Pharmacoepidemiology of Autoimmune Diseases

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ABSTRACT

The current system in place to study safety of medicines after introduction on the market relies on spontaneous reporting. Adverse events occurring long after initiation or cessation of drug use are likely to be missed by this system. In this thesis we explore methods to identify signals of long-term, unexpected adverse events and methods to evaluate these signals.

We utilised data from the UK General Practice Research Database (GPRD), a large primary care database. A review of the literature investigating the validity of medical diagnoses recorded in this database illustrated that the GPRD is a powerful tool to study morbidity in primary care. However, intimate knowledge of the complexities of the database is needed to ensure the best use is made of the database.

Pre-existing hypotheses of drug-induced systemic lupus erythematosus (SLE) were evaluated using the GPRD. Associations between risk of SLE and exposure to hydralazine, minocycline, and carbamazepine were confirmed using both a matched case-control design and the self controlled case series method. Spontaneous reports of drug-induced SLE recorded in the UK Yellow Card database indicated that symptoms of SLE often resolve after withdrawal of the suspected drug.

Using the Smile Plot method to generate signals of drug-induced SLE, we were not able to identify known signals of drug-induced lupus. However, we did identify factors strongly associated with treatment of early symptoms of disease. These findings indicated a high specificity of the Smile Plot method. To improve sensitivity, better hierarchical coding systems for drugs are needed to ensure appropriate grouping.

Lastly, we utilised the GPRD to provide an example of a systematically performed drug safety study. In a small subset of data, we generated hypotheses of drug-induced drug related hypothyroidism. Associations were subsequently evaluated in a larger subset of data. No drugs were clearly associated with risk of drug related hypothyroidism.

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DECLARATION BY CANDIDATE

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I hereby declare that the work presented in this thesis is my own work. With the available GPRD data set in mind, which had been obtained by my colleagues at the London School of Hygiene and Tropical Medicine before I joined the School, I developed the original idea for this PhD project. I performed all the work for this project myself, under the guidance of a number of individuals. These individuals have been acknowledged, as well as all results and quotations from the published or unpublished work of other people. I alone am responsible for the integrity of this work.

Marieke Schoonen

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CHM	Commission on Human Medicines
CI	Confidence interval
CLR	Conditional logistic regression
FDR	False discovery rate
FWER	Family-wise error rate
GPRD	General Practice Research Database
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
OXMIS	Oxford Medical Information Systems
OR	Odds Ratio
SCCS	Self-controlled case series
sd	Standard deviation
SLE	Systemic lupus erythematosus

CHAPTER 1. INTRODUCTION

1.1. DRUG SAFETY

Prescription medicines undergo a thorough process of preclinical and clinical testing before approval for use in patients. The clinical phases of drug development are subdivided in Phases I through III. A small number of (usually) healthy individuals is for the first time exposed to the drug in Phase I. Phase II trials involve testing the drug on a small population of patients of the target disease. The main aims during Phase I and II testing are to obtain information on tolerability, pharmacokinetic characteristics of a drug and required dosage and treatment regimen. During Phase III, randomised clinical trials are carried out. Due to the relatively small number of patients included in these trials, statistical power to detect unexpected and uncommon side effects is low. In addition, side effects occurring after a long time of use or long after cessation of use are unlikely to be identified due to the relatively short duration of these clinical trials. It is not until a drug is introduced on the market when the chance of detecting rare adverse drug reactions increases as the number of exposed patients and length of therapy increases[1].

1.1.1. Adverse Drug Reactions

Adverse drug reactions (ADR) can be divided into two types. Type A reactions are undesirable drug effects that can be explained and predicted based on the pharmacologic action of a drug. Type A reactions are relatively common, dependent on dose and of mild severity. These reactions are likely to be identified during the pre-marketing phases of drug-development. Type B reactions on the other hand are unexpected adverse reactions that are usually not dose-related, of rare occurrence and more serious in terms of morbidity and mortality. An example of a Type B reaction is drug-induced lupus associated with use of procainamide. Because of their nature, Type B reactions are unlikely to be identified during Phases I to III of the drug development process.

1.1.2. Post-Marketing Surveillance

Because the full safety profile of a drug is not known at the time of its approval, safety has to be monitored once the drug is on the market. The importance of post-marketing surveillance is illustrated by public health tragedies such as in the 1960s, when an estimated 10,000 babies were born with congenital malformations due to exposure to thalidomide *in utero*[2]. A more recent example is that of cardiovascular events associated with selective cyclooxygenase inhibitors[3].

Post-marketing surveillance can roughly be divided into two steps[2]. Previously unknown adverse drug reactions are identified using signal detection methods. New signals are then investigated in further detail in analytical studies, for instance to confirm or refute causality, quantify risk, or to identify specific sub-groups of patients that are likely to present with the hypothesized adverse event.

1.1.2.1. Signal Detection

The current system in place to study safety of medicines after their introduction on the market relies predominantly on spontaneous reports. In addition to case reports that are published in the medical literature there are several national and international systems in which health care professionals (and sometimes consumers) have the opportunity to report suspected adverse events. For example, the US Food and Drug Administration (FDA) developed a reporting system called MedWatch in which standard forms are used by health care professionals to voluntarily report adverse events[4]. The largest international database of adverse event reports is held by the World Health Organisation (WHO) at the Uppsala Monitoring Centre in Sweden[5]. This database, containing case reports from over 60 countries, is screened on a regular basis in order to identify new adverse events[6]. As a result of these spontaneous reporting systems several (sometimes serious) adverse events have been newly identified, such as sudden cardiac death associated with sertindole exposure in 1998[7].

Although spontaneous reports databases have proven to be useful tools to identify new adverse drug reactions, the data have a number of limitations. Most importantly, there is substantial under-reporting and reporting rates are subject to bias[5]. Secondly, the data only provide "numerator" data as the total number of adverse events is unknown. The number of available statistical methods to analyse spontaneous reports databases is therefore limited. Thirdly, individual case reports only contain a limited amount of information. For instance, detailed information on pre-existing medical conditions and past drug therapies is often lacking. Assessment of causality is therefore almost impossible.

1.1.2.2. Multiple Comparisons

In signal generation studies of drug safety, one studies large numbers of drugs which are potentially associated with the adverse drug reaction of interest (or alternatively, a large number of adverse events that are potentially associated with the drug of interest). For each individual drug - adverse event association, the significance level equals $100(1-\alpha)\%$ with α usually being 0.05 (i.e. a 95% significance level). However, when the number of potential associations being tested increases, the overall significance level decreases (e.g. when the number of associations tested is 20, the significance level will be $100(1-\alpha)^{20}\% = 36\%$ instead of 95%), and the chance to reject at least one null hypothesis increases (in the example stated above this chance would increase from 5% to 64%). A method commonly used to correct for this problem is called the Bonferroni correction. This method is extremely conservative and when the number of comparisons being made is large, α approaches zero. This may result in over-correction and a loss of statistical power whereby only those associations that are extremely strong are detected[8]. Less conservative methods than the Bonferroni correction have been developed for studies with multiple comparisons. Examples are family wise error rate (FWER) methods and false discovery rate (FDR) methods. In general, FWER methods are utilised when a 'medium' number of comparisons are made. FWER methods are less conservative than the Bonferroni correction, but still result in α approaching zero when a very

large number of comparisons are made. In large scale studies such as signal generation exercises, FDR methods are more useful to correct for multiple comparisons.

1.1.2.3. The UK Yellow Card System

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) and its Commission on Human Medicines (CHM) are in charge of the "Yellow Card" scheme. It is a system of spontaneous reporting whereby health care professionals report suspected adverse events on a "Yellow Card". Health care professionals contributing to this scheme are GPs, dentists, hospital pharmacists (since 1997), community pharmacists (since 1999)[7] and, since late 2005, patients themselves can report suspected adverse drug reactions on a separate yellow card form. Drugs of interest are not only prescription drugs, but also vaccines, over the counter medicines, and herbal preparations. The "Yellow Card" is a standardised form containing patient descriptive information (sex and age), the suspected drug (which drug, dosage, route of administration, indication of therapy, start and stop dates of therapy), and details on the suspected drug reaction including severity, outcome (recovered or not) and dates of start and end of reaction. If known, other drugs taken in the 3 months prior to the reaction are also listed. The reports are anonymised and collected into a central database (formerly ADROIT, Adverse Drug Reactions Online Information and Tracking, currently this database is called "Sentinel").

Although yearly reporting rates (per million residents) for the Yellow Card scheme are known to be high compared to other countries[7], the database is still subject to under-reporting. Only a limited percentage of health care professionals eligible to submit reports will actively do so[7]. For instance, an estimated 33% of practicing GPs submitted reports in the period from 1992 to 1995[7].

1.1.2.4. Signal Evaluation

Once adverse drug reactions have been identified, careful evaluation of signals is needed. A number of epidemiologic study designs are available to evaluate signals (i.e. test hypotheses).

A commonly used study design is the case-control study, in which study subjects are selected based on their disease status. The odds of exposure to the suspected drug is compared between individuals with and without the outcome of interest (i.e. the adverse event). An alternative commonly used observational study design is the cohort study, in which study subjects are selected based on their exposure status. Subjects are then followed over time and the incidence of the outcome (adverse event) in the exposed group is compared to the incidence in the group not exposed to the suspected drug.

An important problem with observational study designs is the potential influence of bias and confounding. When information on these factors has been measured, their effects can be investigated through statistical analyses. However, some factors (e.g. health-seeking behaviour) are difficult to quantify. For studies where unmeasured confounding is likely to play an important role, alternative statistical analysis approaches have been developed. Two important methods are the case-crossover design and the self-controlled case series. Both methods make within-person comparisons, thereby cancelling out the effect of hard to measure factors that are likely to vary between the study group and reference group. The case-crossover design is derived from the case-control method, and compares prevalence of exposure in a predefined time period preceding the event versus prevalence during control periods[9]. The self-controlled case series method on the other hand is derived from the cohort method. The incidence of an outcome during predefined risk periods after exposure is compared to the incidence of disease during baseline periods[10]. A detailed explanation of the self-controlled case series method can be found in Chapter 3.

Intervention (experimental) study designs such as randomised clinical trials can also be used to study drug safety. Although well-designed interventional studies are less sensitive to bias and confounding than observational studies, the main drawback of interventional studies is that they are demanding in terms of time and resources. In case of a pressing drug safety issue when a timely answer is needed, interventional study designs will generally not be utilised.

An important advantage of the case-control, cohort study and case-only study designs is that existing data sources can be utilised to answer newly arisen questions. A number of large health care databases are available to this end. Examples are Medicaid and health maintenance organisation (HMO) databases in the US. In addition, Pharmaceutical companies often hold their own databases of detailed patient information. The intricacies in terms of collection, completeness and quality of data are different for the different databases. However, these databases all contain computerised patient-level data for large numbers of individuals who are followed up for extended periods of time. These databases are therefore excellent data sources for drug safety studies, which often investigate uncommon drug exposures and/or rare adverse events.

1.1.2.5. The General Practice Research Database (GPRD)

The UK-based GPRD is a large primary care database containing anonymised patient level data. Over 98% of patients are registered with the UK National Health Service (NHS). NHS practices contributing to the GPRD are broadly representative of all UK practices in terms of age and sex distribution of patients, and geographical distribution and size of practices[11]. Patient-level data is collected prospectively by each contributing general practice. The quality of data, entered by practice staff and anonymised prior to central collection, is checked before and during contribution of data to the GPRD. If a number of quality criteria are met a practice is said to be "up-to-standard"[12].

A typical data set from the GPRD contains several components. Patient level data are provided in text format, in four separate files; a patient file containing general information including a patient's sex, age, date of birth and registration details. In the patient file, one row of data represents one unique patient. Medical information is recorded in a separate file, which includes dates of consultation and the corresponding OXMIS and Read codes for diagnoses and symptoms. In this medical file one patient may have several rows of data, depending on the number of consults with their GP. Therapy information includes prescriptions using codes from the prescription pricing authority (PPA) with corresponding dates, dosages and method of administration. Each patient may have several rows of therapy data depending on number of prescriptions received. For some patients additional information is available regarding vaccinations, weight, height and blood pressure measurements and laboratory test results. This information is recorded in a separate file which is called the prevention file. All information is entered by practice staff and is anonymised prior to central collection.

Text descriptions of the OXMIS and Read codes for medical diagnoses and symptoms are listed in a medical dictionary. For each drug code, information on drug name, formulation, strength and a list of up to three British National Formulary (BNF) codes are listed in a therapy dictionary.

1.2. EXAMPLES OF POTENTIALLY DRUG-INDUCED DISEASE

1.2.1. Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease of the connective tissue. It is a lifelong disease which can affect multiple organ systems[13]. Around a third of patients initially present with a typical butterfly shaped rash in the face. Other commonly seen early symptoms of the disease include photosensitivity and arthritis [14]. Later in the course of the disease, major organs such as the lungs, heart and kidney may be affected, resulting in potentially life-threatening disease [13]. The majority of SLE patients have chronically active disease, or a relapsing-

remitting course of disease. Several indices have been developed to monitor SLE disease activity and severity of organ damage [15]. SLE can have a major impact on quality of life of patients suffering from active disease [14], with fatigue being an important characteristic of the disease [16].

An important feature of the epidemiology of SLE is the female predominance [14]. Onset of disease often takes place in the decade after puberty, i.e. ages 20 to 30 [14]. However, a study of SLE cases in the GPRD found a peak incidence in women aged 50 to 54 years [17]. Certain ethnic groups are of higher risk to develop SLE, including African-Americans and African Caribbeans, and Asians [13]. The incidence of SLE is generally low, although there are some marked differences in incidence and prevalence between different countries across the world [18]. In the UK, the age-standardised incidence of SLE is estimated to be 7.9 per 100,000 person-years for women, and much lower for men, namely 1.5 per 100,000 [17].

Making a diagnosis of SLE is a complex process and is based on both clinical observation as well as laboratory tests [16]. The American College of Rheumatology has developed a list of eleven disease diagnostic criteria that are specific for SLE [19]. When at least four criteria are met, a patient is considered to have SLE. A number of these criteria are based on laboratory findings such as detection of specific autoantibodies, evidence of proteinuria, or hematologic abnormalities (e.g. leukopenia, thrombocytopenia, haemolytic anaemia). Other criteria include a typical rash, arthritis, photosensitivity, oral ulcers and arthritis.

Due to the wide variety of clinical manifestations of SLE, there is no "one size fits all" treatment regimen [20]. Because there is no curative therapy available for SLE, currently available treatments are targeted at control of disease activity and ideally achieving disease remission [21]. Traditionally, SLE is treated with antimalarials (e.g. hydroxychloroquine) which are especially useful in the treatment of articular and mucocutaneous manifestations of the disease. In addition, azathioprine is used for the treatment of a wide range of manifestations. Other traditional treatments include treatment with cytotoxic drugs such as cyclophosphamide, corticosteroids, and non-

steroidal anti-inflammatory drugs (NSAIDs) to suppress inflammatory and immune mechanisms. Alternative, newer treatments such as biologicals are becoming more important in the treatment of SLE [20]. A number of these traditional and newer treatments are associated with serious side effects which can also greatly affect a patient's quality of life [14].

The pathogenesis of SLE is not fully understood. However, it is clear that genetic as well as environmental factors are important factors in disease susceptibility [13]. Environmental factors important in inducing disease as well as disease flares are exposure to ultraviolet light, exogenous and endogenous estrogen, and possibly infections (including Hepatitis C, Epstein-Barr Virus), and exposure to silica dust [14]. In addition, several prescription medicines have been implicated in the risk of SLE. Patients with the drug-induced form of the disease have widely overlapping symptoms compared to idiopathic SLE.

1.2.1.1. Drug-Induced Lupus

A wide range of prescription drugs has been reported to induce autoimmune disease. A search of the medical literature published in 2005 reveals a total of 52 publications reporting a drug suspected of inducing an autoimmune condition. The majority of these reports (47 out of 52) describe a single case of drug-induced autoimmunity. Eight reports (15%) appeared in non-English journals and are therefore less likely to reach large numbers of health care professionals world wide.

The most extensively documented drug-induced autoimmune disease is systemic lupus erythematosus (SLE). Since the first reports of procainamide and hydralazine-induced lupus in the early 1950s, the list of drugs reported to lead to lupus has been growing[22]. Table 1-1 is reproduced from Rubin (2005)[23] and is the most recent overview of drugs implicated in risk of lupus. Therapeutic class and duration of treatment varies widely among the different drugs on this list. It is thought that drug-induced lupus develops within one month up to several years after start of exposure to the causative drug[24]. In some cases treatment continued for over 10

years before the occurrence of clinically apparent disease[25].

Table 1-1: Drugs implicated in risk of SLE

Agent	Risk
Anti-arrhytmics	
Procainamide	High
Quinidine	Moderate
Disopyramide	Very low
Propafenone	Very low
Anti-hypertensives	
Hydralazine	High
Methyldopa	Low
Captopril	Low
Acebutolol	Low
Enalapril	Very low
Clonidine	Very low
Atenolol	Very low
Labetalol	Very low
Pindolol	Very low
Minoxidil	Very low
Prazosin	Very low
Anti-psychotics	
Chlorpromazine	Low
Phenelzine	Very low
Chlorprothixene	Very low
Lithium carbonate	Very low
Antibiotics	
Isoniazid	Low
Minocycline	Low
Nitrofurantoin	Very low
Anti-convulsants	
Carbamazepine	Low
Phenytoin	Very low
Trimethadione	Very low
Primidone	Very low
Ethosuximide	Very low
Anti-thyroidals	
Propylthiouracil	Low
Anti-inflammatories	
D-Penicillamine	Low
Sulfasalazine	Low
Phenylbutazone	Very low
Diuretics	
Chlorthalidone	Very low
Hydrochlorothiazide	Very low
Miscellaneous	
Anti-tumor necrosis- α	Very low
Lovastatin	Very low
Levodopa	Very low
Aminoglutetheimide	Very low
Interferon- α	Very low
Timolol eye-drops	Very low

After one year of treatment at currently used doses, approximately 20% of procainamide users and 5 to 8% of hydralazine users develop SLE. For the other drugs included in table 1-1, a much smaller percentage of users develops the disease (less than 1%). Risk levels for these drugs are assessed based on number of reports in the literature. Limited evidence is available for quinidine, sulfasalazine, chlorpromazine, penicillamine, methyldopa, carbamazepine, acebutolol, isoniazid, captopril, propylthiouracil and minocycline. Evidence for other drugs is based on a very small amount of case reports and is these drugs are therefore considered to be of "very low" risk. To our knowledge, no large analytical studies have been conducted to confirm suspected associations and to quantify risks associated with exposure to these drugs.

The underlying mechanisms of drug-induced autoimmunity are not clear although it is thought that oxidative metabolites of the suspected drugs play a role in the development of autoimmunity[23]. Many reports of drug-induced lupus describe disappearance of symptoms upon withdrawal of the suspected drug and in some instances, re-challenge resulted in re-appearance of symptoms[22]. Such reports are in support of a causal association between the suspected drugs and risk of lupus.

1.2.2. Hypothyroidism

Hypothyroidism occurs when the thyroid gland is not producing sufficient thyroid hormone to maintain normal body functions [26]. This can be due to primary hypothyroidism (i.e. when the thyroid gland itself fails to work), or secondary hypothyroidism (i.e. when hormones dictating functionality of the thyroid gland are deregulated) [27]. The vast majority (up to 95%) of hypothyroidism cases have the primary form of the disease [27]. Hypothyroidism can also be classified according to the time of disease onset, namely congenital or acquired hypothyroidism. Congenital hypothyroidism occurs when the thyroid gland is not or not properly developed (agenesis or dysgenesis), or when the synthesis of thyroid hormone is impaired due to a genetic defect [28]. Acquired hypothyroidism occurs at a later stage in life and can be due to iodine insufficiency, surgical procedures or other medical treatment which affect functionality and mass of thyroid gland tissue, destruction of the thyroid gland through autoimmune processes,

Worldwide, the major cause of primary hypothyroidism (including congenital hypothyroidism) is dietary iodine insufficiency [26]. However, in geographical areas where the diet provides sufficient iodine (such as the United Kingdom), hypothyroidism is most often caused by medical procedures affecting the thyroid gland (i.e. iatrogenic hypothyroidism), or by autoimmune mechanisms [26]. Although the pathogenesis of autoimmune thyroiditis is not fully understood, it is clear that genetic predisposition plays an important role. Individuals with a family history of autoimmune hypothyroidism have an increased risk of the disease [27].

Symptoms of primary acquired hypothyroidism may develop over the course of years. These symptoms are often widely variable and can be non-specific, including weight gain and constipation due to impaired metabolism, cold intolerance, dry skin and hair, fatigue and slowed mental processing or mental retardation, bradycardia, deafness, and a hoarse voice. Infertility and menorrhagia are also common manifestations [26, 28, 29]. In children with congenital hypothyroidism, skeletal growth and maturation is affected, unless the disease is adequately treated[26]. In

addition, sexual maturation can be delayed due to the lack of thyroid hormone [27]. Mild anaemia is seen in about a quarter of untreated hypothyroidism cases, and approximately ten percent of cases of autoimmune hypothyroidism are affected with pernicious anaemia[26]. Severe cases of hypothyroidism can present with an altered state of consciousness and severe hypothermia. This can ultimately lead to myxoedema coma which, when not promptly treated, may result in death[26].

Both congenital and acquired hypothyroidism are more often diagnosed in women than in men [28]. For congenital hypothyroidism, the female to male ratio is approximately 2:1, whereas for acquired hypothyroidism this ratio is approximately 7:1 [28]. For women, the risk of developing a transient form of hypothyroidism is increased during pregnancy and in the 6 month period directly after delivery [29]. This transient form of hypothyroidism is called postpartum hypothyroidism and is mediated by autoimmune mechanisms [28]. Approximately 7% of women are thought to develop postpartum hypothyroidism after delivery [30]. The incidence of hypothyroidism increases with age, with a marked increase in incidence after the third decade of life [31, 32]. Not many studies have described the distribution of the different subtypes of hypothyroidism in the general population. One recently published study by Carle et al[31] found that 84.4% of incident cases of hypothyroidism in two areas in Denmark were of spontaneous, primary nature with no apparent cause of disease. These cases are generally assumed to be of autoimmune origin [28]. The overall incidence of hypothyroidism (all causes) in this Danish study was 51.8 per 100,000 person-years among women, and 14.9 per 100,000 person-years among men. These estimates are markedly lower than previously reported incidence rates for the UK; 350 per 100,000 (for women) and 60 per 100,000 (for men) were observed in the Whickham study [33] and th Tayside study reported an incidence of 498 per 100,000 (for women) and 88 per 100,000 (for men)[34].

Serum TSH is high in all cases of primary hypothyroidism and measurement of serum TSH is therefore an excellent test to diagnose primary hypothyroidism[27]. It is also

used to distinguish between primary and secondary hypothyroidism, as TSH is not elevated in cases of secondary hypothyroidism [35]. Instead, serum TSH is low or normal with a reduced concentration of T_4. A diagnosis of autoimmune hypothyroidism is confirmed by a positive laboratory test for thyroid autoantibodies, as well as a family history of the disease and/or the presence of other autoimmune diseases [27]. Determining other causes of hypothyroidism can be difficult but may be facilitated by carefully investigating a patient's medical history [27].

Hypothyroidism is treated with thyroid hormone, which is an effective therapy in the majority of cases[36]. Patients with hypothyroidism are primarily treated in primary care, which makes the disease an excellent candidate to be studied in a primary care database such as the GPRD. However, one disadvantage of studying hypothyroidism in this database is that it is difficult to assess the cause of hypothyroidism. This is due to the fact the laboratory measurements such as presence of autoantibodies, or specific histologic characteristics of thyroid gland tissue are not consistently recorded in the database.

The aetiology of hypothyroidism in iodine replete areas is not fully understood, It has been hypothesized that an increase in iodine uptake is associated with an increased risk of the autoimmune form of hypothyroidism [31]. In addition genetic factors are thought to play a role [28]. Environmental factors may also play a role, including several commonly used pharmacologic agents which are known to have an effect on thyroid function. These include lithium, iodine containing drugs such as amiodarone, alpha interferon, propylthiouracil, thionamide, and drugs that interfere with thyroxine absorption in treated hypothyroidism[28, 37, 38].

1.3. RATIONALE FOR RESEARCH

Drug-induced autoimmunity is a good example of a type B adverse drug reaction as its occurrence cannot be predicted based on the pharmacological action of suspected drugs. Furthermore, drug-induced autoimmunity is a rare but serious adverse event. For instance, the estimated incidence rate of SLE is 7.8 cases per 100,000 person

years[39]. Only a fraction of newly diagnosed cases of SLE will be due to exposure to a lupus-inducing drug. In addition to being unexpected and rare, duration of drug treatment may be months to years before the adverse event occurs. As a result, it is questionable whether health care professionals attribute autoimmune disease to drug exposure when a new patient presents.

If long-term unexpected adverse drug reactions remain unrecognised by health care professionals, these will not appear in spontaneous reporting databases. However, the current system in place to study drug safety relies predominantly on spontaneous reports. As a result, long-term unexpected adverse drug reactions are likely to be missed by the current system.

This thesis investigates the use of a data source different from the currently used spontaneous reporting databases, namely the General Practice Research Database. The adverse event of interest in this thesis is drug-induced autoimmunity. The examples given in this introductory chapter, drug-induced lupus and drug-related hypothyroidism, may not be very common diseases but they can be potentially life threatening. In this thesis, we utilise these potential adverse drug reactions as a tool to investigate methods of signal detection and signal evaluation.

1.4. AIMS AND OBJECTIVES

1.4.1. Aims

- To determine whether the GPRD can be used to study drug-induced autoimmune disease
- To examine and compare statistical methods available for evaluating drug safety hypotheses
- To examine a systematic method of signal generation which utilises a large healthcare database instead of a spontaneous reporting database

- To perform a complete drug safety study including a signal generation and a signal evaluation phase

1.4.2. Objectives

- To test pre-existing hypotheses of risk of SLE associated with prescription drugs using a case-control method

- To test pre-existing hypotheses of risk of SLE associated with prescription drugs using a case-only method

- To compare results obtained by the case-control method with those from the self-controlled case series method

- To assess whether a novel signal generation method (the Smile Plot method) is capable of detecting known associations of prescription drugs and risk of SLE

- To investigate whether other drugs than those identified from the literature are associated with risk of SLE.

- To describe suspected adverse drug reactions of drug-induced lupus as reported in the UK Yellow Card database of spontaneous reports.

- To identify previously unknown associations of risk of drug related hypothyroidism and prescription drugs (grouped by BNF-subchapter) using the smile plot method in a subset of data

- To evaluate newly identified signals of drug-induced drug related hypothyroidism in a different subset of data

1.5. OUTLINE OF THESIS

The present chapter provides an overview of drug safety issues and available methods and data sources to study drug safety. Drug-induced autoimmunity is described as an example of an unexpected long-term adverse drug reaction.

For the purpose of this thesis the General Practice Research Database (GPRD) was utilised to study drug-induced autoimmune disease. A review of the literature to study the validity of medical diagnoses recorded in the database is presented in Chapter 2.

The association between prescription drugs and risk of autoimmunity was studied in different data sources and using different statistical analysis methods. Details of these data sources and the methods used are outlined in Chapter 3.

In Chapter 4, the association between selected prescription drugs and risk of systemic lupus erythematosus is investigated. Firstly, GPRD data are analysed in order to evaluate existing hypotheses and to determine whether drug-induced autoimmunity can be studied using this database. Data are analysed using a case-control design as well as the self-controlled case series method. Secondly, both Yellow Card and GPRD data are analysed to identify potential new signals of drugs inducing SLE.

Chapter 5 investigates risk of drug related hypothyroidism associated with exposure to prescription drugs. The total data set of cases with hypothyroid disease and controls is split up in two parts; a small subset that is utilised for signal generation and a larger subset which is used to validate newly identified signals.

Finally, Chapter 6 summarises and discusses the main findings of this thesis and implications for clinical practice and pharmacovigilance.

CHAPTER 2. A LITERATURE REVIEW OF THE VALIDITY AND VALIDATION OF THE GENERAL PRACTICE RESEARCH DATABASE (GPRD)

2.1. INTRODUCTION

Computerised databases of medical records are increasingly used in biomedical research. The General Practice Research Database (GPRD) is a primary care database containing anonymised patient records for about 5% of the UK population. The GPRD's strengths as a research tool include its size, representativeness of patient and practice characteristics[40], and a virtually complete medical history of patients due to the recording of referral to secondary care[41]. The GPRD has been widely used for observational studies, with over 500 studies published to date including a number of high impact papers[42-47].

A typical dataset from the GPRD contains general information on a patient's sex, age, date of birth and registration details. Medical information includes dates of consultation with the corresponding OXMIS and Read codes for diagnoses and symptoms. The therapy information includes prescriptions using codes from the prescription pricing authority (PPA) with corresponding dates, dosages and method of administration. For some patients there is additional information on vaccinations, weight and blood pressure measurements and laboratory test results. All information is entered by practice staff and is anonymised prior to central collection.

The validity of research based on GPRD data depends on the quality of data recorded. Methods available to check this quality can be divided into two groups, internal and external validation. Internal validation uses no information from outside the database. Examples include diagnostic algorithms combining medical codes, disease-appropriate drugs and/or disease-specific signs to establish likelihood of disease, or manual review of computerised records. External validation involves comparing information from outside the database, such as the original doctor's notes, to the computerised information. This anonymised information is obtained by

approaching each practice. Specific validation studies have suggested that diagnostic data in GPRD are of high validity[48, 49]. However, there has not been a review of the literature of all validation studies to assess the totality of evidence. In order to investigate the range of methods used to validate diagnoses in the GPRD, to summarise findings of these validation studies and to assess their quality, we conducted a review of the literature of studies that assessed quality of morbidity data available in the GPRD.

2.2. METHODS

2.2.1. Search Strategy

We searched the databases PubMed and Embase for articles using the GPRD as a data source, published between 1987 and February 2004. Publication listings on the websites of the GPRD (http://www.gprd.com/info/bibliography.asp) and the Boston Collaborative Drug Surveillance Program (http://www.bcdsp.org/publications.html) were scrutinised to identify additional articles. International Society of Pharmacoepidemiology (ISPE) conference procedures, issues of Health Statistics Quarterly, and back issues of Pharmacoepidemiology and Drug Safety that were not incorporated into PubMed were hand-searched. Reference lists of identified articles were examined. In the first search a comprehensive list of free text terms denoting VAMP, General Practice Research Database or UK primary care database was linked to a number of free text and exploded thesaurus terms for validation, accuracy and reproducibility, together with a number of free text and exploded thesaurus terms for patient records, medical records and primary care records. This preliminary search showed that in many published papers case validation was a minor component of the study and was not mentioned in the title, abstract or index terms. Therefore, we broadened our search strategy to identify all epidemiological studies using the GPRD as a primary data source. The complete search strategy can be found in Appendix I.

2.2.2. Study Selection

All publications identified via the search strategy that definitely, or possibly, used the GPRD as a data source were retrieved and the full text was examined. A study was eligible for the review of the literature when a disease diagnosis was verified. The verification process could utilise computerised information only (internal validation), and/or use additional information from outside the database (external validation).

2.2.3. Data Extraction and Quality Assessment

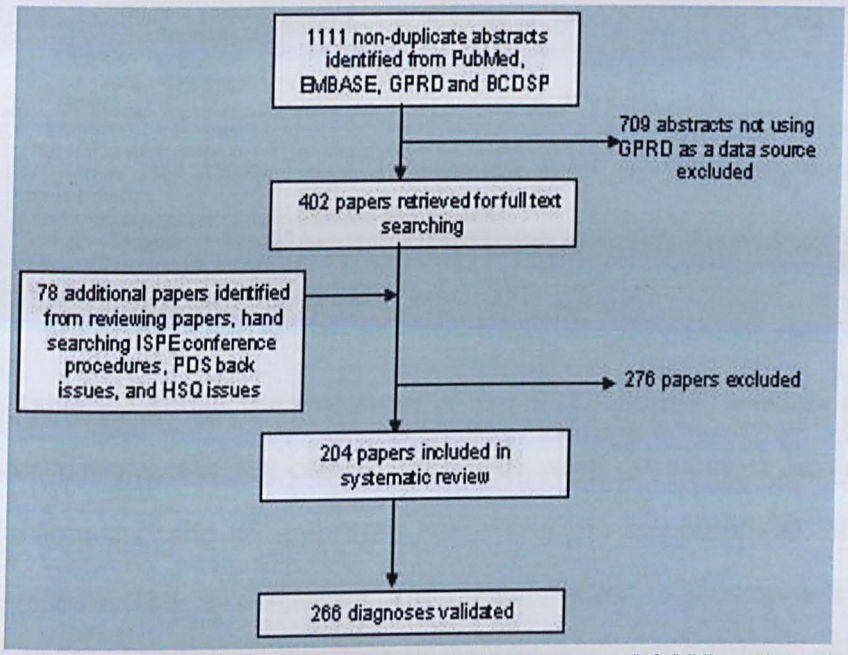
Data extraction was conducted by one reviewer (Marieke Schoonen) using a standardised data extraction sheet (which can be found in Appendix I), and a second reviewer (Andy Hall) assessed a random sample of 20% of the articles to verify the extraction process. All disagreements were resolved after discussion. Data extracted included the disease validated and the method used to identify cases. The specific OXMIS, Read or ICD codes used to identify each condition were not extracted, as describing the validity of a single disease or group of diseases was not the purpose of the review. We extracted information about the validation method used and the outcome of the validation exercise. Validation methods were classified into: 1) manual inspection of computerised records; 2) creation of an algorithm combining computerised information into a measure of likelihood of truly having the disease of interest; 3) retrieval of original medical records or death certificates; 4) sending a questionnaire to the GP; 5) comparison of disease pattern and/or rates to an external data source; 6) comparison of internal disease pattern to clinical knowledge of disease (e.g. seasonality). Wherever possible, quality of the validation exercise was additionally assessed in terms of number and status of independent reviewers, GP response rates to requests for information and whether the reviewers were blinded to exposure in analytical studies.

2.2.4. Data Analysis

Diseases were grouped by the organ system affected, with additional categories for allergy, birth outcome, cancer, death, demography, hospital procedures and

miscellaneous diagnoses. Studies were categorised by validation method used, in order to describe the usefulness of different validation methods.

Figure 2-a: Stream diagram of article search



GPRD, General Practice Research Database (http://www.gprd.com/info/bibliography.asp); BCDSP, Boston Collaborative Drug Surveillance Program, (http://www.bcdsp.org/publications.html); ISPE, International Society of Pharmacoepidemiology; PDS, Pharmacoepidemiology and Drug Safety; HSQ, Health Statistics Quarterly

2.3. RESULTS

We identified a total of 1111 non-duplicate abstracts from the PubMed, EMBASE and website searches, of which we excluded 709 after reviewing the title and abstract (Fig 2-a). We identified another 78 abstracts from reviewing papers and from hand-searching relevant journals and conference procedures. After reviewing the full text, we included 204 of these 480 studies. The main reasons for exclusion were: a publication did not validate the diagnosis under investigation, the GPRD was not used as a data source, the publication was not an original research article, the study reported a validation exercise that had already been published elsewhere, or no diagnosis was investigated (e.g. study of prescriptions). The 204 included papers validated 266 diagnoses (i.e. some papers reported more than one validated diagnosis).

Table 2-1: Characteristics of validation exercises

Validation method	Times used	% Diagnoses validated* (N=266)
Total	424	
Internal validation methods		
Manually review computerised records†	116	44
Algorithm‡	84	32
External validation methods		
Retrieve copy of records	117	44
Original medical records§	107	40
Death certificate	10	4
Questionnaire to GP	55	21
Compare disease pattern/rates to other data source	46	17
Other‖	6	2

*Validation of a diagnosis by use of different methods within one study causes total percentage to be >100
†Manual review: print out of full computer records per case to read
‡Algorithm: a list of medical codes, or a combination of signs, symptoms, and/or disease appropriate therapies used in the database
§Also includes copies of discharge and referral letters
‖Other validation methods included: a questionnaire to patients (external) and investigating whether expected seasonality could be confirmed (internal)

Table 2-1 shows the frequency of use of the different validation methods. For internal validations, the full computer records were manually reviewed for 44% of the 266 diagnoses, and an algorithm combining the computerised information was used to validate 32% of diagnoses. The GP was asked to provide extra information to verify their patients' diagnoses in 145 validation exercises (55%). This external information included a questionnaire, copies of original notes (including referral letters and discharge letters), or death certificates. In 27 exercises the GP was asked for a combination of this information. A total of 95 of these validation exercises (66%) reported GP response rates to requests for information – 40-100% of requests were met by GPs. A small number of studies that manually reviewed computer records, original records, or death certificates hired an expert to review these data. Blinding of reviewers to exposure in analytical studies was in general not reported. The number of cases validated using additional information varied from 10 to 2820.

A total of 135 diagnoses were validated by means of only one method. Of these, researchers relied most often on creating an algorithm combining the computerised information (42 out of 135 diagnoses, 31%). Comparing disease rates and patterns to another data source was the second most frequently used method (22%). Ninety-six of the total 266 diagnoses (36%) were validated using a combination of both internal and external validation methods.

Table 2-2: Number of validation studies per disease category

Disease category	Diagnoses validated	References*	Disease definition specified			Proportion considered valid (%)‡§		
			yes	ICD†	No / unclear	Range (%)	Based on N studies	No. / range of cases
Total	266		112	23	127			
Allergy	6	a1-a6	2	-	4	73	1	120
Birth outcome / Congenital	5	a3 a7-a10	1	-	4	85 - 100	2	123
Blood dyscrasia	8	a6 a11-a17	3	2	3	25 - 95	4	38 - 59
Cancer§	14	a18-a30	6	3	5	88 - 100	8	12 - 316
Cardiovascular disease	48	a31-a69	18	5	25			
Coronary	20	a31-a48	6	3	11	35 - 100	9	10 - 1606
Cerebrovascular	9	a35 a49-a53	5	-	4	48 - 77	5	25 - 101
Venous thromboembolism / hypertension	19	a38 a43 a54-a70	7	2	10	54 - 100	6	14 - 170
Death	13	a35 a56 a71-a81	7	-	6	47 - 94	4	20 - 72
Dermatology	6	a6 a82-a86	4	-	2	74 - 100	3	47 - 84
Endocrinology	11	a4 a43 a60 a87-a94	2	-	9	42 - 99	2	80 - 86
Eye disease	7	a95-a100	2	2	3	16 - 97	6	60 - 341
Gastrointestinal disease	26	a6 a25 a58 a101-a121	12	2	12	8 - 100	14	21 - 860
Gynaecology	4	a122-a125	3	-	1	87	1	366
Hepatic disease	15	a6 a91 a124 a126-a137	13	-	2	13 - 96	10	24 - 2820
Hospital procedures	4	a59 a116 a138	NA	NA	NA	82	1	167
Mental health	18	a60 a78 a102 a139-a150	8	2	8	52 - 92	8	25 - 318
Metabolic disease	5	a43 a70 a90 a138 a151	3	-	2	-	-	-
Musculoskeletal disease	15	a67 a152-a164	6	4	5	33 - 100	10	38 - 1428
Neurology	15	a72 a165-a177	8	2	5	9 - 100	6	11 - 100
Renal	6	a6 a171 a178-a181	2	-	4	8	1	59
Respiratory	22	a3 a4 a80 a81 a182-a190	7	-	15	26 - 95	2	20 - 89
Systemic	6	a4 a191-a195	2	1	3	66 - 76	2	44 - 151
Miscellaneous‖	12	a140 a196-a204	3	-	9	8 - 100	7	12-1191

*More than one diagnosis within the same disease category may be validated within one publication
†Disease criteria specified as ICD codes, although the GPRD uses OXMIS and Read codes for recording medical events
‡Numbers given are the range of values that were reported within the disease category. Not all papers reported these values
§Numbers given are based on validations where the GP was requested to confirm diagnosis or provide copies of records
‖Miscellaneous diagnoses studied were: benign prostatic hyperplasia (1), orchidopexy (1), potentially drug-inducible illnesses (4), indication for referral (2), serious adverse event (3), and NSAID-related adverse event (1)

Table 2-2 shows the number of validation studies per disease category. The definition used to select cases was clearly stated for 42% of the diagnoses. In 9% of the validated diagnoses only an International Classification of Diseases (ICD) code was given. Clarity of disease description was especially low in endocrine and respiratory diseases. Hepatic diseases were generally clearly described. The proportion of computer-identified cases of a disease confirmed by the GP was highly variable both between and within disease categories. Fifty-eight of the 111 studies (52%) that

reported a confirmation rate reached over 80% concordance; the 24 with less than 50% concordance used very strict case criteria.

2.4. DISCUSSION

This review identified a large number of studies in which diagnoses were validated. The search strategy used is likely to have captured all published studies of validations within the GPRD in the specified time period. We found that the most frequently used method was external comparison through requesting additional information from the GP. These external methods only assess positive diagnoses in computer records and therefore measure positive predictive value not specificity (which would require a comparison of computer records and GP records without the diagnoses). Many authors using this method did not seem to appreciate that that they were measuring only positive predictive value and that negative predictive value, sensitivity and specificity remained unknown. Positive predictive value varies with prevalence of the condition and so care is needed in interpretation when geographical variation or change in incidence over time is investigated.

Validation studies requesting copies of medical notes from the GP showed that the proportion of records actually retrieved was highly variable. Low retrieval rates raise the question of generalisability of the results of the validation to all cases, especially as not all GPs offer this service. Thus, even if compliance in providing records is high, this may arise only from a sub-group of practices and therefore of records. For instance, in a study by Van Staa et al[50], 719 practices contributed data during the study period. Only 295 practices (41%) were known to provide additional information, of which 269 (91%) provided the requested information. This may introduce selection bias if data from GPs offering the service are of a different quality to those not providing the service. Thus the predictive value found may only be applicable to the cases coming from these practices. An additional problem with record retrieval from GPs is that it is expensive (currently £70 per single set of notes). This frequently limits the number of records that can be retrieved, leading to

small sample sizes. Very few studies gave confidence intervals around their estimates of positive predictive value.

The second most frequent method used was a manual examination of the computerised record. Very few studies specified the criteria used in this examination to determine "true" cases. Judgements from individual physicians may vary over time and between physicians. Without case criteria specified, there is scope for bias arising from these individual judgements. In addition, manual inspection of computerised records is time consuming and takes away much of the advantage of having automated data.

