the size of the prescription. Interestingly we found a strong correlation in the prescribing rates of anti-parasitic agents, which may be related to similar factors as those found with anti-infective agents.

Differential care regarding other medical conditions and deprivation have also been described [50]. There is evidence to suggest that the prevalence of diabetes[294;295], asthma [296-298], depression [299;300] and epilepsy [301]increases with increasing deprivation. Our results confirm these findings except for the prescription of anti-epileptic and anti-depressive agents. Patients with epilepsy may also receive their medications under another scheme of reimbursement, the long-term illness scheme (which includes patients who suffer from one of a list of scheduled illnesses including diabetes and epilepsy) and hence we may have had an incomplete picture of the prescribing patterns of these patients. The finding that the prescription of anti-depressive agents falls with increasing material deprivation is more difficult to explain, particularly as we found an opposite effect with benzodiazepine prescription rates. There appears to be a tendency with CNS drugs to prescribe symptomatic therapy such as benzodiazepines in the most deprived with a greater use of disease specific therapy such as antipsychotics, anti-epileptics, anti-parkinsonian and antidepressant therapy in those patients with a lower level of deprivation. Thus while depression is more common with increasing deprivation[299;300], we found that the prescribing of specific therapy such as antidepressants did not follow such a pattern. Furthermore a lack of prescribing of specific disease therapies which are not related to deprivation such as thyroid and parkinson's disease, may suggest either under diagnosis or under treatment of that particular disease.

Some of the increased prescribing patterns which we found in this study may be due to an excess of morbidity within a deprived community in addition to

increased consultations among more deprived communities which in turn leads to increased prescribing.

5.5 Conclusions

Our results suggest that even within a population considered to be economically deprived that different levels of deprivation may significantly influence general practitioner prescribing patterns. There is evidence that symptomatic rather than disease specific treatment increases with increasing material deprivation. Further analysis of this population will require validation with individual level social deprivation scores such as those based on individual income, employment status, marital status or receipt of benefits as well as extension to more specific types of therapies using individualised data for this population. This would allow one to also examine the ecological fallacy that the relationship between deprivation and prescribing rates is different when individuals rather than areas are examined.

Chapter 6 - Conclusions

6.1 Introduction

Pharmacoepidemiology grew out of the science of pharmacovigilance and later became further subdivided into studies of drug utilisation and prescribing quality.

The aims of this thesis were two-fold, namely,

1. To demonstrate the usefulness of the GMS prescription database for performing pharmacoepidemiological studies and
2. To examine the influence of material deprivation on prescribing patterns within the GMS.

In the field of pharmacovigilance it was possible to demonstrate the influence of external forces, in particular the media on prescribing patterns within the GMS. The studies also illustrated how media reports or regulatory action taken in one country of the European Union can influence prescribers in another country. The attitudinal survey on adverse drug reaction reporting confirmed the results of other workers[199] and highlighted the need to improve reporting rates. The studies performed on drug utilisation demonstrated the extent of polypharmacy within the GMS population and illustrated the influence of age and gender on prescription rates. The GMS prescription database illustrated how it could be used to examine the utilisation and success of various *Helicobacter pylori* eradication therapies.

The GMS prescription database provided a unique insight into prescribing quality among Irish general practitioners and also demonstrated a wide variability in prescribing practices among general practitioners. The prescription database allowed one to develop a new index of prescribing quality using the principal of drug interactions which was further explored when examining the co-prescribing patterns with sildenafil. It was also possible to estimate adherence to both established and new prescribing guidelines as a measure of prescribing quality.

Finally, using the material deprivation index developed by SAHRU, I was able to demonstrate that even within a population seen as already materially deprived, that prescribing patterns could be influenced by different levels of material deprivation. In particular the prescription of anti-infective agents and symptomatic centrally active agents increased with increasing material deprivation whereas the prescription of disease specific centrally active drugs fell with increasing deprivation.

6.2 Conclusions

The conclusions from my work are as follows

1. The GMS prescription database provides an important resource for performing studies of pharmacovigilance, drug utilization and prescribing quality. Given the level of under-reporting of adverse drug reactions, there is a need for the regulatory authority to be more explicit in its requirements for reporting and to increase the range of knowledge regarding adverse drug reaction reporting in order to create a 'reporting culture' among health professionals. The appointment of personnel with an expertise in pharmacovigilance should be encouraged as a means to improve reporting

rates. Doctors' understanding of ADR frequency rates needs improvement in order that accurate estimates of risk can be explained to patients. A more satisfactory method of explaining the risks associated with medications needs to be developed in order that the public can make informed decisions regarding drug safety issues. Regulatory action and media attention have been shown to influence the prescribing patterns positively (in the case of cotrimoxazole) and negatively (in the case of the inappropriate advice regarding the safety of the third generation oral contraceptive steroids).

2. Multiple drug use is widespread within the GMS, with age, male gender and the major therapeutic drug classes contributing to the consumption of more than 4 drugs per month. By identifying a particular treatment (e.g. *Helicobacter pylori* eradication therapy) and an outcome which can be measured in terms of drug therapy (e.g. lack of anti-ulcer medications), it is possible to use the GMS prescription database for hypothesis testing even if one is constrained by lack of diagnosis.
3. The GMS prescription database has allowed the development of an indicator of prescribing quality which is based on drug interactions and will have universal application. Furthermore there is evidence of good quality prescribing within the GMS as judged by the preferential prescribing of non-interacting drugs in the case of the H_2-antagonists and sildenafil, the low prescribing rate of drugs associated with limited efficacy and the use of a limited range of drugs from a particular class of drug. However there was evidence of poor adherence to guidelines for the secondary prevention of ischaemic heart disease which was further

confounded by an age and gender inequality. Increased prevention, diagnosis and treatment efforts for ischaemic heart disease should be directed toward women and the elderly in primary care.

4. Initial fears regarding the economic impact of the prescription of sildenafil within the GMS were unfounded. Furthermore the relatively high level of co-prescribing of drugs associated with impotence may indicate that such drugs contribute to the patient's condition or that sildenafil is being prescribed to counteract the side effects of these drugs.
5. Even within the 'economically deprived' population of the GMS different levels of material deprivation influence prescribing patterns. The increased prescription of anti-parasitic drugs with increasing deprivation may act as a sensitive indicator of material deprivation. There is evidence that symptomatic central nervous system (CNS) therapy increases with increasing deprivation whereas the therapy of specific CNS disorders such as depression decrease with increasing deprivation. The reasons for these apparent inequalities requires further study. In particular the use of a deprivation index based on individual characteristics, rather than one that is based on area may provide further insight into the influence of deprivation on health and prescribing practices. This would allow one to also examine the 'ecological fallacy' that the relationship between deprivation and prescribing rates is different when individuals rather than areas are examined.

6.3 The future of pharmacoepidemiology

The studies performed regarding drug safety illustrate that communicating information regarding drug safety can be quite complex and is fraught with vested interests such as the pharmaceutical industry, government legislators, healthcare professionals and consumer groups. Despite criticism by the medical profession of the presentation of such issues by the general media, it appears to have a greater effect than information provided by regulatory authorities. With the advent of a centralised European mechanism to license drugs, there is a need to develop an EU perspective on drug safety. It may well be appropriate to develop an independent agency, responsible for drug safety. This would ensure objectivity and avoid any possible conflict of interests. Growing public concern over drug safety and a closer regulation of drug development is creating a need for expertise in pharmacoepidemiology, rather than mere familiarity with a new discipline. Increasingly, physicians and government agencies need to evaluate the risk and benefit of drug therapy in the context of public and political concern when taking decisions that effect economically important marketed drugs. This is illustrated by the recent public concern regarding the withdrawal of cerivastatin from the market [302]. An understanding of pharmacoepidemiology will enhance judgement in decision-making and reduces the chances of retaining unsafe medicines and of banning effective, safe and necessary drugs.

The future of drug safety practised in a scietific manner and the future of new drug development strategies that incorporate epidemiologic evidence of safety in the real world depend on adequate numbers of rigorously trained

pharmacoepidemiologists and expert drug regulators who are fully-fledged public health professionals.

The majority of the general practitioners who were surveyed in the GMS felt that the proposed indicators of prescribing quality could be used to assess prescribing quality and welcomed the idea of a feedback mechanism to individual prescribers. Quality improvement programmes still rely heavily on clinical audit of paper health records, which will be difficult to sustain. The process of data collection, analysis and feedback is often too slow to have a direct impact on patient care. With the increasing computerisation of general practices, it will be possible to speed up this process in the future which may be applied to Irish general practice in a similar manner to COMPASS [303]. Furthermore the GMS prescription database was able to provide a unique insight into the patterns of adherence among general practitioners to prescribing guidelines, illustrating the possible future use of the database in auditing prescribing practice.