The use of specified internal diagnostic algorithms overcomes this concern, particularly since these are clearly described in the studies. This allows the reader to decide whether or not they agree with the judgements made. However, GPs in the GPRD are asked to record a diagnostic code following consultations where a new diagnosis was made or a new treatment initiated[40]. For other consultations, a symptom or sign may be entered instead. For chronic diseases this means the absolute number of diagnostic codes will not necessarily be a proxy for disease severity or natural history. Inclusion of disease-specific therapy and/or symptoms in the algorithm may increase probability of the diagnosis. This could however result in omission of less severe cases who do not require treatment. Differential diagnoses may be recorded before the definite diagnosis[51], leading to misclassification. If an algorithm relies on codes for symptoms, people with overlapping symptoms from a different disease may be included.

Finally some validations compared the disease pattern (sex ratio, symptomatology) or incidence/prevalence rates with estimates from studies not using the GPRD. These are reassuring for descriptive purposes but of course do not exclude the possibility that a balanced misclassification between different diagnoses occurs, i.e. the situation sometimes seen in death certification where the loss of deaths from cause A because of misclassification is balanced by the inclusion of people truly dying of cause B but who are misclassified to cause A. Results of these types of validations

should therefore be treated with caution when used in analytical studies where the precise individual diagnosis is critical.

Information provided in the papers was often limited in terms of the methodology used for the validation. For example patient characteristics such as age may influence data quality but this was rarely explored. In particular manual inspection of the records was poorly described.

Validation of prescription data is of lesser importance than validation of morbidity data, as the GP uses the computer to generate prescriptions. This makes the therapy file virtually complete (except for prescriptions issued in secondary care). Hollowell et al[52] confirmed there is excellent agreement between prescribing data from the GPRD and national data from the UK Prescription Pricing Authority.

In defining diagnoses, research groups use their own sets of criteria and medical codes to select cases. Occasionally, medical codes from the GPRD coding system (OXMIS and Read codes) were mapped onto ICD codes. However, for many diseases it is not clear which codes from the GPRD correspond to specific ICD codes. It is desirable that a table of the medical OXMIS and Read codes used for diagnosis or the mapping of these codes to specific ICD codes be made available at the time of publication, so that others studying the disease can use the same method.

When conducting a case-control study using the GPRD, it is important to apply the same inclusion and exclusion criteria to cases and controls. However, because validation studies typically focus solely on cases, they may produce more detailed criteria for cases compared to controls. For example, a study of Garcia Rodriguez et al[53] established the relation between exposure to nonsteroidal anti-inflammatory drugs and acute liver injury. Cases with acute liver injury were validated by retrieving original medical records. Based on the validation study, 16 of 166 potential cases (10%) were excluded from further analyses due to alcoholism. No validation was carried out for controls, and so no further details on alcohol consumption were identified. This may have led to bias and potentially a false association.

In our review of GPRD validation studies used we made every effort to include all published studies that matched our inclusion criteria. Despite our extensive search strategy and additional hand searches, there is still a possibility we missed out on some publications that should have been included in this review. An additional limitation of our review is that we did not attempt to assess the quality of each the validation studies. Appraisal of quality of included studies is a characteristic of a systematic review, as described in further detail in the Handbook for systematic reviews by the Cochrane Collaboration[54].

The implications from this review for researchers are that although validation studies have shown good predictive value for the majority of diseases studied there needs to be a much clearer description of the methods and case criteria – with disease codes and mapping to ICD where appropriate – to allow the researcher to fully judge the appropriateness and generalisability of the method and to replicate it if desired. We suggest that the careful use of algorithms is likely to be the most cost-effective method of identifying valid cases. It is likely that results from clinical investigations and letters from specialists will be captured in future electronic records - this will greatly strengthen this method of validation and is likely to improve the quality of the data (with fewer data entry errors). It is also clear that most studies should carry out some form of validation, since the positive predictive value of a set of diagnostic codes may change over time and use of historical validations may therefore not be justified.

In conclusion, the GPRD is an enormously powerful tool for the study of morbidity in primary care. Its use is likely to increase, particularly with the recent agreement between GPRD and the Medical Research Council (MRC) that the data can be made available to academic researchers at no (or low) cost[55]. However, intimate knowledge of the use of coding in General Practice and of the complexities of the database is needed to ensure that the best use is made of it.

CHAPTER 3. METHODOLOGY

The association between prescription drugs and risk of autoimmunity was studied using a variety of statistical analysis methods. Details of these methods are outlined in the current chapter.

3.1. STUDY POPULATION

3.1.1. The Yellow Card Database

We received permission to analyse a subset of Yellow Card data for the purpose of this thesis. The subset comprised of reports submitted to the Commission on Human Medicines (CHM) between July 1963 and 10 January 2006 that mentioned SLE as an adverse drug reaction. Detailed reports were received of drugs for which a suspected association with lupus was reported at least 9 times. We did not receive detailed reports of drugs with less than 9 reports.

Detailed reports contained the following information: description of all adverse drug reaction(s) diagnosed in individual, drug suspected of causing the reaction, age range and sex of case, duration of treatment, outcome of reaction (recovered or recovering after treatment or after drug withdrawal, not recovered, fatal, not known), reaction onset time, and names of other drugs also taken by the patient in the past 3 months (if known). Although information on dosage and method of administration may be available for the suspected drug on the original Yellow Card report, this was not included in our data set. For drugs taken concurrently with the suspected drug there was no information on duration of treatment, dosage, and method of administration.

The Yellow Card data set was provided in a Microsoft Excel file format. After adding a unique patient identifier for each report, data were converted to a Stata data set (Stata software Version 9, Statacorp, Texas) to summarise data and perform descriptive analyses. All detailed descriptions of adverse drug reactions were assigned an SLE likelihood code. An SLE likelihood of 1 was assigned to reports with

a definite diagnosis of SLE. Possible SLE symptoms and signs were assigned a likelihood of 2. All other adverse drug reactions reported (e.g. pneumonia, depression, dry mouth) were not of interest to us and therefore excluded in further analyses. An overview of ADRs included in our study is given in Table 3-1.

Table 3-1: Adverse drug reactions listed on Yellow Card reports and their SLE likelihood

Adverse drug reaction listed on report	Likelihood of SLE*
Lupus-like syndrome	1
Systemic lupus erythematosus	1
Systemic lupus erythematosus rash	1
Glomerulonephritis proliferative	2
Antinuclear antibody positive	2
Histone antibody positive	2
Photosensitivity reaction	2
Rash erythematous	2
Cutaneous lupus erythematosus	2

*Likelihood=1 for definite and 2 for possible SLE

All cases with at least one adverse drug reaction with a likelihood of 1 were included in the study. Cases with only a likelihood of 2, such as those with cutaneous lupus erythematosus were excluded. Simple frequency tables were generated to explore and describe the Yellow Card data.

3.1.2. The General Practice Research Database

A detailed description of the General Practice Research Database (GPRD) can be found in Chapters 1 and 2. The base population included all patients registered with a general practice that was contributing data to the GPRD between 1987, the start date of the GRPD, and 2001. A comprehensive list of medical codes for autoimmune diseases was compiled by a team of clinicians and a rheumatology epidemiologist prior to the onset of this project. All subjects with a medical code for an autoimmune disease included in this list were selected from the base population as potential cases. Control subjects originated from the same base population but did not have a record of a medical code for an autoimmune disease at any point in time. Details of case definition, and inclusion and exclusion criteria are outlined under "outcome definition" (SLE, 3.3.1; drug related hypothyroidism, 3.3.2).

Further sections of this chapter describe methodology specific for analysis of the GPRD data.

3.2. DATA MANAGEMENT

Computerised patient-level data go through a number of quality checks before being added to the GPRD[12]. Despite these checks the data are not flawless. Prior to data analysis, our data were cleaned and the values of calendar dates were verified. Data cleaning steps are described in sections 3.2.1 and 3.2.2. Matching of control subjects to autoimmune cases involved additional steps after eligible controls were identified. These additional steps are outlined in sections 3.3.4, 3.3.5 and 3.3.6.

3.2.1. Missing and Incomplete Calendar Dates

Data entered by a GP or practice staff may be incomplete or missing. Missing calendar dates appear as 1 January 1900 in some but not all GPRD records. In order to ensure these missing dates were not used as non-missing values in data analyses, all instances of 1 January 1900 were reset to missing (.) in SAS and Stata. A list of outlying calendar date values for prescriptions as well as doctor's visits was scrutinised. 11 November 1911 was identified as an alternative value for missing date and all instances of this date were also reset to missing.

Incomplete calendar dates with a missing day and month were reset to midpoint of the non-missing year, i.e. 1 July. Calendar dates with missing day and non-missing month and year were reset to the midpoint of the month, i.e. day 15. In addition an indicator variable was created to flag all calendar dates with estimated day and/or month. This indicator variable was used for the self-controlled case series method to determine whether (a) diagnosis date was estimated or (b) prescription date was estimated.

3.2.2. Data Cleaning

Codes for medical diagnoses and symptoms may be erroneous or incomplete. Merging the patient-level medical records with a medical dictionary enabled us to identify these codes, for which a text description was not available. A list of incomplete or erroneous codes was scrutinised in order to identify obvious errors (e.g. where the first or last letter of a code was missing) but no obvious errors were found. Incomplete and erroneous medical codes were reset to missing and the record was retained, as these records represented consultations for unknown symptoms or with unknown outcomes. Similarly, incomplete and erroneous codes for therapy records were identified by merging therapy files with the therapy dictionary. These drug codes were reset to missing but the record was retained as a prescription to unknown drug.

Duplicate medical codes, i.e. identical codes that were recorded on the same day for the same patient, were removed. Duplicates of prescriptions for the same drug on the same day to the same patient were also removed.

3.3. OUTCOME DEFINITION

3.3.1. Systemic Lupus Erythematosus

3.3.1.1. Case Definition

OXMIS and Read codes for SLE were identified from a coding dictionary by four investigators (3 physician epidemiologists and 1 rheumatic disease epidemiologist), and verified by a rheumatologist whose subspecialty is SLE. A full list of codes can be found in Appendix II. Patients with at least one SLE code in their medical history were identified. With the exception of subacute cutaneous lupus (SCLE), codes for cutaneous variants of lupus were not considered to represent SLE. SCLE was retained since a high proportion of SCLE cases develop SLE.

For all statistical analyses utilising matched case-control data (described in further detail in sections 3.5.1 and 3.5.3), we excluded cases with a medical code for a comorbid autoimmune disease anywhere in their records. The reason for this exclusion criterion was that none of the controls had an autoimmune disease in their records either. Details on control definition and matching can be found in section 3.3.3 and onwards.

3.3.1.2. Case Validation

None of the cases were validated by review of original medical records due to financial and time constraints. Case validation based on laboratory test results on ANA and anti-DNA antibody positivity was not feasible as this information was recorded for 19 cases only (<1%). In clinical practice, the diagnosis of lupus is usually based on criteria formulated by the American College of Rheumatology[19]. It is thought that drug-induced lupus, which develops in previously asymptomatic individuals and usually disappears upon discontinuation of the drug is different from idiopathic SLE, which is a life-long disease[23]. Criteria for diagnosis of drug-induced lupus are less strict than those for diagnosis of idiopathic SLE[25]. In our study the diagnosis of SLE was not validated for each case individually and laboratory test results for ANA or anti-DNA antibody positivity were not available for the majority of cases. However this was not considered a critical limitation of our study, because of the less strict diagnostic criteria for drug-induced lupus. In addition, a high proportion of our case population received prescriptions for drugs used for the treatment of lupus (79% non-steroidal anti-inflammatory drugs, 10% corticosteroids, 48% anti-malarials and/or immunosuppressives[17]) and incidence rates based on our data are consistent with other published estimates[17]. We therefore believe the lupus diagnostic codes were valid.

3.3.1.3. Diagnosis Date

The date corresponding to the first SLE record represented the date of diagnosis for the cases. This date served as index date for the matched controls. Further characteristics of control subjects are described in paragraph 3.3.3, 3.3.4 and 3.3.5.

3.3.2. Drug related hypothyroidism

The risk of hypothyroidism associated with prescription drugs was investigated, using GPRD data, in two ways. Firstly, new signals of drug-induced hypothyroidism were generated using a subset of cases and their matched controls. These signals were subsequently evaluated in the remainder of hypothyroidism cases and controls.

3.3.2.1. Definition of Data Subsets

Data were split by geographical area. Practices contributing to the GPRD are located in 11 geographical areas which cover England, Wales, Scotland and Northern Ireland. Incident cases with hypothyroid disease were observed in practices from each of these areas. Cases and their matched controls registered with a practice in the regions "Northern England & Yorkshire", "Eastern England" and "West Midlands" were included in the signal generation data set and patients from practices in Scotland, Wales, Northern Ireland and all other regions of England were included in the signal evaluation data set. Random splitting of data was not considered appropriate as this would have resulted in similar results for signal generation and evaluation.

Decisions on the size of each data subset were based on type II error rate considerations. A type II error is made in the case of a false negative study finding; i.e. to conclude there is no association between drug exposure and risk of drug related hypothyroidism when in fact there is one. This type of error was considered of less importance in the context of signal generation (where minimising the number of false positive signals is of highest importance). However for signal evaluation type II error was considered to be particularly important. Type II error rate is dependent on a number of factors, including study sample size: larger sample sizes result in decreased type II error rates. We therefore included the majority of incident cases with hypothyroid disease (11873 out of the 17791, 66.7%) in the signal evaluation data set. Further details on sample size and power considerations for the signal evaluation study can be found in Section 3.5.1.1. The sample size for the signal generation data set was 5918 incident cases. In order to minimize type I error rate, we utilised a family-wise procedure which is further outlined in Section 3.5.3.

3.3.2.2. Case Definition

The list of diagnostic codes for hypothyroidism (including autoimmuine thyroiditis) can be found in Appendix III. Cases were defined as patients with at least one occurrence of an code for hypothyroidism in their medical records and at least one code for disease specific treatment (i.e. thyroid hormone). Therefore all included cases were treated, symptomatic drug related hypothyroidism cases. We searched the computerised medical case records for codes indicating thyroidectomy or radio-iodine therapy (Appendix IV). Cases with an occurrence of such codes prior to drug related hypothyroidism diagnosis were likely to have iatrogenic instead of autoimmune mediated disease and were therefore excluded from the analyses.

3.3.2.3. Case Validation

Cases were not individually validated by review of medical records due to financial and time constraints. Case validation based on laboratory test results on auto-antibody positivity was not feasible as this information was recorded for 1.3% of the cases.

3.3.2.4. Diagnosis Date

The date corresponding to the first medical record of drug related hypothyroidism represented the date of diagnosis for the cases. This date served as index date for the matched controls. Further characteristics of control subjects are described in paragraph 3.3.3, 3.3.4 and 3.3.5.

3.3.3. Control Definition

Control subjects were selected from the same base population as the cases and did not have a medical code for any autoimmune disease in their records. Exclusion criteria that were applied to cases were also applied to their matched controls: Controls matched to drug related hypothyroidism cases were excluded if they had a positive history of thyroidectomy or radio-iodine therapy prior to the index date.

3.3.4. Control Matching

Each case was matched to up to five non-autoimmune disease controls based on sex, age, practice and calendar year. Case diagnosis date, which was determined as described in further detail below, served as the index date for matched controls. A subject was eligible as a control when the index date occurred during the period of up-to-standard data collection. If no suitable control subject born in the same year as the case was identified, a subject of one year older or one year younger was sought. If still no suitable control was identified, the age difference was expanded to two years older of younger. This process was repeated up to a maximum age difference of 9 years. If there were still no suitable controls, the case was left unmatched or matched to less than 5 controls.

When a matched case was diagnosed with two or more autoimmune diseases, the index date for the earliest autoimmune disease served as the index date at which controls had to contribute data to the database. If at the time of diagnosis of a later autoimmune disease a matched control had left the practice, this control no longer contributed data and was therefore excluded from analyses of the later autoimmune disease.

3.3.5. Inactive Controls

Control subjects not showing any activity in medical, therapy or prevention records in the three years before the index date were assumed to be inactive. Inactive controls may represent healthy subjects who truly don't receive any prescriptions. However, some inactive control subjects are likely to have transferred out of the practice or are seeking medical care elsewhere. We decided to exclude inactive controls from further analyses because including these inactive controls as unexposed to drugs of interest would have, potentially erroneously, strengthened drug-disease associations.

3.3.6. Incident and Prevalent Cases

Cases were eligible as incident if the date of diagnosis occurred during the study period (1987 to 2001), and while the patient was registered with a practice contributing data to the GPRD. Diagnoses recorded on or shortly after registration with a practice may represent diagnoses for pre-existing medical conditions. For a number of acute and chronic diseases, Lewis et al[56] demonstrated there is an inflated incidence rate in the period after registration. The length of time needed for incidence rates to return to baseline varies by disease. In general, the time period is 4 to 6 months for acute conditions, and 10 to 12 months for chronic diseases. In order to avoid misclassification between prevalent and incident conditions, we excluded cases diagnosed within the first 12 months of having UTS data.

Similarly to the cases, the index date of the matched controls occurred at least 12 months after the start of up-to-standard data collection. Controls with less than 12 months of data before the index date were excluded from the analyses.

3.4. EXPOSURE DEFINITION

If a study subject received a prescription for a drug of interest a minimum of one week before diagnosis or index date, this subject was considered to be exposed. No maximum time limit between prescription and diagnosis was set to ensure that all potential exposure time windows were included. The agreement between prescribing data from the GPRD and national data from the UK Prescription Pricing Authority (PPA) is known to be very high[52]. As the prescription data are considered of particularly high quality, it was decided to also include prescriptions from outside the up-to-standard period in the analyses.

3.4.1. Exposures of Interest for Signal Generation

In signal generation studies, all drug exposures are considered potential risk factors for disease (in contrast to signal evaluation studies in which pre-existing hypotheses are tested).

In the GPRD, drug exposures are recorded as numerical codes which are linked to a prescription dictionary. One code represents only one drug name listed in the British National Formulary (BNF), but there can be several different codes that represent the same drug name. There were 41990 codes representing 10310 different drug names that were listed in the BNF during our study period.

As well as being linked to a GPRD drug code, drug names are linked to BNF codes. The BNF is divided into 15 chapters, each of which relate to a body system (e.g. the gastro-intestinal or cardiovascular system) or a therapeutic area (e.g. infections, anaesthesia). BNF chapters are further divided into subchapters, sub-subchapters and paragraphs. A BNF code consists of four two-digit numbers and is based on the BNF chapter, subchapter, sub-subchapter and paragraph under which a drug is listed. For instance, the code for amoxicillin (05.01.01.03) is compiled as follows:

Chapter	05	Infections
Subchapter	01	Antibacterial drugs
Sub-subchapter	01	Penicillins
Paragraph	03	Broad-spectrum penicillins

Some drugs are listed under more than one BNF chapter, for instance: aspirin is used as an antiplatelet drug for the cardiovascular system, and it is also used as an anti-inflammatory for musculoskeletal and joint diseases. Drug names can be linked to a maximum of three different BNF codes.

Instead of studying risk of SLE or drug related hypothyroidism associated with each of the 10310 drug names individually, we grouped the drug exposures by BNF subchapters, i.e. by the first four digits of the BNF codes. At a later stage in the signal generation analysis we refined our grouping by using the full BNF code. Drugs included in more than one BNF chapter and/or subchapter were counted once in each of their respective groups. Grouping of exposures resulted in an increase in potential risk factors to which both cases and controls were exposed. In relation to that,

grouping of drugs increased the proportion of subjects exposed to the potential risk factor, which dramatically increased study power.

3.4.2. Exposures of Interest for SLE Signal Evaluation

We obtained a list of drugs hypothesised to be associated with risk of SLE from the literature. A list of exposures of interest can be found in Table 1-1. The drugs in this table are reported to have 'low', 'moderate' and 'high' approximate risk levels based on available literature[22]. Drugs thought to be of very low risk, such as those where there is only one case report available, were not studied. Risks associated with exposure to drugs reported to exacerbate pre-existing lupus or to initiate lupus flares[23] were also not studied because in the clinical data available in the GPRD, exacerbations of existing disease are difficult to assess reliably.

3.4.2.1. Control Drugs

A selection of drugs that are not known to be linked to risk of SLE were included as 'control drugs' to investigate whether any observed effects were specific to the drugs of interest. Control drugs were chosen based on a number of characteristics. Firstly, drugs commonly prescribed in general practice were chosen, to ensure sufficient statistical power. Secondly, we ensured that use of the drug did not reflect a forthcoming diagnosis of SLE by selecting drugs which are not prescribed for symptoms overlapping with early SLE symptoms. Lastly, therapeutic class played a role in the selection of appropriate control drugs. Inclusion of a control drug of similar therapeutic class as a drug known to induce lupus enabled us to investigate whether effects were class-wide or drug-specific. Trimethoprim was included as a 'control' drug because it is of the same therapeutic class as the SLE-inducing drug minocycline (i.e. an antibiotic). The 'control' drug diazepam is an antiepileptic, as is carbamazepine. The third 'control' drug, the asthma drug salbutamol, is of a different therapeutic class from any of the lupus-inducing drugs but it was chosen because asthma symptoms do not overlap with early SLE symptoms and prescription of the drug should occur independently of case or control status.

3.4.3. Exposures of Interest for Signal Evaluation investigating Drug Related Hypothyroidism

During the signal evaluation phase of our study of risk of drug related hypothyroidism associated with prescription drugs, we investigated new hypotheses which were identified during the signal generation phase.

3.5. STATISTICAL ANALYSES

3.5.1. Conditional Logistic Regression

Conditional logistic regression was performed to model the risk of SLE (or drug related hypothyroidism) associated with exposure to drugs of interest during the study period and 1 week or more before diagnosis date (index date for the matched controls). Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated using Stata Software Version 9.0 (StataCorp, Texas). When there were sufficient numbers of exposed study subjects, a drug was studied in further detail by investigating the effect of number of prescriptions (as a proxy for cumulative dose), time between first and last prescription (as a proxy for duration of exposure) and time since cessation of the drug. In all analyses, unexposed subjects served as the reference category. Categorisation of variables was based on their frequency distribution in the control group. For instance, number of prescriptions was categorised into four groups; unexposed individuals served as the reference group and those exposed were categorised into three groups based on tertiles of number of prescriptions in the controls. Years of available prescription data before diagnosis date was also categorised into 4 groups with cut-off points based on quartiles in the controls. However, values were rounded off to the nearest year or 6 months for ease of interpretation. Similarly, number of consultations in the year before diagnosis was categorised into four groups based on quartile values in the controls. No missing values were observed for the categorised variables, hence sample size was not affected in analyses which included categorised variables in the model (e.g. conditional logistic regression models that were adjusted for confounding variables).

We investigated potential trends in risk of SLE (or drug related hypothyroidism) with increasing number of prescriptions in two ways. Firstly, we performed a test for trend by adding the grouped variable for number of prescriptions to the conditional logistic regression model as a continuous variable. The p-value relating to the risk estimate for this 'continuous' variable served as the p for trend. This test for trend assumes linearity of the underlying (ungrouped) continuous variable for number of prescriptions. When the odds ratios for the separate categories of number of prescriptions are suggesting a non-linear trend, but the p for trend suggests statistical significance, interpretation can be difficult. This situation may occur when individual categories contain a limited number of subjects, or when the risk estimate for one specific category has an extreme value relative to the other categories. A more informative measure in that case is the risk of SLE (or drug related hypothyroidism) per 10 prescriptions for the drug of interest. In order to calculate this risk, we grouped number of prescriptions in an alternative way; unexposed cases and controls remained the reference category and every 10 prescriptions were combined into a new group. For instance, the maximum number of prescriptions for anxiolytics (BNF code 04.01.02.00) was 514, hence there were 52 exposure categories. The regrouped variable for number of prescriptions was added in the model as a continuous variable to obtain risk of disease per 10 prescriptions.

The potential confounders age, sex, practice and calendar time were included in the study design as matching variables. Two additional factors were added to the model as *a priori* confounding factors: Years of available prescription data before diagnosis date (index date for the controls) was included because with more years of available prescription data, a study subject is more likely to receive a prescription for a drug of interest and more likely to be diagnosed with SLE; Number of consultations in the year preceding diagnosis date (index date for the controls) was included as a confounder because with more consultations a study subject is more likely to receive a prescription for any drug, including a drug of interest and more likely to be diagnosed with SLE (or drug related hypothyroidism).

Age at diagnosis was categorised into younger and older age based on the median value for each disease (<45 years or ≥45 years for the SLE data and <55 or ≥55 for the drug related hypothyroidism data, respectively). Age at diagnosis and sex were then investigated in two ways. Firstly, potential effect-modifying effects were examined. Stratum-specific ORs for men and women and for younger and older age were calculated and a test for interaction was performed. Secondly, age- and sex distributions of exposed subjects were compared to those of unexposed subjects, to identify whether drug-induced lupus (drug-induced drug related hypothyroidism) can be distinguished from idiopathic lupus by means of its age- and sex distribution. For age, a two-sided t-test was performed to compare the mean age in exposed versus unexposed cases and separately for controls. A chi-squared test was performed to investigate differences in the proportions of males and females for exposed and unexposed cases and separately for controls. When expected values were less than five, a Fisher's Exact test was performed instead of a chi-squared test.

3.5.1.1. Statistical Power

The GPRD data set obtained for this project included all possible autoimmune cases diagnosed between 1987, when data collection of the GPRD was initiated, and 2001. This data set included approximately 1500 matched incident cases of SLE and approximately 18000 matched incident cases of drug related hypothyroidism. The total number of cases with hypothyroid disease was divided in two subsets as described in paragraph 3.3.2.1. This resulted in a sample size of about 6000 cases for signal generation and 12000 for signal evaluation.

Using the formula below (from Schlesselman[57]), power curves were generated in order to assess the minimum relative risk we would be able to detect with the sample size available to us.

$$N = \frac{[Z_\alpha \sqrt{\left(1+\frac{1}{c}\right)p'q'} + Z_\beta \sqrt{p_1 q_1 + \frac{p_0 q_0}{c}}]^2}{(p_1 - p_0)}$$

where

N = Number of cases needed for the study sample

Z_α = Value of Z in a standard normal distribution where $\alpha = 0.05$

c = Number of controls per case

p_0 = Proportion of controls exposed

q_0 = Proportion of controls unexposed

R = Minimum risk to be detected

$$p_1 = \frac{p_0 R}{1 + p_0(R-1)}$$

$$q_1 = 1 - p_1$$

$$p' = \frac{p_1 + cp_0}{1+c}$$

$$q' = 1 - p'$$

Z_β = Value of Z in standard normal distribution where $\beta = 1 - power$

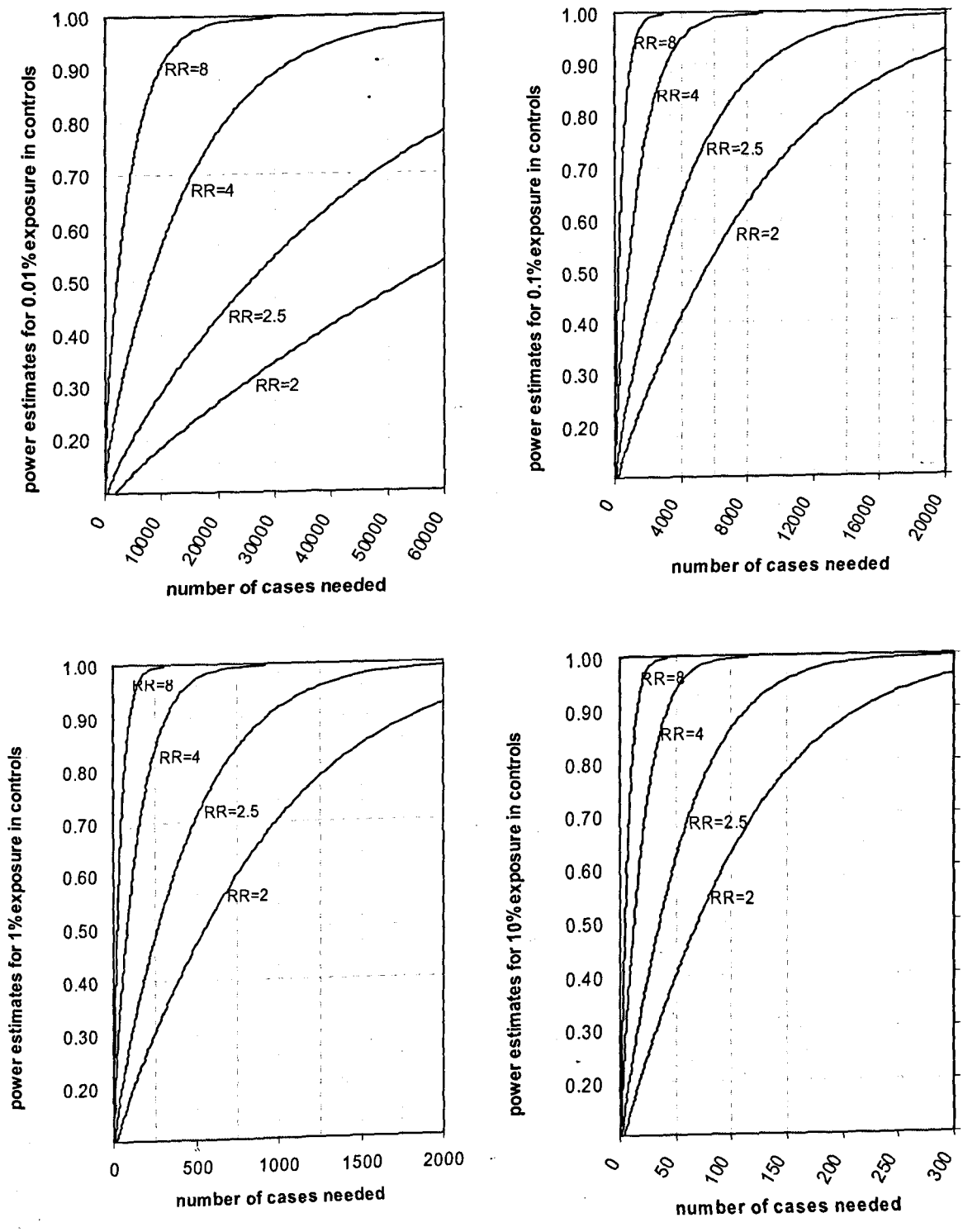


Figure 3-a: Power curves for various levels of exposure in control subjects

Figure 3-a depicts power curves for four different levels of drug exposure in controls (0.01%, 0.1%, 1% and 10%), at an α of 0.05. For each level of exposure, power associated with four levels of risk (RR=2, RR=2.5, RR=4 and RR=8) was calculated. Study power of 80% was considered sufficient.

For the signal evaluation study of drug related hypothyroidism (sample size ≈ 12000), there was sufficient study power to detect a relative risk of >4 associated with drugs of low exposure prevalence (i.e. used by 0.01% of the controls). For drugs with higher exposure prevalence (0.1% and higher) there was sufficient power to detect a relative risk of 2 or higher.

Study power for risk of SLE was insufficient when 0.01% of the controls were exposed to the exposure of interest. Study power was limited to relative risks of >4 for drugs with a relatively low exposure prevalence of 0.1%. There was sufficient power to detect relative risks of 2 or more for drugs with exposure an prevalence of 1% or more.

3.5.2. Self-Controlled Case Series

The case series method is derived from the cohort method and compares, within an individual, the incidence of an outcome during (exposed) risk periods versus the incidence during (unexposed) periods which serve as baseline time[10]. Individuals without the outcome of interest (control subjects) do not contribute information to the risk estimate. Unexposed cases also do not contribute information regarding the association between exposure and risk of disease. However, unexposed cases may be included to adjust for confounding by age. It is particularly important to include unexposed cases when those who are exposed are all of the same age, e.g. when investigating risk of intussusception associated with oral polio vaccination[58]. Because the case series method makes comparisons within one person, factors that are difficult to measure (e.g. consultation behaviour), or vary between individuals (e.g. coexistence of other autoimmune diseases), do not affect the risk estimates.

We utilised the self-controlled case series method to investigate the association between risk of lupus and exposure to a variety of prescription drugs. Definition of outcome and exposure, and details of the statistical analysis methods are provided below.

3.5.2.1. Outcome Definition

Cases were identified by selecting patients with at least one code for SLE in their medical history (for further details, see section 3.3.1.1). In order to avoid misclassification between prevalent and incident conditions, we excluded cases diagnosed within the first 12 months of having UTS data (see paragraph 3.3.6 for further detail). Case inclusion and exclusion criteria for the self-controlled case series analysis were the same as described for the matched case-control analysis (section 3.3.1.1), with the exception that cases with comorbid autoimmune disease were included in the SCCS analyses. In the case-control analyses these cases were excluded to avoid confounding.

3.5.2.2. Exposure Definition

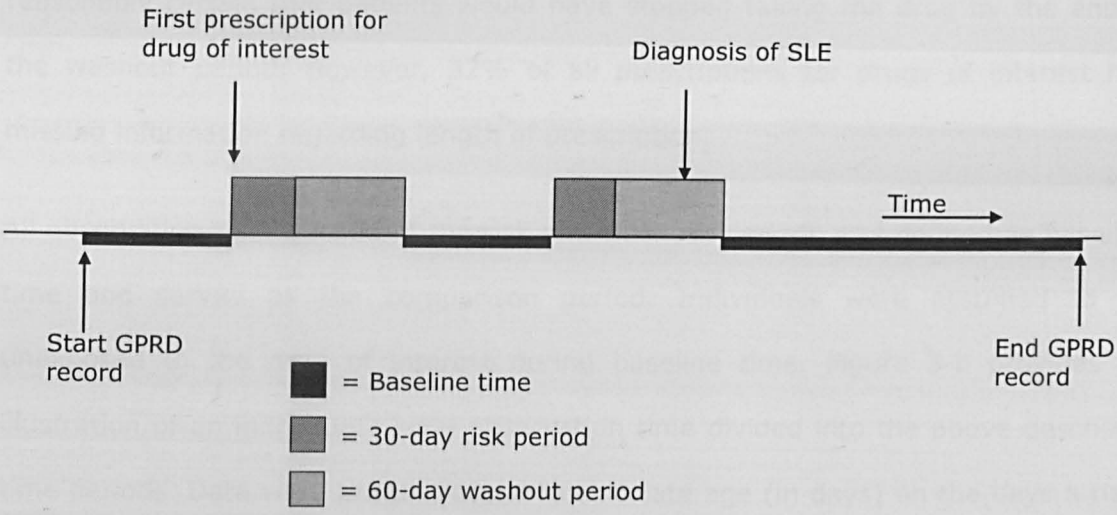
Exposures of interest were drugs known to be associated with risk of SLE, as well as three 'control drugs'. A more detailed description of exposures of interest and control drugs can be found in paragraph 3.4.2. Because we observed a wide variation in age among the exposed cases (see also table 4-5), it was not necessary to include unexposed cases for adjustment of confounding by age. Our analyses were therefore based on exposed cases only. For each drug of interest, a separate data set was created containing only cases who received one or more prescriptions for the drug. Prescriptions issued on the same day for the same drug were combined to represent one exposure. Because timing is very important in the case series method (see Whitaker et al[59] and section 3.5.2.3), we double checked that none of the prescriptions for the drugs of interest had a missing or estimated diagnosis date. In the whole of our data set, there were three missing prescription dates. These missing dates were not in association with the drugs of interest.

3.5.2.3. Definition of Exposure time

The start of an individual's GPRD record was defined as the first date on which a patient's practice was considered to contribute up-to-standard data, or the date on which a patient registered with the practice (whichever occurred latest). The end of

an individual's record was defined as the date on which the patient transferred out of their general practice or the date of the last data upload of the practice to the GPRD (whichever came earliest). The total observation time, running from the start to the end of the GPRD record, was divided into intervals of defined length. There were three types of intervals, namely: risk periods, washout periods, and baseline periods.

Figure 3-b: Graphic representation of the case series method



The figure shows an example of one individual who received two prescriptions for the drug of interest during the observation period. A 30 day risk period started on the day of the first prescription, and a further 60 day washout period followed the risk period. All other observation time served as reference time in which the individual was not exposed. In this example, SLE was diagnosed within the 60-day washout period after receiving the second prescription.

A risk period started on the day a prescription for a drug of interest was issued and ended 30 days later. New risk periods started on the issue dates of each subsequent prescription for the drug of interest, i.e. a case had as many 30-day risk periods as the number of issued prescriptions during the observation time. The length of the risk period was chosen somewhat arbitrarily because the time lag between taking a drug and developing SLE is not known. We chose 30 days to reflect the usual prescription length for all drugs of interest. The median value for prescription length was 28 days (inter-quartile range, 5 to 30).

An additional 60-day washout period, starting on day 31 after each prescription was issued and ending on day 90, was included in the analyses. The reason to include the washout period was twofold; we did not know the exact date on which a patient

started and ended taking a drug of interest (we only know the date a prescription was issued). In addition, when a patient is on long term medication for a chronic condition, a GP sometimes chooses to issue repeat prescriptions that cover several months instead of a limited time period of one month. The length of the washout period was again based on the distribution of prescription length for all drugs of interest: 99% of prescriptions had a duration of 90 days or less so we were reasonably certain that patients would have stopped taking the drug by the end of the washout period. However, 32% of all prescriptions for drugs of interest had missing information regarding length of prescription.

All observation time outside of the risk and washout periods was defined as baseline time and served as the comparison period. Individuals were assumed to be unexposed to the drug of interest during baseline time. Figure 3-b provides an illustration of an individual's total observation time divided into the above described time periods. Data were pre-processed to calculate age (in days) on the days a risk, washout and baseline period started and ended.

3.5.2.4. Statistical Analysis

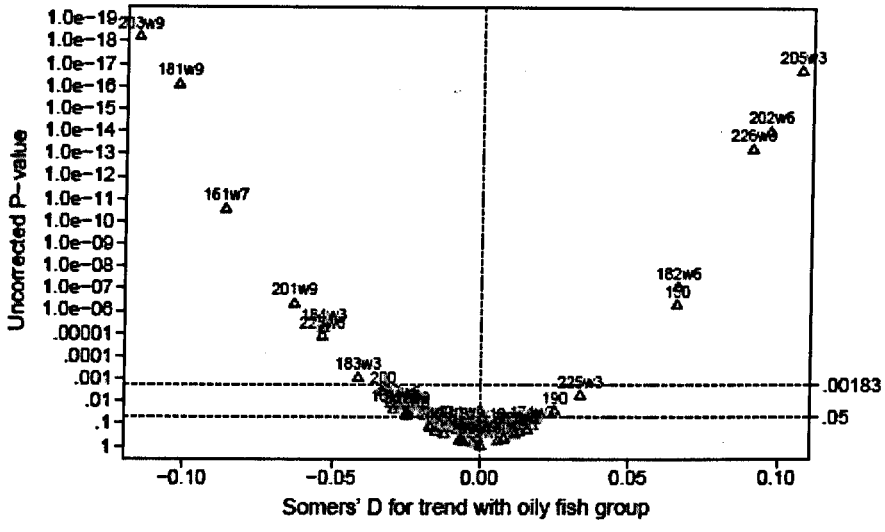
We compared the incidence rate of SLE during high risk and washout periods to the rate during baseline periods. All observation time, including the period after diagnosis of SLE, was included to estimate these relative incidence rate ratios (IRR) (Figure 3-b). We adjusted for age using 5-year age bands. For risk associated with exposure to carbamazepine we stratified the analysis by sex to investigate its effect on risk of disease. All analyses were performed in Stata using the "xtpoisson" command for conditional Poisson regression.

3.5.3. Signal Generation Using the "Smile Plot" Method

A smile plot is a graph of p-values plotted against risk estimates corresponding to these p-values. The smileplot package was developed by R Newson[60] in order to facilitate the interpretation of multiple test procedures. The package is downloadable from (http://www.stata-journal.com/software/sj3-2) as an add-in to the statistical

software package Stata (from version 7, Statacorp, Texas). An example of a smile plot can be seen in Figure 3-c. Observations in the upper right hand corner of Figure 3-c represent drugs with a large estimated risk and strong evidence for an association with the disease of interest.

Figure 3-c: Example of a smile plot



From: Newson et al [60]. This figure presents correlation between oily fish consumption and red blood cell fatty acid percentages, expressed in Somers' D. The labels in this graph represent different fatty acids. The vertical line represents the null (i.e. no correlation); the p-values corresponding to correlation estimates are on the y-axis (on a reverse logarithmic scale). In addition to the x-axis, which lists Somers' D, there are two horizontal lines. One is marked ".05" and represents the uncorrected level of significance. The top horizontal line (in this graph marked with ".00183") represents the 'new' significance level: a stricter level obtained using defined criteria to correct for multiple comparisons. In our study of drug-induced autoimmune disease the graph will contain the following elements; the x-axis will list odds ratios instead of Somers' D, and the labels in the graph will represent individual BNF subchapters instead of fatty acids. The vertical reference line will represent the null (OR=1, i.e. no risk). All other elements of the graph will be the same as presented here.

The basis for each smile plot is an input data set. This data set contains a unique id variable for each exposure of interest, a risk estimate for each exposure, and p-value corresponding to each risk estimate. The risk estimates may be univariable or may be adjusted for confounding factors. Additional measures such as 95% confidence limits for the risk estimates and number of individuals exposed to each risk factor may be incorporated in the input data set, but these are not used to generate the graph.

Once the input data set has been created, one has to choose a method of controlling for multiple comparisons. A range of multiple test procedures is available in the smile plot package. These can be divided into family wise error rate (FWER) and false

discovery rate (FDR) methods (see also section 1.1.2.2). The methods calculate a corrected significance level. For one comparison, the significance level α is 0.05. With an increasing number of comparisons, the significance level becomes 'stricter', i.e. the corrected p value below which a null hypothesis is rejected is smaller than 0.05.

To create smile plots of risk of autoimmune disease associated with prescription drugs, we analysed the GPRD autoimmune case-control data using conditional logistic regression (as described in section 3.5.1). Exposures of interest were drugs grouped by BNF subchapter or full BNF code (see Paragraph 3.4.1 and Appendix V for a list of BNF subchapters). For each exposure, we estimated risk of SLE (or drug related hypothyroidism), adjusted for confounding factors, and the p value corresponding to the risk estimate. We also recorded the number of cases and controls exposed to each BNF subchapter, the 95% confidence limits corresponding to each Odds Ratio, as well a unique identifier for each exposure. The risk estimates, p values and additional variables were then compiled in a new data set (the input data set).

Smile plots were generated for each input data set. We explored all step-up FDR methods available in the smile plot package to correct for multiple comparisons, namely: the Simes, Yekutieli, and Krieger methods. We decided to use the method resulting in conservative corrected p values, which was the Yekutieli method.

Separate smile plots (and thus input data sets) were generated to investigate the effect of time between exposure and onset of disease. One input data set contained risk estimates and p values based on all exposures up to one week before diagnosis of SLE (or drug related hypothyroidism). We also generated an input data set based on exposures that took place one year or more before diagnosis.