As health service research and audit develops, pharmacoepidemiology is well placed to receive external funding. In Ireland we do not have universal cover and information regarding inexpensive and acute prescribing is not readily accessible for the 'private' sector. However, studies routinely based on European health computerised databases have become available only in the last decade with resources in the UK, Netherlands, Italy and the Scandinavian countries. Although useful, most of these databases are far from ideal as they have been set up mainly for administrative purposes, such as reimbursement with drug utilisation data being obtained as 'spin-off ' information. A key aim of Health Services Research is to provide clinically effective care to the

whole population by implementation of best practice. Record linkage is essential to the identification of inappropriate variation in clinical practice and research on behaviour to change strategies to improve the implementation of effective care. Clinical information systems will need to become active rather than passive aids to the efficient delivery of appropriate care and can be used to investigate how organisational or management systems act as either facilitators or barriers to change. The evolving science of health informatics uses record linkage to investigate how best to bring together information about individual patients with evidence about best practice in order to improve shared decision making. With the introduction of record linkage, the GMS prescription database will be in a position to implement and develop health services research. The pivotal datasets of an 'exposure' database of dispensed prescriptions, and an 'outcome' database of hospital admissions will then be available to conduct appropriate pharmacovigilance studies. The significant number of patients within this dataset would allow it to make a significant contribution to the evaluation of drug safety, allowing accurate quantification of the risks of adverse drug reactions which occur at low frequency in the population. Record-linkage can also facilitate outcomes research, general epidemiological studies and even economic evaluation.

Dunn coined the term Record Linkage in 1946 to describe the linking of all of the records in a person's life[25]. With the introduction of a national individual identity number in Ireland, there is the potential to link a patient's medical records with their prescription data in the GMS prescription database. We may then be in a position to assemble the pages of a person's 'book of life' into a volume whereby diagnosis will be linked to a particular prescription. It

will then be possible to examine prescriber behaviour in even greater detail. Record linkage will make it possible to identify people with apparently similar conditions who may be receiving different treatments and then to explore the possible reasons for these different treatments in terms of the knowledge and attitudes of prescribers.

Confidentiality of patient records can be handled successfully at a technical level such as the encoding of data by third parties, and making the anonomysed data available only to researchers[304]. However, in many countries political acceptance may be more difficult to achieve. For example, although patient specific information is captured in some of the current databases in Sweden, due to legal restrictions this valuable information is not saved or stored and, thus, not available for health services research. EURO DURG researchers have reported difficulties arising from confidentiality laws in five of 10 European countries[305]. It is also feared that implementation of Directive 95/46/EC of 24th October 1995, on the protection of individuals with regard to the processing of personal data and on the free movement of such data in the European Union, may adversely affect researcher access to patient health data.

The GMS prescription database provides an important source of prescription data for epidemiologic studies. It provides reliable data to expand the knowledge about the use and effects of drugs in the general population and could with the appropriate safeguards and consent be used to examine individual doctor or individual patient prescribing in Ireland and thus will have an important role to play in the continued development of pharmacoepidemiology in Ireland.

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APPENDIX A

Questionnaire posted to Doctors regarding their attitudes to the reporting of adverse drug reactions

1. Have you ever diagnosed an adverse drug reaction in a patient under your care?

   YES ☐**NO**☐

2. Have you sent a report of a suspected adverse drug reaction to :

The Irish Medicines Board? **YES** (in the last 5 yrs) ☐ **YES**(more than 5 years ago) ☐ **NO**(Never) ☐

A pharmaceutical manufacturer? **YES** (in the last 5 yrs) ☐**YES**(more than 5 years ago) ☐ **NO**(Never) ☐

3. Have you ever suspected an adverse drug reaction but not reported it?

YES ☐**NO** ☐

(if 'yes' go to question 4, if 'No' go to question 5)

4. If you have suspected, but not reported, an adverse drug reaction was it because:

(tick as many as applicable)

You were uncertain that the reaction had been definitely caused by the drug?

YES☐**NO**☐

You considered the adverse drug reaction to be too trivial to report?

YES☐**NO**☐

You considered the adverse drug reaction to be too well known to report?

YES☐**NO**☐

You were unaware of the existence of a national adverse drug

reaction reporting scheme?

YES ☐**NO**☐

You were unaware of the need to report adverse drug reactions?

YES☐**NO**☐

You did not know how to report adverse drug reactions?

YES□NO□

Reporting adverse drug reactions is too bureaucratic a process?

YES□NO□

You do not have enough time to report adverse drug reactions?

YES □NO□

You were concerned that your report could be used in a

legal case for damages by the patient?

YES□NO□

5. Which of the following hypothetical situations would prompt you to report an adverse drug reaction? (Assume, in each case, that the patient has no other medical problems and is taking no other medicines).

Deep vein thrombosis in a 22 year old patient three months

after taking a combined oral contraceptive.

YES□NO□NOT SURE□

Hypoglycaemic coma, requiring hospitalisation, in a

previously well controlled insulin dependent diabetic.

YES□NO□NOT SURE□

Acute pancreatitis in a 55 yr old male 6 weeks after

starting treatment with a tricyclic antidepressant.

YES□NO□NOT SURE

Agranulocytosis in a 65 yr old patient who has been taking

spironolactone for three months.

YES□NO□NOT SURE□

Myalgia in a 40-yr old patient who has been taking a new

statin (HMG CoA reductase inhibitor) for 6 months.

YES□NO□NOT SURE□

Weight loss in a 44-yr old patient 8 weeks after starting treatment with a new selective serotonin reuptake inhibitor.

YES□NO□NOT SURE□

A morbilliform rash in a patient 6 days after starting a course of amoxycillin for a urinary tract infection.

YES□NO□NOT SURE□

Swollen ankles in a hypertensive patient who has been taking a calcium channel blocker for 4 months.

YES□NO□NOT SURE□

A sore tongue in a patient 2 weeks after starting treatment with a new antiepileptic agent.

YES□NO□NOT SURE□

Local hypertrichosis in a patient who has been using a new topical antifungal for 3 months.

YES□NO□NOT SURE□

Angiodema in a patient one day after starting treatment with a new angiotensin-converting enzyme inhibitor

YES□NO□NOT SURE□

Bronchospasm in an asthmatic patient after taking one dose of a new

selective beta-blocker.

YES□NO□NOT SURE□

Temporary taste disturbance in a patient while taking

regular doses of paracetamol.

YES□NO□NOT SURE□

Dyspepsia in a patient taking loperamide.

YES□NO□NOT SURE□

Sudden unexpected death in a patient 10 days after starting

treatment with a new antipsychotic drug.

YES□NO□NOT SURE□

Pseudomembranous colitis in a patient 3 weeks after starting

treatment with a new proton pump inhibitor.

YES□NO□NOT SURE□

6 Are you aware of any criteria from the Irish Medicines Board specifying which adverse reaction you should report.

YES□NO□

7. Would you report an adverse drug reaction if:

The medicine has been prescribed for your patient by another physician?

YES□NO□

The patient had purchased the medicine

(without prescription) themselves.

YES□NO□

8. What would you understand by the following expressions of risk that are used to describe the frequency of adverse drug reactions in text books and prescribing literature?

Expression	Incidence 1 in 10 patients	Incidence 1 in 100 patients	Incidence 1 in 1,000 patients	Incidence 1 in 10,000 patients	Incidence 1 in 100,000 patients
'Occasional'	□	□	□	□	□
'Rare'	□	□	□	□	□
'Common'	□	□	□	□	□
'Very Rare'	□	□	□	□	□

9. What is your age?
10. Are you principally based in:

General Practice(primary health care) □

Specialist or hospital practice □

Other (please specify) □

11. Are you currently engaged in medical practice involving the prescribing of medicines?

YES□NO □

12. If you are a GP, do you have a GMS list?

YES□NO□

Many Thanks for your help and Co-operation

Appendix B

Survey of General Practitioners regarding the appropriateness of a number of prescribing indicators

Cover Letter sent with Questionnaire

Department of Pharmacology and Therapeutics

Trinity College Dublin

Dear Doctor,

Drug prescribing is an integral part of the provision of health care and represents a relatively safe, effective and inexpensive mode of treatment. Some measure of prescribing quality is needed. The majority of indicators assume that a concensus among doctors has been reached about evidence-based prescribing. Prescribing indicators may be used to improve the quality and effectiveness of prescribing and also to reduce prescribing costs.