The effect of sex and age at diagnosis was investigated by means of stratification. Separate smile plots were generated for women and men, and for younger and older age at diagnosis. The cut point to divide age at diagnosis in 'younger' and 'older' age groups was based on the median age at diagnosis for each disease (<45 years or

≥45 years for the SLE data and <55 or ≥55 for the drug related hypothyroidism data, respectively).

3.5.4. Signal Evaluation

Our study of prescription drugs and risk of drug related hypothyroidism consisted of two phases: firstly, we generated new signals using the smile plot method as described above. Potential signals were subsequently evaluated in a larger data subset. A description of how the total drug related hypothyroidism case-control data were divided in subsets can be found in section 3.3.2.1.

Signals were evaluated using conditional logistic regression (see section 3.5.1). Each BNF subchapter was divided in BNF codes and risk of drug related hypothyroidism was determined for each individual BNF code. In addition, risk associated with number of prescriptions (grouped) was investigated in order to assess a potential dose-response relationship. Potential effect modification by sex was investigated by performing stratified analyses (see section 3.5.1 for further detail).

CHAPTER 4. RISK OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ASSOCIATED WITH PRESCRIPTION MEDICINE

Exposure to a wide range of prescription drugs has been linked to the induction of auto-antibodies and, to a lesser extent, clinically apparent autoimmune disease. The most extensively documented drug-induced autoimmune disease is systemic lupus erythematosus (SLE). Prescription drugs from several therapeutic classes have been reported to lead to lupus[22]. To date there has not been a large observational study to confirm the findings of these case reports or to quantify risks associated with exposure to the drugs of interest.

In this chapter, the risk of lupus associated with prescription drugs is investigated. Two separate data sources are utilised: Firstly, existing hypotheses are evaluated in GPRD data using a case-control and a case-only approach. A new method to generate new hypotheses is presented, also using GPRD data. Secondly, a subset of Yellow Card spontaneous reports is described.

4.1. MATCHED CASE-CONTROL STUDY

We identified 875 incident cases of lupus with 3632 matched controls (Table 4-1). 82.8% of the cases were female with a mean age at diagnosis of 44.2 years (sd, 15.1). Male cases were on average 6.6 years older at diagnosis (mean age 50.9 years, sd 15.5, $p < 0.0001$). Control subjects had a mean age of 45.3 years (sd, 15.1).

Table 4-1: Demographic characteristics and univariable Odds Ratios (ORs) with 95% Confidence Intervals (CIs) for the association between selected variables and risk of lupus

		Study subjects (%)		
		Case (N=875)	Control (N=3632)	OR*(95% CI)
Sex†	Female	721 (82.4%)	3012 (82.9%)	
Age at diagnosis, years†	Age (SD)	45.4 (15.1)	45.3 (15.1)	
	Range	4.5 - 85.5	4.5 - 88.4	
Time in database, years‡	1 - 3	209 (23.9)	1112 (30.6)	1.00 (reference)
	3 - 4.5	165 (18.9)	770 (21.2)	1.37 (1.03 - 1.83)
	4.5 - 7	246 (28.1)	950 (26.2)	2.43 (1.79 - 3.30)
	> 7	255 (29.1)	800 (22.0)	4.27 (3.03 - 6.02)
				p < 0.001
Consultation rate§	0 - 6	55 (6.29)	1060 (29.19)	1.00 (reference)
	7 - 12	105 (12.00)	672 (18.50)	4.27 (2.95 - 6.18)
	13 - 24	194 (22.17)	826 (22.74)	8.51 (5.95 - 12.2)
	> 24	521 (59.54)	1074 (29.57)	28.2 (19.4 - 40.8)
				p < 0.001

* Univariable OR for risk of SLE
† Variable used to match cases and controls, therefore univariable OR is not reported
‡ Time (in years) in database before diagnosis
§ Number of consultations per year in the year preceding diagnosis date (index date for the controls)

The observation period from study entry to index date was longer for cases than controls, the mean for cases being 5.5 years and for controls being 4.9 years. Cases consulted their general practitioners more frequently in the year prior to the index date. The mean number of consultations for cases in the year before the index date was 40.4, while for controls the average number was 21.2.

Conditional logistic regression was used to examine the association between lupus and exposure to drugs at any point up to one week before the diagnosis or index date. Crude and adjusted ORs are shown in Table 4-2. Neither cases nor controls were exposed to procainamide, propylthiouracil or acebutolol therefore risk associated with these drugs could not be estimated. For isoniazid, only cases were exposed. Very few subjects were exposed to a further five drugs of interest, resulting in wide confidence intervals (e.g. hydralazine, OR = 6.62, 95% CI 1.03 - 42.74). For three drugs of interest more than 10 cases and controls were exposed. Large numbers of both cases and controls were exposed to the 'control' drugs.

Table 4-2: Crude and adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the association between lupus and exposure to selected drugs before diagnosis or index date

Drug name	Study Subjects: Case (N=875)	Study Subjects: Control (N=3632)	Unadjusted OR* (95% CI)	Adjusted OR*†‡ (95% CI)
Drugs thought to induce SLE§				
Hydralazine	4	2	8.91 (1.62 - 48.94)	6.62 (1.03 - 42.74)
Minocycline	50	49	4.35 (2.90 - 6.52)	4.23 (2.65 - 6.75)
Carbamazepine	28	49	2.39 (1.48 - 3.85)	1.88 (1.09 - 3.22)
Quinidine	2	2	3.94 (0.55 - 28.17)	1.41 (0.17 - 11.95)
Methyldopa	2	7	1.39 (0.29 - 6.70)	1.40 (0.28 - 7.11)
Captopril	11	24	1.97 (0.95 - 4.09)	1.30 (0.57 - 2.96)
Chlorpromazine	7	16	1.95 (0.78 - 4.87)	0.86 (0.32 - 2.33)
Procainamide	0	0	-	-
Propylthiouracil	0	0	-	-
Acebutolol	0	0	-	-
Isoniazid	3	0	-	-
Drugs not thought to induce SLE				
Trimethoprim	201	583	1.63 (1.35 - 1.97)	1.00 (0.80 - 1.24)
Diazepam	86	228	1.66 (1.26 - 2.18)	0.92 (0.68 - 1.26)
Salbutamol	135	411	1.44 (1.16 - 1.79)	0.96 (0.76 - 1.22)

*Reference category is the unexposed group for each drug
†ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date
‡Control drugs additionally adjusted for exposure to SLE-inducing drug
§Drugs are reported to have high, moderate or low risk of inducing lupus [22]

For hydralazine, minocycline, carbamazepine and quinidine, drugs thought to induce lupus based on the literature, the crude ORs were greater than 2 and were statistically significant apart from quinidine. Exposure to methyldopa, captopril and chlorpromazine was not clearly associated with risks of lupus (ORs not statistically significant with values between 1 and 2). Simultaneous adjustment for number of consultations in the year preceding diagnosis or index date, and for number of years of available therapy data before diagnosis or index date, generally reduced the ORs. After adjustment for confounding factors a more than twofold increased risk was seen for two of the drugs thought to induce SLE (hydralazine, OR = 6.62, 95% CI 1.03 - 42.7; minocycline, OR = 4.23, 95% CI 2.65 - 6.75).

Exposure to carbamazepine was associated with a significantly increased risk. Risks associated with use of quinidine, methyldopa and captopril were slightly, but not significantly, increased (ORs between 1.00 and 2.00). The estimate for chlorpromazine shifted from an increased to a slightly decreased risk after adjustment for confounding factors.

In general, crude ORs for the 'control' drugs trimethoprim, diazepam and salbutamol showed an increased risk of lupus of less than double compared to unexposed individuals. However, after adjustment for confounding factors (including use of lupus-inducing drugs) these associations were no longer apparent.

The stratum-specific estimates for men and women are shown in Table 4-3. Very few men were both diagnosed with lupus and exposed to the drugs of interest. The sex-specific estimates were different from the overall adjusted ORs for hydralazine, carbamazepine, captopril and chlorpromazine. For hydralazine, both women and men had an increased risk of SLE. Although the OR for men was higher than for women there was little evidence of effect modification (p for interaction = 0.387). For carbamazepine, women had an increased risk of SLE whereas there was no evidence of an association in men. The test for interaction suggested the effect of carbamazepine varied with gender (p = 0.047). A test for interaction between captopril use and sex was not significant (p = 0.203). The male : female ratio for cases exposed to chlorpromazine was significantly different from the ratio among unexposed cases (ratio exposed 1 : 0.77, ratio unexposed 1 : 4.7, p = 0.027). There was no clear association observed for the 'control' drugs in women or men.

Table 4-3: Sex-specific adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the association between lupus and exposure to selected drugs before diagnosis or index date

	Women			Men		
Drug name	**Case (N=721)**	**Control (N=3012)**	**OR (95% CI)*†‡**	**Case (N=154)**	**Control (N=620)**	**OR (95% CI)*†‡**
Drugs reported to induce SLE§						
Hydralazine	2	1	2.87 (0.26 - 31.71)	2	1	13.1 (1.04 - 166)
Minocycline	45	44	4.29 (2.61 - 7.06)	5	5	4.47 (1.08 - 18.58)
Carbamazepine	25	39	2.47 (1.37 - 4.48)	3	10	0.60 (0.15 - 2.38)
Quinidine	2	2	1.36 (0.16 - 11.65)	0	0	-
Methyldopa	2	7	1.43 (0.28 - 7.26)	0	0	-
Captopril	9	16	1.84 (0.71 - 4.76)	2	8	0.53 (0.09 - 3.21)
Chlorpromazine	3	12	0.51 (0.12 - 2.15)	4	4	1.75 (0.40 - 7.69)
'Control' drugs; not known to induce SLE						
Trimethoprim	190	541	1.05 (0.84 - 1.32)	11	42	0.59 (0.28 - 1.26)
Diazepam	73	203	0.87 (0.62 - 1.21)	13	25	1.34 (0.59 - 3.03)
Salbutamol	105	335	0.88 (0.68 - 1.15)	30	76	1.29 (0.75 - 2.22)

*Reference category is the unexposed group for each drug
†ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date
‡Control drugs additionally adjusted for exposure to SLE-inducing drug
§Drugs are reported to have high, moderate or low risk of inducing lupus [22]

Stratum-specific estimates for younger and older age at diagnosis could not be obtained for all drugs because of the small number of exposed subjects (data not shown). The highest number of minocycline users was amongst those less than 45

years old (34/446 cases exposed, 41/1849 controls). Risk of lupus in this group was 3.38 (95% CI 1.94 - 5.90). In contrast, the older age group of ≥45 years had fewer minocycline users (16/429 cases and 8/1783 controls) but a suggestion of a higher risk was observed (OR=7.93, 95% CI 3.12 - 20.17, p interaction = 0.117). Cases using captopril before diagnosis were on average 13 years older than non-users (mean age 58.1 (sd 11.3), p = 0.0058) but the risk estimate for the older age group was similar to the overall risk estimate (data not shown). Risk associated with captopril in the younger age group could not be estimated as only one case was exposed and no controls.

Table 4-4: Odds Ratios (OR) and 95% Confidence Intervals (CI) for number of prescriptions and risk of SLE

		Study subjects			
Drug name	**No. of prescriptions***	**Case N=875**	**Control N=3632**	**Unadjusted OR (95% CI)**	**Adjusted OR †‡ (95% CI)**
Drugs thought to induce SLE					
Minocycline	unexposed	825	3583	1.00 (Reference)	1.00 (Reference)
	1	17	22	3.43 (1.81 - 6.51)	3.03 (1.49 - 6.17)
	2-3	13	12	4.31 (1.94 - 9.60)	6.10 (2.20 - 16.93)
	>=4	20	15	5.67 (2.88 - 11.14)	5.00 (2.37 - 10.51)
				p < 0.001	p < 0.001
Carbamazepine	unexposed	847	3583	1.00 (Reference)	1.00 (Reference)
	1	9	16	2.39 (1.05 - 5.45)	1.55 (0.62 - 3.84)
	2-6	4	17	0.96 (0.32 - 2.89)	0.94 (0.27 - 3.25)
	>=7	15	16	3.83 (1.88 - 7.80)	3.04 (1.34 - 6.85)
				p < 0.001	p = 0.011
Captopril	unexposed	864	3608	1.00 (Reference)	1.00 (Reference)
	1-13 Rx	8	13	2.58 (1.06 - 6.26)	2.13 (0.79 - 5.73)
	>=14 Rx	3	11	1.20 (0.32 - 4.40)	0.56 (0.14 - 2.29)
				p = 0.180	p = 0.970
Chlorpromazine	unexposed	868	3616	1.00 (Reference)	1.00 (Reference)
	1 Rx	4	11	1.60 (0.49 - 5.27)	0.63 (0.17 - 2.26)
	>=2 Rx	3	5	2.65 (0.63 - 11.2)	1.48 (0.29 - 7.42)
				p = 0.124	p = 0.987
Drugs not known to induce SLE					
Trimethoprim	unexposed	674	3049	1.00 (Reference)	1.00 (Reference)
	1 Rx	121	385	1.47 (1.17 - 1.84)	0.97 (0.75 - 1.25)
	2 Rx	40	105	1.85 (1.26 - 2.70)	1.10 (0.72 - 1.67)
	>=3 Rx	40	93	2.13 (1.43 - 3.18)	1.00 (0.64 - 1.56)
				p < 0.001	p = 0.918
Diazepam	unexposed	789	3404	1.00 (Reference)	1.00 (Reference)
	1	50	118	1.85 (1.30 - 2.62	1.10 (0.74 - 1.63)
	2-3	19	53	1.64 (0.96 - 2.81)	0.79 (0.44 - 1.42)
	>=4	17	57	1.28 (0.74 - 2.23)	0.73 (0.40 - 1.33)
				p = 0.009	p = 0.297
Salbutamol	unexposed	740	3221	1.00 (Reference)	1.00 (Reference)
	1 Rx	40	161	1.08 (0.75 - 1.56)	0.85 (0.57 - 1.26)
	2-6 Rx	52	126	1.85 (1.31 - 2.59)	1.23 (0.84 - 1.79)
	>=7 Rx	43	124	1.49 (1.04 - 2.15)	0.83 (0.55 - 1.25)
				p < 0.001	p = 0.744

* Categorisation no. of prescriptions based on distribution in controls
† Adjusted for years in database before diagnosis and no. of consultations in year prior diagnosis
‡ Drugs not known to induce SLE additionally adjusted for use of SLE drug yes/no

For drugs where there were sufficient numbers of cases and controls exposed, the effect of number of prescriptions on risk of lupus was investigated (Table 4-4). For

minocycline there was a clear trend of increasing risk with increasing number of prescriptions (adjusted OR per 10 prescriptions 3.10, 95% CI 2.10 - 4.55, p for trend < 0.001). For carbamazepine there was some evidence of a trend in ORs for grouped number of prescriptions (adjusted OR per 10 prescriptions 1.27, 95% CI 1.04 - 1.57, p for trend = 0.011). For chlorpromazine there was a suggestion of increasing risk with increasing number of prescriptions, however the OR per 10 prescriptions and the test for trend did not confirm this association (adjusted OR per 10 prescriptions 1.18, 95% CI 0.64 - 2.20), p for trend = 0.987). Number of prescriptions for captopril did not show a clear association with risk of SLE nor did the 'control' drugs. Results for time between first and last prescription as a proxy for duration are very similar to cumulative dose (data not shown).

Current use of minocycline was associated with a 4-fold increased risk (OR = 4.05, 95% CI 1.04 - 15.76) and current use of chlorpromazine was associated with a 2-fold increased risk (OR = 2.27, 95% CI 0.27 - 19.02). Increasing time since cessation of drug use was associated with a decreased risk of lupus for minocycline and chlorpromazine, which was confirmed by a test for trend (minocycline p = 0.009, chlorpromazine p = 0.031). For carbamazepine there was a suggestion of a decrease in risk of lupus with increasing time since cessation but a test for trend did not confirm this association (p = 0.120). Time since cessation of use of captopril and all of the 'control' drugs was not clearly associated with risk of lupus (data not shown).

4.2. SELF-CONTROLLED CASE SERIES METHOD

The matched case-control analyses (results described in section 4.1) included 875 incident cases of SLE. Although there were a further 632 incident cases identified from the GPRD, these were unsuitable for the case-control analyses because there was no suitable control available (N=135) and/or the case was diagnosed with another autoimmune disease (N=567). For the self-controlled case series analyses, all incident cases were eligible for inclusion in the analyses. Table 4-5 summarises the characteristics of cases exposed to the drugs of interest. Due to the limited

number of exposed cases for each drug, we chose to report median values and the inter-quartile range (instead of means and standard deviations) for length of observation time, number of repeat prescriptions and age.

Table 4-5: Self-Controlled Case Series: characteristics of SLE cases and their exposures

Drug name	No. of exposed cases at timing of first prescription*		Median length of observation time†, year	No. of repeat prescriptions		Median age at first prescription†, year
	Pre (%)	Post (%)		Median†	Max‡	
Drugs thought to induce SLE§						
Hydralazine	7 (100)	0 (0)	3.5 (2.1 - 6.5)	6 (3 - 26)	49	68 (64 - 72)
Minocycline	38 (67)	19 (33)	5.2 (2.6 - 8.0)	3 (1 - 6)	73	38 (30 - 47)
Carbamazepine	34 (56)	27 (44)	4.3 (2.8 - 6.8)	10 (2 - 28)	94	46 (35 - 57)
Methyldopa	1 (100)	0 (0)	6.0	40		73
Captopril	15 (60)	10 (40)	4.6 (2.1 - 6.3)	13 (4 - 29)	103	66 (54 - 74)
Chlorpromazine	8 (40)	12 (60)	6.6 (3.3 - 9.1)	2 (1 - 13)	48	44 (39 - 61)
Propylthiouracil	1 (100)	0 (0)	8.5	18		42
Acebutolol	3 (100)	0 (0)	8.2 (3.4 - 9.3)	10 (1 - 99)	99	67 (52 - 72)
Isoniazid	3 (43)	4 (57)	4.4 (1.4 - 7.6)	6 (1 - 7)	10	38 (34 - 60)
Penicillamine	6 (67)	3 (33)	4.7 (3.4 - 7.5)	4 (2 - 6)	22	51 (49 - 61)
Sulfasalazine	38 (63)	22 (37)	4.8 (3.2 - 7.7)	5 (2 - 12.5)	77	47 (37 - 54)
Drugs not thought to induce SLE						
Trimethoprim	124 (36)	220 (64)	5.3 (3.3 - 7.6)	1 (1 - 2)	23	50 (37 - 62)
Diazepam	61 (41)	89 (59)	5.3 (3.1 - 8.0)	2 (1 - 4)	167	50 (40 - 61)
Salbutamol	142 (54)	122 (46)	4.4 (2.7 - 7.0)	3 (1 - 10)	357	49 (38 - 60)

*Number of exposed cases who received their first prescription before or after diagnosis of SLE
†Numbers in parentheses: inter-quartile range
‡Max, maximum
§Drugs are reported to have high, moderate or low risk of inducing lupus[22]

For drugs thought to induce SLE[22], the majority of cases received their first prescription before onset of SLE, apart from chlorpromazine (12 out of 20 exposed cases received their first prescription after diagnosis of SLE), and isoniazid (4 out of 7 cases received their first prescription after diagnosis of SLE). For the 'control drugs' trimethoprim and diazepam however, the majority of cases received their first prescription after diagnosis of SLE. For the 'control drug' salbutamol, the proportion of cases receiving their first prescription before diagnosis was approximately equal to those receiving their first prescription after diagnosis of SLE (54% versus 46%, respectively). Observation time was of similar length for all studied drugs, apart from chlorpromazine. Although the inter-quartile range overlapped with the range for all other drugs, chlorpromazine users had on average a slightly longer observation time.

Table 4-6: Incidence Rate Ratios (IRR) of SLE associated with prescription drug exposure during defined time periods

Exposure period* (No. of exposed cases)	No. of SLE diagnoses	IRR† (95% CI)
Drugs thought to induce SLE‡		
Hydralazine (N=7)		
Unexposed period	2	1.00 (Reference)
0 - 30	1	1.42 (0.10 - 20.54)
31 - 90	4	4.23 (0.57 - 31.34)
Minocycline (N=57)		
Unexposed period	36	1.00 (Reference)
0 - 30	8	2.14 (0.90 - 5.09)
31 - 90	13	2.57 (1.25 - 5.27)
Carbamazepine (N=61)		
Unexposed period	31	1.00 (Reference)
0 - 30	12	1.60 (0.66 - 3.87)
31 - 90	18	1.93 (0.87 - 4.26)
Captopril (N=25)		
Unexposed period	15	1.00 (Reference)
0 - 30	1	0.09 (0.01 - 0.85)
31 - 90	9	0.77 (0.20 - 2.91)
Chlorpromazine (N=20)		
Unexposed period	15	1.00 (Reference)
0 - 30	2	1.28 (0.19 - 8.48)
31 - 90	3	1.58 (0.34 - 7.27)
Isoniazid (N=7)		
Unexposed period	6	1.00 (Reference)
0 - 30	0	-
31 - 90	1	0.34 (0.02 - 5.66)
Penicillamine (N=9)		
Unexposed period	7	1.00 (Reference)
0 - 30	0	-
31 - 90	2	2.20 (0.30 - 15.9)
Sulfasalazine (N=60)		
Unexposed period	39	1.00 (Reference)
0 - 30	5	0.77 (0.27 - 2.19)
31 - 90	16	2.26 (1.12 - 4.56)
Drugs thought not to induce SLE		
Trimethoprim (N=344)		
Unexposed period	316	1.00 (Reference)
0 - 30	9	0.80 (0.41 - 1.58)
31 - 90	19	0.94 (0.58 - 1.51)
Diazepam (N=149)		
Unexposed period	114	1.00 (Reference)
0 - 30	13	1.63 (0.83 - 3.20)
31 - 90	22	1.86 (1.06 - 3.23)
Salbutamol (N=264)		
Unexposed period	179	1.00 (Reference)
0 - 30	34	1.43 (0.92 - 2.23)
31 - 90	51	1.59 (1.09 - 2.33)

*Period expressed in days since prescription was issued
†IRR = Incidence Rate Ratio
‡ Drugs are reported to have high, moderate or low risk of inducing lupus[22]

Cases exposed to carbamazepine and captopril received a substantial number of prescriptions, whereas cases exposed to minocycline and chlorpromazine as well as the 'control drugs' generally received a limited number of prescriptions. Median age at first prescription again varied between the different drugs. These differences mostly reflect the indications for which the drugs are prescribed. For instance: hydralazine, methyldopa and captopril are drugs prescribed for high blood pressure; a condition that is mostly diagnosed in an older population.

In Table 4-5, the values for acebutolol, methyldopa, and propylthiouracil are based on only three exposed cases and random variation is likely to play a large role in any observed differences in observation time, number of repeat prescriptions and median age at first prescription.

Table 4-6 summarises the results of the self-controlled case series analyses. A limited number of cases were diagnosed with SLE during the defined risk period for most drugs thought to induce lupus[22]. This resulted in wide confidence intervals. In the case population exposed to isoniazid and penicillamine, no SLE diagnoses were made during the defined 30-day risk period and we could therefore not estimate the incidence rate ratio in this period. All risk estimates for the washout period, including those for the 'control drugs' were higher than those for the risk periods.

Among users of hydralazine, no increased risk of SLE was seen during the risk period. However, a 4-fold increased risk was observed during the washout period. The 95% confidence interval included one. For minocycline, risk during both of the exposed periods was twofold compared to unexposed time. For carbamazepine, there was a suggestion of a moderately increased risk in both the risk and washout periods, but the IRRs were not statistically significant. When the analysis was stratified by sex, risk estimates for women were similar to the overall results ($IRR_{risk\ period}$ = 1.30, 95% CI 0.50 – 3.42; $IRR_{washout\ period}$ = 1.74, 95% CI 0.74 – 4.11). The risk estimates for the seven exposed men however were substantially higher. Two men were diagnosed with SLE during the risk period and two during the washout period. The diagnosis date for the other three men occurred during baseline (unexposed) time. This resulted in the following risk estimates: $IRR_{risk\ period}$ = 7.43 (95% CI 0.81 – 68.1), $IRR_{washout\ period}$ = 4.29 (95% CI 0.50 – 36.53). Although these estimates are based on a small number of exposed men (and, consequently, have very wide confidence intervals), their magnitude is in support of a true increase of risk, especially during the period immediately after receiving a prescription.

There was a suggestion of a moderately increased risk of SLE (IRR less than 2) associated with use of chlorpromazine. An approximately twofold increase in risk was

observed during the washout period for penicillamine and sulfasalazine. Risk of SLE associated with use of captopril appeared to be decreased in both the 30-day risk period and the washout period.

We did not observe an increased risk of SLE during the washout period for trimethoprim. However, for the other two 'control drugs' a modest but statistically significant increase in risk of SLE was observed during the washout period.

4.3. SIGNAL GENERATION USING "SMILE PLOTS"

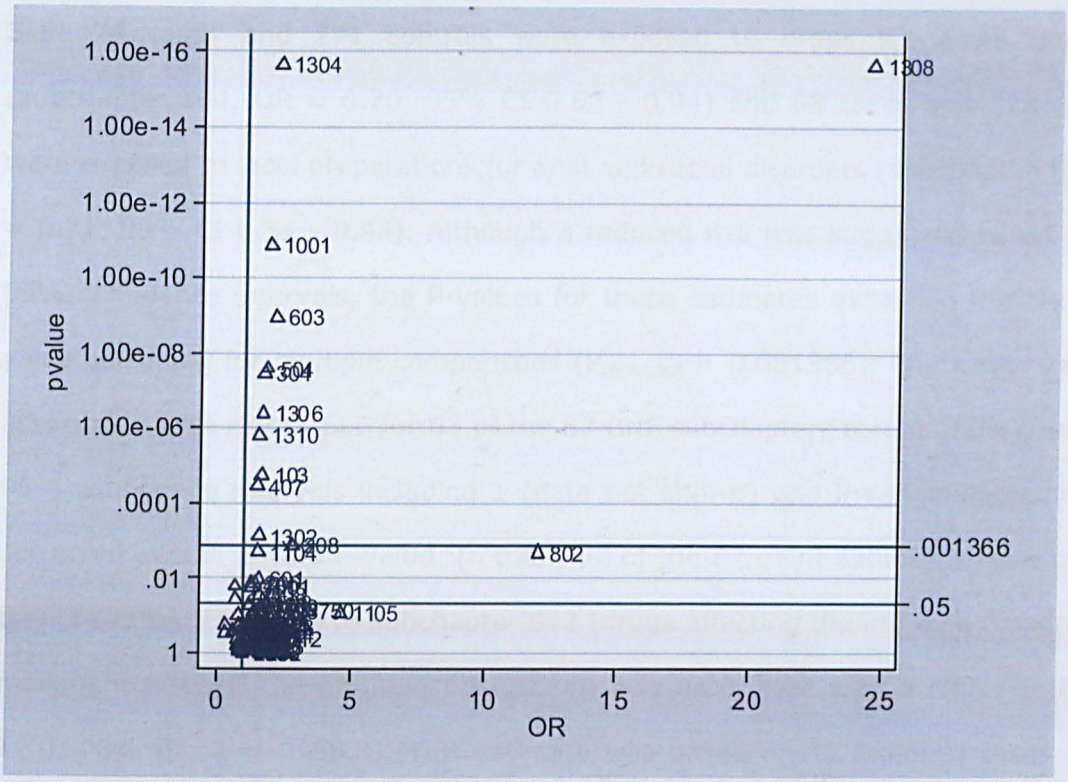
For the signal generation analyses, we used the same cases and controls as for the matched case-control study. Characteristics of the 875 cases and 3632 matched controls can be found in Paragraph 4.1 and Table 4-1.

4.3.1. Exposure to Drugs Prescribed One Week or More Before Diagnosis

Firstly, we investigated risk of SLE associated with exposure to drugs, grouped by BNF subchapter, one week or more before diagnosis. Further details of the BNF subchapters can be found in Appendix V. There were 87 subchapters to which both cases and controls were exposed. Conditional logistic regression was performed to obtain adjusted risk estimates for each of these subchapters. A graphical presentation of the risk estimates and corresponding P-values can be found in Figure 4-a.

There was a suggestion of an increased risk of SLE, with P-values smaller than the corrected overall critical P-value, for twelve BNF subchapters (located in the upper right corner of Figure 4-a). Five of these twelve signals were subchapters of BNF chapter 13, which covers drugs for the skin. Furthermore, seven of the twelve signals were subchapters containing drugs prescribed to reduce inflammation such as corticosteroids and aspirin (subchapters 1304, 603, 1001, 504, 1306, 103 and 407). Further details of the twelve signals can be found in Table 4-7.

Figure 4-a: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis date



Odds Ratios (OR) are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 87; Corrected overall critical P-value: 0.00136596; Number of rejected P-values: 12.

Table 4-7: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis date

Label	BNF subchapter * (BNF chapter)	Case (N=875)	Control (N=3632)	OR (95% CI)†‡	P value¶
1308	Sunscreens and camouflagers (Skin)	63	10	24.5 (11.4 - 52.9)	2.22E-16
208	Anticoagulants and protamine (Cardiovascular system)	29	26	2.81 (1.50 - 5.26)	1.27E-03
1304	Topical local corticosteroids (Skin)	489	1099	2.23 (1.87 - 2.66)	2.22E-16
603	Corticosteroids (Endocrine system)	168	238	2.14 (1.68 - 2.73)	1.12E-09
1001	Drugs used in rheumatic diseases and gout (Musculoskeletal and joint diseases)	586	1504	1.91 (1.58 - 2.30)	1.34E-11
504	Antiprotozoal drugs (Infections)	228	469	1.82 (1.47 - 2.24)	2.57E-08
304	Antihistamines, hyposensitisation, and allergic emergencies (Respiratory system)	290	617	1.73 (1.42 - 2.10)	3.48E-08
1306	Acne and rosacea (Skin)	267	609	1.66 (1.37 - 2.03)	4.13E-07
103	Ulcer-healing drugs (Gastrointestinal system)	181	371	1.66 (1.32 - 2.09)	1.84E-05
1302	Emollient and barrier preparations (Skin)	135	273	1.57 (1.21 - 2.04)	7.39E-04
1310	Anti-infective skin preparations (Skin)	370	943	1.55 (1.30 - 1.85)	1.50E-06
407	Analgesics (Central nervous system)	571	1586	1.48 (1.23 - 1.79)	3.48E-05

*BNF subchapters identified as signals in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 1.37E-03

For two BNF subchapters, the 95% confidence intervals suggested reduced risks of SLE: 74 cases and 271 controls were exposed to drugs for acute diarrhoea (subchapter 104, OR = 0.70, 95% CI 0.52 - 0.94) and 68 cases and 225 controls were exposed to local preparations for anal and rectal disorders (subchapter 107, OR = 0.71, 95% CI 0.51 - 0.98). Although a reduced risk was suggested based on the 95% confidence intervals, the P-values for these estimates exceeded the critical P-value corrected for multiple comparisons ($P_{corrected}$ = 0.001366). There was no clear association with risk of SLE for 63 of the 87 BNF subchapters tested (72%), with the 95% confidence intervals including 1 (data not shown) and P-values exceeding the corrected overall critical P-value. In total, 62 of the 87 point estimates were greater than 1 (71%). Exposure to subchapter 802 (drugs affecting the immune response for malignant disease and immunosuppression) was associated with a high risk (OR = 12.0, 95% CI: 2.46 - 58.8). This estimate was based on 12 exposed cases and 2 exposed controls, and the P-value exceeded the corrected overall critical P-value (P = 2.03E-03, $P_{corrected}$ = 1.37E-03).

Table 4-8: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis date for male cases and controls

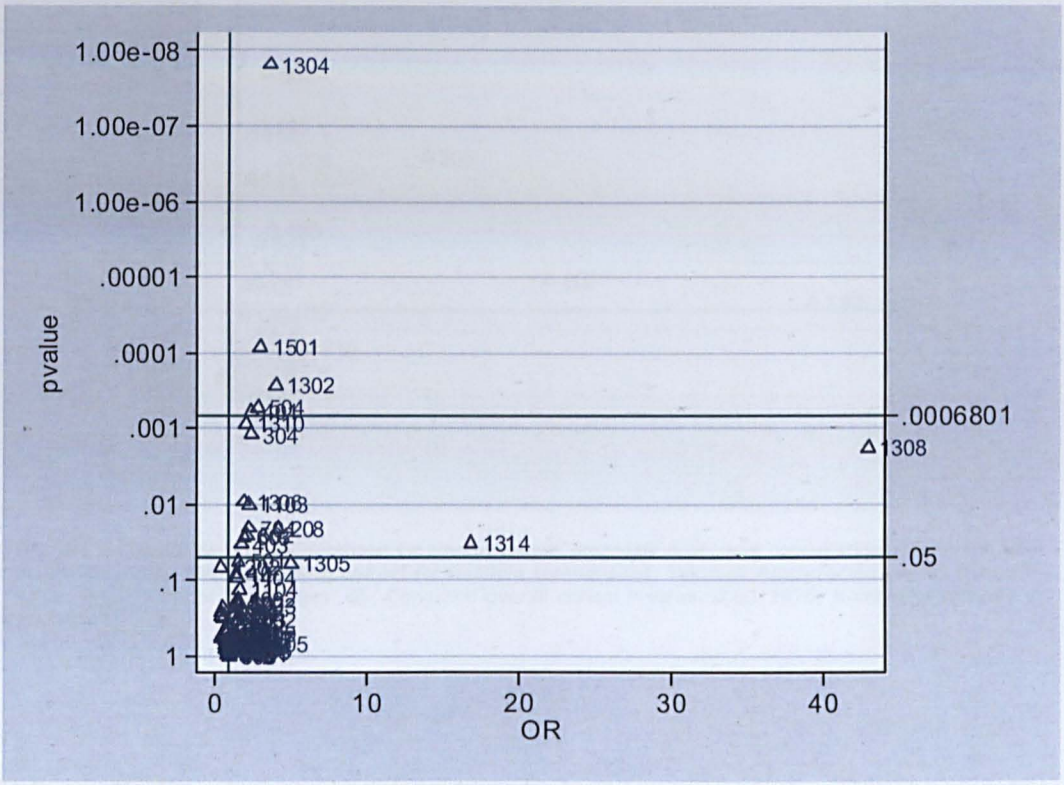
Label	BNF subchapter* (BNF chapter)	Case (N=154)	Control (N=620)	OR (95% CI)†‡	P value¶
1302	Emollient and barrier preparations (Skin)	28	27	4.08 (1.92 - 8.69)	2.65E-04
1304	Topical local corticosteroids (Skin)	89	163	3.67 (2.34 - 5.75)	1.52E-08
1501	General anaesthesia (Anaesthesia)	35	39	3.04 (1.75 - 5.30)	8.50E-05
504	Antiprotozoal drugs (Infections)	28	37	2.91 (1.59 - 5.32)	5.37E-04
401	Hypnotics and anxiolytics (Central nervous system)	44	59	2.46 (1.47 - 4.11)	6.02E-04

*BNF subchapters identified as signals in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 6.69E-04

In the sex-stratified analyses, we found similar results for women as compared to the overall results (data not shown). For men, less signals were identified but two previously undetected BNF subchapters were among the identified signals: BNF subchapter 401 (hypnotics and anxiolytics) and BNF subchapter 1501 (general anaesthesia) (Figure 4-b and Table 4-8). Apart from the four drugs temazepam, diazepam, lorazepam and butobarbitone/promethazine hydrochloride which are listed

in subchapter 401 as well as 1501, there are no further similarities between the two subchapters. Eight cases and one control were exposed to sunscreens and camouflagers (BNF subchapter 1308, OR = 42.9, 95% CI, 4.05 - 455). Although the point estimate and 95% confidence interval for subchapter 1308 suggested a strong association with risk of SLE, the P-value (P=1.80E-03) exceeded the corrected overall critical P-value ($P_{corrected}$ = 6.80E-04). Similarly, exposure to herbal preparations for the skin (subchapter 1314) was associated with an increased risk of SLE (OR = 16.9, 95% CI: 1.27 - 224). The estimate was based on three exposed cases and one exposed control, and the P-value (P=3.24E-02) again exceeded the corrected overall critical P-value of 6.80E-04.

Figure 4-b: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis date in men

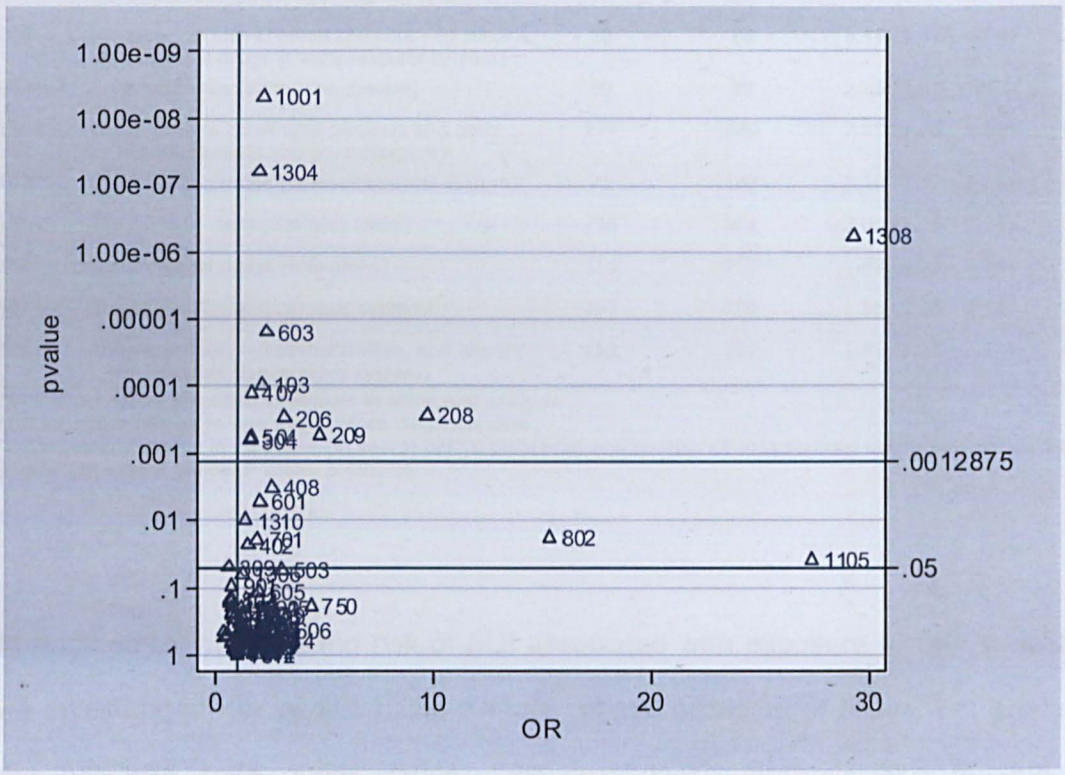


ORs are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 76; Corrected overall critical P-value: 0.0006801; Number of rejected P-values: 5

Stratifying the data by age at diagnosis gave similar results for cases and controls diagnosed at age 45 and over, compared to the overall results (data not shown). Although subchapters 103, 208 and 407 were not identified as signals in the older

cases and controls, the point estimates and 95% confidence intervals for these subchapters did suggest an increased risk of SLE. Among the signals for older cases and controls, there was one subchapter that was not identified in the full data set: 60 older cases and 112 older controls were exposed to subchapter 1104 (corticosteroids and other anti-inflammatory preparations for the eye, OR = 1.97, 95% CI: 1.35 - 2.87, P = 4.49E-04, $P_{corrected}$ = 1.15E-03).

Figure 4-c: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis date for individuals under 45 years old



ORs are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 85; Corrected overall critical P-value: 0.0012875; Number of rejected P-values: 11

The results for younger cases and controls (diagnosed before the age of 45) can be found in Figure 4-c and Table 4-9. The majority of signals for younger study subjects were similar to signals observed in the full data set. However, we observed three new signals, all of the BNF chapter of treatments for the cardiovascular system (subchapter 206: nitrates, calcium-channel blockers and other antianginal drugs, subchapter 208: anticoagulants and protamine and subchapter 209: antiplatelet drugs). Subchapter 209 contains aspirin, which has anti-inflammatory properties in

addition to its antiplatelet action. Two other identified signals are also subchapters that include aspirin (subchapters 407 and 1001).