I have been investigating the value of such indicators of prescribing quality which can be applied to prescription data. AS part of my research thesis I am surveying general practitioners on their opinions regarding the usefulness of such indicators to measure prescribing quality. Some of these may be sensible in theory but may not make much practical sense. I would be grateful if you could take a few minutes of your time to complete the enclosed questionnaire and return it in the stamped addressed envelope provided at your earliest convenience. If you have any comments regarding any further indicators of prescribing quality/ the usefulness of such indicators, they will be gratefully received.

Thank you for taking the time to complete the questionnaire.

Yours Sincerely

Dr David Williams

Lecturer in Clinical Pharmacology and Therapeutics

Proposed Indicators of prescribing quality

The following have been proposed as objective indicators of good prescribing practice. For each of the following, please indicate your preference on a scale of 1 to 5 on the usefulness of such indicators as measures of good prescribing (please circle your preference).

1. Low rate of prescribing of cerebral and peripheral vasodilators e.g. Inositol Nicotinate (*Hexopal, Hexogen*), Cinnarizine (*Stugeron*), Naftidofuryl (*Praxilene*).

Poor Indicator **Good Indicator**

1 2 3 4 5

2. Low rate of prescribing of appetite suppressants e.g. Phentermine *(Ionamin)*

Poor Indicator **Good Indicator**

1 2 3 4 5

3. Low rate of prescribing of topical nonsteroidal anti-inflammatory drugs e.g Diclofenac (*Voltarol emugel)*, Piroxicam *(Feldene gel)*

Poor Indicator **Good Indicator**

1 2 3 4 5

4. Low rate of prescribing of long-acting sulphonylureas e.g Chlorpropramide, Glibenclamide *(Daonil)* compared to short-acting sulphonylureas e.g. Gliclazide *(Diamicron)*, Glipazide *(Glibenese)*, Tolbutamide *(Rastinon).*

Poor Indicator **Good Indicator**

1 2 3 4 5

5. Low rate of prescribing of amoxycillin+clavulanic acid *(Augmentin)* compared to oral amoxycillin.

Poor Indicator **Good Indicator**

1 2 3 4 5

6. High rate of prescribing of trimethoprim *(Ipral, Monotrim)* compared to oral cotrimoxazole*(Septrin)*.

Poor Indicator **Good Indicator**

1 2 3 4 5

7. High rate of prescribing of atenolol (Tenormin, Amolin) as a % of all β-blockers.

Poor Indicator **Good Indicator**

1 2 3 4 5

8. High rate of prescribing of diclofenac *(Voltarol)*, ibuprofen *(Brufen)*, indomethacin *(Indocid)* and naproxen *(Naprosyn)* as a % of all NSAIDs.

Poor Indicator **Good Indicator**

1 2 3 4 5

9. High rate of generic prescribing

Poor Indicator **Good Indicator**

1 2 3 4 5

10. High rate of prescribing of aspirin in patients who are receiving nitrate therapy.

Poor Indicator **Good Indicator**

1 2 3 4 5

11. Low rate of prescribing of Hypnosedatives e.g Nitrazepam *(Mogadon)*, Flurazepam *(Dalmane)*, Zopiclone *(Zimovane)*, and anxiolytics e.g. Diazepam (Valium), Bromazepam *(Lexotan)*, Alprazolam *(Xanax)*.

Poor Indicator **Good Indicator**

1 2 3 4 5

12. Low rate of prescribing hypnosedatives e.g Nitrazepam *(Mogadon),* Flurazepam *(Dalmane),* Zopiclone *(Zimovane)* for more than 4 weeks duration.

Poor Indicator **Good Indicator**

1 2 3 4 5

13. High ratio of prescribing of inhaled corticosteroids to inhaled bronchodilators in asthmatic patients.

Poor Indicator **Good Indicator**

1 2 3 4 5

14. High ratio of prescribing of Hormone Replacement Therapy (HRT) in post menopausal women.

Poor Indicator **Good Indicator**

1 2 3 4 5

15. Low rate of prescribing of quinolone antibiotics e.g Ciprofloxacin *(Ciproxin*), Ofloxacin *(Tarivid)* as a % of all antibiotics.

Poor Indicator **Good Indicator**

1 2 3 4 5

16. Low rate of prescribing of aspirin in children (<12 yrs)

Poor Indicator **Good Indicator**

1 2 3 4 5

Do you have any comments on the above indicators/any suggestions of other indicators which may be used to measure good quality prescribing?

Thank You