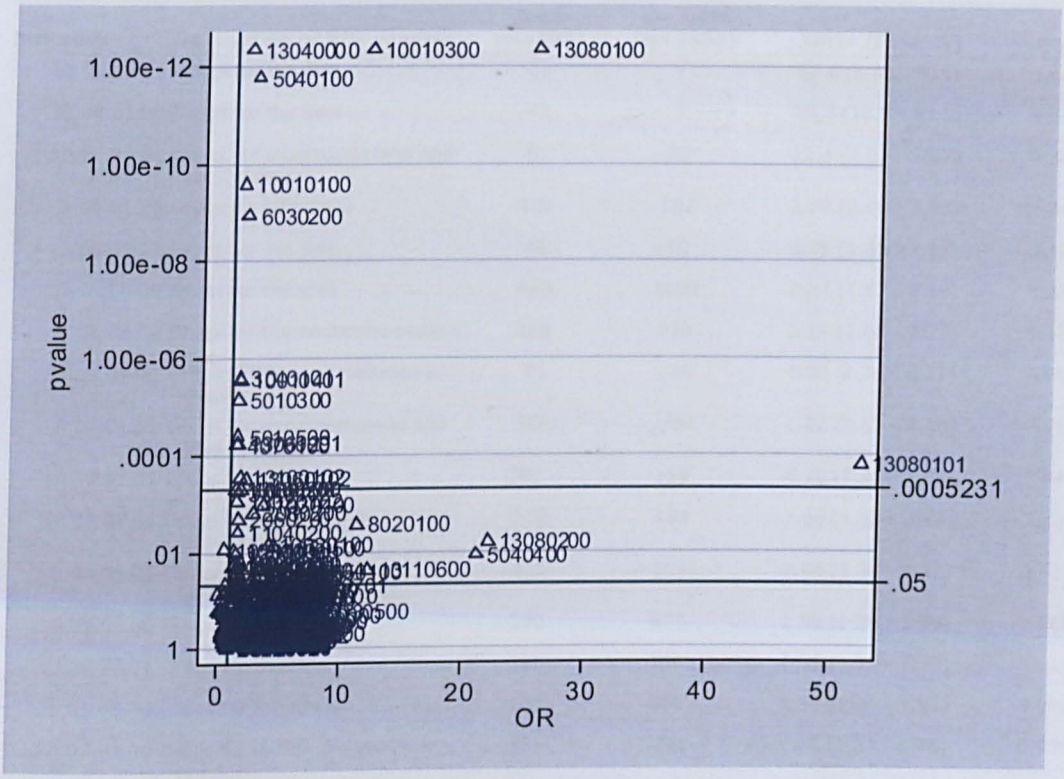
Table 4-9: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF subchapters one week or more before diagnosis in cases and controls under the age of 45

Label	BNF subchapter* (BNF chapter)	Case (N=446)	Control (N=1849)	OR†‡ (95% CI)	P-value¶
1308	Sunscreens and camouflagers (Skin)	21	3	29.2 (7.79 - 110)	5.71E-07
208	Anticoagulants and protamine (Cardiovascular system)	16	4	9.70 (2.86 - 33.0)	2.69E-04
209	Antiplatelet drugs (Cardiovascular system)	17	12	4.80 (1.98 - 11.6)	5.30E-04
206	Nitrates, calcium-channel blockers and other antianginal drugs (Cardiovascular system)	30	28	3.18 (1.70 - 5.94)	2.99E-04
603	Corticosteroids (Endocrine system)	69	99	2.35 (1.60 - 3.47)	1.55E-05
1001	Drugs used in rheumatic diseases and gout (Musculoskeletal and joint diseases)	279	640	2.20 (1.69 - 2.87)	4.73E-09
103	Ulcer-healing drugs (Gastrointestinal system)	71	107	2.18 (1.47 - 3.22)	9.50E-05
1304	Topical local corticosteroids (Skin)	236	561	2.00 (1.56 - 2.57)	6.19E-08
504	Antiprotozoal drugs (Infections)	115	257	1.67 (1.25 - 2.24)	5.91E-04
407	Analgesics (Central nervous system)	281	706	1.66 (1.28 - 2.16)	1.26E-04
304	Antihistamines, hyposensitisation, and allergic emergencies (Respiratory system)	152	352	1.61 (1.23 - 2.12)	6.37E-04

*BNF subchapters identified as signals in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 6.69E-04

In addition to investigating risk of SLE associated with exposure to BNF subchapters, we investigated risk of SLE using a more refined grouping of drugs, i.e. grouping by the full BNF code. Odds ratios, 95% confidence intervals and P-values were calculated for exposure to BNF codes one week or more before diagnosis date. Risk estimates and corresponding P-values for all BNF codes are presented in a smile plot (Figure 4-d). There were 264 BNF codes to which both cases and controls were exposed. Seventeen of these (6.4%) were identified as signals because the P-value was smaller than the overall corrected critical P-value.

Figure 4-d: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of SLE associated with exposure to BNF codes one week or more before diagnosis date



ORs are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 264; Corrected overall critical P-value: 0.0005231; Number of rejected P-values: 17

Appendix VI provides lists of drugs for the BNF codes that were identified as signals. Seven of the identified signals were codes of BNF chapter 13, which covers drugs for the skin. A further three signals were BNF codes of chapter 10 (drugs for musculoskeletal and joint diseases). The signals identified when using the more refined grouping of drugs by BNF code (Table 4-10) are similar to those based on grouping drugs by subchapter presented in Table 4-7. Fifteen of the seventeen BNF code signals were derived from BNF subchapters listed in Table 4-7. The risk estimates of twelve of those were higher than the risk estimates for the associated subchapter and the confidence intervals were wider. Two signals, BNF code 5.01.03.00 and 5.01.05.00, had not been identified in the previous analysis although both were from the same BNF subchapter (501, antibacterial drugs).

Table 4-10: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF code one week or more before diagnosis date.

BNF code*	Description of BNF chapter	Cases (N=875)	Controls (N=3632)	OR†‡ (95% CI)	P value¶
13.08.01.01	Drugs for the skin	21	1	52.6 (6.68 - 415)	1.68E-04
13.08.01.00	Drugs for the skin	47	7	25.7 (10.7 - 61.9)	4.38E-13
10.01.03.00	Drugs for musculoskeletal and joint diseases	81	20	12.1 (7.03 - 20.7)	4.38E-13
5.04.01.00	Drugs for infections	134	182	2.77 (2.09 - 3.67)	1.64E-12
13.06.01.02	Drugs for the skin	44	70	2.26 (1.45 - 3.52)	3.12E-04
13.04.00.00	Drugs for the skin	489	1099	2.23 (1.87 - 2.66)	4.38E-13
6.03.02.00	Drugs for the endocrine system	168	238	2.14 (1.68 - 2.73)	1.12E-09
1.03.05.00	Drugs for the gastrointestinal system	76	128	1.89 (1.32 - 2.71)	4.98E-04
10.01.01.00	Drugs for musculoskeletal and joint diseases	566	1461	1.82 (1.51 - 2.19)	2.51E-10
13.10.01.02	Drugs for the skin	87	159	1.78 (1.30 - 2.43)	2.94E-04
10.01.04.01	Drugs for musculoskeletal and joint diseases	218	430	1.68 (1.35 - 2.08)	2.75E-06
3.04.01.01	Drugs for the respiratory system	235	502	1.64 (1.34 - 2.02)	2.51E-06
5.01.03.00	Drugs for infections	292	673	1.56 (1.29 - 1.90)	6.90E-06
13.06.02.01	Drugs for the skin	226	526	1.53 (1.25 - 1.89)	5.61E-05
5.01.05.00	Drugs for infections	282	688	1.50 (1.24 - 1.82)	4.08E-05
4.07.01.00	Drugs for the central nervous system	473	1228	1.46 (1.21 - 1.75)	5.93E-05
13.10.02.00	Drugs for the skin	211	492	1.45 (1.18 - 1.79)	4.98E-04

*BNF codes identified as signals in the smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 5.23E-04

For a further 31 BNF codes there was a suggestion of an increased risk of SLE based on the 95% confidence intervals. However, the P-values for these estimates exceeded the corrected overall critical P-value (data not shown). There was also one BNF code for which a decreased risk of SLE was suggested based on the 95% confidence interval (BNF code 1.02.01.00, 40 cases and 158 controls exposed, OR = 0.58, 95% CI: 0.39 - 0.87). Again the P-value for this BNF code exceeded the critical P-value corrected for multiple comparisons.

In the sex-stratified analyses we identified similar signals for women as compared to the overall results (data not shown). For men, only three BNF codes were identified as signals. BNF code 13.04.00.00 (topical local corticosteroids for the skin) was identified as a signal both in men and in the overall analysis. The other two BNF codes identified as signals in men, codes 13.02.01.02 (non-proprietary emollient preparations) and 15.01.04.01 (Sedative and analgesic peri-operative drugs), did not

arise in the overall analysis but appeared to be strongly associated with risk of SLE since the risk estimates were large. Further details of BNF code signals in men are listed in Table 4-11.

Table 4-11: Odds ratios (OR), 95% Confidence Intervals (CI) and P-values for exposure to BNF codes one week or more before diagnosis in men

BNF code*	Cases (N=154)	Controls (N=620)	OR†‡ (95% CI)	P-value¶
13.02.01.02	28	25	4.87 (2.18 - 10.9)	1.16E-04
13.04.00.00	89	163	3.67 (2.34 - 5.75)	1.52E-08
15.01.04.01	35	38	3.20 (1.82 - 5.61)	4.96E-05

*BNF codes identified as signals in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 1.55E-04

When data were stratified by younger and older age at diagnosis, results for those aged less than 45 years at the time of diagnosis (index) date were similar to the overall analysis (data not shown). This was in contrast to the signal generation results for BNF subchapters, when we identified three signals of drugs aimed at the cardiovascular system in the younger cases and controls (subchapters 206, 208 and 209. See also Table 4-9).

For those aged 45 and older at diagnosis, one new BNF code was identified as a signal: 38 older cases and 49 controls were exposed to BNF code 11.04.02.00 (OR= 2.58 95% CI: 1.58 - 4.21, P = 1.58E-04, $P_{corrected}$ = 3.52E-04). This is in line with the results for older study subjects exposed to BNF subchapters where subchapter 1104 was identified as a signal.

Table 4-12: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF codes for specific drugs one week or more before diagnosis date

Drug name* BNF code	Cases (N=875)	Controls (N=3632)	OR†‡ (95% CI)	P-value¶
Carbamazepine				
4.02.03.00	30	59	1.65 (0.99 - 2.77)	5.63E-02
4.07.03.00	135	303	1.25 (0.97 - 1.61)	7.99E-02
4.08.01.00	44	84	1.61 (1.05 - 2.47)	2.82E-02
Minocycline				
5.01.03.00	292	673	1.56 (1.29 - 1.90)	6.90E-06§
12.03.02.00	46	84	1.41 (0.94 - 2.12)	9.89E-02
13.06.02.01	226	526	1.53 (1.25 - 1.89)	5.61E-05§
Trimethoprim				
5.01.08.00	267	770	1.07 (0.88 - 1.29)	5.07E-01
11.03.01.00	157	402	1.25 (0.99 - 1.58)	5.68E-02
Diazepam				
4.01.02.00	126	300	1.17 (0.90 - 1.52)	2.41E-01
4.08.02.00	2	2	1.32 (0.15 - 12.0)	8.03E-01
4.08.03.00	1	1	0.66 (0.04 - 11.0)	7.71E-01
10.02.02.00	122	302	1.11 (0.85 - 1.45)	4.37E-01
15.01.04.01	173	396	1.32 (1.05 - 1.66)	1.80E-02
Salbutamol				
3.01.01.01	153	455	0.97 (0.78 - 1.22)	8.03E-01
3.01.04.00	4	10	1.38 (0.36 - 5.31)	6.41E-01
3.01.05.02	23	61	0.91 (0.52 - 1.61)	7.52E-01
3.02.00.00	81	227	0.95 (0.70 - 1.28)	7.25E-01
7.01.03.00	17	57	0.82 (0.45 - 1.50)	5.14E-01

*Choice of drugs further explained in section 4.1
†OR for exposures one week or more before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value = 5.23E-04
§ P-value < 5.23E-04, therefore BNF code identified as signal

In sections 4.1 and 4.2 of this thesis we presented results for risk of SLE associated with specific drugs (instead of drugs grouped by BNF code). In Table 4-12, signal generation results are presented for the BNF codes representing these drugs. Both carbamazepine and minocycline were identified as risk factors for SLE in section 4.1. However, the BNF codes representing carbamazepine are not identified as signals using the smile plot method. For minocycline on the other hand, two of the three BNF codes are identified as signals. There were five BNF codes representing the 'control drug' diazepam or combined preparations that included diazepam. None of these BNF codes were identified as signals. However, the point estimates for four of the five codes were greater than 1, and the 95% confidence interval for BNF code 15.01.04.01 suggested an increased risk of SLE. BNF codes representing the 'control drug' salbutamol were not identified as signals. The point estimates were less than 1 apart from one code to which few cases and controls were exposed. Two BNF codes represented trimethoprim. The point estimate and 95% confidence interval of one of

these codes (11.03.01.00) suggested an increased risk of SLE. However, the P-value exceeded the value of the corrected overall critical P-value.

4.3.2. Exposure to Drugs One Year or More Before Diagnosis

Initial symptoms of SLE may be vague and overlapping with a number of other conditions. Therefore, considerable amounts of time may pass before the GP identifies the patient's symptoms as SLE. In the signal generation analyses described above, we investigated exposures as recent as one week before diagnosis. Drugs prescribed for early symptoms of SLE may have been identified as signals. Below we describe the results of signal generation in which recent exposures, i.e. drugs prescribed in the year before diagnosis, were excluded from the analyses.

When excluding recent exposures, five subchapters were identified as signals. All of these subchapters were also identified as signals when including recent exposures of up to one week before diagnosis (Figure 4-e and Table 4-13). The risk estimates were of similar magnitude to those obtained when including recent exposures.

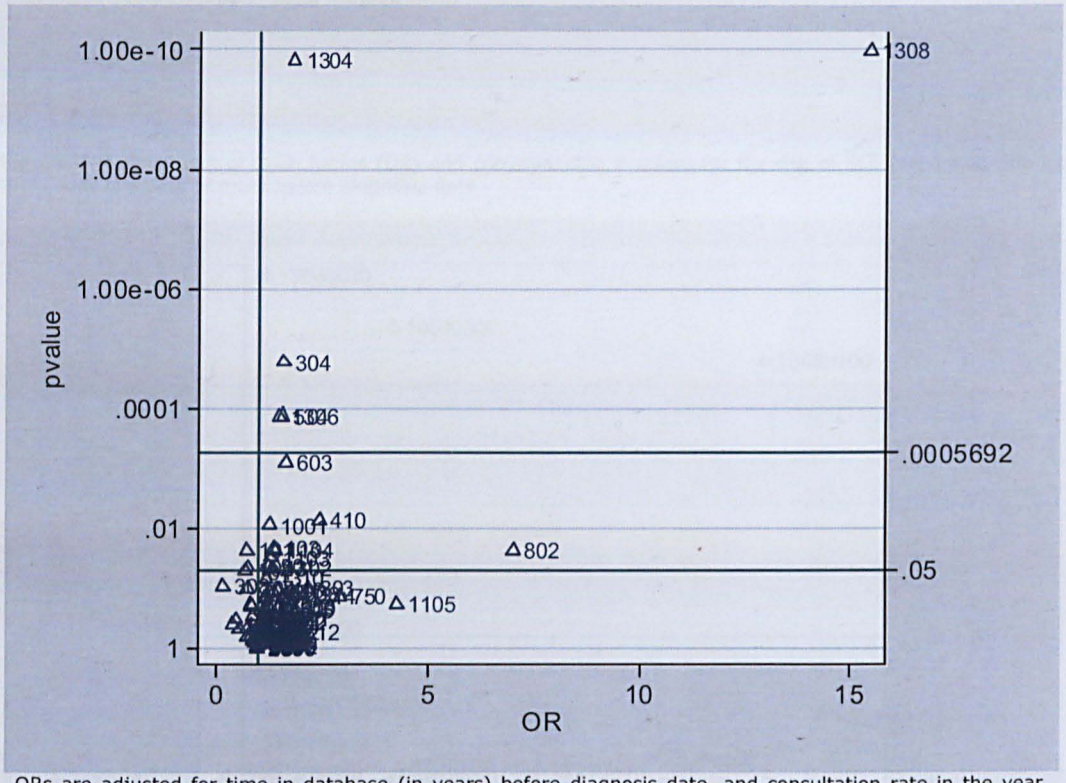
Table 4-13: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF subchapters one year or more before diagnosis date

Label	BNF subchapter* (BNF chapter)	Cases (N=875)	Controls (N=3632)	OR†‡ (95% CI)	P-value¶
1308	Sunscreens and camouflagers (Skin)	35	9	15.4 (6.74 - 35.4)	1.00E-10
1304	Topical local corticosteroids (Skin)	393	932	1.80 (1.51 - 2.16)	1.55E-10
304	Antihistamines, hyposensitisation, and allergic emergencies (Respiratory system)	236	520	1.58 (1.28 - 1.94)	1.66E-05
504	Antiprotozoal drugs (Infections)	173	381	1.57 (1.25 - 1.97)	1.31E-04
1306	Acne and rosacea (Skin)	219	516	1.50 (1.22 - 1.86)	1.37E-04

*BNF subchapters identified as signal in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value: 5.69E-04

Compared to the signal generation analyses that included recent exposures, we identified less signals but those identified were from the same subchapters. The risk estimates were lower and confidence intervals were wider compared to estimates obtained when including recent exposures. The same pattern was seen for sex- and age-stratified analyses.

Figure 4-e: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of SLE associated with exposure to BNF subchapters one year or more before diagnosis



ORs are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 87; Corrected overall critical P-value: 0.0056915; Number of rejected P-values: 5

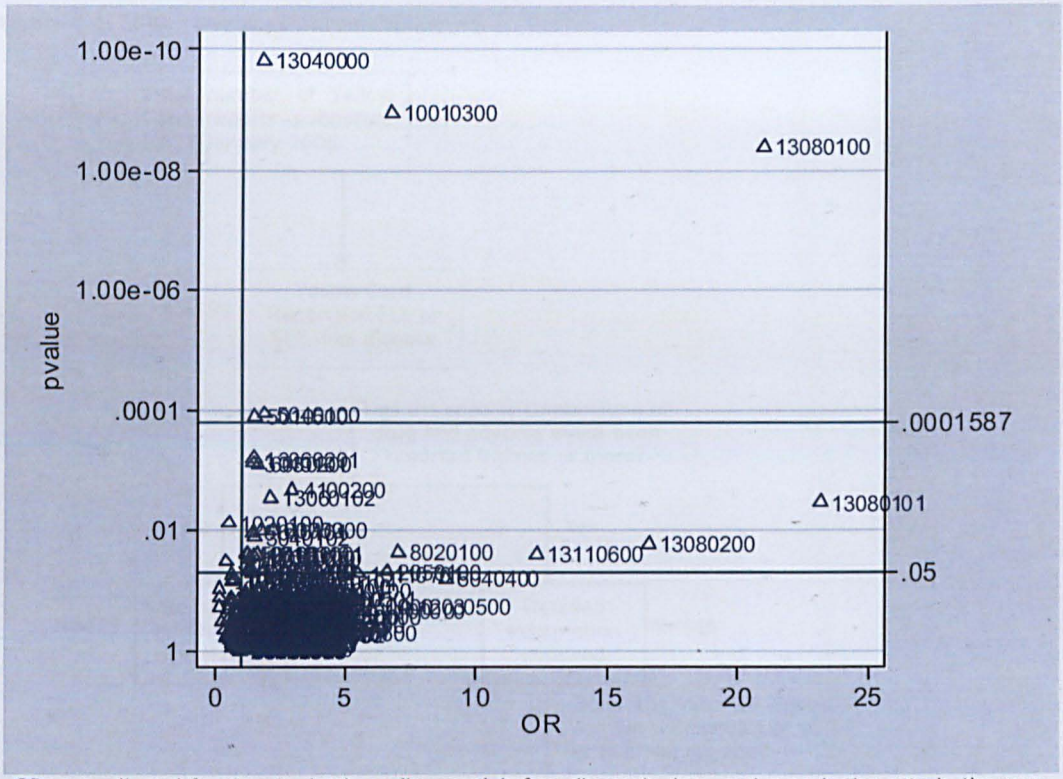
In Figure 4-f and Table 4-14, results are presented for signal generation of full BNF codes, excluding recent exposures from the analyses. We identified fewer signals as compared to the analyses that included recent exposures. The observed associations with risk of SLE are weaker as compared to the analyses that include recent exposures.

Table 4-14: Odds Ratios (OR), 95% Confidence Intervals (CI) and P-values for the risk of SLE associated with exposure to BNF codes one year or more before diagnosis date

BNF code*	Description BNF chapter	Cases (N=875)	Controls (N=3632)	OR†‡ (95% CI)	P-value¶
13.08.01.00	Drugs for the skin	27	6	20.94 (7.60 - 57.71)	4.05E-09
10.01.03.00	Drugs for musculoskeletal and joint diseases	42	19	6.70 (3.63 - 12.34)	1.10E-09
5.04.01.00	Drugs for infections	84	144	1.90 (1.37 - 2.62)	1.12E-04
13.04.00.00	Drugs for the skin	393	932	1.80 (1.51 - 2.16)	1.55E-10
5.01.05.00	Drugs for infections	243	576	1.50 (1.22 - 1.84)	1.28E-04

*BNF codes identified as signals in smile plot analysis
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis
¶Corrected overall critical P-value = 1.59E-04

Figure 4-f: Smile plot of Odds Ratios (OR) and corresponding P-values for the risk of SLE associated with exposure to BNF codes one year or more before diagnosis date



ORs are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 257; Corrected overall critical P-value: 0.0056915; Number of rejected P-values: 5

4.4. DESCRIPTION OF SIGNALS IN THE YELLOW CARD DATABASE

A total of 528480 Yellow Card reports were submitted between July 1963 and 10 January 2006 by health care professionals and, since recently, patients. SLE or SLE-like disease was the reported adverse drug reaction on 859 of these (0.16%). We received detailed records for 446 of the 859 reports (Figure 4-g). After inspection we

excluded 25 of the 446 detailed records, because the recorded adverse event was cutaneous lupus, which is not considered a form of SLE. The drug terbinafine was listed as the suspected drug on all of these 25 excluded reports. A further six reports were excluded because they concerned conditions other than SLE, namely: rheumatoid arthritis (N=2, suspected drugs: minocycline and procainamide), arthropathy (N=1, suspected drug: labetalol), arthritis (N=1, suspected drug: minocycline), myalgia (N=1, suspected drug: procainamide) and pneumonia (N=1, suspected drug: procainamide).

Figure 4-g: Stream diagram of Yellow Card reports

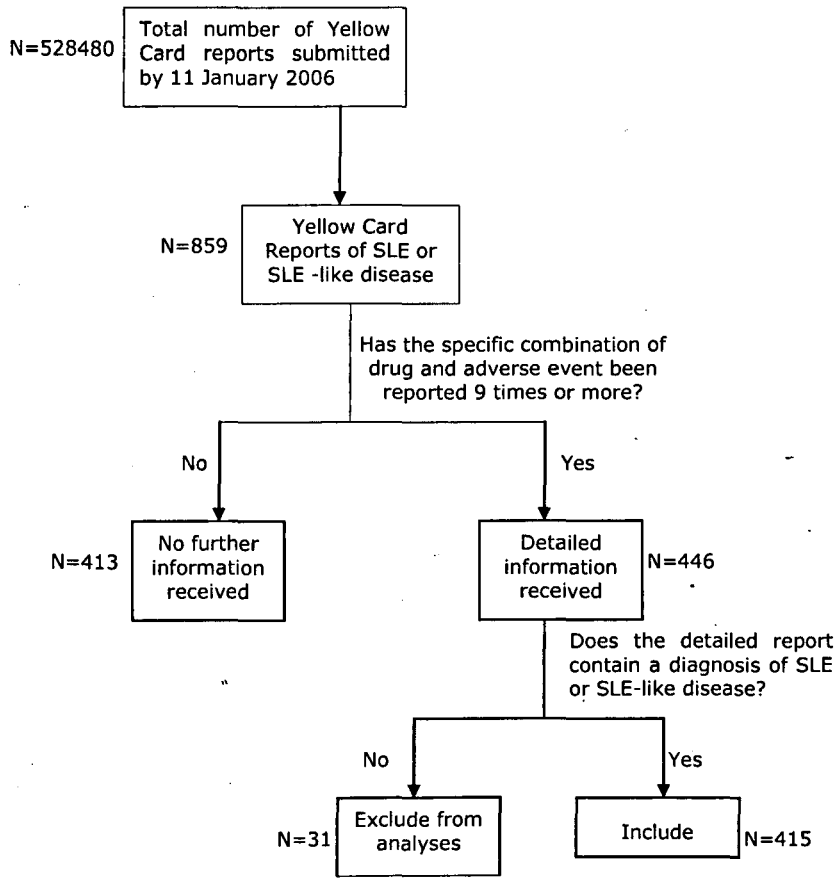


Table 4-15 lists the total number of included reports for each drug. The drug with the largest number of reports of a suspected association with SLE was hydralazine (42% of the total number of reports). The male to female ratio of reports for each drug can also be found in Table 4-15. An equal number of Yellow Cards reporting procainamide in association with SLE were submitted for men and women. For sulfasalazine and penicillamine on the other hand, the majority of reports were for female cases, and all twelve reports submitted for infliximab involved female cases.

Table 4-15: Number and sex distribution of Yellow Cards reporting SLE or SLE-like disease by suspected drug

			Outcome of disease				Time to onset of SLE, days§	
Suspected drug*	**No. of reports**	**Male : Female ratio†**	**Reco-vered/ reco-vering**	**Not reco-vered**	**Fatal**	**Not known‡**	**Median time (range)‖**	**% Missing**
Hydralazine	173	1 : 2.1	127	1	4	4	639 (3 - 2268)	82.7
Minocycline¶	138	1 : 2.9	105	18	0	14	161 (1 - 6570)	80.4
Practolol	21	1 : 2.0	15	0	0	6		100.0
Procainamide	20	1 : 1.0	10	0	0	10	(189, 480, 848)	85.0
Sulfasalazine	17	1 : 7.5	14	0	0	3		100.0
Carbamazepine	17	1 : 2.4	8	1	0	8	(1, 49, 80, 114)	76.5
Infliximab	12		4	2	0	6	(68, 186, 207, 277)	66.7
Penicillamine	9	1 : 8.0	6	1	0	2	(1460)	88.9
Labetalol**	8	1 : 6.0	6	0	0	2	(12)	87.5
Overall (%)	415	1 : 2.5	295 (71.1)	23 (5.5)	4 (1.0)	92 (22.2)		

*Drugs for which at least 9 reports of drug-induced SLE were submitted
†4 reports of unknown gender for hydralazine, and one report of unknown gender for minocycline and labetalol
‡The outcome was reported to be "not known", i.e. information on the outcome of disease was not missing
§Time from initiation of therapy to diagnosis of SLE
‖When the total of reported values 4 or less, the list of values is given instead of the range
¶One report for minocycline had missing information on outcome of disease
**One of the 9 reports for labetalol reported arthropathy rather than SLE and was excluded

Information on outcome of disease was available for 414 of the 415 reports. The majority of cases recovered or was recovering at the time of submission of the Yellow Card. Four cases had a fatal outcome of disease, all of whom were exposed to hydralazine.

Information on time between initiation of therapy and onset of SLE was missing on the majority of reports (Table 4-15). In addition, information on duration of therapy was missing on 72% of reports (data not shown). However, we did have information on both duration and time to onset of SLE for 27 of the 173 hydralazine reports. Seventeen of the 27 cases continued to take hydralazine for 1 up to 522 days after onset of SLE symptoms. A further five cases stopped taking hydralazine on the day

that SLE symptoms started. The remaining 5 cases developed SLE symptoms after cessation of hydralazine use. Time since cessation ranged from 4 days to nearly 4 years. Of these 27 cases, 23 recovered from SLE or were recovering at the time of submission of the Yellow Card report. Four cases had an unknown outcome of disease.

Table 4-16 presents the number of reports for each drug by age category. Overall, 27% of reports did not contain information on age of the case. The majority of cases taking minocycline (an antibiotic which is primarily prescribed for acne) were aged 15 to 44. All reports concerning cases aged 75 and over were for exposure to hydralazine which is an anti-hypertensive.

Table 4-16: Age distribution of patients for each drug suspected of inducing SLE

		Age group (years)							
Suspected drug*	**Number of reports**	**1-4**	**5-14**	**15-44**	**45-54**	**55-64**	**65-74**	**75+**	**Missing**
Hydralazine	173	0	0	12	31	45	33	6	46
Minocycline	138	0	3	119	4	1	0	0	11
Practolol	21	0	0	0	1	4	0	0	16
Procainamide	20	0	0	0	2	2	2	0	14
Sulfasalazine	17	0	0	5	0	4	2	0	6
Carbamazepine	17	1	1	7	3	0	0	0	5
Infliximab	12	0	0	3	2	2	0	0	5
Penicillamine	9	0	0	2	3	0	1	0	3
Labetalol†	8	0	0	1	0	1	1	0	5
Overall	415	1	4	149	46	59	39	6	111
(%)		(0.2)	(1.0)	(35.9)	(11.1)	(14.2)	(9.4)	(1.4)	(26.7)

*Drugs for which at least 9 reports of drug-induced SLE were submitted
†One of the 9 reports for labetalol reported arthropathy rather than SLE and was excluded

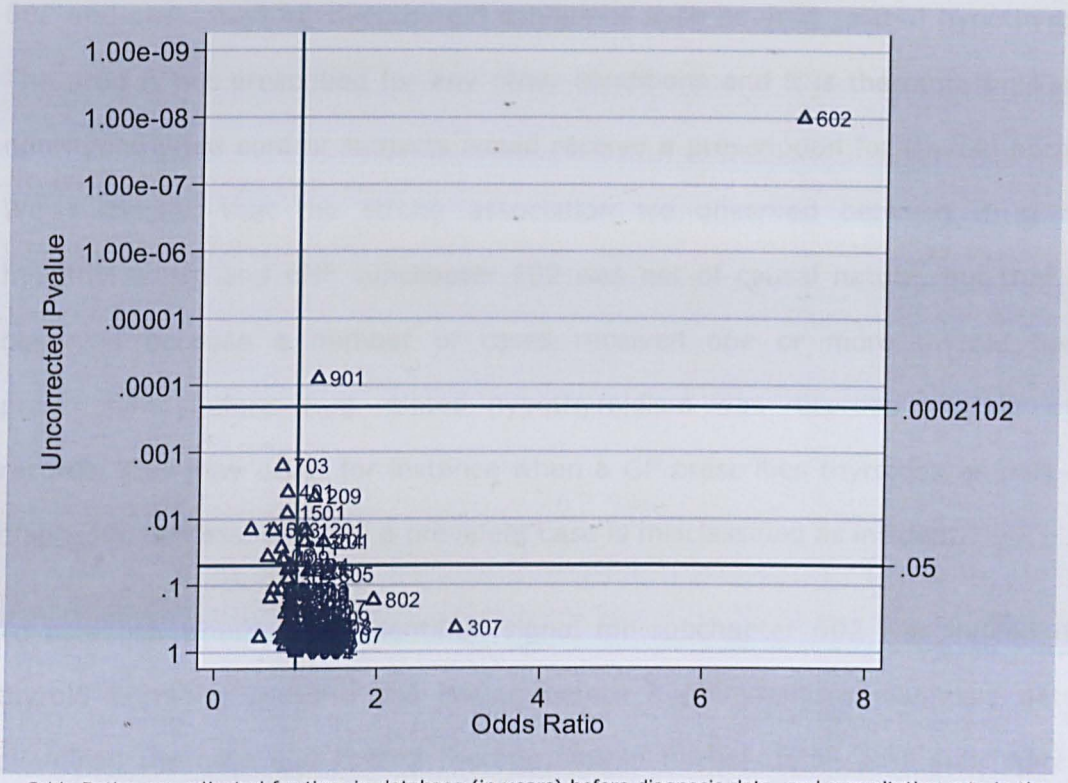
CHAPTER 5. RISK OF HYPOTHYROIDISM ASSOCIATED WITH PRESCRIPTION MEDICINE

We investigated risk of drug related hypothyroidism associated with exposure to prescription drugs. The total GPRD data set of hypothyroid cases and matched controls was divided in two. Firstly, a small subset was analysed to generate potential signals of drug-induced drug related hypothyroidism. Subsequently, the remainder of the data were analysed to evaluate newly identified signals. Results of the analyses are described in this chapter.

5.1. SIGNAL GENERATION USING THE "SMILE PLOT" METHOD

Initial analyses demonstrated that exposure to one particular BNF subchapter was associated with an extreme increased risk of drug related hypothyroidism: seven cases and none of the controls were exposed to subchapter 350, which resulted in an odds ratio of 5.83E+09 (confidence limits approaching zero to infinity). BNF subchapter 350 included non-pharmacologic care products for the throat such as a tracheostomy protector, dressing and brush. The specific subchapter was in use in earlier versions of the BNF, but in the most recent version (March 2007) it is no longer included. Further examination of the seven cases exposed to subchapter 350 revealed that these cases had undergone surgical operations or had been diagnosed with malignant neoplasms in the anatomical proximity of the thyroid gland, (e.g. laryngectomy, malignant neoplasms of the larynx). The medical codes referring to these conditions were considered to be indicative of potentially iatrogenic thyroid disease and cases and controls with an occurrence of such codes in their records were excluded from the analyses (see Appendix IV under "Further medical codes for potentially iatrogenic drug related hypothyroidism").

Figure 5-a: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of drug related hypothyroidism associated with exposure to BNF subchapters one week or more before diagnosis date



Odds Ratios are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 93; Corrected overall critical P-value: 0.0056915; Number of rejected P-values: 2. A description of all value labels in the plot (i.e. BNF subchapters) can be found in Appendix V.

After applying these refined case and control exclusion criteria, we re-ran the analyses. Overall results (i.e. data including both male and female subjects of all ages at diagnosis) are presented in Figure 5-a.

Two BNF subchapters were clearly associated with drug related hypothyroidism, namely the subchapter containing thyroid and antithyroid drugs (subchapter 602), and the subchapter containing drugs for anaemias and some other blood disorders (subchapter 901). 1221 cases and 763 controls were exposed to subchapter 602, resulting in an OR of 7.17 (95% CI: 6.42 - 8.01). 710 cases and 1937 controls were exposed to subchapter 901, resulting in an OR of 1.25 (95% CI: 1.11 – 1.37). Results were consistent throughout the age- and sex stratified analyses (data not shown).

The drug thyroxine is a thyroid hormone which is categorised under BNF subchapter 602 and prescribed for hypothyroid conditions such as drug related hypothyroidism. The drug is not prescribed for any other conditions and it is therefore unlikely that non-hypothyroid control subjects would receive a prescription for thyroid hormones. We suspected that the strong association we observed between drug related hypothyroidism and BNF subchapter 602 was not of causal nature, but that it was observed because a number of cases received one or more thyroid hormone prescriptions before drug related hypothyroidism was recorded in their medical records. This may occur for instance when a GP prescribes thyroxine as part of the diagnostic process, or when a prevalent case is misclassified as incident.

To establish whether the identified signal for subchapter 602 was indeed due to thyroid hormone prescriptions issued before hypothyroidism diagnosis date, we examined the case and control therapy files in further detail. BNF subchapter 602 consists of two different BNF codes, namely 06.02.01.00 (thyroid hormones) and 06.02.02.00 (antithyroid drugs). No controls received prescriptions for thyroid hormones. Of the 5918 incident drug related hypothyroidism cases in the signal generation data set, 1514 cases (26%) received their first thyroid hormone prescription before diagnosis of drug related hypothyroidism. The median number of days this first prescription preceded the diagnosis date was 373.5 (inter-quartile range, 67 to 1285). 763 cases (4.3% of the 5918 incident cases) received their first thyroid hormone prescription more than one year before diagnosis. The median number of prescriptions issued before diagnosis date was 6 (inter-quartile range: 1 to 23). 396 cases received only one prescription for thyroid hormone before their drug related hypothyroidism diagnosis was recorded. More than half of the cases (58%) received their first thyroid hormone prescription on the same date as the first code for drug related hypothyroidism was recorded in their medical records. All other cases (16%) received a thyroid hormone prescription after diagnosis of drug related hypothyroidism. For those receiving a prescription after diagnosis date, the median time between diagnosis and prescription was 21 days (inter-quartile range, 7 to 62). Overall, for 5091 cases (86%) their first thyroid hormone prescription was no more

than one year apart from the first recorded medical code for drug related hypothyroidism. These results confirmed our hypothesis that thyroid hormone prescription is a strong marker of drug related hypothyroidism and not a cause of disease. Therefore, instead of considering thyroid hormone prescription as a potential risk factor for disease, we incorporated the date of first prescription in the definition of the diagnosis date. We re-defined diagnosis date as the first occurrence of a code for drug related hypothyroidism in the medical records, or the first occurrence of a thyroid hormone prescription in the therapy records, whichever came earliest.

Table 5-1: Demographic characteristics and univariable Odds Ratios (ORs) with 95% Confidence Intervals (CIs) for the association between selected variables and risk of drug related hypothyroidism in the signal generation data set

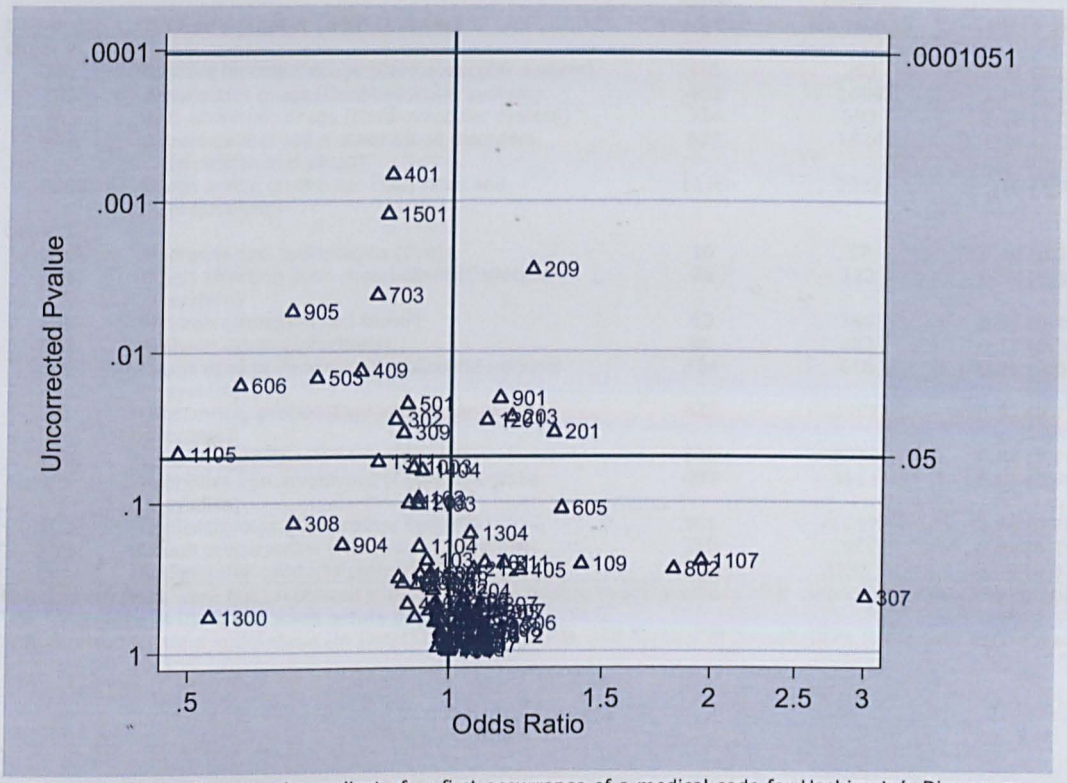
		Study subjects (%)		
		Case (N=4,088)	Control (N=16,945)	OR*(95% CI)
Sex†	Female	3432 (84.4)	14300 (83.9)	
Mean age at diagnosis, years†	Age (SD)	55.1 (17.1)	54.5 (16.6)	
	Range			
Time in database, years‡	1 - 3	638 (15.6)	3791 (22.4)	1.00 (reference)
	3 - 4.5	1141 (27.9)	5114 (30.2)	1.70 (1.48 - 1.95)
	4.5 - 7	1251 (30.6)	4597 (27.1)	2.97 (2.56 - 3.45)
	> 7	1058 (25.9)	3443 (20.3)	4.16 (3.53 - 4.90)
				p < 0.001
Consultation rate§	0 - 1	346 (8.5)	4596 (27.1)	1.00 (reference)
	2 - 3	704 (17.2)	3896 (23.0)	2.62 (2.28 - 3.02)
	4 - 6	1112 (27.2)	3660 (21.6)	4.59 (4.01 - 5.25)
	> 6	1926 (47.1)	4793 (28.3)	6.36 (5.58 - 7.24)
				p < 0.001

* Univariable OR for risk of drug related hypothyroidism
† Variable used to match cases and controls, therefore univariable OR is not reported
‡ Time (in years) in database before diagnosis
§ Number of consultations per year in the year preceding diagnosis date (index date for the controls)

Using these 'new' diagnoses dates, we reassessed whether cases were incident or prevalent. Originally, we had identified a total of 17791 incident cases of drug related hypothyroidism. After applying the new definition of diagnosis date, there were a total of 18606 incident cases. The total of incident cases was divided in 2 subsets based on geographical location of the practice as described in Section 3.3.2.1. Results for signal generation using the smaller subset of data are described below.

The final signal generation data subset contained 4088 incident cases with hypothyroid disease and 16945 matched controls. The demographic characteristics of cases and controls included in this final data set are summarised in Table 5-1.

Figure 5-b: Smile plot of Odds Ratios (OR) and corresponding P-values for risk of drug related hypothyroidism associated with exposure to BNF subchapters one week or more before 'new' diagnosis date



Diagnosis date defined as the earliest of: a first occurrence of a medical code for Hashimoto's Disease or a first occurrence of a prescription for thyroxine. Odds Ratios (OR) are adjusted for time in database (in years) before diagnosis date, and consultation rate in the year before diagnosis. Method used to correct for multiple comparisons: Yekutieli; Uncorrected overall critical P-value: 0.05; Number of P-values: 93; Corrected overall critical P-value: 0.00010511; Number of rejected P-values: 0.

Figure 5-b presents the association between drug related hypothyroidism and exposure to prescription drugs, grouped by BNF subchapter, one week or more before diagnosis date. Of the 93 BNF subchapters investigated, none of the P-values were smaller than the critical P-value corrected for multiple comparisons; i.e. no BNF subchapter was clearly associated with risk of drug related hypothyroidism. This pattern was consistent throughout the sex- and age-specific analyses (data not shown). In addition, none of the BNF subchapters were found to be strongly associated with risk of drug related hypothyroidism (i.e an Odds Ratio of greater than 5 or less than 0.2, regardless of whether the P-value did or did not exceed the overall corrected critical P-value). Results were consistent across the sex- and age-stratified analyses (data not shown).

Table 5-2: Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association between selected BNF subchapters and risk of drug related hypothyroidism in the signal generation data subset

Label	BNF subchapter (BNF chapter)*	Case N=4,088	Control N=16,945	OR†‡ (95% CI)
OR > 1				
201	Positive inotropic drugs (Cardiovascular system)	105	263	1.31 (1.02 - 1.69)
209	Antiplatelet drugs (Cardiovascular system)	402	1068	1.24 (1.08 - 1.42)
203	Anti-arrhytmic drugs (Cardiovascular system)	334	893	1.18 (1.02 - 1.36)
901	Anaemias and some other blood disorders (Nutrition and blood)	627	1824	1.14 (1.02 - 1.27)
1201	Drugs acting on the ear (Ear, nose and oropharynx)	1115	3522	1.10 (1.01 - 1.20)
OR < 1				
1105	Mydratics and cycloplegics (Eye)	10	57	0.48 (0.24 - 0.99)
606	Drugs affecting bone metabolism (Endocrine system)	26	122	0.57 (0.36 - 0.90)
905	Minerals (Nutrition and blood)	63	260	0.65 (0.49 - 0.88)
503	Antiviral drugs (Infections)	66	283	0.70 (0.53 - 0.93)
409	Drugs used in Parkinsonism (Central nervous system)	154	616	0.79 (0.65 - 0.95)
703	(Obstetrics, gynaecology and urinary tract disorders)	623	2471	0.82 (0.72 - 0.94)
1501	General anaesthesia (Anaesthesia)	646	2278	0.84 (0.76 - 0.93)
401	Hypnotics and Anxiolytics (Central nervous system)	882	3111	0.85 (0.78 - 0.93)
302	Corticosteroids (Respiratory system)	361	1267	0.86 (0.76 - 0.98)
309	Cough preparations (Respiratory system)	570	1940	0.88 (0.79 - 0.99)
501	Antibacterial products (Infections)	3310	12551	0.89 (0.81 - 0.98)

*BNF subchapters were not associated with risk of drug related hypothyroidism after correction for multiple comparisons
†OR for exposures up to one week before diagnosis date
‡OR adjusted for time in database (in years) before diagnosis, and number of consultations in the year before diagnosis

Table 5-2 lists all BNF subchapters that were found to have a 95% confidence interval excluding the null in the signal generation exercise. In Figure 5-b, these subchapters are located in the upper half (in between the horizontal line for P=0.05 and the line for the overall critical P-value corrected for multiple comparisons, P=1.05E-04). Although all confidence intervals for BNF subchapters listed in Table 5-2 suggest statistical significance, these subchapters were not identified as signals in the signal generation exercise because of the threshold we defined to take account of multiple comparisons. Table 5-2 was compiled to facilitate the signal evaluation exercise which will be described in section 5.2.

5.2. SIGNAL EVALUATION

When we originally designed our study to investigate associations between prescription drugs and risk of drug related hypothyroidism, we expected to observe signals of drug-induced hypothyroidism during the signal evaluation phase. We planned to subsequently evaluate these newly generated hypotheses in a larger subset of the data. Because no signals were observed during signal generation, we selected alternative BNF subchapters to evaluate in the second phase of this study.

An obvious alternative choice of BNF subchapters would have been those that were strongly associated with risk of disease (i.e. an OR greater than 5 or less than 0.2) but for which no statistical significance was observed. The larger number of individuals included the signal evaluation data subset (described in section 3.3.2.1) ensured greater statistical power to evaluate associations, i.e. to have more certainty when accepting a null hypothesis ("there is no association between BNF subchapter X and risk of drug related hypothyroidism"). However, in Phase I of our study we also did not observe any such strong associations. We therefore decided to evaluate BNF subchapters that were associated with risk of drug related hypothyroidism based on their 95% confidence interval, but were not identified as a signal because the P-values exceeded the threshold value we set to adjust for multiple comparisons. All BNF subchapters meeting these requirements are listed in Table 5-2. Of these, we selected two to evaluate in further detail: subchapter 901 (drugs for anaemias and some other blood disorders) for which there was a suggestion of a mildly increased risk of drug related hypothyroidism (OR = 1.14, 95% CI 1.02 – 1.27), and subchapter 401 (hypnotics and anxiolytics) for which there was a suggestion of a decreased risk of drug related hypothyroidism (OR = 0.85, 95% CI 0.78 – 0.93) in the signal generation phase of this study.

The signal evaluation data set contained 8,199 cases with a code for hypothyroidism and 33,950 matched controls (Table 5-3). 83.8% of the cases were female with a mean age at diagnosis of 55.1 years old (sd = 17.4). Male cases were on average 5.9 years older at diagnosis (mean age: 61.0, sd 17.3, $p < 0.0001$). The observation period from study entry to index date was on average 34 weeks longer for cases than controls ($p < 0.001$). Cases consulted their GP significantly more often in the year before diagnosis than the matched controls.

Table 5-3: Demographic characteristics and univariable Odds Ratios (ORs) with 95% Confidence Intervals (CIs) for the association between selected variables and risk of drug related hypothyroidism in the signal evaluation data set

		Study subjects (%)		
		Case (N=8,199)	Control (N=33,950)	OR*(95% CI)
Sex†	Female	6872 (83.8)	28569 (84.2)	
Mean age at diagnosis, years†	Age (SD)	56.1 (17.5)	55.6 (17.2)	
	Range	2 - 99	2 - 101	
Time in database, years‡	1 - 3	1,389 (16.9)	8,224 (24.2)	1.00 (reference)
	3 - 4.5	2,478 (30.2)	10,853 (32.0)	1.85 (1.68 - 2.04)
	4.5 - 7	2,523 (30.8)	9,233 (27.2)	3.19 (2.87 - 3.55)
	> 7	1,809 (22.1)	5,640 (16.6)	4.56 (4.04 - 5.14)
				p < 0.001
Consultation rate§	0 - 1	731 (8.9)	9,529 (28.1)	1.00 (reference)
	2 - 3	1,467 (17.9)	7,335 (21.6)	2.79 (2.53 - 3.07)
	4 - 6	2,148 (26.2)	7,318 (21.6)	4.29 (3.91 - 4.71)
	> 6	3,853 (47.0)	9,768 (28.8)	6.17 (5.64 - 6.75)
				p < 0.001

* Univariable OR for risk of drug related hypothyroidism
† Variable used to match cases and controls, therefore univariable OR is not reported
‡ Time (in years) in database before diagnosis
§ Number of consultations per year in the year preceding diagnosis date (index date for the controls)

Using conditional logistic regression, we investigated risk of drug related hypothyroidism associated with exposure to two BNF subchapters one week or more before diagnosis. We investigated exposure to the individual BNF codes classified under the subchapter of interest. Crude and adjusted odds ratios and 95% confidence intervals are listed in Table 5-4. Of the exposures categorized under BNF subchapter 901, the code for oral iron had the highest exposure rate (approximately 10% of controls) and approximately 2 percent of control subjects was exposed to "Drugs used in megaloblastic anaemia". Among exposures grouped under subchapter 401, both the BNF codes for hypnotics and for anxiolytics had relatively high exposure rates of over 10% in the control subjects. As can be seen in the power curves in section 3-a, statistical power in this study was sufficient (i.e. > 80%) to

detect odds ratios of 1.5 or more for oral iron, "Drugs used in megaloblastic anaemias", hypnotics, and anxiolytics.

Table 5-4: Odds Ratios (OR) and 95% Confidence Intervals (CI) for the risk of drug related hypothyroidism associated with selected BNF codes

BNF code	Description	Case N=8,199	Control N=33,950	Crude OR * (95% CI)	Adjusted OR*† (95% CI)
Drugs for anaemias and some other blood disorders (subchapter 901)					
09.01.01.01	Oral iron	1267	3533	1.67 (1.55 - 1.80)	1.26 (1.17 - 1.37)
09.01.01.02	Parenteral iron	18	37	2.01 (1.14 - 3.55)	1.36 (0.75 - 2.46)
09.01.02.00	Drugs used in megaloblastic anaemias	222	626	1.49 (1.27 - 1.76)	1.14 (0.96 - 1.36)
09.01.03.00	Drugs used in hypoplastic, haemolytic and renal anaemias	40	111	1.48 (1.02 - 2.15)	1.18 (0.80 - 1.74)
Hypnotics and anxiolytics (subchapter 401)					
04.01.01.00	Hypnotics	1273	4249	1.25 (1.16 - 1.35)	0.94 (0.88 - 1.02)
04.01.02.00	Anxiolytics	1080	3594	1.31 (1.22 - 1.41)	0.91 (0.84 - 0.98)
04.01.03.00	Barbiturates	9	23	1.55 (0.71 - 3.40)	1.18 (0.52 - 2.67)

*Reference category is the unexposed group for each drug
†ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date

Crude odds ratios suggested a mildly increased risk of drug related hypothyroidism associated with all BNF codes included in subchapters 901 and 401. However, after correction for confounding factors, the association was no longer apparent for BNF codes included in subchapter 901 ("Drugs for anaemias and some other blood disorders") apart from oral iron (code 09.01.01.01). As for BNF codes included in subchapter 401 (hypnotics and anxiolytics), the direction of the association shifted to a slightly decreased risk of drug related hypothyroidism after adjustment for confounding factors. Results of the sex-stratified analyses showed a similar pattern (data not shown). The sex-specific risk estimates were of similar magnitude with the exception of one BNF code: Among the male study subjects, 29 cases and 41 controls were exposed to "Drugs used in megaloblastic anaemias". After adjustment for confounding factors, we observed a more than twofold increased risk in men (OR = 2.47, 95% CI: 1.47 to 4.15). Results for women were similar to the overall results (data not shown). A test for interaction did not confirm that the effect of BNF subchapter 09.01.02.00 varied with gender (p=0.501).

Risk of drug related hypothyroidism associated with number of prescriptions (as a proxy for cumulative dose) is summarised in Table 5-5. Although the odds ratios for categorised number of prescriptions for oral iron did not show a clear pattern of

increasing risk with increasing cumulative dose, we did observe a trend (adjusted OR per 10 prescriptions 1.11, 95% CI 1.06 - 1.17, p for trend < 0.001). Sex-stratified analyses showed a similar pattern (data not shown). When we stratified our data by younger (<55 years) and older (≥55 years) age at diagnosis, a clear pattern was observed for younger cases.

Table 5-5: Odds Ratios and 95% Confidence Intervals (CI) for the risk of drug related hypothyroidism associated with grouped number of prescriptions for selected BNF codes

BNF code	Number of prescriptions*	Case N=8,199	Control N=33,950	Crude OR (95% CI)	Adjusted OR† (95% CI)
Drugs for anaemias and some other blood disorders (subchapter 901)					
09.01.01.01	Unexposed	6932	30417	1.00 (Reference)	1.00 (Reference)
	1	491	1430	1.60 (1.43 - 1.78)	1.28 (1.14 - 1.43)
	2 to 3	416	1077	1.83 (1.62 - 2.07)	1.34 (1.18 - 1.52)
	> 3	360	1026	1.61 (1.42 - 1.84)	1.17 (1.02 - 1.33)
				P_{trend} < 0.001	P_{trend} < 0.001
09.01.01.02	Unexposed	8181	33913	1.00 (Reference)	1.00 (Reference)
	1	13	21	2.53 (1.25 - 5.10)	1.82 (0.87 - 3.80)
	2 to 4	1	10	0.45 (0.06 - 3.52)	0.33 (0.04 - 2.62)
	> 4	4	6	2.66 (0.75 - 9.50)	1.46 (0.40 - 5.28)
				P_{trend} = 0.054	P_{trend} = 0.554
09.01.02.00	Unexposed	7977	33324	1.00 (Reference)	1.00 (Reference)
	1	92	290	1.36 (1.06 - 1.75)	1.06 (0.82 - 1.38)
	2 to 5	72	178	1.74 (1.31 - 2.31)	1.34 (0.99 - 1.80)
	> 5	58	158	1.45 (1.07 - 1.98)	1.08 (0.78 - 1.49)
				P_{trend} < 0.001	P_{trend} = 0.135
09.01.03.00	Unexposed	8159	33839	1.00 (Reference)	1.00 (Reference)
	1 to 2	19	52	1.51 (0.89 - 2.58)	1.20 (0.69 - 2.10)
	3 to 15	16	32	2.08 (1.13 - 3.86)	1.69 (0.89 - 3.21)
	> 15	5	27	0.67 (0.23 - 1.94)	0.53 (0.18 - 1.55)
				P_{trend} = 0.144	P_{trend} = 0.718
Hypnotics and anxiolytics (subchapter 401)					
04.01.01.00	Unexposed	6926	29701	1.00 (Reference)	1.00 (Reference)
	1-2 Rx	538	1742	1.35 (1.22 - 1.50)	1.01 (0.91 - 1.12)
	3-18 Rx	363	1291	1.22 (1.08 - 1.38)	0.88 (0.78 - 1.00)
	>18 Rx	372	1216	1.29 (1.14 - 1.46)	0.91 (0.80 - 1.04)
				P_{trend} < 0.001	P_{trend} = 0.047
04.01.02.00	Unexposed	7119	30356	1.00 (Reference)	1.00 (Reference)
	1-2 Rx	541	1,807	1.31 (1.18 - 1.45)	0.94 (0.84 - 1.04)
	3-10 Rx	291	925	1.38 (1.20 - 1.58)	0.91 (0.79 - 1.05)
	>10 Rx	248	862	1.24 (1.07 - 1.44)	0.85 (0.72 - 0.99)
				P_{trend} < 0.001	P_{trend} = 0.01
04.01.03.00	Unexposed	8190	33927	1.00 (Reference)	1.00 (Reference)
	1-12 Rx	5	7	2.83 (0.88 - 9.16)	2.04 (0.60 - 6.96)
	13-40 Rx	2	8	1.04 (0.22 - 4.98)	0.85 (0.16 - 4.54)
	>40 Rx	2	8	0.96 (0.20 - 4.60)	0.75 (0.16 - 3.56)
				P_{trend} = 0.611	P_{trend} = 0.954

* Data categorised based on tertiles of number of prescriptions in the control group, with the unexposed as the reference category

†ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date

Results for risk of drug related hypothyroidism associated with exposure to oral iron in the younger cases can be found in Table 5-6. Risk in the grouped variable of number of prescriptions for oral iron increased with increasing number of prescriptions. In addition, the p for trend and the adjusted odds ratio per 10 prescriptions were statistically significant in this younger case population. A test for

interaction confirmed effect modification by age at diagnosis: the interaction term for the highest exposure category (4 or more prescriptions) was statistically significant (p=0.005), with no interaction in the other two exposure categories (1 prescription: p for interaction = 0.649, 2 or 3 prescriptions: p for interaction = 0.970). This effect modification was largely confined to the female population, as there were only 14 male cases and 15 male controls exposed to oral iron in the younger age group.

Table 5-6: Crude and adjusted Odds Ratios (OR) and 95% Confidence intervals for the association between oral iron and exposure and risk of drug related hypothyroidism in cases diagnosed before age 55.

Exposure to oral iron*	Case (N=4039)	Control (N=17,179)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Exposed before diagnosis date	822	2311	1.77 (1.60-1.94)	1.34 (1.21-1.48)
Number of prescriptions				
Unexposed	3,217	14,868	1.00 (Reference)	1.00 (Reference)
1	314	984	1.56 (1.36-1.79)	1.27 (1.10 - 1.47)
2 - 3	295	793	1.87 (1.61-2.16)	1.36 (1.17 - 1.59)
4 or more	213	534	2.05 (1.72-2.44)	1.41 (1.18 - 1.70)
			P_{trend} < 0.001	P_{trend} < 0.001
OR per 10 prescriptions			1.63 (1.49-1.78)	1.26 (1.16 - 1.39)

*The unexposed category served as the reference group in all analyses
†Odds ratios adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date

There was a suggestion of a decreased risk of drug related hypothyroidism with an increasing number of prescriptions for anxiolytics (BNF code 04.01.02.00). This trend remained after adjustment for confounding factors (P for trend = 0.01): risk in the highest exposure category (more than 10 prescriptions) was significantly lower compared to unexposed individuals (OR = 0.85, 95% CI 0.72 - 0.99). However, the adjusted OR per 10 prescriptions did not confirm this association (OR = 0.99, 95% CI 0.97 - 1.00). Number of prescriptions for any of the other BNF codes classified under subchapter 401 (hypnotics and anxiolytics) was not associated with risk of drug related hypothyroidism.

CHAPTER 6. DISCUSSION

6.1. RISK OF SLE ASSOCIATED WITH PRESCRIPTION DRUGS

The risk of Systemic Lupus Erythematosus associated with exposure to prescription drugs was investigated using two data sources and a variety of analysis methods. Firstly, we evaluated existing hypotheses (identified from the literature) in GPRD data, for which we used a case-control and a case-only approach. Secondly, we performed signal generation using the Smile Plot method which had not previously been utilised for the purpose of drug safety. We also described findings on Yellow Card spontaneous reports of suspected cases of drug-induced lupus. In this chapter, we will present and discuss the key findings of these studies.

6.1.1. Matched Case-Control Study

6.1.1.1. Main Findings

In our large matched case-control study investigating the association between lupus and exposure to prescription drugs, we found statistically significant risks for exposure to hydralazine, minocycline and carbamazepine. For the latter two a cumulative dose - response relationship was observed. Gender influenced the association between use of carbamazepine and risk of lupus.

6.1.1.2. Discussion

This matched case - control study was the first large observational study to investigate risk of SLE associated with prescription medicines thought to induce the disease. We showed a sex-specific effect of carbamazepine which has not previously been reported. Comparison studies using a different data source are not available to this date. However, associations between drugs and risk of SLE that have been hypothesised in case reports were confirmed in our study. This led us to believe the GPRD is a useful data source to study drug-induced SLE. However when both the disease and the exposures (i.e. drug prescriptions) of interest are uncommon, study

power to detect moderately increased risks or to perform relevant subgroup analyses is limited, even in this very large data set.

In clinical practice, the diagnosis of idiopathic lupus is based on criteria formulated by the ACR[19]. It is thought that drug-induced lupus, which develops in previously asymptomatic individuals and usually disappears upon discontinuation of the drug, is different from idiopathic SLE, which is a life-long disease[23]. Criteria for diagnosis of drug-induced lupus are less strict than those for diagnosis of idiopathic SLE[25]. In our study the diagnosis of SLE was not validated for each case individually and laboratory test results for ANA or anti-DNA antibody positivity were not available for the majority of cases. However this was not considered an important limitation of our study, because of the less strict diagnostic criteria for drug-induced lupus. In addition, a high proportion of our case population received prescriptions for drugs used for the treatment of lupus (79% non-steroidal anti-inflammatory drugs, 10% corticosteroids, 48% anti-malarials and/or immunosuppressives[17]) and incidence rates based on our data are consistent with other published estimates[17].

Risk of SLE associated with sulfasalazine exposure and penicillamine exposure could not be studied in our study population because of the selection criteria for cases and controls. Study subjects were not diagnosed with other autoimmune diseases and would therefore by definition not receive drugs which are prescribed specifically for autoimmune conditions, such as sulfasalazine and penicillamine. We did note that 5 cases and 3 controls received prescriptions for sulfasalazine, which may be the result of misclassification of an autoimmune disease as non-autoimmune.

Although causality can not be determined on the basis of our findings, the magnitude of the risks observed for hydralazine and minocycline as well as the cumulative dose-response relationship observed for minocycline and carbamazepine are in support of a causal relationship. We ensured that drug exposures took place before onset of SLE by excluding prevalent cases. Symptoms are reported to disappear after cessation of drug use in a number of drug-induced lupus patients[61] and occasionally re-challenge with the drug results in reappearance of symptoms[25, 62]. Because the

GPRD does not contain codes for recovery from disease we were not able to investigate causality in this manner. However, we did note that use of hydralazine was discontinued upon diagnosis in three of the four cases using the drug.

We included consultation behaviour as a confounding factor in our models, even though one could argue it is on the causal pathway between drug exposure and induction of SLE. We believe it was correct to adjust for consultation behaviour as after adjustment, the increased risk of lupus disappeared for the 'control' drugs, but not for the drugs thought to induce SLE.

A GPRD-based study of minocycline-induced lupus in a population of acne patients[63] reported an 8.5-fold increased risk of lupus for use of minocycline at the time of SLE diagnosis. Excluding past users of minocycline from our study results in a similar unadjusted 8-fold increased risk. Adjustment for confounders reduced this risk to 4, highlighting the importance of including consultation behaviour and length of therapy history in analyses of drug-induced disease utilising the GPRD.

Numerous previous case reports have suggested that lupus can be induced by a range of prescription medications. To our knowledge no sufficiently large observational studies assessing such associations have been published. We observed a substantially increased risk of lupus associated with exposure to hydralazine and minocycline and moderately increased risk for carbamazepine, quinidine, methyldopa and captopril. This study provides evidence that the increased risks observed are likely to be causal given the lack of an increased risk observed with deliberately selected 'control' drugs. For several other drugs previously suggested to increase the risk of lupus, we lacked statistical power to reliably confirm or exclude an effect even utilising a database that includes over 20 million person years of observation.

6.1.2. Self-Controlled Case Series

In the previous section of this thesis we discussed the association between risk of SLE and exposure to prescription drugs, based on results from a matched case-control study. In the current section, we will discuss the same hypothesized

associations between prescription drugs and risk of SLE. This discussion will be based on findings resulting from a different statistical analysis method, namely a self-controlled case series. In both the case-control and case series methods we utilised incident cases of SLE who were identified from the GPRD. In the previously discussed case-control study the reference group consisted of individually matched control subjects. Some factors, such as health-seeking behaviour, were likely to have varied between cases and their matched controls. If these factors were associated with both risk of SLE and the chance of receiving a prescription for a drug of interest, bias may have affected SLE risk estimates. In addition, the matched controls in this case-control study were defined as those not having an autoimmune disease, and therefore by definition did not receive medication specific for autoimmune conditions other than SLE (some of which have been implicated in risk of SLE). In contrast, the self-controlled case series utilised within-person comparisons to obtain risk estimates of drug-induced SLE. Factors such as health-seeking behaviour or coexistence of other autoimmune conditions were assumed to be constant within each person during the observation time and did therefore not bias the results. In theory, factors that change over time within one individual, such as disease severity and symptoms, may still confound the associations investigated in a self-controlled case series.

6.1.2.1. Main Findings

In this case series investigating relative incidence of SLE associated with exposure to prescription drugs we found a suggestion of a positive association for hydralazine, minocycline, carbamazepine, penicillamine and sulfasalazine. The effects of these drugs did not appear to be immediate. In the washout period of 30 to 60 days after receiving a prescription for minocycline and sulfasalazine, the relative incidence of SLE was more than double compared to baseline (unexposed) periods. For hydralazine, the relative incidence rate during the washout period was more than four-fold compared to baseline.

6.1.2.2. Discussion

No large observational studies have previously quantified the time between exposure to drugs of interest and the development of clinically apparent SLE. In our large data set of incident SLE cases, the number of subjects exposed to the drugs of interest was limited, resulting in limited statistical power. Although incidence rates in pre-specified time intervals after receiving a prescription could not be estimated with great precision, we did observe an increased risk for a number of drugs implicated with risk of SLE.

The main strength of this study is that we estimated relative incidence rates of SLE by making within-person comparisons. Unlike studies that make inter-person comparisons such as our previously described matched case-control study of SLE and prescription drugs (described in further detail in sections 4.1 and 6.1.1), risk estimates of this case series were not affected by confounders such as comorbid autoimmune disease or health-seeking behaviour[59]. However, our results may still have been affected by factors that change over time within one individual, such as SLE symptoms and severity. Because the majority of drugs of interest were indicated for conditions that are independent of SLE symptoms and severity (for instance: hyralazine is indicated for hypertension, minocycline is indicated for acne), we believe the extent of confounding in our anlayses is limited. Compared to our matched case-control study, risk estimates of the case series were lower, suggesting that residual confounding may have resulted in an overestimation of risk in the case-control study.

A number of limitations of both the study design and our data have to be taken into account when interpreting the results of the self-controlled case series of SLE. In terms of limitations of the data, we have already mentioned the limited number of cases exposed to the drugs of interest. This limitation can not be overcome at the current time, because the database used in our study, the GPRD, is the largest longitudinal patient-level database available for pharmacoepidemiology research[12].

In the future, when more data will have been recorded in the GPRD, we will be able to expand our study including additional exposed cases.

One disadvantage of our data was the difficulty of assessing the exact date on which SLE became clinically apparent. In our self-controlled case series we used the first occurrence of a medical code for SLE as the diagnosis date. In reality however, a patient may have had symptoms for a number of weeks (or even months) before this patient consulted with their GP, and/or before a GP ruled out all other potential disease diagnoses. This may have resulted in a substantial delay between onset of symptoms and a computerised medical record of an SLE diagnosis. While computerised information for prescriptions and prescription dates is known to be accurate[52] [40], this accuracy may not always be the case for the SLE diagnosis date. If the diagnosis of SLE is recorded at a later date than the actual onset of the disease, but prescription dates are correct, then the relative incidence rate of SLE may have appeared to be higher in a period later than our pre-specified 'high risk' period. This may explain why, for all drugs of interest, the relative incidence rate during the 'washout' period (i.e. 31 to 90 days after receiving a prescription) was higher compared to the relative incidence rate in the 'high risk' period (the 30 day period after issuing a prescription) as well as the baseline period. This pattern was seen for drugs implicated in risk of SLE, as well as the 'control drugs' which are thought not to induce SLE. These results had not been anticipated at the analysis stage of our study and we therefore did not include further 'high risk' or 'washout' periods in our design.

Some limitations with regard to the statistical analysis method should be noted. The self-controlled case series method was originally designed to study adverse events following vaccination[64]. A major underlying assumption of the method is that the probability of exposure (i.e. receiving a prescription for a drug of interest) is independent of the outcome (i.e. a diagnosis of lupus)[59]. In our study of drug-induced SLE several scenarios are plausible in which this independence may not be present. For instance, the increased risk of SLE associated with exposure to

minocycline has been reported in a number of international peer-reviewed papers and autoimmune disease textbooks[22, 23, 25, 61-63, 65-68]. If a GP is aware of these publications and observes a patient on minocycline to develop symptoms of SLE, the GP may switch the patient over to an alternative anti-acne treatment, thereby influencing this patient's chance of receiving further minocycline prescriptions. The potential effect on risk estimates is dependent on the timing of a GP's decision to switch a patient over. For instance, if the patient stops receiving prescriptions for minocycline as soon as their GP suspects a diagnosis of SLE (but the actual diagnosis has not yet been recorded in the database), the patient would no longer have a chance to have their SLE diagnosis recorded while they are receiving minocycline and we may find an artificially low incidence rate of SLE during exposed periods.

An adapted method of the self-controlled case series method is currently being developed to investigate 'censoring events', i.e. events for which the occurrence (e.g. diagnosis of SLE) influences the chance of being subsequently exposed to a risk factor of interest (e.g. drug prescription). This adapted method takes account of missing exposure data and has been shown to work in simple situations where the number of cases is relatively large and the number of repeat exposures is limited (Farrington et al, in press). We performed some preliminary analyses using this adapted method in close collaboration with those who developed it. With our sparse yet complex data due to the large number of repeat prescriptions, the method is not yet operational and needs further development. When the method is finalised it would be interesting to apply to our data and compare risk estimates to those obtained using the original self-controlled case series method. If results are markedly different, this would mean a GP indeed changes his or her prescribing behaviour after occurrence of an SLE diagnosis and we would have to treat prescriptions issued after diagnosis date as censored (Farrington et al, in press). We are looking forward to collaborating closely with Dr. Whitaker and Prof. Farrington to further develop this method in the near future.

In the self-controlled case series analyses reported here we assumed that risk of SLE returned to baseline at the end of each washout period. This assumption may not have been correct: it has been reported that patients on hydralazine are at increased risk of developing SLE when exposed to a cumulative dose of 100g or more[65]. An adapted version of the self-controlled case series method is available to take account of cumulative exposure levels[59]. Instead of assuming that risk returns to baseline at the end of each washout period and before the next prescription, this adapted method calculates relative incidence rates separately for each risk, washout, and 'in between' period (which we previously called baseline period). The time prior to the first prescription serves as baseline (unexposed) time. When we applied this adapted method to our data, the model was not able to calculate risk estimates, most likely due to the low number of exposed subjects who each had large numbers of repeat prescriptions. We were unable to investigate the effect of cumulative exposures on the risk of SLE using the self-controlled case series approach.

In this case-only approach we were able to investigate risk of SLE associated with exposure to drugs prescribed for comorbid autoimmune conditions. Associations have been hypothesized in the literature for sulfasalazine and penicillamine, which are both used for the treatment of Rheumatoid Arthritis[65] [23]. Quantitative risk measures and/or estimates of time to onset of SLE after exposure to these drugs have not been previously reported. Our results suggest an approximately twofold increased risk of SLE associated with penicillamine and sulfasalazine exposure.

In the self-controlled case series, individuals without the outcome of interest and without the exposure of interest do not contribute information to the risk estimate. In addition, incident cases who are on drugs taken daily for many years continuously also do not contribute any information to the risk estimate, because these cases will not have any baseline (unexposed) comparison time. Similarly, when repeat prescriptions are a limited number of days apart, but long enough for a risk and washout period to pass by, the amount of baseline time will be limited. In this situation, the cases do contribute information to the risk estimates. However,

analyses are likely to be less robust as compared to analyses in which substantial amounts of unexposed time was available to calculate baseline incidence.

The majority of drugs implicated in the risk of SLE are used to treat lifelong conditions (or prevent exacerbations) and users of these drugs are likely to be exposed during the majority of observation time. For instance, carbamazepine is an anti-epileptic drug and it prevents the occurrence of epileptic seizures by maintaining a certain dose at all times[69]. Other drugs implicated in risk of SLE that may be used on a continuous basis are hydralazine, methyldopa, captopril and acebutolol (all are used in the treatment of hypertension), minocycline (when used to treat acne), chlorpromazine (when used in the long-term treatment of schizophrenia), propylthiouracil (when used in long-term treatment of hyperthyroidism), and penicillamine and sulfasalazine (used to suppress the rheumatic disease process). In addition, one of the 'control drugs', salbutamol, is prescribed for maintenance of asthma. For these drugs, the self-controlled case series method may not be the most appropriate statistical analysis method to asses associations with risk of SLE because of the limited amount of unexposed baseline time.

Although both the case-control study and the self-controlled case series utilised the same set of incident SLE cases from the GPRD, risk estimates of these two studies are not directly comparable. First of all, the measures obtained in the two analyses are different, namely an odds ratio for the case control study and an incidence rate ratio for the case series. In order to calculate the odds ratio, we considered exposures taking place before diagnosis of SLE. For the incidence rate ratio on the other hand, we considered prescriptions received at any point during a person's observation time in the GPRD, including time after diagnosis of SLE. In addition, the sample of cases contributing to the risk estimates was different in the two study designs. In the matched case-control study only discordant case-control pairs contributed information, whereas in the case series only exposed cases were included. Despite these differences, it is helpful to compare results of both studies of SLE and prescription drugs in terms of direction of risk estimates, whether the

estimates are statistically significant, and size of the risk estimates (i.e. whether exposures are mildly or strongly associated with risk of disease). These comparisons can provide useful information when interpreting results of both the case-control and case-series analyses. For instance, we suspected that the results of the matched case-control study were affected by bias. In the self-controlled case series, where these biases did not play a role, we observed different (lower) risk estimates. This finding made us believe that the risk observed in the case-control study may have been overestimated due to residual (unmeasured) confounding that could not be accounted for in the logistic regression models. We will further discuss potential sources of residual confounding in section 6.1.3.2.

When comparing sex-specific risk estimates for carbamazepine from the case-control and case series analyses, results are inconclusive. In the case-control analyses, we observed an interaction with sex whereby women appeared to have an increased risk of SLE after carbamazepine exposure. No clear association was seen in men. In the self-controlled case series however the observed effect was in the opposite direction; no clear effect was seen in women whereas the relative incidence rate in men was strongly increased in both the high risk and washout periods. However, results of both analysis methods were based on a limited number of cases (the number of exposed male subjects in the case-control study: 3 cases and 10 controls, in the case series: 7 cases) and our findings may have been due to chance. Further studies investigating sex-specific risk of SLE associated with carbamazepine exposure will have to be conducted to clarify our conflicting results.

Although the risk estimates obtained from this case series have to be interpreted with caution due to a limited number of exposed study subjects, the results contribute valuable information to the current body of knowledge on drug-induced SLE. Hypotheses of associations between drugs and risk of SLE that were identified from the literature were previously confirmed using a case-control approach. With our case series analysis we were able to further confirm some of these pre-existing hypotheses.

6.1.3. Smile Plots and Systemic Lupus Erythematosus

In sections 6.1.1 and 6.1.2 of this thesis, we evaluated pre-existing hypotheses of drugs that may induce SLE which were identified from the literature. We were able to confirm some of these hypotheses. In this section, we discuss results from a signal generation exercise in which we also investigated the association between prescription medicine and risk of SLE. The purpose of this exercise was twofold, namely: to investigate whether the smile plot method was capable of detecting known associations, and to investigate whether any other drugs, in addition to those hypothesised in the literature, were associated with risk of SLE.

6.1.3.1. Main Findings

We found a strong association between exposure to sunscreens and camouflagers and risk of SLE. Other BNF subchapters that were identified as potential signals were not as strongly associated with risk of disease. Among the identified BNF subchapters were those for corticosteroids (for topical local use, as well as systemic corticosteroids), drugs used in musculoskeletal diseases, and antiprotozoal drugs. When excluding recent exposures taking place in the year before diagnosis of SLE, some of these associations were still apparent, especially the association between sunscreens and camouflagers and risk of SLE. However, the risk estimates were lower compared to those including recent exposures.

The risk estimate for the BNF subchapter which includes minocycline, a drug known to be associated with risk of SLE, only provided weak evidence for an association. When investigating risk associated with full BNF code (i.e. a finer sub-categorisation of drugs), we were also not able to identify many of the known associations between drugs and risk of lupus.

6.1.3.2. Discussion

The majority of signals we identified in this exercise involved drugs that are commonly prescribed to treat (early) symptoms of SLE. These 'signals' are most likely markers of disease rather than causative factors in the aetiology of SLE.

Although we believe these BNF subchapters are not associated with risk of disease in a causal manner, the drugs are in some way connected with SLE and cannot be considered false-positive signals. Drugs in three of the BNF subchapters that were identified as signals, subchapters 103, 1306 and 208, could not be directly linked to early symptoms of SLE and warranted further investigation.

Although stomach ulcers are not a symptom of SLE, we did observe an association between the BNF subchapter for ulcer-healing drugs (subchapter 103) and SLE. Two of the subchapters encoding aspirin and non-steroidal anti-inflammatory drugs (NSAIDS, subchapters 407 and 1001) were also identified as a 'signal'/marker of SLE. Known and relatively common side effects of aspirin and NSAIDS include gastro-intestinal side-effects, e.g. stomach ulcers. So, due to use of aspirin and NSAIDS, cases were at higher risk of developing gastro-intestinal conditions than their matched controls. These gastro-intestinal side effects were likely to have been treated with for instance ulcer-healing drugs. It is therefore not surprising we identified subchapter 103 as a 'signal'/marker of SLE.

Two BNF subchapters, those for anticoagulants and protamine (208), and drugs treating acne and rosacea (1306), were observed to be associated with SLE. Unlike the previously discussed associations, the drugs in these subchapters could not be directly or indirectly linked to symptoms of SLE. With subchapter 208 we may have identified a previously unknown association. However, our observation may be a chance finding because only a limited number of cases and controls were exposed to the subchapter of interest. When the signal generation exercise was repeated using refined grouping of drugs, we no longer observed a signal for any of the BNF codes categorised under subchapter 208. There are two possible explanations for this negative finding; a true association may not exist, or perhaps the sample size was too limited (due to refined grouping) to detect an association. Further studies are needed to clarify our findings.

The subchapter for drugs treating acne and rosacea (subchapter 1306) includes the drug minocycline, a drug that is known to be associated with risk of SLE[62, 63]. We

believe our identification of subchapter 1306 as a signal most likely represents this association between minocycline and SLE. When we excluded recent exposures to subchapter 1306 from the analyses, the association was also identified as a signal. In addition, when we repeated our signal generation exercise using refined grouping of drugs (grouping by full BNF codes instead of BNF subchapters), two of the three codes that include minocycline were identified as a signal. In our previously described case-control and self-controlled case series we had already identified this increased risk of SLE associated with minocycline use. The risk estimates in both of the previous analyses were higher compared to the estimates reported in the signal generation exercise. Due to the grouping of drugs by subchapter or full BNF code, we included drugs other than minocycline that were not associated with risk of SLE and may have caused a dilution of the effect of minocycline. However, further studies investigating risk of SLE associated with each of the drugs comprised in subchapter 1306 are needed, to ensure the identified signals do not represent a class effect.

An important limitation of our signal generation analysis was the grouping of exposures based on BNF subchapter. Drugs with an opposite effect in the human body may be incorporated in the same subchapter. For example, the BNF subchapter for drugs used in diabetes (subchapter 601) contains both insulin (required for glucose absorption) and glucagon (which counteracts the effects of hypoglycaemia). An additional limitation of grouping by BNF subchapter is that it combines drugs with the same effect but a different mechanism of action into one exposure category. An example is the BNF subchapter for "Antisecretory drugs and mucosal protectants" (subchapter 103). This subchapter includes proton pump inhibitors, which are used in the treatment of gastric and duodenal ulcers. The drug inhibits gastric acid secretion by blocking an enzyme system in a certain type of gastric cells. Another type of drugs, also used for the treatment of gastric and duodenal ulcers and categorised under subchapter 103, is the H_2-receptor antagonist. This drugs reduces gastric acid output by blocking an entirely different pathway in the cell; the histamine H_2-receptor. Other examples are the subchapter for Antiepileptics (408, including carbamazepine and an additional wide range of different drugs with often unknown

mechanism of action) and that for hypertension and heart failure (205, including hydralazine but also beta-blockers, calcium channel blockers, Angiotensin-converting enzyme (ACE) inhibitors). Combining these different entities into one exposure category may result in 'dilution' of the effect which may explain why we did not identify the subchapters for hydralazine and carbamazepine as a signal.

The strong association seen for sunscreens and camouflagers, which was also apparent when we excluded recent exposures from the analyses, indicated that a number of cases sought medical treatment for symptoms of SLE more than one year before the diagnosis. This raises questions about the accuracy of the SLE diagnosis date as recorded in the database. We also found an association (albeit less pronounced) for anti-malarials, which are drugs that may be used in the treatment of SLE. Again, the association was apparent when excluding recent exposures from the analyses. In our signal generation analyses we used the first occurrence of a medical code for SLE as the diagnosis date, but it may be more appropriate to redefine this diagnosis date to the date of a first prescription for disease specific treatment. In practice this may not always be feasible, as many of the treatments for SLE are non-specific, i.e. also used for the treatment of a number of other conditions.

All smile plots depicting the risk of SLE associated with various groups of drugs were based on risk estimates and p-values that were adjusted for confounding factors. The majority of point estimates suggested an increased risk of SLE, instead of being randomly dispersed around the null. It is highly unlikely that the majority of BNF subchapters are truly associated with risk of SLE. A more plausible explanation is that residual confounding affected our risk estimates. In the previously discussed self-controlled case series of SLE and exposure to specific drugs, we already suggested there may be an effect of residual confounding in the case-control analysis. The findings of this signal generation exercise provide further evidence of an influence of unmeasured bias.

A potential source of the residual confounding in this study is confounding by indication. It is possible that a GP preferentially prescribed a certain drug to

individuals who were predisposed to develop SLE, whereas others not likely to develop SLE may have received an alternative drug[70]. Although this source of confounding is an important problem in many pharmacoepidemiological studies, it is unlikely that it influenced the majority of our risk estimates in the same direction, i.e. an overestimate of the risk. Another source of residual confounding may be related to a non-random difference between the case and control groups in terms of the proportion of individuals with contraindications for a specific drug. If the proportion of controls with contraindications for a drug is larger than this proportion among cases, we would find a spurious association between use of this drug and risk of SLE (because the odds of exposure would be lower in controls compared to cases). Again, it is unlikely that this source of bias affected all of the exposure categories in a similar way.

A more plausible explanation for the apparent residual confounding in our study is related to a differential disparity between cases and controls in terms of health-seeking behaviour. Behavioural factors are difficult to measure in computerised medical records. However, in the study of drugs and risk of SLE, these behavioural factors may play a large role: patients who are more prone to visit their GP are more likely to receive prescriptions to any drug and they are also more likely to be diagnosed with SLE. In our analyses, we adjusted for the effect of health-seeking behaviour by using the number of visits in the year before SLE diagnosis as a proxy. The time period of one year before diagnosis to measure this number of visits may not have been ideal. As illustrated by our analysis excluding drug exposures in the year before SLE index date, several cases had symptoms of SLE (such as photo-sensitivity) long before the index date and occurrence of these symptoms may have affected a case's health-seeking behaviour. It would have therefore been more appropriate to measure health-seeking behaviour in a period before onset of SLE symptoms, for instance in the 2 years to 1 year before index date. However, many of the matched controls did not have two years or more of recorded data before the index date. Adjusting our analyses for health-seeking behaviour using this alternative

proxy variable would have resulted in the loss of a substantial number of controls from the analysis, and thereby a substantial loss of statistical power.

Although there is no gold standard available against which we can check our results of the smile plot analysis, we can comment on sensitivity and specificity by referring to evidence from the literature and from our previously reported case-control and case series analyses (sections 4.1, 4.2, 6.1.1 and 6.1.2). In these previous analyses, we confirmed a number of associations that had also been reported in the literature. Of the confirmed associations, only one was identified as a signal using the 'Smile Plot' method, namely the subchapter for minocycline. Other BNF subchapters comprising drugs that are known to be associated with risk of SLE were not identified as signals in this smile plot analysis, i.e. a number of false negative associations were among our results.

In summary, when we utilised the 'Smile Plot' method to generate signals of drug-induced lupus we observed a number of highly specific associations between drugs and risk of SLE, most of which were not causal. In order to interpret our results we needed intricate knowledge of the disease, as well as an understanding of the indications and side-effects of drugs that were identified as signals. After ruling out the majority of potential signals because they were in fact markers of disease, there were only two signals left that needed further scrutiny. One signal, for the BNF subchapter containing minocycline, has been previously reported in the literature and we therefore believe this signal is true-positive. The other signal may have been erroneously identified. Among the 87 exposures investigated, the number of false-positive signals identified with this 'Smile Plot' analysis is not more than one, from which we can derive that the specificity of this method is high. On the other hand, a number of known associations were not identified in the smile plots. From these false-negative findings we conclude that the sensitivity of the method is currently not optimal. Better hierarchical coding systems for drugs are needed to allow for appropriate grouping of drugs which will improve sensitivity of the method.

6.1.4. Signals of Drug-Induced SLE in the Yellow Card Database

So far, we have discussed risk of SLE associated with prescription drugs based on data from the General Practice Research Database. In this section we discuss signals of drug-induced SLE which were observed in the Yellow Card database. Although both the GPRD and the Yellow Card database comprise data from the United Kingdom, the nature of the data collection process is entirely different. In the GPRD, data are collected on a daily basis as part of routine clinical practice. The Yellow Card database on the other hand contains spontaneous reports of suspected adverse drug reactions which are voluntarily sent in by health care professionals (and, more recently, by patients as well).

6.1.4.1. Main Findings

Numerous reports of drug-induced lupus have been submitted as part of the Yellow Card scheme. The majority of these reports listed hydralazine or minocycline as the suspected drug. The majority of cases (71%) were reported to recover when the drug suspected of causing lupus was withdrawn. Four individuals who developed SLE after being exposed to hydralazine were reported to have died from the disease. Missing information was a common factor among all Yellow Card reports: time to onset of SLE was missing on the vast majority of reports (83%), as well as information on duration of therapy (72%).

6.1.4.2. Discussion

The Yellow Card database does not contain information on the total number of persons exposed to drugs of interest at any one time. In addition, spontaneous reporting databases such as the Yellow Card database are subject to substantial under-reporting[71]. Given this lack of denominator data and inaccurate numerator data, it is not possible to calculate a quantitative risk measure of SLE associated with exposure to the suspected drugs. It is also not informative to directly compare the number of reports for drug-induced lupus across the different suspected drugs, again

because denominator data is lacking, and the prevalence of use for each of the drugs is likely to be different.

Some methods have been employed to identify signals of adverse drug reactions in spontaneous reporting databases. Examples are the proportional reporting ratio (PRR) used by the MHRA to investigate data in the Yellow Card database[72], the Empirical Bayesian Geometric Mean (EBGM)[73] employed by the FDA to investigate the MedWatch data, as well as application of data mining algorithms to the spontaneous reporting data[74]. Despite the sometimes sophisticated statistical methodology, these methods are generally applied to poor quality data and can therefore not assess causality but merely signals of adverse drug reactions[8]. The above mentioned methods are beyond the scope of this thesis. Our analysis of the Yellow Card data was purely descriptive and provided a source of comparison for signals identified from the literature and from the GPRD.

Signals of drug-induced lupus identified from the Yellow Card database showed overlap with signals that have been reported in the literature. Unfortunately we were not given permission to view reports of drugs that were suspected of inducing lupus in less than nine occasions. We can therefore not comment on the completeness of the Yellow Card data as compared to information available in the literature. However, it should be noted that both the Yellow Card database as well as the published literature collect data based on voluntary, non-systematic reporting mechanisms. Data from both sources are therefore likely to be incomplete and subject to biases related to (for instance) the severity of the adverse event, the number of years a drug has been on the market, the frequency of use of a suspected drug, the background rate of the condition in the general population, etc. For example, consider the number of reports (N=20) for procainamide. Procainamide is prescribed for arrhythmias of the heart which occur relatively commonly. It is known that approximately 30% of procainamide users will develop lupus within one year of starting therapy[65]. If we would assume that all instances of procainamide-induced lupus were recorded in the Yellow Card database, an estimated 70 individuals would

have been exposed to procainamide in the UK during the nearly 25 years that the Yellow Card Scheme has been in operation. This number is very low and illustrates the problem of under-reporting.

Compared to our previously discussed signal generation exercise utilising GPRD data, the Yellow Card data revealed a larger number of signals of drug-induced SLE. This is primarily due to the current limitations of the smile plot method as discussed in section 6.1.3. However, it should be noted here that healthcare professionals are encouraged to submit Yellow Card reports as soon as an adverse drug reaction is suspected (instead of reporting only those associations for which causality has been proven). Due to the nature of data collection, it is likely that false positive reports are included in the Yellow Card database.

An important strength of the Yellow Card data was the availability of information on disease outcome. In our earlier signal evaluation analyses of GPRD data, this information could not be derived because the GPRD medical coding dictionary does not include codes for disease remission. The Yellow Card data indicated that symptoms of lupus disappear after withdrawal of the suspected drug, which is an important confirmation of what has been reported in the literature.

6.1.5. Risk of SLE Associated With Prescription Drugs: the Full Picture

Numerous reports in the literature have suggested an association between certain prescription drugs and risk of SLE[22, 23, 25, 61-63, 65-67, 75-77]. We utilised data from the GPRD to evaluate these pre-existing hypotheses. Data were analysed using two different study designs; a matched case-control study and a self-controlled case series. Results of both these studies suggested an increased risk of SLE associated with minocycline, hydralazine and carbamazepine. In addition, the self-controlled case series suggested an increased risk of SLE associated with use of penicillamine and sulfasalazine. Results for other drugs of interest were inconclusive and need further investigation.

The case-control and the self-controlled case series designs each provided complimentary pieces of information regarding the hypothesised associations between drugs and risk of SLE. The matched case-control study was especially useful to investigate the effect of cumulative dose on risk of SLE. The self-controlled case series on the other hand provided information on the timing of SLE in relation to exposure to drugs of interest. However, with both the statistical analysis methods we obtained wide confidence intervals around our point estimates due to the low incidence of SLE and the low exposure prevalence of the drugs of interest (i.e. low statistical power). At the present time, no larger data set than the GPRD is available to study the hypothesised associations. In the current age of computerised medical records it is thinkable that other (and larger) sources will become available in the future, perhaps through pooling of national data and linkage of several data sources[78]. If such data sources become available it will be possible to gain further understanding of the hypothesized associations and obtain more evidence to assess causality.

A few limitations should be noted regarding the use of computerised medical records to study SLE. In chapter 2 of this thesis we already discussed some general limitations of the GPRD in terms of its validity. With regard to studying SLE, a few additional points are important to mention. The results of both the case-control and case series analysis methods are dependent on accurate recording of diagnosis date and prescription dates. As discussed in section 6.1.2, the exact SLE diagnosis date is particularly difficult to establish when using computerised information.

When studying the association between exposures and risk of disease, it is important to ensure only true cases of the disease of interest are included in the study. We therefore formulated strict criteria defining cases of SLE. The set of diagnostic codes we included in our definition may have excluded codes that were preferred by GPs to describe the symptoms of drug-induced lupus. For instance, cutaneous lupus is not considered to be true SLE and was therefore not included in our case definition.

However, approximately 25% of cases of drug-induced lupus have shown symptoms of cutaneous lupus[23] and may have been recorded as such in the GPRD.

Our analysis of the Yellow Card database provided an additional understanding of the association between drugs and risk of SLE. In the majority of reports, symptoms of SLE were observed to resolve after withdrawal of the suspected drug. In four reports of drug-induced SLE it was thought the patient died as a result of the adverse drug reaction.

6.2. RISK OF HYPOTHYROIDISM ASSOCIATED WITH PRESCRIPTION DRUGS

In section 6.1 we discussed associations between prescription medicines and risk of SLE. A number of pre-existing hypotheses, identified from the literature, formed the basis of these investigations. First, we evaluated hypotheses using a matched case-control and a case-only study design to analyse GPRD data. We then used the same data set to demonstrate the use of a novel method to detect signals of drug-induced disease. In addition, we described signals of drug-induced SLE in a spontaneous reporting database and compared these to our observations in GPRD data.

In the current section, we will discuss a two phase study of drug related hypothyroidism. Instead of relying on spontaneous reports or published literature to identify new signals of drug-induced disease, we generated signals using a subset of data from the GPRD. Newly identified signals were subsequently verified in a different data subset. The main purpose of this two phase study design was to provide an example of an entirely systematically performed drug safety investigation. This is in contrast to the current practice of pharmacovigilance, where all signal evaluation studies are preceded by identification of a signal in a non-standardised and subjective way.

6.2.1. Signal Generation

6.2.1.1. Main Findings

In our signal generation analyses of a subset of drug related hypothyroidism cases and matched controls we did not identify BNF subchapters that were potentially causally associated with risk of disease. However, we did identify a BNF subchapter which is strongly associated with risk of iatrogenic drug related hypothyroidism; the subchapter for non-pharmacologic care products for the throat. We refined our case and control selection criteria to exclude those with diagnostic codes indicative of iatrogenic drug related hypothyroidism. When using the redefined case and control selection criteria, thyroid hormone prescriptions were found to be strongly associated with drug related hypothyroidism. This association was not causal, but rather an indication of forthcoming drug related hypothyroidism. The date of first thyroid hormone prescription was therefore incorporated into the definition of diagnosis date. Using the new definition of diagnosis date, no signals of drug-induced drug related hypothyroidism were identified.

6.2.1.2. Discussion

When performing a signal generation exercise it is highly undesirable to identify spurious associations between drugs and adverse events. In the worst case, falsely identified positive associations may lead to erroneous withdrawal of drugs from the market and denial of 'safe' medicines from patients who could have benefited from the drug. With respect to identification of spurious associations the Smile Plot method can be regarded as a useful method; it detected no false-positive associations of drug-induced hypothyroidism, and one potentially false-positive signal of drug-induced lupus (discussed in section 6.1.3).

As discussed in section 6.1.3, an important limitation of the Smile Plot method, when utilised to identify signals of drug-induced disease, is the classification system we used to categorise drug exposures. Drug exposures were grouped by BNF subchapter because this classification system was incorporated in the GPRD drug dictionary. An

alternative classification system that is currently available and widely used is the Anatomical Therapeutic Chemical (ATC) classification[79]. This classification system arranges prescription drugs in five levels, according to the organ or system on which they act (which is the highest level) and their chemical, pharmacological and therapeutic properties. The ATC classification has been developed for the purpose of drug utilisation studies and not specifically to study drug safety. The hierarchical organisation of ATC codes is very similar to the BNF classification system (BNF also uses the target organ or system as the highest classification level) and because of these similarities we believe there will be little improvement in the sensitivity of the Smile Plot method when using ATC codes instead of BNF codes.

In contrast to our earlier findings in the Smile Plots investigating drug-induced SLE, the point estimates for drug related hypothyroidism were generally dispersed around the no effect level (OR=1). This is a pattern one would expect to see when none of the investigated risk factors are truly associated with risk of disease. It is therefore unlikely that our risk estimates were affected by residual confounding, unlike our observation for signals of drug-induced SLE.

Prior to redefinition of the diagnosis date, we observed subchapter 901 to be a potential signal of drug-induced drug related hypothyroidism. After redefinition, this subchapter was no longer identified as a signal but the 95% confidence interval around the risk estimate excluded 1 and suggested an increased risk of drug related hypothyroidism associated with its use. Subchapter 901 includes drugs prescribed for anaemia and some other blood disorders. In hypothyroidism, anaemia is a common feature[26] and it is possible we identified subchapter 901 because it is prescribed for early symptoms of hypothyroidism.

Approximately four percent of cases who were identified as incident received their first thyroxine prescription more than one year before a recorded diagnosis of hypothyroidism. These cases may in reality be prevalent cases who were misclassified as incident. This is possible when a hypothyroidism patient who is on thyroxine newly registers with a GP. It is plausible that a GP does not enter a medical

code for hypothyroidism retrospectively, but records such a code only when the patient develops new symptoms of the disease. Based on the computerised records this patient will appear to be newly diagnosed with hypothyroidism, despite having several prescriptions of thyroxine preceding the apparent 'diagnosis date'. We made a similar observation of potentially prevalent cases of SLE, based on prescriptions for anti-malarials that were received more than a year before the recorded diagnosis date.

6.2.2. Signal Evaluation

The main purpose of our two phase study design was to provide an example of an entirely systematically performed drug safety investigation. When we originally designed our study, we anticipated identifying signals of drug-induced hypothyroidism. These signals would subsequently be evaluated in a larger subset of the data. However, in the first phase of the study we did not observe signals of drug-induced disease. In a real life setting, the drug safety study would have ended here. However, for the purpose of this thesis we did proceed with a signal evaluation phase. Two BNF subchapters for which the 95% confidence intervals suggested an association with risk of drug related hypothyroidism were selected for evaluation in the second phase of this study. When interpreting the results of this signal evaluation study it is important to keep in mind that these subchapters were not identified as signals due to the threshold we defined to take account of multiple comparisons.

6.2.2.1. Main Findings

When investigating the BNF subchapter for "Drugs used in anaemias and some other blood disorders" in further detail, we found evidence for an increasing risk of drug related hypothyroidism with an increasing number of prescriptions for oral iron. This association was confined to individuals diagnosed with drug related hypothyroidism before the age of 55 and there was a statistically significant interaction between age group (younger or older than 55 years) and an iron cumulative dose of 4 or more prescriptions. In terms of exposure to hypnotics and anxiolytics, we found limited

evidence for an inverse association between cumulative dose and risk of drug related hypothyroidism.

6.2.2.2. Discussion

The weak evidence for an inverse dose-response relationship for hypnotics and anxiolytics may be in support of a causal association between use of these drugs and a decreased risk of drug related hypothyroidism. However, it is important to consider the clinical characteristics of drug related hypothyroidism when interpreting our results. Firstly, it should be noted that clinical manifestations of hypothyroid disease can be non-specific[27], which may cause substantial time to pass before a diagnosis of hypothyroidism is made. One of the common clinical manifestations of hypothyroidism is slowed mental processing[28]. Individuals with undiagnosed or subclinical hypothyroid disease[80] are therefore less likely to require the use of sedatives such as hypnotics and anxiolytics. When early symptoms of a disease influence the likelihood of being exposed to a certain drug, there is potential for bias. This particular type of bias is called protopathic bias[70] and may explain the inverse cumulative dose-response association we found between hypnotics and anxiolytics and the risk of drug related hypothyroidism.

Hypothyroidism is reported to occur in approximately 1 per 1600 to 3 per 1000 pregnancies [81, 82]. In addition, postpartum thyroiditis has been reported to occur in approximately 20 to 50 per 1000 pregnancies. In women developing postpartum hypothyroidism, a hyperthyroid stage is often seen 2 to 4 months postpartum, followed by a euthyroid and/or hypothyroid stage. Not all cases have disease remission [27]. When a woman is pregnant or planning a pregnancy, her GP will often prescribed supplements including oral iron and folic acid. This may explain why we observed an association between exposure to the subchapter for these drugs and a risk of drug related hypothyroidism among individuals less than 55 years of age, the majority of them being women of childbearing age. The prescriptions for oral iron and folic acid were most likely a marker for pregnancy instead of causative factors in the aetiology of drug related hypothyroidism.

6.2.3. Risk of Hypothyroidism Associated with Prescription Drugs: the Full Picture

In our signal generation analysis we did not identify BNF subchapters that were associated with risk of drug related hypothyroidism. In the subsequent signal evaluation analyses, the stratified analyses revealed a strong cumulative dose-response association between the subchapter encoding supplements prescribed for pregnancy and risk of drug related hypothyroidism. This association reflects the increased risk of hypothyroidism during and immediately after pregnancy. The cumulative dose-response investigations for hypnotics and anxiolytics illustrated an example of protopathic bias.

6.3. IMPLICATIONS FOR PHARMACOVIGILANCE

6.3.1. Signal generation

Using GPRD data for signal detection has a number of advantages compared to the use of spontaneous reporting databases. Firstly, GPRD data are collected routinely and in a prospective manner. Information is therefore less likely to be incomplete and/or subject to underreporting compared to data from spontaneous reporting databases. Secondly, the total number of individuals in the GPRD database receiving a prescription for a drug of interest can be determined, i.e. "denominator" data are available. In addition, the GPRD contains detailed information on unexposed individuals with and without the outcome of interest, as well as exposed individuals without the outcome of interest. This provides an opportunity to select appropriate comparison groups to perform (for instance) case-control or cohort studies. Lastly, the information captured in the GPRD is more detailed and complete than information on spontaneous reports. For instance, the GPRD can provide insight in timing of events (e.g. lag time between exposure and occurrence of a potential adverse event), underlying medical conditions and comorbidities, information on cumulative exposure and duration of exposure, and concurrent or past use of other drugs. However, for certain adverse events (e.g. SLE) it is difficult to assess whether the

symptoms resolved after withdrawal of a drug, because this type of information is not recorded.

The large size of the GPRD and the relatively high incidence of hypothyroidism enabled us to create two data subsets without compromising substantially on study power and significance level. We were able to use one data subset for signal generation and to subsequently evaluate signals in the second data subset. In practice this may not always be the case, however. Adverse drug reactions that are identified during the post-marketing phases of a drug are likely to be rare, because any common events would have already been identified during the pre-marketing phases (when a relatively small numbers of individuals are exposed). Often the adverse drug reaction of interest (e.g. SLE) will be too rare to split the total set of cases recorded in the GPRD into subsets. When studying such rare events, we suggest using two separate large longitudinal databases with prospectively recorded patient-level data. One of the data sets (the smaller of the two) will serve to generate signals, and the other to evaluate newly identified signals.

Our method to split the total set of cases with hypothyroid disease and matched controls was non-random (i.e. by geographical location of the patient's general practice). Random splitting of data would have essentially guaranteed similar results for both the signal generation and evaluation phases of our study (if a difference was observed between the randomly split data subsets, this would have been due to random variation). Several variables were considered for splitting the data non-randomly. Age-group or sex were not deemed appropriate characteristics, because these factors were likely to be associated with both risk of hypothyroidism and likelihood of receiving a prescription for a drug of interest. We also did not split our data by calendar period. From previous analyses we knew that the incidence of hypothyroidism increased substantially over time during our study period[32], and prescription patterns are also likely to have changed over time. Non-random splitting by geographical area seemed the most appropriate. Although the incidence of hypothyroidism varied across the United Kingdom during our study period[32], we

have no reason to believe that exposure to prescription drugs varied substantially between different regions.

Identification of signals of ADRs involves considering both the apparent strength of the signal as well as the severity/importance of the adverse event[83]. Despite its current weaknesses in terms of grouping of exposures, we believe the Smile Plot method can be helpful in this decision making process. Firstly, the plots are based on data of much higher quality and completeness than data from spontaneous reporting databases. Secondly, the methods used to generate data points on the plot are well-accepted and widely used statistical analysis methods (unlike the numerous data mining algorithms which are difficult to validate[71]. Lastly, the smile plots can be generated in relatively little time thereby providing timely results that are easy to interpret.

In our signal generation studies of drug-induced hypothyroidism and drug-induced lupus, we chose the adverse event as the starting point of our study and conducted a matched case-control study to identify which exposures were associated with this adverse event. However, the focus of signal generation generally is to identify which adverse events are associated with a specific product (or class of drugs). In order to answer this question, one can generate signals of ADRs in association with a particular medicine. This can be easily done by adapting the analysis method described in section 3.5.5 of this thesis: instead of a conducting a case-control study (estimating odds ratios of the association between a specific ADR and several drug exposures), one could conduct a cohort study. Risk ratios are estimated by comparing incidence of several diseases in the exposed group to the incidence of these diseases in the comparison group(s). The obtained risk ratios and corresponding P-values can then be plotted in a Smile Plot and a method to correct for multiple comparisons applied.

In our earlier discussion of the Smile Plot method we identified the grouping of drug exposures to be the main limitation. The cohort study approach does not involve grouping of drug exposures, but instead involves grouping of diseases. This can be

done by using a well-developed and widely used hierarchical coding system of diseases: the ICD classification. Although this classification system will likely have its own limitations but it may be superior to the drug classification systems available to date, resulting in a higher sensitivity of the Smile Plot method. An additional strength of using the cohort approach to generate Smile Plots is that the study design allows for several comparison groups. For example, one can have (1) an unexposed population based cohort, (2) a cohort of individuals who are exposed to a different drug of the same class or (3) a comparison cohort of unexposed individuals who have the same underlying condition for which the suspected drug is prescribed. Although cohort studies may be subject to bias and confounding in a similar way as case-control studies, the use of well-selected different comparison groups can facilitate a better understanding of these biases and confounding.

6.3.2. Signal evaluation

Because causality can not be established based on signal generation studies, signal evaluation will always be an essential component of pharmacovigilance. One individual signal evaluation study will also not be sufficient to establish causality. In this thesis we presented two different methods to evaluate potential associations between drugs and adverse events; a case-control and a self-controlled case series approach. These methods can be applied to the same data source which is an efficient use of resources. In addition, when using the two analysis methods alongside each other, we illustrated how the results of one study may facilitate interpretation the results of the other study.

Most signal evaluation studies will be of observational nature due to ethical and/or practical reasons. Observational studies will often be subject to bias and confounding. A particular type of bias which is of importance in observational studies of drug safety is confounding by indication. This type of bias may be overcome by removing the effect of difficult to measure factors which are likely to vary between a cases (or exposed individuals) and the comparison group. Inter-personal variations are

removed from the analysis when making within-person comparisons, for example by using the self-controlled case series method.

Despite the large size of the GPRD, the sample size of SLE cases was too small to perform relevant subgroup analyses or to detect moderately increased risks.

6.4. RECOMMENDATIONS FOR CLINICIANS AND DRUG SAFETY SCIENTISTS

6.4.1.1. Recommendations for clinicians

It is important for GPs to consider drug-induced lupus as a potential diagnosis when a patient on one (or more) of the drugs listed in Table 1-1 presents with lupus-like symptoms. We will publish the matched case-control study of the associations between prescription drugs and risk of SLE in an international peer-reviewed medical journal. This publication will further inform the medical community of potential risk of SLE associated with a wide range of drugs. Based on the findings presented in this thesis we do not recommend routine testing for autoantibodies in the blood of patients on drugs suspected of causing drug-induced lupus. The findings for drug-related hypothyroidism presented in this thesis do not warrant any recommendations for endocrinologists or general practitioners.

6.4.1.2. Recommendations for drug safety scientists

The methods explored in this thesis provide a useful addition to the currently used set of methods to monitor safety of medicines. In terms of signal evaluation, use of the case-series method should be considered when studying a potential adverse event with an acute onset of symptoms.

Further studies are needed to investigate sensitivity and specificity of Smile Plots when these are generated from cohort study results. The smile plot method provides an easy to interpret visual aid for interpretation of large quantities of data and with improved sensitivity and specificity this tool should not be disregarded in the detection of previously unknown adverse events.

Currently, the GPRD is not used to its full potential for the study of drug safety. Although the data are being utilised for evaluation of hypothesized drug- adverse event associations, no signal detection studies have been reported to date. Use of the GPRD for signal detection would be an important improvement of the current practice of pharmacovigilance.

6.5. CONCLUSION

The GPRD is the largest primary care medical records database currently available. It is a powerful tool to study morbidity in primary care. However, intimate knowledge of the use of coding in General Practice and of the complexities of the database is needed to ensure that the best use is made of it.

Known and suspected associations of drug-induced SLE were reproduced in the GPRD. However, in our study of drug-induced SLE both the disease and the exposures (i.e. drug prescriptions) of interest were uncommon, resulting in a limited study power to detect moderately increased risks or to perform relevant subgroup Results from a matched case-control study indicated strong associations with risk of SLE for hydralazine, carbamazepine and minocycline. These associations were confirmed in a self-controlled case series but the risk estimates were lower compared to those observed in the case-control study. This difference in risk estimates is most likely due to an overestimate of risk in the case-control study, as a result of the effect of unmeasured confounders including health-seeking behaviour. Despite the large size of the GPRD, the sample size of SLE cases was too small to investigate potential associations and bias using conventional stratification.

Known associations between drugs and risk of SLE were not identified as signals when using the Smile Plot method. This signal generation method was found to have a high specificity as illustrated by the highly limited number of falsely identified positive associations for both drug-induced SLE and drug-induced hypothyroidism. However, the sensitivity of the Smile Plot method is low. Sensitivity may be improved when improved hierarchical classification systems for drugs become available.

Alternatively, smile plots may be created from risk estimates of a cohort study rather than a case-control study in order to avoid use of inadequate drug classification systems.

Spontaneous reports of drug-induced SLE recorded in the UK Yellow Card database indicated that symptoms of SLE often resolve after withdrawal of the suspected drug. This is important information that could not be gathered from our studies utilising GPRD data.

BIBLIOGRAPHY

[1] Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet. 2004 May 22;363(9422):1728-31.

[2] Mann RD, Andrews EB. Introduction. In: Mann R, Andrews E, eds. *Pharmacovigilance*. Chichester, England: John Wiley & Sons Ltd 2002:3 - 10.

[3] Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001 Aug 22-29;286(8):954-9.

[4] Kennedy DL, Goldman SA, Lillie RB. Spontaneous Reporting in the United States. In: Strom BL, ed. *Pharmacoepidemiology*. 3 ed. Chichester, England: John Wiley & Sons 2000:151-74.

[5] Wiholm B-E, Olsson S, Moore N, Waller P. Spontaneous Reporting Systems Outside the US. In: Strom BL, ed. *Pharmacoepidemiology*. 3 ed. Chichester, England: John Wiley & Sons 2000:175-92.

[6] Edwards RE, Olsson S. WHO Programme - Global Monitoring. In: Mann R, Andrews E, eds. *Pharmacovigilance Part II: Signal Generation*. Chichester, England: John Wiley & Sons Ltd 2002:169 - 82.

[7] Davis S, Raine JM. Spontaneous Reporting - UK. In: Mann R, Andrews E, eds. *Pharmacovigilance*. Chichester, England: John Wiley & Sons Ltd 2002:195 - 208.

[8] Evans SJW. Statistics: Analysis and Presentation of Safety Data. In: Talbot J, Waller P, eds. *Stephens' Detection of New Adverse Drug Reactions*. 5 ed. Chichester, England: John Wiley & Sons Ltd 2004:301 - 28.

[9] Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. American journal of epidemiology. 1991 Jan 15;133(2):144-53.

[10] Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. American journal of epidemiology. 1996 Jun 1;143(11):1165-73.

[11] Office for National Statistics. Analyses of morbidity and treatment data, including time trends, England and Wales. Key Health Statistics from General Practice. 1998;Series MB6(No. 2).

[12] Walley T, Mantgani A. The UK General Practice Research Database. Lancet. 1997 Oct 11;350(9084):1097-9.

[13] D'Cruz DP, Khamashta MA, Hughes GRV. Systemic Lupus Erythematosus. Lancet. 2007;369:587-96.

[14] Petri MA. Systemic Lupus Erythematosus: Clinical Aspects. In: Koopman WJ, Moreland LW, eds. *Arthritis & Allied Conditions*. 15th ed. Philadelphia: Lippincott Williams & Wilkins 2005:1473-96.

[15] Grossman JM, Kalunian KC. Definition, Classification, Activity, and Damage Indices. In: Wallace DJ, Hannahs Hahn B, eds. *Dubois' Lupus Eythematosus*. 6 ed. Philadelphia: Lippincott Williams & Wilkins 2002:19-31.

[16] Lahita RG. Clinical Presentation of Systemic Lupus Erythematosus. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of Rheumatology*. 5 ed. Philadelphia: W.B. Saunders Company 1997:1028-39.

[17] Somers EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999. 2007:612-8.

[18] Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2005;15:308-18.

[19] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982 Nov;25(11):1271-7.

[20] Mosca M, Ruiz-Irastorza G, Khamashta MA, Hughes GRV. Treatment of systemic lupus erythematosus. International Immunopharmacology. 2001;1:1065-75.

[21] Iannou Y, Isenberg DA. Current concepts for the management of systemic lupus erythematosus in adults: a therapeutic challenge. Postgrad Med J. 2002;78:599-606.

[22] Rubin RL. Etiology and mechanisms of drug-induced lupus. Current opinion in rheumatology. 1999 Sep;11(5):357-63.

[23] Rubin RL. Drug-induced lupus. Toxicology. 2005 Apr 15;209(2):135-47.

[24] Young P. Musculoskeletal disorders. In: Lee A, ed. *Adverse Drug Reactions*. London: Pharmaceutical Press 2001:157 - 75.

[25] Rubin R. Drug-induced Lupus. In: Wallace D, Hahn B, eds. *Dubois' Lupus Erythematosus*. 6th ed. Philadelphia: Lippincott Williams &Wilkins 2002:885-916.

[26] Chiu AC, Sherman SI. Clinical Manifestations and Differential Diagnosis of Hypothyroidism. In: Falk SA, ed. *Thyroid Disease Endocrinology, Surgery, Nuclear Medicine and Radiotherapy*. 2 ed. Philadelphia: Lippincott-Raven 1997:379 - 91.

[27] Kim G, Davies TF. Hypothyroidism. In: Besser GM, Thorner MO, eds. *Comprehensive Clinical Endocrinology*. Third edition ed. Printed in Spain: Mosby, Elsevier Science Limited 2002:151 - 64.

[28] Roberts CGP, Ladenson PW. Hypothyroidism. Lancet. 2004 March 6;363:793 - 803.

[29] Wahid ST, Robinson ACJ. Hypothyroidism. In: Robinson S, Meeran K, eds. *Endocrinology Specialist Handbook*. London: Martin Dunitz 2002:243-56.

[30] Fitzgerald PA. Endocrinology. In: McPhee SJ, Papadakis MA, Tierney Jr LM, eds. *Current Medical Diagnosis & Treatment*. 46 ed. New York: McGraw-Hill 2007:1123-218.

[31] Carle A, Laurberg P, Bulow Pedersen I, Knudsen N, Perrild H, Ovesen L, et al. Epidemiology of subtypes of hypothyroidism in Denmark. European Journal of Endocrinology. 2006;154:21-8.

[32] Papadopoulos Somers EC. Epidemiology and comorbidity of selected autoimmune diseases in the United Kingdom [Ph.D. Thesis]. London: London School of Hygiene and Tropical Medicine; 2006.

[33] Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clinical Endocrinology. 1995;43:55-68.

[34] Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. Journal of Clinical Endocrinology and Metabolism. 2004;89:3879-84.

[35] Utiger R. The Thyroid: Physiology, Thyrotoxicosis, Hypothyroidism and The Painful Thyroid. In: Felig P, Frohman L, eds. *Endocrinology and Metabolism*. 4th Edition ed. United States of America: McGraw-Hill 2001:316 - 29.

[36] Toft AD. Thyroxine therapy. New England Journal of Medicine. 1994;331:174 - 80.

[37] Singer PA. Clinical Approach to Thyroid Testing. In: Falk SA, ed. *Thyroid Disease Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy*. 2 ed. Philadelphia: Lippincott-Raven 1997:41 - 52.

[38] Watt J. Endocrine Disorders. In: Lee A, ed. *Adverse Drug Reactions*. London: Pharmaceutical Press 2001:119 - 35.

[39] Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997 Sep;84(3):223-43.

[40] Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. J Public Health Med. 1999 Sep;21(3):299-304.

[41] Lis Y, Mann RD. The VAMP Research multi-purpose database in the U.K. J Clin Epidemiol. 1995 Mar;48(3):431-43.

[42] Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. The New England journal of medicine. 2003 Oct 23;349(17):1628-35.

[43] Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG, et al. MMR vaccination and pervasive developmental disorders: a case-control study. Lancet. 2004 Sep 11-17;364(9438):963-9.

[44] Cassell JA, Mercer CH, Sutcliffe L, Petersen I, Islam A, Brook MG, et al. Trends in sexually transmitted infections in general practice 1990-2000: population based study using data from the UK general practice research database. BMJ. 2006 Feb 11;332(7537):332-4.

[45] Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ. 2005 Feb 19;330(7488):389.

[46] Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of beta-blockers and risk of fractures. JAMA. 2004 Sep 15;292(11):1326-32.

[47] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet. 2000 Nov 11;356(9242):1627-31.

[48] Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ. 1991 Mar 30;302(6779):766-8.

[49] Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology and drug safety. 1992;1:347-9.

[50] van Staa T, Abenheim L. The quality of information recorded on a UK database of primary care records: A study of hospitalisations due to hypoglycemia and other conditions. Pharmacoepidemiology and drug safety. 1994;3:15-21.

[51] Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). Thorax. 1999 May;54(5):413-9.

[52] Hollowell J. The General Practice Research Database: quality of morbidity data. Popul Trends. 1997 Spring(87):36-40.

[53] Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. Arch Intern Med. 1994 Feb 14;154(3):311-6.

[54] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of interventions 4.2.6 [updated September 2006]. Chichester: John Wiley & Sons 2006.

[55] Kmietowicz Z. UK academics gain free access to database of patients. BMJ. 2005 October 22, 2005;331(7522):924-.

[56] Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiology and drug safety. 2005 Jul;14(7):443-51.

[57] Schlesselman JJ, Stolley PD. Case-control studies. Design, conduct, analysis. New York: Oxford University Press 1982.

[58] Andrews N, Miller E, Waight P, Farrington P, Crowcroft N, Stowe J, et al. Does oral polio vaccine cause intussusception in infants? Evidence from a sequence of three self-controlled cases series studies in the United Kingdom. Eur J Epidemiol. 2001;17(8):701-6.

[59] Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Statistics in medicine. 2006 May 30;25(10):1768-97.

[60] Newson R. Mulitple-test procedures and smile plots. The Stata Journal. 2003;3(2):109-32.

[61] Rubin RL. Environmentally induced systemic lupus erythematosus. In: Kaufman L, Varga J, eds. *Rheumatic diseases and the environment.* London: Arnold Publishers 1999:83-100.

[62] Schlienger RG, Bircher AJ, Meier CR. Minocycline-induced lupus. A systematic review. Dermatology. 2000;200(3):223-31.

[63] Sturkenboom MC, Meier CR, Jick H, Stricker BH. Minocycline and lupuslike syndrome in acne patients. Arch Intern Med. 1999 Mar 8;159(5):493-7.

[64] Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics. 1995 Mar;51(1):228-35.

[65] Yung RL, Richardson BC. Drug-induced lupus. Rheum Dis Clin North Am. 1994 Feb;20(1):61-86.

[66] Yung RL, Richardson BC. Drug-induced rheumatic syndromes. *Bulletin on the rheumatic diseases* 2002:http://www.arthritis.org/research/bulletin/vol51no4/_4_fullversion.htm.

[67] Antonov D, Kazandjieva J, Etugov D, Gospodinov D, Tsankov N. Drug-induced lupus erythematosus. Clinics in dermatology. 2004 Mar-Apr;22(2):157-66.

[68] Vaile J, Russell A. Chapter 42: Drug-induced autoimmunity. In: Lahita R, ed. *Textbook of the autoimmune diseases*. Philadelphia: Lippincott 2000:783-98.

[69] Joint Formulary Committee. British National Formulary. 53 ed. London: British Medical Association

Royal Pharmaceutical Society of Great Britain 2007.

[70] Collet J-P, Boivin J-F. Bias and Confounding in Pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. 3 ed. Chichester, England: John Wiley & Sons 2000:765-84.

[71] Stephenson WP, Hauben M. Data mining for signals in spontaneous reporting databases: proceed with caution. Pharmacoepidemiology and drug safety. 2007 Apr;16(4):359-65.

[72] Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiology and drug safety. 2001 Oct-Nov;10(6):483-6.

[73] DuMouchel W. Bayesian Data Mining in Large Frequency Tables, With an Application to the FDA Spontaneous Reporting System. The American Statistician. 1999;53(3):177 - 200.

[74] Hauben M, Patadia V, Gerrits C, Walsh L, Reich L. Data mining in pharmacovigilance: the need for a balanced perspective. Drug Saf. 2005;28(10):835-42.

[75] Pichler WJ. Drug-induced autoimmunity. Current opinion in allergy and clinical immunology. 2003 Aug;3(4):249-53.

[76] Shapiro M, Sosis AC, Junkins-Hopkins JM, Werth VP. Lupus erythematosus induced by medications, ultraviolet radiation, and other exogenous agents: a review, with special focus on the development of subacute cutaneous lupus erythematosus in a genetically predisposed individual. International journal of dermatology. 2004 Feb;43(2):87-94.

[77] Srivastava M, Rencic A, Diglio G, Santana H, Bonitz P, Watson R, et al. Drug-induced, Ro/SSA-positive cutaneous lupus erythematosus. Archives of dermatology. 2003 Jan;139(1):45-9.

[78] Askling J, Fored CM, Geborek P, Jacobsson LT, van Vollenhoven R, Feltelius N, et al. Swedish registers to examine drug safety and clinical issues in RA. Annals of the rheumatic diseases. 2006 Jun;65(6):707-12.

[79] WHO Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs. 2007 [cited May 2007]; Available from: http://www.whocc.no/atcddd/

[80] Mitchell ML, Klein RZ. The sequelae of untreated maternal hypothyroidism. European journal of endocrinology / European Federation of Endocrine Societies. 2004 Nov;151 Suppl 3:U45-8.

[81] Montoro M. Management of hypothyroidism during pregnancy. Clin Obstet Gynecol. 1997;40:65 - 80.

[82] Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstetrics and gynecology. 2006 Nov;108(5):1283-92.

[83] Waller PC, Arlett P. Responding to signals. In: Mann R, Andrews E, eds. *Pharmacovigilance Part I: Basis of Pharmacovigilance*. Chichester: John Wiley & Sons Ltd 2002:105 -28.

APPENDIX I-A. MEDLINE AND EMBASE SEARCH STRATEGIES

FOR GPRD LITERATURE REVIEW

	Search History EMBASE
1	exp REPRODUCIBILITY/ or exp RELIABILITY/ or exp "sensitivity and specificity"/ or exp diagnostic error/ or exp validation process/
2	exp information processing/ or exp Medical Information/ or exp Patient information/ or exp factual database/ or exp information system/
3	(GPRD or General Practice Research Database or General Practice Database or VAMP or Value Added Medical Products or GP Research Database or GP Ddatabase).af.
4	(accurac$ or quality or valid$ or systematic comparison or agreement between or complete$ or evaluat$ or reprduci$ or predict$ or sensit$ or specific$ or misdiagnos$ or compar$ or false positiv$ or false negativ$ or reference value).af.
5	(medical record$ or primary care record$ or patient record$ or diagnos#s).af.
6	1 or 4
7	2 or 5
8	3 and 6 and 7

	Search History PubMed
1	"Medical record*" OR "primary care record*" OR "patient record*" OR "diagnoses" OR "diagnosis" OR "medical history" OR "Medical Records" [MeSH] OR "Medical record administrators" [MeSH] OR "records" [MeSH] OR "registries" [MeSH] OR "diagnosis" [MeSH] OR "documentation" [MeSH]
2	GPRD OR "General Practice Research Database" OR "Practice Research Database" OR "General Practice Database" OR VAMP OR "Value Added Medical Products" OR "GP Database" OR "UK Database of Primary Care Records"
3	"accurac*" OR "qualit*" OR "valid*" OR "systematic comparison" OR "agreement between" OR "complete*" OR "evaluat*" OR "reproduci*" OR "predictive value" OR "sensit*" OR "specific*" OR "misdiagnos*" OR "compar*" OR "false positiv*" OR "false negativ*" OR "reference value" OR "evaluation studies" [MeSH] OR "evaluation studies" [PT] OR "reproducibility of results" [MeSH] OR "validation studies" [PT] OR "software validation" [MeSH] OR "sensitivity and specificity" [MeSH] OR "predictive value of tests" [MeSH] OR "reference values" [MeSH]
4	Search "Epidemiology"[MeSH] OR "epidemiology"[Subheading] OR epidemiol*
5	#1 AND #2 AND #3
6	(#2 AND #4) NOT #5

APPENDIX I-B: DATA EXTRACTION SHEET FOR GPRD

LITERATURE REVIEW

Author + Year	
Reference #	
Validation period	
Boston group y/n	
Disease(s) to validate	1 2 3
Patient criteria defined y/n	1 2 3
Validation method	1 2 3
# of reviewers	
Blinded to results	
Outcome measures 1 Response rate 2 Confirm. rate	
Lab results used	
Hospital records	
Appropriate gold standard	
External validity	
Comments	

APPENDIX I-C: LITERATURE REFERENCES GPRD LITERATURE REVIEW

a1. Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, et al. Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case-control studies using the General Practice Research Database and the Doctors' Independent Network. *Clin Exp Allergy* 2003;33(11):1518-25.

a2. Hajat S, Haines A, Atkinson RW, Bremner SA, Anderson HR, Emberlin J. Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. *Am J Epidemiol* 2001;153(7):704-14.

a3. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;54(5):413-9.

a4. Hollowell J. The General Practice Research Database: quality of morbidity data. *Popul Trends* 1997(87):36-40.

a5. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med* 2004;164(3):317-9.

a6. Perez-Gutthann S, Garcia-Rodriguez LA, Duque-Oliart A, Varas-Lorenzo C. Low-dose diclofenac, naproxen, and ibuprofen cohort study. *Pharmacotherapy* 1999;19(7):854-9.

a7. Jick SS, Terris BZ. Anticonvulsants and congenital malformations. *Pharmacotherapy* 1997;17(3):561-4.

a8. Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. *Pharmacotherapy* 1999;19(2):221-2.

a9. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150(5):476-81.

a10. Wood SL, Jick H, Sauve R. The risk of stillbirth in pregnancies before and after the onset of diabetes. *Diabet Med* 2003;20(9):703-7.

a11. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol* 2003;55(1):107-11.

a12. Blackburn SC, Oliart AD, Garcia Rodriguez LA, Perez Gutthann S. Antiepileptics and blood dyscrasias: a cohort study. *Pharmacotherapy* 1998;18(6):1277-83.

a13. Hollowell J, Ruigomez A, Johansson S, Wallander MA, Garcia-Rodriguez LA. The incidence of bleeding complications associated with warfarin treatment in general practice in the United Kingdom. *Br J Gen Pract* 2003;53(489):312-4.

a14. Huerta C, Zhao SZ, Garcia Rodriguez LA. Risk of acute liver injury in patients with diabetes. *Pharmacotherapy* 2002;22(9):1091-6.

a15. Jick H, Myers MW, Dean AD. The risk of sulfasalazine- and mesalazine-associated blood disorders. *Pharmacotherapy* 1995;15(2):176-81.

a16. Myers MW, Vasilakis C, Kaufman MR, Jick H. Antihypertensive drugs and the risk of idiopathic aplastic anaemia. *Br J Clin Pharmacol* 2000;49(6):604-8.

a17. van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, Leufkens HG. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. *Am J Hematol* 2003;72(4):248-54.

a18. Garcia Rodriguez LA, Huerta-Alvarez C. Reduced incidence of colorectal adenoma among long-term users of nonsteroidal antiinflammatory drugs: a pooled analysis of published studies and a new population-based study. *Epidemiology* 2000;11(4):376-81.

a19. Garcia Rodriguez LA, Gonzalez-Perez A. Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13(4):649-53.

a20. Garcia-Rodriguez LA, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. *Epidemiology* 2001;12(1):88-93.

a21. Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel blockers and risk of cancer. *Lancet* 1997;349(9051):525-8.

a22. Kaye JA, Derby LE, del Mar Melero-Montes M, Quinn M, Jick H. The incidence of breast cancer in the General Practice Research Database compared with national cancer registration data. *Br J Cancer* 2000;83(11):1556-8.

a23. Kaye JA, Myers MW, Jick H. Acetaminophen and the risk of renal and bladder cancer in the general practice research database. *Epidemiology* 2001;12(6):690-4.

a24. Kaye JA, Meier CR, Walker AM, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. *Br J Cancer* 2002;86(9):1436-9.

a25. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology* 2001;121(5):1080-7.

a26. Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998;45(6):608-12.

a27. Meier CR, Derby LE, Jick SS, Jick H. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000;160(3):349-53.

a28. Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. *Pharmacotherapy* 2002;22(3):303-9.

a29. Ronquist G, Rodriguez LA, Ruigomez A, Johansson S, Wallander MA, Frithz G, et al. Association between captopril, other antihypertensive drugs and risk of prostate cancer. *Prostate* 2004;58(1):50-6.

a30. Logie J, Dolin P, Boudiaf N. An evaluation of the U.K. General Practice Research Database (GPRD) for studying the incidence of male breast cancer. *Pharmacoepidemiol Drug Saf* 2003;12 Suppl 1:S50-1.

a31. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol* 1999;47(3):307-13.

a32. Ellis C, Gnani S, Majeed A. Prevalence and management of heart failure in England and Wales, 1994-98. *Health Statistics Quarterly* 2001;11:17-24.

a33. Garcia Rodriguez LA, Varas C, Patrono C. Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. *Epidemiology* 2000;11(4):382-7.

a34. Hall G, Chukwujindu J, Richardson J, Lis Y, Wild R. Micturin (terodiline hydrochloride), torsades de pointe and other arrhythmias - a study using the VAMP database. *Pharmacoepidemiol Drug Saf* 1993;2:127-232.

a35. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004;62(4):563-8.

a36. Jick H, Jick S, Myers MW, Vasilakis C. Risk of acute myocardial infarction and low-dose combined oral contraceptives. *Lancet* 1996;347(9001):627-8.

a37. Jick H, Derby LE, Gurewich V, Vasilakis C. The risk of myocardial infarction associated with antihypertensive drug treatment in persons with uncomplicated essential hypertension. *Pharmacotherapy* 1996;16(3):321-6.

a38. Jick H, Vasilakis C, Derby LE. Antihypertensive drugs and fatal myocardial infarction in persons with uncomplicated hypertension. *Epidemiology* 1997;8(4):446-8.

a39. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998;339(11):719-24.

a40. Johansson S, Wallander MA, Ruigomez A, Garcia Rodriguez LA. Incidence of newly diagnosed heart failure in UK general practice. *Eur J Heart Fail* 2001;3(2):225-31.

a41. Majeed A, Moser K. Prevalence and management of heart failure in general practice in England and Wales 1994-96. *Health Statistics Quarterly* 1999;4:5-8.

a42. Majeed A, Moser K, Maxwell R. Age, sex and practice variations in the use of statins in general practice in England and Wales. *J Public Health Med* 2000;22(3):275-9.

a43. Mann RD, Lis Y, Chukwujindu J, Chanter DO. A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. *J Clin Epidemiol* 1994;47(3):307-12.

a44. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet* 1998;351(9114):1467-71.

a45. Meier CR, Derby LE, Jick SS, Vasilakis C, Jick H. Antibiotics and risk of subsequent first-time acute myocardial infarction. *Jama* 1999;281(5):427-31.

a46. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol* 2002;55(4):358-63.

a47. Ryan R, Majeed A. Prevalence of ischaemic heart disease and its management with statins and aspirin in general practice in England and Wales, 1994 and 1998. *Health Statistics Quarterly* 2001;12:34-39.

a48. Schlienger RG, Jick H, Meier CR. Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction. *Br J Clin Pharmacol* 2002;54(3):327-32.

a49. de Abajo FJ, Jick H, Derby L, Jick S, Schmitz S. Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol* 2000;50(1):43-7.

a50. Derby LE, Myers MW, Jick H. Use of dexfenfluramine, fenfluramine and phentermine and the risk of stroke. *Br J Clin Pharmacol* 1999;47(5):565-9.

a51. Gibbs RG, Todd JC, Irvine C, Lawrenson R, Newson R, Greenhalgh RM, et al. Relationship between the regional and national incidence of transient ischaemic attack and stroke and performance of carotid endarterectomy. *Eur J Vasc Endovasc Surg* 1998;16(1):47-52.

a52. Gibbs RG, Newson R, Lawrenson R, Greenhalgh RM, Davies AH. Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database. *Stroke* 2001;32(5):1085-90.

a53. Jick SS, Myers MW, Jick H. Risk of idiopathic cerebral haemorrhage in women on oral contraceptives with differing progestagen components. *Lancet* 1999;354(9175):302-3.

a54. Black C, Kaye JA, Jick H. Clinical risk factors for venous thromboembolus in users of the combined oral contraceptive pill. *Br J Clin Pharmacol* 2002;53(6):637-40.

a55. Farmer RD, Williams TJ, Simpson EL, Nightingale AL. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of general practice research database. *BMJ* 2000;321(7259):477-9.

a56. Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995;346(8990):1589-93.

a57. Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000;321(7270):1190-5.

a58. Jick SS. The risk of gastrointestinal bleed, myocardial infarction, and newly diagnosed hypertension in users of meloxicam, diclofenac, naproxen, and piroxicam. *Pharmacotherapy* 2000;20(7):741-4.

a59. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. *Br J Clin Pharmacol* 2000;49(6):591-6.

a60. Moser K, Majeed A. Prevalence of treated chronic diseases in general practice in England and Wales - trends over time and variations by the ONS area classification. *Health Statist Quart* 1999;2:25-32.

a61. Perez Gutthann S, Garcia Rodriguez LA, Castellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997;314(7083):796-800.

a62. Ryan R, Majeed A. Prevalence of treated hypertension in general practice in England and Wales, 1994 and 1998. *Health Statistics Quarterly* 2002;16:14-18.

a63. Seaman HE, de Vries CS, Farmer RD. The risk of venous thromboembolism in women prescribed cyproterone acetate in combination with ethinyl estradiol: a nested cohort analysis and case-control study. *Hum Reprod* 2003;18(3):522-6.

a64. Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. *Contraception* 1999;59(2):79-83.

a65. Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. *Lancet* 1999;354(9190):1610-1.

a66. Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001;358(9291):1427-9.

a67. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med* 2002;162(10):1105-10.

a68. Yang CC, Jick SS, Jick H. Statins and the risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 2002;53(1):101-5.

a69. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000;356(9237):1219-23.

a70. MacDonald TM, Morant SV, Pettitt D. Prevalence of clinically recognized hypertension (HT) and Dyslipidaemia (DL) in the UK. *Pharmacoepidemiol Drug Saf* 2003;12 Suppl 1:S25-6.

a71. Derby LE, Jick H, Dean AD. Antidepressant drugs and suicide. *J Clin Psychopharmacol* 1992;12(4):235-40.

a72. Derby LE, Tennis P, Jick H. Sudden unexplained death among subjects with refractory epilepsy. *Epilepsia* 1996;37(10):931-5.

a73. Donovan S. The use of the General Practice Research Database (GPRD) to examine potential links between antidepressant medication and the incidence of suicide. *Drug Informat J* 1996;30:785-792.

a74. Haste F, Charlton J, Jenkins R. Potential for suicide prevention in primary care? An analysis of factors associated with suicide. *Br J Gen Pract* 1998;48(436):1759-63.

a75. Jick SS, Dean AD, Jick H. Antidepressants and suicide. *BMJ* 1995;310(6974):215-8.

a76. Lanes SF, Garcia Rodriguez LA, Huerta C. Respiratory medications and risk of asthma death. *Thorax* 2002;57(8):683-6.

a77. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. A UK general practice database study of prevalence and mortality of people with neural tube defects. *Clin Rehabil* 2000;14(6):627-30.

a78. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. *Drug Saf* 2004;27(3):203-13.

a79. Ruigomez A, Garcia Rodriguez LA, Hasselgren G, Johansson S, Wallander MA. Overall mortality among patients surviving an episode of peptic ulcer bleeding. *J Epidemiol Community Health* 2000;54(2):130-3.

a80. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, et al. Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000;55(9):789-94.

a81. Soriano JB, Kiri VA, Maier WC, Strachan D. Increasing prevalence of asthma in UK primary care during the 1990s. *Int J Tuberc Lung Dis* 2003;7(5):415-21.

a82. Castellsague J, Garcia-Rodriguez LA, Duque A, Perez Gutthann S. Risk of serious skin disorders among users of oral antifungals: a population-based study. *BMC Dermatol* 2002;2(1):14.

a83. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. *Arch Dermatol* 2003;139(11):1425-9.

a84. Margolis DJ, Bilker W, Knauss J, Baumgarten M, Strom BL. The incidence and prevalence of pressure ulcers among elderly patients in general medical practice. *Ann Epidemiol* 2002;12(5):321-5.

a85. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. *J Am Acad Dermatol* 2002;46(3):381-6.

a86. Smith S, Smith G, Heatlie H, Bashford J, Ashcroft D, Millson D. Head lice diagnosed in general practice in the West Midlands between 1993 and 2000: a survey using the General Practice Research Database. *Commun Dis Public Health* 2003;6(2):139-43.

a87. Carter M, Moser K, Kelly S. Health of older people: disease prevalence, prescription and referral rates, England and Wales 1996. *Health Statistics Quarterly* 1999;4:9-15.

a88. Eland IA, Alvarez CH, Stricker BH, Rodriguez LA. The risk of acute pancreatitis associated with acid-suppressing drugs. *Br J Clin Pharmacol* 2000;49(5):473-8.

a89. Garcia Rodriguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994;308(6927):503-6.

a90. Jick H, Hall GC, Dean AD, Jick SS, Derby LE. A comparison of the risk of hypoglycemia between users of human and animal insulins. 1. Experience in the United Kingdom. *Pharmacotherapy* 1990;10(6):395-7.

a91. Jick SS, Stender M, Myers MW. Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. *Diabetes Care* 1999;22(12):2067-71.

a92. Kornegay CJ, Vasilakis-Scaramozza C, Jick H. Incident diabetes associated with antipsychotic use in the United Kingdom general practice research database. *J Clin Psychiatry* 2002;63(9):758-62.

a93. Newnham A, Ryan R, Khunti K, Majeed A. Prevalence of diagnosed diabetes mellitus in general practice in England and Wales. *Health Statistics Quarterly* 2002;14:5-13.

a94. Ruigomez A, Garcia Rodriguez LA. Presence of diabetes related complication at the time of NIDDM diagnosis: an important prognostic factor. *Eur J Epidemiol* 1998;14(5):439-45.

a95. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. *J Allergy Clin Immunol* 2000;105(5):912-6.

a96. Deschaseaux-Voinet C, Lafuma A, Berdeaux G. Cost and effectiveness of brinzolamide versus dorzolamide in current practice: an analysis based on the UK-GPRD database. *J Med Econ* 2003;6:69-78.

a97. Garcia Rodriguez LA, Mannino S, Wallander MA. Ocular safety of antiulcer drugs. *Lancet* 1995;345(8956):1059-60.

a98. Garcia Rodriguez LA, Mannino S, Wallander MA, Lindblom B. A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996;42(2):213-6.

a99. Huerta C, Rodriguez LA. Incidence of ocular melanoma in the general population and in glaucoma patients. *J Epidemiol Community Health* 2001;55(5):338-9.

a100. Ruigomez A, Garcia Rodriguez LA, Dev VJ, Arellano F, Raniwala J. Are schizophrenia or antipsychotic drugs a risk factor for cataracts? *Epidemiology* 2000;11(6):620-3.

a101. Andrews N, Miller E, Waight P, Farrington P, Crowcroft N, Stowe J, et al. Does oral polio vaccine cause intussusception in infants? Evidence from a sequence of three self-controlled cases series studies in the United Kingdom. *Eur J Epidemiol* 2001;17(8):701-6.

a102. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ* 2002;325(7361):419-21.

a103. Card T, West J, Hubbard R, Logan RF. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study. *Gut* 2004;53(2):251-5.

a104. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999;319(7217):1106-9.

a105. Derby LE, Jick H. Appendectomy protects against ulcerative colitis. *Epidemiology* 1998;9(2):205-7.

a106. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343(8900):769-72.

a107. Garcia Rodriguez LA, Ruigomez A. Gastric acid, acid-suppressing drugs, and bacterial gastroenteritis: how much of a risk? *Epidemiology* 1997;8(5):571-4.

a108. Garcia Rodriguez LA, Ruigomez A, Hasselgren G, Wallander MA, Johansson S. Comparison of mortality from peptic ulcer bleed between patients with or without peptic ulcer antecedents. *Epidemiology* 1998;9(4):452-6.

a109. Garcia Rodriguez LA, Ruigomez A. Secondary prevention of upper gastrointestinal bleeding associated with maintenance acid-suppressing treatment in patients with peptic ulcer bleed. *Epidemiology* 1999;10(3):228-32.

a110. Garcia Rodriguez LA, Ruigomez A, Wallander MA, Johansson S, Olbe L. Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome. *Scand J Gastroenterol* 2000;35(3):306-11.

a111. Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology* 2001;12(5):570-6.

a112. Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001;110 Suppl 3A:20S-7S.

a113. Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S. Risk of irritable bowel syndrome among asthma patients. *Pharmacoepidemiol Drug Saf* 2002;11(1):31-5.

a114. Huerta C, Garcia Rodriguez LA, Wallander MA, Johansson S. Users of oral steroids are at a reduced risk of developing irritable bowel syndrome. *Pharmacoepidemiol Drug Saf* 2003;12(7):583-8.

a115. Jick H, Vasilakis-Scaramozza C, Jick SS. Live attenuated polio vaccine and the risk of intussusception. *Br J Clin Pharmacol* 2001;52(4):451-3.

a116. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf* 2002;11(3):211-8.

a117. Lewis JD, Aberra FN, Lichtenstein GR, Bilker WB, Brensinger C, Strom BL. Seasonal variation in flares of inflammatory bowel disease. *Gastroenterology* 2004;126(3):665-73.

a118. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ* 1999;318(7183):565-6.

a119. Ruigomez A, Garcia Rodriguez LA, Johansson S, Wallander MA. Is hormone replacement therapy associated with an increased risk of irritable bowel syndrome? *Maturitas* 2003;44(2):133-40.

a120. Talley NJ, Jones M, Nuyts G, Dubois D. Risk factors for chronic constipation based on a general practice sample. *Am J Gastroenterol* 2003;98(5):1107-11.

a121. Walker AM, Szneke P, Bianchi LA, Field LG, Sutherland LR, Dreyer NA. 5-Aminosalicylates, sulfasalazine, steroid use, and complications in patients with ulcerative colitis. *Am J Gastroenterol* 1997;92(5):816-20.

a122. del Mar Melero-Montes M, Jick H. Hyperemesis Gravidarum and the Sex of the Offspring. *Epidemiology* 2000;12(1):123-124.

a123. Lawrence M, Jones L, Lancaster T, Daly E, Banks E. Hormone replacement therapy: patterns of use studied through British general practice computerized records. *Fam Pract* 1999;16(4):335-42.

a124. Seaman HE, de Vries CS, Farmer RD. The risk of liver disorders in women prescribed cyproterone acetate in combination with ethinyloestradiol (Dianette): a nested case-control study using the GPRD. *Pharmacoepidemiol Drug Saf* 2003;12(7):541-50.

a125. Wyatt KM, Dimmock PW, Frischer M, Jones PW, O'Brien SP. Prescribing patterns in premenstrual syndrome. *BMC Womens Health* 2002;2(1):4.

a126. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. *Med J Aust* 1993;158(9):596-600.

a127. Derby LE, Jick H, Henry DA, Dean AD. Erythromycin-associated cholestatic hepatitis. *Med J Aust* 1993;158(9):600-2.

a128. Derby LE, Gutthann SP, Jick H, Dean AD. Liver disorders in patients receiving chlorpromazine or isoniazid. *Pharmacotherapy* 1993;13(4):353-8.

a129. Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med* 1994;154(3):311-6.

a130. Garcia Rodriguez LA, Stricker BH, Zimmerman HJ. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996;156(12):1327-32.

a131. Garcia Rodriguez LA, Wallander MA, Stricker BH. The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol* 1997;43(2):183-8.

a132. Garcia Rodriguez LA, Duque A, Castellsague J, Perez-Gutthann S, Stricker BH. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999;48(6):847-52.

a133. Huerta C, Garcia Rodriguez LA. Risk of clinical blood dyscrasia in a cohort of antibiotic users. *Pharmacotherapy* 2002;22(5):630-6.

a134. Jick H, Derby LE, Garcia Rodriguez LA, Jick SS, Dean AD. Liver disease associated with diclofenac, naproxen, and piroxicam. *Pharmacotherapy* 1992;12(3):207-12.

a135. Meier CR, Krahenbuhl S, Schlienger RG, Jick H. Association between body mass index and liver disorders: an epidemiological study. *J Hepatol* 2002;37(6):741-7.

a136. Myers MW, Jick H. Terfenadine and risk of acute liver disease. *Br J Clin Pharmacol* 1998;46(3):251-3.

a137. Seaman HE, Lawrenson RA, Williams TJ, MacRae KD, Farmer RD. The risk of liver damage associated with minocycline: a comparative study. *J Clin Pharmacol* 2001;41(8):852-60.

a138. van Staa T, Abenheim L. The quality of information recorded on a UK database of primary care records: A study of hospitalisations due to hypoglycemia and other conditions. *Pharmacoepidemiol Drug Saf* 1994;3:15-21.

a139. Blumentals WA, Brown RR, Gomez-Caminero A. Antihypertensive treatment and erectile dysfunction in a cohort of type II diabetes patients. *Int J Impot Res* 2003;15(5):314-7.

a140. Clifford GM, Farmer RD. Drug or symptom-induced depression in men treated with alpha 1-blockers for benign prostatic hyperplasia? A nested case-control study. *Pharmacoepidemiol Drug Saf* 2002;11(1):55-61.

a141. Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG, et al. Validation of the diagnosis of autism in general practitioner records. *BMC Public Health* 2004;4(1):5.

a142. Frischer M, Akram G. Prevalence of comorbid mental illness and drug use recorded in general practice: preliminary findings from the General Practice Research Database. *Drugs: education, prevention and policy* 2001;8:276-280.

a143. Howard LM, Kumar C, Leese M, Thornicroft G. The general fertility rate in women with psychotic disorders. *Am J Psychiatry* 2002;159(6):991-7.

a144. Jick SS, Vasilakis C, Martinez C, Jick H. A study of the relation of exposure to quinolones and suicidal behaviour. *Br J Clin Pharmacol* 1998;45(1):77-81.

a145. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000;136(10):1231-6.

a146. Kaye JA, del Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001;322(7284):460-3.

a147. .Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. *BMJ* 1993;307(6895):32-4.

a148. Seshadri S, Zornberg GL, Derby LE, Myers MW, Jick H, Drachman DA. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. *Arch Neurol* 2001;58(3):435-40.

a149. Turnbull S, Ward A, Treasure J, Jick H, Derby L. The demand for eating disorder care. An epidemiological study using the general practice research database. *Br J Psychiatry* 1996;169(6):705-12.

a150. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003;163(16):1926-32.

a151. van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. *J Clin Epidemiol* 1997;50(6):735-41.

a152. Bailey K, Ellis C, Majeed A. Trends in the treatment of osteoporsis and types of drug treatments prescribed in general practice in England and Wales, 1994 to 1998. *Health Statistics Quarterly* 2002;16:5-13.

a153. Black C, Jick H. Etiology and frequency of rhabdomyolysis. *Pharmacotherapy* 2002;22(12):1524-6.

a154. Card T, Logan RF, Rodrigues LC, Wheeler JG. Antibiotic use and the development of Crohn's disease. *Gut* 2004;53(2):246-50.

a155. Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12(5):565-9.

a156. Meier CR, Jick H. Omeprazole, H2 blockers, and polyarthralgia: case-control study. *BMJ* 1997;315(7118):1283.

a157. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997;44(2):175-8.

a158. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. *Jama* 2000;283(24):3205-10.

a159. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003;163(15):1801-7.

a160. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15(6):993-1000.

a161. van Staa T, Abenhaim L, Cooper C, Zhang B, Leufkens B. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf* 2000;9(5):359-366.

a162. van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* 2002;17(3):465-71.

a163. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18(5):913-8.

a164. Sturkenboom MC, Fautrel B, Rozenberg S, Begaud B, Roullet E, Heinzlef O. Vaccinations against hepatitis B and rheumatoid arthritis. *Pharmacoepidemiol Drug Saf* 2003;12 Suppl 1:S71-2.

a165. Cleary P, Shorvon S, Tallis R. Late-onset seizures as a predictor of subsequent stroke. *Lancet* 2004;363(9416):1184-6.

a166. Davey G, Sedgwick P, Maier W, Visick G, Strachan DP, Anderson HR. Association between migraine and asthma: matched case-control study. *Br J Gen Pract* 2002;52(482):723-7.

a167. Gaist D, Garcia Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *Eur J Clin Pharmacol* 2001;56(12):931-3.

a168. Gasse C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy* 2000;20(6):629-34.

a169. Jick SS, Jick H, Knauss TA, Dean AD. Antidepressants and convulsions. *J Clin Psychopharmacol* 1992;12(4):241-5.

a170. Jick H, Derby LE, Vasilakis C, Fife D. The risk of seizures associated with tramadol. *Pharmacotherapy* 1998;18(3):607-11.

a171. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. *Neuroepidemiology* 2001;20(2):138-43.

a172. Marrie RA, Wolfson C, Sturkenboom MC, Gout O, Heinzlef O, Roullet E, et al. Multiple sclerosis and antecedent infections: a case-control study. *Neurology* 2000;54(12):2307-10.

a173. Purcell B, Gaitatzis A, Sander J, Majeed A. Epilepsy prevalence and prescribing patterns in England and Wales. *Health Statistics Quarterly* 2002;15:23-30.

a174. Shorvon SD, Tallis RC, Wallace HK. Antiepileptic drugs: coprescription of proconvulsant drugs and oral contraceptives: a national study of antiepileptic drug prescribing practice. *J Neurol Neurosurg Psychiatry* 2002;72(1):114-5.

a175. Tallis R, Hall G, Craig I, Dean A. How common are epileptic seizures in old age? *Age Ageing* 1991;20(6):442-8.

a176. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 1998;352(9145):1970-3.

a177. Mannino S, Garcia Rodriguez L, Jick S. NSAIDs, quinolones and convulsions: an epidemiologic approach. *Post Marketing Surveillance* 1992;6:119-128.

a178. Clifford GM, Logie J, Farmer RD. How do symptoms indicative of BPH progress in real life practice? The UK experience. *Eur Urol* 2000;38 Suppl 1:48-53.

a179. Garcia Rodriguez LA, Wallander MA, Johanson S, Bjorck S. Renal disease and acid-suppressing drugs. *Pharmacoepidemiol Drug Saf* 1997;6(4):247-51.

a180. Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. *J Antimicrob Chemother* 2001;48(6):895-901.

a181. Orlander JD, Jick SS, Dean AD, Jick H. Urinary tract infections and estrogen use in older women. *J Am Geriatr Soc* 1992;40(8):817-20.

a182. Gupta D, Hansell A, Nichols T, Duong T, Ayres JG, Strachan D. Epidemiology of pneumothorax in England. *Thorax* 2000;55(8):666-71.

a183. Hoare J, Bruce M, Majeed A. Prevalence of treated asthma and its management in general practice in England and Wales, 1994-1998. *Health Statistics Quarterly* 2003;17:15-22.

a184. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000;161(1):5-8.

a185. Huerta C, Garcia Rodriguez LA, Moller CS, Arellano FM. The risk of obstructive airways disease in a glaucoma population. *Pharmacoepidemiol Drug Saf* 2001;10(2):157-63.

a186. Majeed A, Moser K. Prescribing for patients with asthma by general practitioners in England an Wales 1994-96. *Health Statistics Quarterly* 1999;1:16-20.

a187. Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. *Eur J Epidemiol* 2001;17(12):1075-80.

a188. Soriano JB, Kiri VA, Pride NB, Vestbo J. Inhaled corticosteroids with/without long-acting beta-agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med* 2003;2(1):67-74.

a189. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003;124(2):474-81.

a190. Metlay JP, Kinman JL. Failure to validate pneumococcal pneumonia diagnoses in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2003;12 Suppl 1:S163-4.

a191. Meier CR, Sturkenboom MC, Cohen AS, Jick H. Postmenopausal estrogen replacement therapy and the risk of developing systemic lupus erythematosus or discoid lupus. *J Rheumatol* 1998;25(8):1515-9.

a192. Meier CR, Napalkov PN, Wegmuller Y, Jefferson T, Jick H. Population-based study on incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom. *Eur J Clin Microbiol Infect Dis* 2000;19(11):834-42.

a193. Sturkenboom MC, Meier CR, Jick H, Stricker BH. Minocycline and lupuslike syndrome in acne patients. *Arch Intern Med* 1999;159(5):493-7.

a194. Sturkenboom MC, Fautrel B, Rozenberg S, Begaud B, Roullet E, Heinzlef O. Vaccinations against Hepatitis B and Lupus Erythematosus. *Pharmacoepidemiol Drug Saf* 2000;9 Suppl 1:S71.

a195. Mines DI, Wang L, Guo D, Xue S. The incidence of myasthenia gravis (MG) in the General Practice Research Database (GPRD): a validation study. *Pharmacoepidemiol Drug Saf* 2003;12 Suppl 1:S10-1.

a196. Bradbury BD, Jick SS. Itraconazole and fluconazole and certain rare, serious adverse events. *Pharmacotherapy* 2002;22(6):697-700.

a197. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302(6779):766-8.

a198. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. *Pharmacoepidemiol Drug Saf* 1992;1:347-349.

a199. Jick H, Derby LE, Garcia Rodriguez LA, Jick SS, Dean AD. Nonsteroidal antiinflammatory drugs and certain rare, serious adverse events: a cohort study. *Pharmacotherapy* 1993;13(3):212-7.

a200. Jick SS, Jick H, Dean AD. A follow-up safety study of ciprofloxacin users. *Pharmacotherapy* 1993;13(5):461-4.

a201. Jick H, Derby LE. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy* 1995;15(4):428-32.

a202. Jick S. Ciprofloxacin safety in a pediatric population. *Pediatr Infect Dis J* 1997;16(1):130-3.

a203. Toledano MB, Hansell AL, Jarup L, Quinn M, Jick S, Elliott P. Temporal trends in orchidopexy, Great Britain, 1992-1998. *Environ Health Perspect* 2003;111(1):129-32.

a204. van Staa TP, Leufkens H, Abenhaim L, Cooper C. Postmarketing surveillance of the safety of cyclic etidronate. *Pharmacotherapy* 1998;18(5):1121-8.

APPENDIX II. OXMIS AND READ CODES FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Medical codes for systemic lupus erythematosus	
Oxmis codes	
7341AC	ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS
7341C	LUPUS ENDOCARDITIS
7341AD	LUPUS ERYTHEMATOSUS ACUTE
7341	LUPUS ERYTHEMATOSUS DISSEMINATED
7341AA	LUPUS ERYTHEMATOSUS SYSTEMIC
7341AB	NEPHRITIS LUPUS
6954	SYSTEMIC LUPUS ERYTHEMATOSUS
7341A	SYSTEMIC LUPUS ERYTHEMATOSUS WITH RENAL
Read codes	
Nyu4300	[X]OTHER FORMS OF SYSTEMIC LUPUS ERYTHEMATOSUS
N000000	DISSEMINATED LUPUS ERYTHEMATOSUS
N000200	DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS
H57y400	LUNG DISEASE WITH SYSTEMIC LUPUS ERYTHEMATOSUS
M154.00	LUPUS ERYTHEMATOSUS
M154z00	LUPUS ERYTHEMATOSUS NOS
K01x411	LUPUS NEPHRITIS
F396100	MYOPATHY DUE TO DISSEMINATED LUPUS ERYTHEMATOSUS
K01x400	NEPHROTIC SYNDROME IN SYSTEMIC LUPUS ERYTHEMATOSUS
F371000	POLYNEUROPATHY IN DISSEMINATED LUPUS ERYTHEMATOSUS
M154700	SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS
N000.00	SYSTEMIC LUPUS ERYTHEMATOSUS
N000z00	SYSTEMIC LUPUS ERYTHEMATOSUS NOS
N000300	SYSTEMIC LUPUS ERYTHEMATOSUS WITH ORGAN OR SYS INVOLV
N000400	SYSTEMIC LUPUS ERYTHEMATOSUS WITH PERICARDITIS

APPENDIX III. OXMIS AND READ CODES FOR HYPOTHYROIDISM, (INCLUDING AUTOIMMUNE THYROIDITIS)

Medical codes for hypothyroidism (including autoimmune hypothyroiditis)	
Oxmis codes	
245 B	HASHIMOTO'S DISEASE
244 AC	HYPOTHYROIDISM ACQUIRED
244 AG	HYPOTHYROIDISM COMPENSATED
244	MYXOEDEMA
245 E	THYROIDITIS
245 EA	THYROIDITIS ACUTE
245 A	THYROIDITIS AUTOIMMUNE
Read codes	
Cyu1400	[X]OTHER CHRONIC THYROIDITIS
Cyu1100	[X]OTHER SP CIFIED HYPOTHYROIDISM
Fyu1500	[X]SYSTEMIC ATROPHY AFFECTING THE CNS IN MYXOEDEMA
C050000	ACUTE NONSUPPURATIVE THYROIDITIS
C050.00	ACUTE THYROIDITIS
C050z00	ACUTE THYROIDITIS NOS
C046.00	AUTOIMMUNE MYXOEDEMA
C052.11	AUTOIMMUNE THYROIDITIS
F144100	CEREBELLAR ATAXIA DUE TO MYXOEDEMA
F11x500	CEREBRAL DEGENERATION DUE TO MYXOEDEMA
C052.00	CHRONIC LYMPHOCYTIC THYROIDITIS
C05y400	CHRONIC THYROIDITIS WITH TRANSIENT THYROTOXICOSIS
C051.11	DE QUERVAIN'S THYROIDITIS
C052.12	HASHIMOTO'S DISEASE
C04..13	HYPOTHYROIDISM
C04z.00	HYPOTHYROIDISM NOS
F381400	MYASTHENIC SYNDROME DUE TO HYPOTHYROIDISM
C04..11	MYXOEDEMA
C04z100	MYXOEDEMA COMA
C04y.00	OTHER ACQUIRED HYPOTHYROIDISM
C05y.00	OTHER AND UNSPECIFIED CHRONIC THYROIDITIS
C053.11	RIEDEL'S THYROIDITIS
C051.00	SUBACUTE THYROIDITIS
C05..00	THYROIDITIS
C05z.00	THYROIDITIS NOS

APPENDIX IV. EXCLUSION CRITERIA FOR CASES WITH HYPOTHYROID DISEASE AND MATCHED CONTROLS

A priori identified medical codes for potentially iatrogenic hypothyroidism	
7110111	BILATERAL SUBTOTAL THYROIDECTOMY
K0722	DISSECTION NECK WITH THYROIDECTOMY
K0714FH	FUND HOLDING PARTIAL THYROIDECTOMY
K0722FH	FUND HOLDING THYROIDECTOMY ABERRENT GLAN
K0721FH	FUND HOLDING TOTAL THYROIDECTOMY
7110200	HEMITHYROIDECTOMY
K0716	HEMITHYROIDECTOMY
5A16.11	I131 RADIOTHERAPY
K998 A	I-131 THYROID ABLATION
5A16.12	IODINE 131 RADIOTHERAPY
7110y00	OTHER SPECIFIED THYROIDECTOMY
7110500	PARTIAL THYROIDECTOMY NEC
K998 T	RADIOIODINE THERAPY
7110100	SUBTOTAL THYROIDECTOMY
K998	THYROID ABLATION RADIOIODINE
K072	THYROIDECTOMY
7110600	THYROIDECTOMY NEC
7110z00	THYROIDECTOMY NOS
K071 D	THYROIDECTOMY OF ABERRENT THYROID GLAND
7110.00	THYROIDECTOMY OPERATIONS
K071	THYROIDECTOMY PARTIAL
K071 B	THYROIDECTOMY SUBTOTAL
7110000	TOTAL THYROIDECTOMY
K0721	TOTAL THYROIDECTOMY

Further medical codes for potentially iatrogenic hypothyroidism	
BBa0.00	[M]Craniopharyngioma
ZV10100	[V]Personal history of malig neop of trachea/bronchus/lung
ZV10016	[V]Personal history of malignant neoplasm of oesophagus
ZV10113	[V]Personal history of malignant neoplasm of trachea
Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
PA37.00	Atresia of oesophagus with tracheo-oesophageal fistula
7432400	Attention to artificial voicebox in larynx
2121	BENIGN NEOPLASM LARYNX
B721.00	Benign neoplasm of larynx
B722.00	Benign neoplasm of trachea
B710100	Benign neoplasm of upper 1/3 of oesophagus
2109	BENIGN NEOPLASM PHARYNX
B721z11	Benign papilloma of larynx
B800900	Carcinoma in situ of hypopharynx
B810.00	Carcinoma in situ of larynx
B810z00	Carcinoma in situ of larynx NOS
B800.00	Carcinoma in situ of lip, oral cavity and pharynx
B800z00	Carcinoma in situ of lip, oral cavity and pharynx NOS
B800700	Carcinoma in situ of nasopharynx
B800800	Carcinoma in situ of oropharynx
B800.12	Carcinoma in situ of pharynx
B811.00	Carcinoma in situ of trachea
B801000	Carcinoma in situ of upper 1/3 oesophagus
B0...11	Carcinoma of lip, oral cavity and pharynx
744D100	Changing of tracheooesophageal valve
7433400	Chondroplasty of larynx
7606100	Closure of fistula of oesophagus NEC
7606000	Closure of tracheooesophageal fistula

Further medical codes for potentially iatrogenic hypothyroidism	
PA36.00	Cong.absence of oesophagus with tracheo-oesophageal fistula
PA32z00	Congenital oesophageal fistula NOS
PA32111	Congenital tracheo-oesophageal fistula
2262CP	CRANIOPHARYNGIOMA
ZD64700	Development of oesophageal voice exercises
7432200	Division of larynx stenosis and insertion of prosthesis
7431100	Excision lesion larynx using lateral pharyngotomy approach
7430.00	Excision of larynx
7430z00	Excision of larynx NOS
7431000	Excision of lesion of larynx using thyrotomy as approach
7420.00	Excision of pharynx
7420z00	Excision of pharynx NOS
7606011	Excision of tracheooesophageal fistula
7443.00	Exteriorisation of trachea
7443z00	Exteriorisation of trachea NOS
7601211	Herzen oesophagectomy and interposition of jejunal loop
7422011	Hynes pharyngoplasty
7422212	Hynes pharyngoplasty
7432300	Implantation of artificial voice box into larynx
7601212	Judine oesophagectomy and interposition of jejunal loop
7430.11	Laryngectomy
1619C	LARYNX CARCINOMA
743..00	Larynx operations
743z.00	Larynx operations NOS
2311A	LEIOMYOMA LARYNX
B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
150 A	MALIGNANT NEOPLASM OESOPHAGUS
B220000	Malignant neoplasm of cartilage of trachea
B100.00	Malignant neoplasm of cervical oesophagus
B542100	Malignant neoplasm of craniopharyngeal duct
B08..00	Malignant neoplasm of hypopharynx
B08z.00	Malignant neoplasm of hypopharynx NOS
B0z2.00	Malignant neoplasm of laryngopharynx
B21..00	Malignant neoplasm of larynx
B21z.00	Malignant neoplasm of larynx NOS
B21y.00	Malignant neoplasm of larynx, other specified site
B066.00	Malignant neoplasm of lateral wall of oropharynx
B0...00	Malignant neoplasm of lip, oral cavity and pharynx
B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
B220100	Malignant neoplasm of mucosa of trachea
B10..00	Malignant neoplasm of oesophagus
B10z.00	Malignant neoplasm of oesophagus NOS
B06..00	Malignant neoplasm of oropharynx
B06z.00	Malignant neoplasm of oropharynx NOS
B06y.00	Malignant neoplasm of oropharynx, other specified sites
B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
B08y.00	Malignant neoplasm of other specified hypopharyngeal site
B10y.00	Malignant neoplasm of other specified part of oesophagus
B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
B062300	Malignant neoplasm of palatopharyngeal arch
B0z0.00	Malignant neoplasm of pharynx unspecified
B083.00	Malignant neoplasm of posterior pharynx
B067.00	Malignant neoplasm of posterior wall of oropharynx
B101.00	Malignant neoplasm of thoracic oesophagus
B220.00	Malignant neoplasm of trachea
B220z00	Malignant neoplasm of trachea NOS
B22..00	Malignant neoplasm of trachea, bronchus and lung
B103.00	Malignant neoplasm of upper third of oesophagus
149 AT	MALIGNANT NEOPLASM PHARYNX
B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
B084.00	Malignant neoplasm, overlapping lesion of hypopharynx
B214.00	Malignant neoplasm, overlapping lesion of larynx
7601111	McKewown total oesophagectomy
B901z00	Neop of uncertain behaviour lip, oral cavity and pharynx NOS
B901.00	Neop of uncertain behaviour of lip, oral cavity and pharynx
B907z00	Neop of uncertain behaviour of trachea, bronchus or lung NOS
B920.00	Neop uncertain behaviour pituitary and craniopharyngeal duct
B920z00	Neop uncertain behaviour pituitary and craniopharyngeal NOS
1619A	NEOPLASM MALIGNANT LARYNX
1620A	NEOPLASM MALIGNANT TRACHEA
B920100	Neoplasm of uncertain behaviour of craniopharyngeal duct
B901900	Neoplasm of uncertain behaviour of hypopharynx
B906.00	Neoplasm of uncertain behaviour of larynx
B906z00	Neoplasm of uncertain behaviour of larynx NOS
B901800	Neoplasm of uncertain behaviour of oropharynx

Further medical codes for potentially iatrogenic hypothyroidism	
B901.12	Neoplasm of uncertain behaviour of pharynx
B907000	Neoplasm of uncertain behaviour of trachea
B907.00	Neoplasm of uncertain behaviour trachea, bronchus and lung
B10z.11	Oesophageal cancer
ZT12100	Oesophageal voice
ZD64800	Oesophageal voice injection exercises
ZD64900	Oesophageal voice insufflation exercises
K291	OESOPHAGECTOMY
7602z11	Oesophagectomy NEC
ZC65900	Oesophagostomy feeding
PA32100	Oesophagotracheal fistula
150 C	OESOPHAGUS CARCINOMA
7431200	Open destruction of lesion of larynx
7444000	Open destruction of lesion of trachea
7423000	Open excision of lesion of pharynx
7440000	Open excision of lesion of trachea
7431.00	Open extirpation of lesion of larynx
7431z00	Open extirpation of lesion of larynx NOS
7442000	Open insertion of tubal prosthesis in trachea
7442.00	Open placement of prosthesis in trachea
7442z00	Open placement of prosthesis in trachea NOS
7442200	Open removal of tubal prosthesis from trachea
7442100	Open renewal of tubal prosthesis in trachea
7433500	Operation on cartilage of larynx NEC
7422211	Orticochea pharyngoplasty
7433z00	Other open operation on larynx NOS
7444z00	Other open operation on trachea NOS
7433.00	Other open operations on larynx
7423.00	Other open operations on pharynx
7444.00	Other open operations on trachea
744Cz00	Other operation on bronchus or trachea NOS
7437z00	Other operation on larynx NOS
7426z00	Other operation on pharynx NOS
744C.00	Other operations on bronchus or trachea
7437.00	Other operations on larynx
7430y00	Other specified excision of larynx
7420y00	Other specified excision of pharynx
7443y00	Other specified exteriorisation of trachea
PA3y.00	Other specified oesophageal atresia, stenosis or fistula
7431y00	Other specified open extirpation of lesion of larynx
7433y00	Other specified open operation on larynx
743y.00	Other specified operations on larynx
742y.00	Other specified operations on pharynx
7444y00	Other specified other open operation on trachea
744Cy00	Other specified other operation on bronchus or trachea
7437y00	Other specified other operation on larynx
7426y00	Other specified other operation on pharynx
7602y00	Other specified partial excision of oesophagus
7440y00	Other specified partial excision of trachea
7441y00	Other specified plastic operation on trachea
7432y00	Other specified reconstruction of larynx
7422y00	Other specified repair of pharynx
7601y00	Other specified total excision of oesophagus
7602.00	Partial excision of oesophagus
7602z00	Partial excision of oesophagus NOS
7440.00	Partial excision of trachea
7440z00	Partial excision of trachea NOS
7602.11	Partial oesophagectomy
7602000	Partial oesophagectomy and end to end anastomosis of oesoph
7602500	Partial oesophagectomy and interposition of colon NEC
7602200	Partial oesophagectomy+anastom oesophagus to transp jejunum
7602300	Partial oesophagectomy+anastomosis oesophagus to jejunum NEC
7602400	Partial oesophagectomy+interposition microvasc attach colon
7602100	Partial oesophagectomy+interposition microvasc attach jejun
7420100	Partial pharyngectomy
7420.11	Pharyngectomy
K2841	PHARYNGECTOMY PARTIAL
K2843	PHARYNGECTOMY TOTAL
7420000	Pharyngolaryngectomy
7420300	Pharyngolaryngooesophagectomy
7420300	Pharyngolaryngooesophagectomy
7422.11	Pharyngoplasty
K2862	PHARYNGOPLASTY
7422200	Pharyngoplasty using lateral pharyngeal flap
7422100	Pharyngoplasty using posterior pharyngeal flap
7422000	Pharyngoplasty using posterior pharyngeal implant
149 C	PHARYNX CARCINOMA

Further medical codes for potentially iatrogenic hypothyroidism	
K289	PHARYNX OPERATION
742z.00	Pharynx operations NOS
7441z00	Plastic operation on trachea NOS
7441.00	Plastic operations on trachea
7422300	Plastic repair of pharynx NEC
7432.00	Reconstruction of larynx
7432z00	Reconstruction of larynx NOS
7422.13	Reconstruction of pharynx operations
7422900	Reconstruction of pharynx with colon pull-up
7422500	Reconstruction of pharynx with distant pedicle flap
7422611	Reconstruction of pharynx with free flap
7422700	Reconstruction of pharynx with free jejunal transfer
7422600	Reconstruction of pharynx with microvascular transfered flap
7422800	Reconstruction of pharynx with stomach pull-up
7441000	Reconstruction of trachea & anastomosis HFQ
7441200	Reconstruction of trachea NEC
7441.11	Reconstruction of trachea operations
7441100	Reconstruction of trachea using graft
7441300	Reconstruction of trachea with skin flap
7422z00	Repair of pharynx NOS
7601213	Roux oesophagectomy and interposition of jejunal loop
150 B	SARCOMA OESOPHAGUS
B561500	Secondary and unspec malig neop paratracheal lymph nodes
ZT12211	T-E voice - Tracheo-oesophageal voice
7601100	Tot oesophagectomy+interposition microvasc attached jejunum
7601.00	Total excision of oesophagus
7601z00	Total excision of oesophagus NOS
7601.11	Total oesophagectomy
7601000	Total oesophagectomy and anastomosis of pharynx to stomach
7601000	Total oesophagectomy and anastomosis of pharynx to stomach
7601400	Total oesophagectomy and interposition of colon NEC
7601200	Total oesophagectomy and interposition of jejunum NEC
7601300	Total oesophagectomy+interposition microvasc attached colon
7420011	Total pharyngectomy
7420400	Total pharyngectomy
1620C	TRACHEA CARCINOMA
K249 AA	TRACHEA OPERATION
7502C	TRACHEO-OESOPHAGEAL FISTULA
J10y200	Tracheo-oesophageal fistula
H5y0400	Tracheo-oesophageal fistula following tracheostomy
ZT12200	Tracheo-oesophageal voice
5B76.00	U-S therapy - larynx lesion

APPENDIX V. DESCRIPTION OF BNF SUBCHAPTERS

BNF subchapter	Drug indications
Gastrointestinal system (chapter 1)	
101	dyspepsia and gastro-oesophageal reflux disease
102	antispasmodics and other drugs altering gut motility
103	ulcer-healing drugs
104	acute diarrhoea
105	chronic bowel disorders
106	laxatives
107	local preparations for anal and rectal disorders
109	drugs affecting intestinal secretions
Cardiovascular system (chapter 2)	
201	positive inotropic drugs
202	diuretics
203	anti-arrhytmic drugs
204	beta-adrenoreceptor blocking drugs
205	hypertension and heart failure
206	nitrates, calcium-channel blockers and other antianginal drugs
207	symptathomimetics
208	anticoagulants and protamine
209	antiplatelet drugs
211	antifibrinolytic drugs and haemostatics
212	lipid-regulating drugs
213	local sclerosants
Respiratory system (chapter 3)	
301	bronchodilators
302	corticosteroids
303	cromoglicate and related therapy and leukotriene receptor antagonists
304	antihistamines, hyposensitisation, and allergic emergencies
306	oxygen
307	mucolytics
308	aromatic inhalations
309	cough preparations
310	systemic nasal decongestants
350	miscellaneous care products for the respiratory system
Central nervous system (chapter 4)	
401	hypnotics and anxiolytics
402	drugs used in psychoses and related disorders
403	antidepressant drugs
405	drugs in the treatment of obesity
406	drugs used in nausea and vertigo
407	analgesics
408	antiepileptics
409	drugs used in parkinsonism and related disorders
410	drugs used in substance dependance
Infections (chapter 5)	
501	antibacterial drugs
502	antifungal drugs
503	antiviral drugs
504	antiprotozoal drugs
505	antihelminthics
Endocrine system (chapter 6)	
601	drugs used in diabetes
602	thyroid and antithyroid drugs
603	corticosteroids
604	sex hormones

BNF subchapter	Drug indications
605	hypothalamic and pituitary hormones and anti-oestrogens
606	drugs affecting bone metabolism
607	other endocrine drugs
Obstetrics, gynaecology and urinary tract disorders (chapter 7)	
701	drugs used in obstetrics
702	treatment of vaginal and vulval conditions
703	contraceptives
704	drugs for genito-urinary disorders
750	
Malignant disease and immunosuppression (chapter 8)	
801	cytotoxic drugs
802	drugs affecting the immune response
803	sex hormones and hormone antagonists in malignant disease
Nutrition and blood (chapter 9)	
901	anaemias and some other blood disorders
902	fluids and electrolytes
904	oral nutrition
905	minerals
906	vitamins
907	bitters and tonics
908	metabolic disorders
910	
911	
Musculoskeletal and joint diseases (chapter 10)	
1001	drugs used in rheumatic diseases and gout
1002	drugs used in neuromuscular disorders
1003	drugs for the relief of soft-tissue inflammation
Eye (chapter 11)	
1103	anti-infective eye preparations
1104	corticosteroids and other anti-inflammatory preparations
1105	mydratics and cycloplegics
1106	treatment of glaucoma
1107	local anaesthetics
1108	miscellaneous opthalmic preparations
1150	
Ear, nose and oropharynx (chapter 12)	
1201	drugs acting on the ear
1202	drugs acting on the nose
1203	drugs acting on the oropharynx
Skin (chapter 13)	
1301	management of skin conditions
1302	emollient and barrier preparations
1303	topical local anaesthetics and antipruritics
1304	topical local corticosteroids
1305	preparations for eczema an psoriasis
1306	acne and rosacea
1307	preparations for warts and calluses
1308	sunscreens and camouflagers
1309	shampoos and other preparations for scalp and hair conditions
1310	anti-infective skin preparations
1311	skin cleansers and antisceptics
1312	antiperspirants
1314	herbal preparations
1315	soap and cleansers
Immunological products and vaccines (chapter 14)	
1404	vaccines and antisera

BNF subchapter	Drug indications
1405	immunoglobulins
Anaesthesia (chapter 15)	
1501	general anaesthesia
1502	local anaesthesia

APPENDIX VI. DRUGS BY BNF CODE

Drugs included in BNF code 1.03.05.00

AMOXICILLIN+CLARITHROM & LANSOP
CLARITHROMYCINmetronid + lanzop
LANSOPRAZOLE
OMEPRAZOLE
RABEPRAZOLE
CLARITHROMYCIN+LANSOP & AMOXI
ESOMEPRAZOLE
LANSOPRAZOLE+AMOXI & CLARITH
PANTOPRAZOLE

Drugs included in BNF code 3.04.01.01

ACRIVASTINE
CETIRIZINE
FEXOFENADINE
LORATADINE
TERFENADINE
ASTEMIZOLE
DESLORATADINE
LEVOCETIRIZINE
MIZOLASTINE

Drugs included in BNF code 4.07.01.00

ACETYLSALICYLIC ACID
ACETYLSALICYLIC ACID/ CODEINE PHOSPHATE
AMBUCETAMIDE/PARACETAMOL
ASPIRIN
ASPIRIN /CALCIUM CARBONATE /CITRIC ACID
ASPIRIN 600MG/GLYCINE 300MG
ASPIRIN E/C
ASPIRIN PAED
ASPIRIN SACHETS
ASPIRIN/CAFFEINE CIT./CODEINE PHOSPHATE
ASPIRIN/CAFFEINE/DEXTROPROPOXYPHENE
ASPIRIN/CHLORMEZANONE
ASPIRIN/CODEINE
ASPIRIN/CODEINE/PAEDIATRIC
ASPIRIN/PAPAVERETUM
ASPIRIN+ CAFFEINE
ASPIRIN+ CODEINE & CAFFEINE
ASPIRIN+ GLYCINE
ASPIRIN+ OTHERS
ASPIRIN+ PARACETAMOL
ASPIRIN+NA BICARB&CITRIC AC
ASPRIN E/C
CAF/COD/NICOT/PARACETAMOL(ACETAMINOPHEN)
CAFF/HOMATROP/PARACETAMOL(ACETAMINOPHEN)
CARISOPRODOL/PARACETAMOL (ACETAMINOPHEN)
CHLORMEZANONE+ PARACETAMOL
CODEINE 30/PARACETAMOL 500/ACETAMINOPHEN
CODEINE COMPOUND SOLUBLE
CODEINE PHOSPHATE+ ASPIRIN & CAFFEINE
CODEINE PHOSPHATE+ADDITIONAL INGREDS
CODEINE PHOSPHATEPARACET,DOXYLAMI,CAF
CODEINE/PARACETAMOL (ACETAMINOPHEN)
ACETYLSALICYLIC ACID 300MG/GLYCINE 133MG
ALOXIPRIN
AMBUCETAMIDE+ PARACETAMOL
ASPIRIN /CAFFEINE /QUININE SULPHATE
ASPIRIN 300MG/LYSINE 245MG
ASPIRIN DISPERSIBLE
ASPIRIN M/F
ASPIRIN S/R
ASPIRIN/ANHYDROUS CITRIC ACID/CALCIUM
ASPIRIN/CAFFEINE DISPERSIBLE
ASPIRIN/CAFFEINE/DEXTROPROPOXYPHENE NAPS
ASPIRIN/CODEI/PARACETAMOL(ACETAMINOPHEN)
ASPIRIN/CODEINE PHOSPHATE/CAFFEINE
ASPIRIN/ETHOHEPTAZINE CITRAT/MEPROBAMATE
ASPIRIN/PARACETAMOL (ACETAMINOPHEN)
ASPIRIN+ CODEINE
ASPIRIN+ CYCLIZINE
ASPIRIN+ METHOCARBAMOL
ASPIRIN+ PAPAVERETUM
ASPIRIN+ALOXIPRIN &CAFFEINE
ASPIRINCALCIUM CARBONATE
BENORILATE
CAFF/CODEINE/PARACETAMOL (ACETAMINOPHEN)
CAFFEINE/CODEINE/DIPHENHYDRAMINE
CHLORMEZANONE+ ASPIRIN
CO-CODAPRIN
CODEINE COMPOUND
CODEINE PHOSPHATE+ ASPIRIN
CODEINE PHOSPHATE+ PARACETAMOL
CODEINE PHOSPHATEPARACET,DIPHENH,CAFF
CODEINE SOLUBLE
CODEINE/PARACETAMOL (ACETAMINOPHEN)8/500

CODEINE/PARACETAMOL(ACETAMINOPHEN)/CITRA
CODYDRAGESIC
CO-METHIAMOL
DEXTROPROPOXYPHENE HCL+ PARACETAMOL
DEXTROPROPOXYPHENE NAPSYLATE+ ASPIRIN & CAFFEINE
DICHLORALPHENAZONE/ISOMETHEPTENE MUCATE
DIHYDROCODEINE TARTRATE/ASPIRIN
ETHOHEPTAZINE CITRATE/ASPIRIN
FENOPROFEN
ISOMETHEPTENE MUCATE+ PARACETAMOL
MEPROBAMATE+ETHOHEPTAZINE&ASPIR
MORAZONE HYDROCHLORIDE+ PARACETAMOL
NAPROXENSODIUM
PAPAVERETUM+ ASPIRIN
PARACETAMOL (ACETAMINOP)/CODEINE 450/8.1
PARACETAMOL (ACETAMINOPHEN)
PARACETAMOL (ACETAMINOPHEN)/CODEINE
PARACETAMOL(ACETA/DYHYDROCODEINE500/20MG
PARACETAMOL(ACETAM/PHENYLEP/DEXTROMETHOR
PARACETAMOL(ACETAMINOPHEN)/CAFF/CODEINE
PARACETAMOL(ACETAMINOPHEN)/OXYPHENBUTAZO
PARACETAMOL/ ACETAMINOPHEN
PARACETAMOL/ ACETAMINOPHEN/CAFFEINE
PARACETAMOL+ ASPIRIN
PARACETAMOL+ ASPIRIN & CODEINE
PARACETAMOL+ CHLORMEZANONE
PARACETAMOL+ CODEINE & CAFFEINE
PARACETAMOL+ DEXTROPROPOXYPHENE
PARACETAMOL+ DIPHENHYDRAMINE
PARACETAMOL+ METHIONINE
PARACETAMOL+ PHENYLEPHRINE
PARACETAMOL+ PSEUDOEPHEDRINE
PARACETAMOL+ SODIUM SALICYLATE
PARACETAMOL+ADDITIONAL INGREDS
PARACETAMOL+DIPHEN,EPHED&CAFF
PARACETAMOL+GUAIFEN&PHENYLEPHR
PARACETAMOL+PHENYLEPH VIT C+CAF
PARACETAMOL+PHENYLEPHRNE&CAFFIN
PARACETAMOL+PHENYLPROP&DIPHENHY
PARACETAMOL+PHENYLPROPANOLAMINE
PARACETAMOL+PROMETH&DEXTRO'PHAN
PARACETAMOL+PSEUDOEPH&DIPHENHYD
PARACETAMOLCODEINE,DIPHENHY,CAF
PARACETAMOLCODEINE,HYOSCINE,CAF
PENTAZOCINE+ PARACETAMOL
PHENYLEPHRINE+ADDITIONAL INGREDS
PROMETHAZINE HYDROCHLORIDE+ PARACETAMOL
PSEUDOEPHEDRINE+ PARACETAMOL
SODIUM SALICYLATE

CODEINE/PARACETAMOL(ACETAMINOPHEN)15/500
CO-DYDRAMOL
CO-PROXAMOL
DEXTROPROPOXYPHENE NAPSYLATE/ASPIRIN
DEXTROPROPOXYPHENE/PARACETAMOL (ACETAMIN
DICHLORALPHENAZONE+ PARACETAMOL
DIHYDROCODEINE+ PARACETAMOL
ETHOHEPTAZINE/PARACETAMOL(ACETAMINOPHEN)
IBUPROFEN
MENTHOL
METHOCARBAMOL+ ASPIRIN
MYOLGIN
NEFOPAM
PARACETAMOL
PARACETAMOL (ACETAMINOPH)/CODEINE 500/10
PARACETAMOL (ACETAMINOPHEN) PAEDIATRIC
PARACETAMOL& ASCORBIC ACID
PARACETAMOL(ACETA/DYHYDROCODEINE500/30MG
PARACETAMOL(ACETAMINOPH)/MEPROBAMATE/CAF
PARACETAMOL(ACETAMINOPHEN)/DICHLORALPHEN
PARACETAMOL(ACETOMINOPHEN)CAFFEI/CODEINE
PARACETAMOL/ ACETAMINOPHEN SOLUBLE
PARACETAMOL/ ACETAMINOPHEN/CO
PARACETAMOL+ ASPIRIN & CAFFEINE
PARACETAMOL+ CAFFEINE
PARACETAMOL+ CODEINE
PARACETAMOL+ CODEINE PHOSPHATE
PARACETAMOL+ DIHYDROCODEINE
PARACETAMOL+ ISOMETHEPTENE
PARACETAMOL+ PENTAZOCINE
PARACETAMOL+ PROMETHAZINE HCL
PARACETAMOL+ SODIUM BICARBONATE
PARACETAMOL+ VITAMIN C
PARACETAMOL+DIPHEN & PHENYL
PARACETAMOL+DIPHEN,PSUEDO,PHOLC
PARACETAMOL+NaBICARB & CAFFEINE
PARACETAMOL+PHENYLEPH&ASCORB AC
PARACETAMOL+PHENYLPROP &DEXTROM
PARACETAMOL+PHENYLPROP&PHENYLTO
PARACETAMOL+PROMETH HCL COL/FR
PARACETAMOL+PSEUDOEPH&ASCORBIC
PARACETAMOL+PSEUDOEPH+PHOLCODIN
PARACETAMOLCODEINE,DOXYLAMI,CAF
PARACETAMOLPSEUDOEPH&OTHERS
PHENYLBUTAZON/PARACETAMOL(ACETAMINOPHEN)
PHENYLPROPANOLAMINE+ PARACETAMOL
PROMETHAZINE HYDROCHLORIDE+PARACET COL/FREE
SALICYLAMIDE/PARACETAMOL

Drugs included in BNF code 5.01.03.00

BLENMIX
BROMHEXINE HCL/OXYTETRACYCLINE HCL
CHLORTETRACYCLINE
CHLORTETRACYCLINE HCl/DEMECLOCYCLINE HCl
CHLORTETRACYCLINE HYDROCHLORIDE
CHLORTETRACYCLINE+DEMECLOCYC&TETRACYC
CLOMOCYCLINE
DEMECLOCYCLINE
DEMECLOCYCLINE HYDROCHLORIDE
DEMECLOCYCLINE HYDROCHLORIDE DROPS
DEMECLOCYCLINE+CHLORTET & TETRACYC
DOXYCYCLINE
DOXYCYCLINE HCl
DOXYCYCLINE HYCLATE
DOXYCYCLINE MONOHYDRATE
LYMECYCLINE
METACYCLINE
METHACYCLINE HYDROCHLORIDE
MINOCYCLINE
NYSTATIN+ TETRACYCLINE HCL
OXYTETRACYCLINE
OXYTETRACYCLINE/EPHEDRINE/IPECACUANHA
OXYTETRACYCLINE/PROCAINE HYDROCHLORIDE
OXYTETRACYCLINE+ BROMHEXINE HCL
TETRACYCLINE
TETRACYCLINE HCl
TETRACYCLINE HCl/AMPHOTERICIN
TETRACYCLINE HCL/PANCREATIC CONCENTRATE
TETRACYCLINE HYDROCHLORIDE
TETRACYCLINE/CHLORTETRACY/DEMECLOCYCLINE
TETRACYCLINE/NOVOBIOCIN
TETRACYCLINE/PROCAINE HYDROCHLORIDE
TETRACYCLINE+ AMPHOTERACIN
TETRACYCLINE+ NYSTATIN
TETRACYCLINE+ PANCREATIC ENZYMES
TETRACYCLINE+CHORTET&DEMECLOCYC
AMOXICILLIN+CLARITHROM & LANSOP
AZITHROMYCIN
CLARITHROMYCIN
CLARITHROMYCIN 500MG VIAL I/V
CLARITHROMYCIN+LANSOP & AMOXI
CLARITHROMYCINmetronid + lanzop
ERYTHROMYCIN
ERYTHROMYCIN E/C
ERYTHROMYCIN ETHYL SUCCINATE
ERYTHROMYCIN ETHYL SUCCINATE S/F
ERYTHROMYCIN ETHYLSUCCINATE
ERYTHROMYCIN ETHYLSUCCINATECOATED
ERYTHROMYCIN LACTOBIONATE
ERYTHROMYCIN SACHET S/F
ERYTHROMYCIN STEARATE
ERYTHROMYCINESTOLATE
ERYTHROMYCINSPRINKLE
LANSOPRAZOLE+AMOXI & CLARITH
SPIRAMYCIN
TELITHROMYCIN

Drugs included in BNF code 5.01.05.00

AMOXICILLIN+CLARITHROM & LANSOP	ERYTHROMYCIN ETHYLSUCCINATE
AZITHROMYCIN	ERYTHROMYCIN ETHYLSUCCINATECOATED
CLARITHROMYCIN	ERYTHROMYCIN LACTOBIONATE
CLARITHROMYCIN 500MG VIAL I/V	ERYTHROMYCIN SACHET S/F
CLARITHROMYCIN+LANSOP & AMOXI	ERYTHROMYCIN STEARATE
CLARITHROMYCINmetronid + lanzop	ERYTHROMYCINESTOLATE
ERYTHROMYCIN	ERYTHROMYCINSPRINKLE
ERYTHROMYCIN E/C	LANSOPRAZOLE+AMOXI & CLARITH
ERYTHROMYCIN ETHYL SUCCINATE	SPIRAMYCIN
ERYTHROMYCIN ETHYL SUCCINATE S/F	TELITHROMYCIN

Drugs included in BNF code 5.04.01.00

AMODIAQUINE
ATOVAQUONE+PROGUANIL HYDROCHLR
CHLOROQUINE
CHLOROQUINE AND PROGUANIL
CHLOROQUINE PHOSPHATE
CHLOROQUINE SULPHATE F/C
CHLOROQUINEPHOSPHATE
CHLOROQUINESULPHATE
DAPSONE+ PYRIMETHAMINE
HALOFANTRINE
HYDROXYCHLOROQUINE SULPHATE
MEFLOQUINE
MEFLOQUINE HYDROCHLORIDE
PRIMAQUINE PHOSPHATE
PROGUANIL
PROGUANIL AND CHLOROQUINE
PROGUANIL HYDROCHLORIDE
PROGUANIL+ ATOVAQUONE
PYRIMETHAMINE
PYRIMETHAMINE+ DAPSONE
PYRIMETHAMINE+ SULFADOXINE
QUININE BISULPHATE
QUININE DIHYDROCHLORIDE
QUININE SULPHATE
QUININEBISULPHATE
QUININEDIHYDROCHLORIDE
QUININEHCL
QUININESULPHATE
TETRACYCLINE

Drugs included in BNF code 6.03.02.00

BETAMETHASONE
BETAMETHASONE SODIUM PHOSPHATE
BETAMETHASONE VALERATE
CORTISONE ACETATE
DEFLAZACORT
DEXAMETHASONE
DEXAMETHASONE SODIUM PHOSPHATE
HYDROCORTISONE
HYDROCORTISONE ACETATE
HYDROCORTISONE NA PHOSPHATE
HYDROCORTISONE NA SUCCINATE
HYDROCORTISONE SODIUM PHOSPHATE
HYDROCORTISONE SODIUM SUCCINATE
METHYLPREDNISOLONE
METHYLPREDNISOLONE ACETATE
METHYLPREDNISOLONE SODIUM SUCC
PREDNISOLONE
PREDNISOLONE ACETATE
PREDNISOLONE E/C
PREDNISOLONE SODIUM PHOSPHATE
PREDNISOLONEACETATE
PREDNISOLONESTEAGLATE
PREDNISONE
TRIAMCINOLONE
TRIAMCINOLONE ACETONIDE

Drugs included in BNF code 10.01.01.00

ACECLOFENAC
ACEMETACIN
ACETYLSALICYLIC ACID
ALOXIPRIN
ASPIRIN
ASPIRIN+ GLYCINE
ASPIRIN+NA BICARB&CITRIC AC
AZAPROPAZONE
BENORILATE
BENOXAPROFEN
CELECOXIB
CHOLINE MG TRISALICYLATE
CODEINE PHOSPHATE/IBUPROFEN
DEXKETOPROFEN
DICLOFENAC
DICLOFENAC POTASSIUM
DICLOFENAC SODIUM
DICLOFENAC SODIUM (3ML)
DICLOFENAC SODIUM M/R
DICLOFENAC& MISOPROSTOL
DICLOFENACDISPERSIBLE
DICLOFENACSODIUM
DIFLUNISAL
ETODOLAC
FENBUFEN
FENCLOFENAC
FENOPROFEN
FENOPROFEN (AS CALCIUM SALT)
FENOPROFEN DISPERSIBLE
FEPRAZONE
FLUFENAMIC ACID
FLURBIPROFEN
IBUPROFEN
IBUPROFEN F/C
IBUPROFEN S/R
IBUPROFEN& CODEINE
IBUPROFEN(AS LYSINE)
IBUPROFEN/CODEINE PHOSPHATE
INDOMETACIN
INDOMETHACIN

INDOPROFEN
LORNOXICAM
MELOXICAM
NAPROXEN
NAPROXEN+MISOPROSTOL(combin)
PARACETAMOL(ACETAMINOPHEN)/OXYPHENBUTAZO
PHENYLBUTAZONE
PHENYLBUTAZONE/AL HYDROXI/MG TRISILICATE
PHENYLBUTAZONE/PARACETAMOL(ACETAMINOPHEN
PIROXICAM(BETA-CYCLODEXTRIN)
SALSALATE
SODIUM SALICYLATE
SUPROFEN
TENOXICAM
TOLFENAMIC ACID
TOLMETIN (AS SODIUM SALT)
KETOPROFEN
MEFENAMIC ACID
NABUMETONE
NAPROXEN& MISOPROSTOL
OXYPHENBUTAZONE
PHENYLBUTAZON/PARACETAMOL(ACETAMINOPHEN)
PHENYLBUTAZONE ALKA
PHENYLBUTAZONE/LIGNOCAINE
PIROXICAM
SALICYLAMIDE/PARACETAMOL
SALSALATE (SALICYL SALICYLATE)
SULINDAC
SUTOPROFEN
TIAPROFENIC ACID
TOLMETIN

Drugs included in BNF code 10.01.03.00

URANOFIN
CHLOROQUINEPHOSPHATE
ETANERCEPT
INFLIXIMAB
METHOTREXATE SODIUM
SODIUM AUROTHIOMALATE
SULPHASALAZINE
AZATHIOPRINE
CICLOSPORIN
HYDROXYCHLOROQUINE SULPHATE
LEFLUNOMIDE
PENICILLAMINE
SULFASALAZINE

Drugs included in BNF code 10.01.04.01

AZAPROPAZONE
DICLOFENAC
KETOPROFEN
PIROXICAM
COLCHICINE
INDOMETACIN
NAPROXEN
SULINDAC

Drugs included in BNF code 11.04.02.00

ADRENALINE ACID TARTRATE+ ZN SULPH & BORIC	NAPHAZOLINE HYDROCHLORIDE+ HAMAMELIS
ANTAZOLINE SULPHATE/NAPHAZOLINE NITRATE	NAPHAZOLINE/WITCH HAZEL/BORIC A/GLYCEROL
ANTAZOLINE+ NAPHAZOLINE	NEDOCROMIL SODIUM
ANTAZOLINE+ XYLOMETAZOLINE	OXYPHENBUTAZONE
AZELASTINE	OXYPHENBUTAZONE+ CHLORAMPHENICOL
EMEDASTINE DIFUMARATE	SODIUM BICARBONATE DROPS
HAMAMELIS WATER	SODIUM BICARBONATE OPHTHALMIC
INDOMETHACIN DROPS	SODIUM CROMOGLICATE
KETOTIFEN	SODIUM CROMOGLYCATE (EYE)
LEVOCABASTINE	TETRAHYDROZOLINE HCl
LODOXAMIDE	TETRAHYDROZOLINE/BENZALKONIUM
NAPHAZOLINE HCl DROPS	XYLOMETAZOLINE HYDROCHLORIDE+ ANTAZOLINE SULPH.
NAPHAZOLINE HYDROCHLORIDE	ZINC SULPHATE/HAMAMELIS/BENZALKONIUM Cl

Drugs included BNF code 13.02.01.02

ALLANTOIN+ HEXACHLOROPHENE
ALMOND OIL
ALMOND OIL+ LIQUID PARAFFIN
AMMONIA+ PHENOL
AQUEOUS
ARACHIS OIL
ARACHIS OIL+ LIQUID PARAFFIN
Aveeno
CETOMACROGOL
CHAMOMILE+LANOLIN &HYDROXBENZ
DEIONISED WATER+GLYCERIN+BENZ ALC
DEIONISED WATER+GLYCERIN+PRO.GLYCOL
DIMETICONE& BENZYL ALCOHOL
E45
EMOLLIENT
EMOLLIENT+ CHLOROCRESOL
EMOLLIENT+ HYDROXYBENZOATES
EMOLLIENT+ LACTIC ACID
EMOLLIENT+H-A LANOLIN+PRESERV
EMOLLIENT+LANOLIN &HYDROXBENZ
EMOLLIENTHYPOALLERGENIC LAN
EMULSIFYINGOINT+ PHENOXYETHANOL
ESSENTIAL FATTY ACIDSESTERIFIED
HERBAL EMOLLIENT
HYDROUS
LIGHT LIQUID PARAFFIN
LIGHT LIQUID PARAFFIN+ ISOPROPYLMYRISTATE
LIGHT LIQUID PARAFFIN+ALMOND OIL
LIGHT LIQUID PARAFFIN+BENZALCHLOR&TRICLOS
LIQUID PARAFFIN
LIQUID PARAFFIN+ ACET WOOL ALCOHOLS
LIQUID PARAFFIN+ BENZALKONIUM CL
LIQUID PARAFFIN+ ISOPROPYLMYRISTATE
LIQUID PARAFFIN+ANTIMICROBIALS
LIQUID PARAFFINBENZ CHL & ISOP MYR
LUBRICANT+ PARAFFIN
MINERAL OIL+LANOLIN &HYDROXBENZ
OILY
PARAFFIN AND WOOL FAT+CETOSTEARYL ALCOHOL
PETROLEUMWHITE
PROPYLENE GLYCOL+ UREA & OTHER INGRD
PYRROLIDONE CARBOXYLIC ACID
SIMPLE
SODIUM LAURYL ETHER SULPHATE+ OTHERS
SODIUM PYRROLIDONE
SOYA
SOYA+ LAUROMACROGOLS
SOYA+ TAR
TANNIC ACID+ MENTHOL&PHENOL
TOCOPHERYL
UREA
UREA+ LACTIC ACID
UREA+ SODIUM CHLORIDE
UREACETRI+CHLOROCRS+DEME
UREAWITH LAUROMACROGOIS
Vaseline Dermacare
WHITE SOFT PARAFFIN
WHITE SOFT PARAFFIN+ LIQUID PARAFFIN
WHITE SOFT PARAFFIN+COCONUT OIL+GLYCERL
WHITE SOFT PARAFFIN+LIGHT LIQ PARRAFIN
WOOL ALCOHOLS
YELLOW SOFT PARAFFINPARAFFIN AND WAX
ZINC OXIDE
ZINC OXIDE+ C.L.O. & LANOLIN
ZINC OXIDE+ LANOLIN

Drugs included in BNF code 13.04.00.00

ALCLOMETASONE DIPROPIONATE
BECLOMETASONE
BECLOMETASONE+ CHLORTETRACYCLINE
BECLOMETASONE+ CLIOQUINOL
BECLOMETHASONE DIPROPIONATE
BECLOMETHASONE/CLIOQUINOL
BENZALKONIUM/SALICYLIC ACI/TRIAMCINOLONE
BETAMETHASONE
BETAMETHASONE
BETAMETHASONE (AS SODIUM PHOSPHATE)
BETAMETHASONE BENZOATE
BETAMETHASONE DIPROPIONATE
BETAMETHASONE DIPROPIONATE& SALICYLIC ACID
BETAMETHASONE DIPROPIONATE + FLUOCIN, GENT + SAL AC
BETAMETHASONE DIPROPIONATEDUOPACK
BETAMETHASONE IN EMULSIFYING OINTMENT
BETAMETHASONE IN WHITE SOFT PARAFFIN
BETAMETHASONE IN WHITE SOFT PARAFFIN OIL
BETAMETHASONE PREPARATION
BETAMETHASONE VAL 0.1%/NEOMYCIN SUL 0.5%
BETAMETHASONE VAL/WHITE SOFT PARAFFIN
BETAMETHASONE VALERATE
BETAMETHASONE VALERATE/CHLORHEXIDINE
BETAMETHASONE VALERATE/NEOMYCIN SULPHATE
BETAMETHASONE VALERATE/WEAK TAR PASTE
BETAMETHASONE VALERATE+ CLIOQUINOL
BETAMETHASONE VALERATE+ CLOTRIMAZOLE
BETAMETHASONE VALERATE+ FUSIDIC ACID
BETAMETHASONE VALERATE+ NEOMYCIN
BETAMETHASONE/CHLORHEXIDIN/CETOMACROGOL
BETAMETHASONE/CHLORHEXIDINE/PARAFFIN
BETAMETHASONE/CLIOQUINOL

BETAMETHASONE/COAL TAR/WHITE SOFT PARAFF
BETAMETHASONE/UREA/LAVENDER/CETOMACROGOL
CALAMINE 20.88%/HYDROCORTISONE 0.5%
CHLORHEXIDINE/HYDROCORTISONE/NYSTATIN
CHLORTETRACYCLINE/CLOBETASONE BUTYRATE
CLIOQUINOL
CLIOQUINOL/HYDROCORTISONE ACETATE
CLIOQUINOL+ FLUOCINOLONE
CLIOQUINOL+ HYDROCORTISONE
CLOBETASOL PROPIONATE+ NEOMYCIN
CLOBETASONE BUTYRATE+ OXYTET & NYSTATIN
CLOTRIMAZOLE+ HYDROCORTISONE
CORTICOSTEROIDS
CROTAMITON+ HYDROCORTISONE
DESOXIMETASONE
DESOXIMETASONE+ NEOMYCIN
DIFLUCORTOLONE VALERATE
DIMETHICONE IN CLOBETASOL PROPIONATE
DITHRANOL/CLOBETASOL PROPI/PARAFFIN SOFT
ECONAZOLE+ TRIAMCINOLONE
FLUOCINOLONE
FLUOCINOLONE ACETONIDE
FLUOCINOLONE ACETONIDE+ CLIOQUINOL
FLUOCINOLONE/CETOMACROGOL B/CLIOQUINOL
FLUOCINONIDE
FLUOCORTOLONE ACETONIDE
FLUOCORTOLONE/FLUOCORTOLONE HEXANOATE
FLURANDRENOLONE+ CLIOQUINOL
FRAMYCETIN SULPH/HYDROCORTISONE ACETATE
FUSIDIC ACID/HYDROCORTISONE ACETATE
GENTAMICIN+ HYDROCORTISONE
HALQUINOL/TRIAMCINOLONE
HYDROCORTISONE
HYDROCORTISONE 1% IN WEAK COAL TAR PASTE
HYDROCORTISONE BUTYRATE+ CHLORQUINALDOL
HYDROCORTISONE IN CETOMACROGOL FORMULA A
HYDROCORTISONE IN DIMETHICONE
HYDROCORTISONE IN WATER-MISCIBLE BASIS
HYDROCORTISONE NON-GREASY
HYDROCORTISONE/NEOMYCIN
HYDROCORTISONE/TYROTHRICIN
HYDROCORTISONE+ CLIOQUINOL
HYDROCORTISONE+ CROTAMITON
HYDROCORTISONE+ ECONAZOLE NITRATE
HYDROCORTISONE+ FUSIDIC ACID
HYDROCORTISONE+ MICONAZOLE NITRATE
HYDROCORTISONE+ NYSTATIN &CHLORHEX
HYDROCORTISONE+ PRAMOCAINE HCL
HYDROCORTISONE+ UREA
HYDROCORTISONE+ UREA & NaCl
HYDROCORTISONE+NEOMYC+NYSTAT+POLYM
HYDROCORTISONE+NYSTAT+DIMETICONE+
MICONAZOLE+ HYDROCORTISONE
NEOMYCIN SULPHATE/HYDROCORTISONE
NYSTATIN/TRIAMCINOLONE ACETONIDE
NYSTATIN+HYDROCORT &CHLORHEX
NYSTATIN+NEOMY+BACITRAC+H.C.
BETAMETHASONE/SALICYCLIC ACID 2%
BUDESONIDE
CALAMINE/HYDROCORTISONE 1%
CHLORQUINALDOL/HYDROCORTISONE
CHLORTETRACYCLINE/HYDROCORTISONE/PARAFF
CLIOQUINOL 3%/HYDROCORTISONE ACET 0.5%
CLIOQUINOL+ BETAMETHASONE
CLIOQUINOL+ FLURANDRENOLONE
CLOBETASOL PROPIONATE
CLOBETASONE BUTYRATE
CLOBETASONE/NYSTATIN/OXTETRACYLINE
CLOTRIMAZOLE+BETAMATHASONE
CORTICOSTEROIDS 0.02%/HEPARINOID 0.2%/SA
DESONIDE
DESOXIMETASONE& SALICYLIC ACID
DESOXYMETHASONE
DIFLUCORTOLONE VALERATE FATTY
DITHRANOL 0.1% IN CLOBETASONE BUTYRATE
ECONAZOLE+ HYDROCORTISONE
FLUCLOROLONE ACETONIDE
FLUOCINOLONE ACE 0.025%/NEOMYCIN SU 0.5%
FLUOCINOLONE ACETONIDE/NEOMYCIN SULPHATE
FLUOCINOLONE ACETONIDE+ NEOMYCIN
FLUOCINOLONE/LAVENDER OIL/CETOMACROGOL
FLUOCORTOLONE
FLUOCORTOLONE HEXANOATE & PIVALATE
FLURANDRENOLONE
FLUTICASONE
FRAMYCETIN+ HYDROCORTISONE
FUSIDIC ACID+ HYDROCORTISONE
HALCINONIDE
HEPARIN SODIUM/HYDROCORTISONE ACETATE
HYDROCORTISONE 1% IN COAL TAR MILD
HYDROCORTISONE BUTYRATE
HYDROCORTISONE IN AQUEOUS CREAM
HYDROCORTISONE IN COAL TAR PASTE
HYDROCORTISONE IN SILICONE BARRIER
HYDROCORTISONE IN WHITE SOFT PARAFFIN
HYDROCORTISONE/CHLORTETRACYCLINE/PARAFFI
HYDROCORTISONE/NEOMYCIN/ZINC BACITRACIN
HYDROCORTISONE+ CALAMINE
HYDROCORTISONE+ CLOTRIMAZOLE
HYDROCORTISONE+ DIMETICONE
HYDROCORTISONE+ FRAMYCETIN
HYDROCORTISONE+ GENTAMICIN
HYDROCORTISONE+ NEOMYCIN
HYDROCORTISONE+ OXYTETRACYCLIN
HYDROCORTISONE+ SODIUM FUSIDATE
HYDROCORTISONE+ UREA & LACTIC ACID
HYDROCORTISONE+K.HYDROXYQUNINOLINE
HYDROCORTISONE+NEOMYCIN&BACITRACIN
METHYLPREDNISOLONE+ NEOMYCIN
MOMETASONE
NEOMYCIN SULPHATE+NYSTAT+BACITRA+H.C.
NYSTATIN+CLOBETASOL&NEOMYCIN
NYSTATIN+HYDROCORT &NEOMYCIN
OXYTETRACYCLINE+ HYDROCORTISONE

OXYTETRACYCLINE+HYDROCORT &NYSTATIN
TRIAMCINOLONE 0.1%/CHLORTETRACYCLINE 3%
TRIAMCINOLONE ACETONIDE
TRIAMCINOLONE ACETONIDE+ NYSTATIN
TRIAMCINOLONE ACETONIDE+GRAMICIDIN+NEOMYCIN
TRIAMCINOLONE/GRAMICIDIN/NEOMYCIN/NYSTAT
UREA 10%/HYDROCORTISONE 1%
SODIUM FUSIDATE+ HYDROCORTISONE
TRIAMCINOLONE ACETONID/CHLORTETRACYCLINE
TRIAMCINOLONE ACETONIDE/HALQUINOL
TRIAMCINOLONE ACETONIDE+CHLORTETRACYCLINE
TRIAMCINOLONE ACETONIDE+NEOMY+NYSTAT+GRAMIC
TRIAMCINOLONE+NEOMYC&UNDECYLENATE
UREA+HYDROCORT&LACTIC AC

Drugs included in BNF code 13.06.01.02

BENZOYL PEROXIDE+ ERYTHROMYCIN
CLINDAMYCIN PHOSPHATE
ERYTHROMYCIN+ BENZOYL PEROXIDE
ISOTRETINOIN+ ERYTHROMYCIN
TETRACYCLINE
BENZOYL PEROXIDE+ MICONAZOLE NITRATE
ERYTHROMYCIN
ERYTHROMYCIN+ ZINC ACETATE
MICONAZOLE+ BENZOYL PEROXIDE

Drugs included in BNF code 13.06.02.01

DOXYCYCLINE HYCLATE
ERYTHROMYCIN+ TRETINOIN
MINOCYCLINE
ERYTHROMYCIN
ERYTHROMYCINESTOLATE
TETRACYCLINE

Drugs included in BNF code 13.08.01.00

AMINOBENZOIC ACID
AMINOBENZOIC ACID/ PADIMATE-O/ UVB SPF 10
AVOBENZONE/ EtHex P-METHOXYCINNAMATE
EtHex P-METHOXYCINNAMATE/ AVOBENZONE/ TITA
METHOXYCINNAMATE/ OXYBENZONE/ Et Hex SALIC
PADIMATE-O 3.2%
P-METHOXYCINNAMATE/ AVOBENZONE/ TITANIUM D
P-METHOXYCINNAMATE/ METHOXYDIBENZ/ FACIAL
SUN PROTECTION MILK/FACTOR 6
SUN PROTECTION/FACTOR 4
SUN PROTECTION/LIPS/FACTOR 8
SUN PROTECTON/SPF 12
TITANIUM DIOXIDE
AMINOBENZOIC ACID/ PADIMATE-O
AMINOBENZOIC ACID/ PADIMATE-O/ UVB SPF 25
AVOBENZONE/ OXYBENZONE/ PADIMATE/ TITANIUM
ETHYL p-DIMETHYL AMINOBENZ/ TITANIUM DIOX
MEXENONE
P-METHOXYCINNAMATE/ AVOBENZONE/ TITANIUM
P-METHOXYCINNAMATE/ METHOXYDIBEN/ TITANIUM
SUN PROTECTION
SUN PROTECTION/FACIAL/SPF 8
SUN PROTECTION/FACTOR 8
SUN PROTECTION/SPF 8
TITANIUM DIOX/RED FERR OXIDE/BURNT SUGA
TITANIUM DIOXIDE PASTE

Drugs included in BNF code 13.08.01.01

Almay SPF12, SPF30 and SPF30
Ambre Solaire SPF25 and SPF60
Delph Children's SPF30
E45 Sun Block SPF25 and SPF50
ETHYLHEXYL-P-METHOXYCINNAMATE+ AVOBENZONE
HYDROQUINONE+PADIMATE-O+OXYBENZO
METHOXYCINNAMATE+AVOBENZONE&TITANIUM
METHYLBENZYLIDENE CAMPHOR+ AVOBENZONE+ TITANIUM
OXYBENZONE+ PADIMATE O
Ambre Solaire HP SPF10 and SPF12
Ambre Solaire SPF60/sun intol skin
Delph SPF15, SPF20, SPF25 and SPF30
E45 SUN SPF15
ETHYLHEXYL-P-METHOXYCINNAMATE+ AVOBENZONE+ TITANIUM
METHOXYCINNAMATE+ AVOBENZONE
METHYL PHENYLBENZOXAZOLE
METHYLBENZYLIDENE CAMPHOR+ BUTYLMETHOXYDIBENZO
PADIMATE O+ AMINO BENZOIC ACID

PADIMATE O+ OXYBENZONE
Piz Buin SPF12, SPF20 and SPF30
Roc total sunblock SPF16 and SPF25
Spectraban Ultra SPF28
Sunsense Ultra SPF60
Uvistat SPF10, SPF15, SPF20 and SPF8
PADIMATE O+OXYBENZONE&M'CINNAM
Roc
Spectraban 15, Spectraban 25
Sun E45 SPF15, SPF25 and SPF50
Uvistat Babysun SPF22

Drugs included in BNF code 13.10.01.02

CHLORTETRACYCLINE
CHLORTETRACYCLINE+ HYDROCORTISONE
GENTAMICIN
OXYTETRACYCLINE
TETRACYCLINE
CHLORTETRACYCLINE HYDROCHLORIDE
FUSIDIC ACID
METRONIDAZOLE
SODIUM FUSIDATE

Drugs included in BNF code 13.10.02.00

4-NITROPHENOL
AMPHOTERICIN
BENZOIC ACID& SALICYLIC ACID
BIFONAZOLE
CHLORPHENESIN
CLOTRIMAZOLE
DICHLOROPHEN+ TRICLOSAN
ECONAZOLE NITRATE
HYDROCORTISONE+ CLOTRIMAZOLE
KETOCONAZOLE
MICONAZOLE NITRATE
NYSTATIN
NYSTATIN/ZINC OXIDE
NYSTATIN+ TOLNAFTATE
SALICYLIC ACID
SALICYLIC ACID/METHYL HYDROXYBENZOATE
SULCONAZOLE NITRATE 1%
TIOCONAZOLE
TOLNAFTATE 1%/ ZINC NAPHTHENATE 8%
UNDECENOIC ACID 2.5%/ DICHLOROPHEN 0.25%
WHITFIELDS
ZINC UNDECENOATE 20%/ UNDECENOIC ACID 5%
AMOROLFINE
BENZOIC ACID
BENZOIC ACIDCOMPOUND
BUCLOSAMIDE/SALICYLIC ACID
CHLORQUINALDOL
CLOTRIMAZOLE+ HYDROCORTISONE
ECONAZOLE
HALQUINOL
HYDROCORTISONE+NEOMYC+NYSTAT+POLYM
MICONAZOLE
NATAMYCIN
NYSTATIN/CLIOQUINOL
NYSTATIN+ CHLORHEXIDINE HCL
NYSTATIN+ ZINC OXIDE
SALICYLIC ACID/BENZOIC (WHITFIELD'S)
SULCONAZOLE NITRATE
TERBINAFINE
TOLNAFTATE
UNDECENOATES
UNDECENOIC ACIDDIBROMPROPAMIDINE
ZINC UNDECENOATE

Drugs included in BNF code 15.01.04.01

CLOMETHIAZOLE
DROPERIDOL
FENTANYL+ DROPERIDOL
MIDAZOLAM
TEMAZEPAM
DIAZEPAM
DROPERIDOL+ FENTANYL
LORAZEPAM
PROMETHAZINE HYDROCHLORIDE
TRIMEPRAZINE TARTRATE