A Study on the Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Summary

Pharmacoepidemiology is the science of the use and the effects of drugs in large human populations. Although originally confined to post-marketing drug surveillance of rare or long-latency adverse drug events, the science is gaining increased importance and is regularly applied to assess drug utilization patterns and cost-effectiveness, to characterize target populations of drugs in development, to evaluate undiscovered beneficial or detrimental drug effects, or to provide evidence of effectiveness when randomized controlled trials face ethical or practical barriers.

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are rare but life-threatening mucocutaneous diseases that predominantly occur as adverse reactions to newly administered drugs. The current knowledge of SJS/TEN is sparse, mainly due to the rare nature of SJS/TEN and the long-time unclear classification of the disease. As a consequence many aspects of SJS/TEN remain unclear despite the severe impact of SJS/TEN on affected patients.

The aim of this comprehensive SJS/TEN project presented within this thesis was to contribute to the general understanding of SJS/TEN, thereby focusing on the epidemiology and potential culprit drugs. The project comprises five individual observational studies using data from the Clinical Practice Research Datalink (CPRD). This United Kingdom (UK)-based database contains longitudinal primary-care records of millions of patients, representative of the UK population. Information is recorded by general practitioners and includes demographics, lifestyle factors, medical diagnoses, referrals to secondary care, laboratory and diagnostic results, and a complete history of drug prescriptions.

In Study 3.1 we comprehensively validated incident SJS/TEN diagnoses recorded in the CPRD between 1995 and 2013. The aim of this study was to assess whether SJS/TEN can be studied using CPRD data, and to establish a large and valid SJS/TEN case population. Using diagnoses from secondary care as a gold standard, we managed to compose a case population consisting of 551 SJS/TEN patients with a positive predictive value of 90% in cooperation with two specialised clinicians.

Summary

In Study 3.2 we calculated an overall incidence rate in the UK of 5.76 SJS/TEN cases/1'000'000 person-years, whereby incidence rates were highest in patients aged <10 or ≥80 years. In a case-control analysis, we further found that patients of black, Asian, or mixed ethnicity were at increased risk of SJS/TEN when compared to Caucasians, and observed associations between SJS/TEN and pre-existing depression, lupus erythematosus, chronic kidney disease, recent pneumonia, and active cancer.

In the Studies 3.3, 3.4, and 3.5, we conducted case-control analyses to assess associations between SJS/TEN and drugs which have previously been associated with SJS/TEN. We furthermore calculated cumulative incidences of SJS/TEN for each of these drugs to assess the absolute risk of SJS/TEN among drug users.

Study 3.3 confirms associations between SJS/TEN and the aromatic antiepileptics carbamazepine, phenytoin, and lamotrigine, with absolute risks of 20-46 SJS/TEN cases/100'000 new users. Conversely to previous reports we did not find any exposed cases for valproate, gabapentin and pregabalin despite high number of new users (>40'000).

While previous case-control studies reported a strong association between SJS/TEN and cotrimoxazole (sulfamethoxazole+trimethoprim), Study 3.4 was the first to show an association between SJS/TEN and trimethoprim as a single agent with an absolute risk of 1 SJS/TEN case/100'000 users. Only few patients were exposed to sulfonamide antibiotics in the CPRD which is why we were not able to study associations for sulfamethoxazole and other anti-infective sulfonamides. This study further corroborates previously reported associations between SJS/TEN and use of penicillins, quinolones, cephalosporins, and macrolides (0.3-1.0 SJS/TEN cases/100'000 users).

Study 3.5 confirms the previously reported association between SJS/TEN and allopurinol with an absolute risk of 6 SJS/TEN cases/100'000 new users. Further drugs identified as possible triggers of SJS/TEN were coxibs (1.9 cases/100'000 new users), sulfasalazine (4.3 cases/100'000 new users), mesalamine (3.8 cases/100'000 new users), mirtazapine (1.6 cases/100'000 new users), and fluoxetine (0.2 cases/100'000 new users). We further observed an association between SJS/TEN and proton pump inhibitors (0.5-1.3 cases/100'000 new users). However, proton pumps are often used in

combination with other drugs (e.g nonsteroidal anti-inflammatory drugs) which could potentially confound such an association. Only little evidence previously suggested associations between SJS/TEN and these drugs. For various other drugs which have been suggested as culprit drugs of SJS/TEN in case reports (oxicam analgesics, benzodiazepines, citalopram, sertraline, paroxetine, venlafaxine, and phosphodiesterase-5 inhibitors), we did not find any exposed SJS/TEN cases despite a high number of new users (>100'000) in the CPRD. Our results suggest that these drugs appear to be at least relatively safe in terms of SJS/TEN.

In summary, the population-based observational studies presented in this thesis contribute to the understanding of the epidemiology of SJS/TEN yielding the first calculated incidence rates of SJS/TEN in the UK and information on patients at higher risk of SJS/TEN. They further include comprehensive analyses of culprit drugs of SJS/TEN, which provide important evidence for the successful treatment of SJS/TEN patients, as early discontinuation of the culprit drug is crucial and often decisive for the outcome of SJS/TEN.

Abbreviations

ADR	Adverse drug reaction
AED	Antiepileptic drug
ALDEN	Algorithm of drug causality in epidermal necrolysis
BCDSP	Boston Collaborative Drug Surveillance Program
BSA	Body surface area
CI	Confidence interval
CKD	Chronic kidney disease
COX	Cyclooxygenase
CPRD	Clinical Practice Research Datalink
CYP	Cytochrome
EM	Erythema multiforme
EMM	Erythema multiforme majus
FDA	Food and Drug Administration
GP	General practitioner
GPRD	General Practice Research Database
HES	Hospital episode statistics
HLA	Human leukocyte antigen
ICD	International Statistical Classification
IR	Incidence rate
ISAC	Independent Scientific Advisory Committee
IVIG	Intravenous immunoglobulin
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency

Abbreviations

NK	Natural killer cells
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
py	Person-years
RCT	Randomised controlled trial
SAS	Statistical Analysis Software
SCORTEN	Severity-of-illness score for toxic epidermal necrolysis
sFasL	Soluble Fas-ligand
SJS	Stevens-Johnson syndrome
SSRI	Selective serotonin reuptake inhibitor
TCR	T-cell receptor
TEN	Toxic epidermal necrolysis
THIN	The Health Improvement Network
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States
VAMP	Value Added Medical Products

Chapter 1

Introduction

1 Introduction

1.1 Pharmacoepidemiology

1.1.1 Rise of a new science

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people. It is a combination of clinical pharmacology, the study of the effects of drugs in humans, and epidemiology, the study of the distribution and determinants of diseases in populations. Pharmacoepidemiology emerged in the mid 1960's when the fast growth of the pharmaceutical armoury, along with increasing possibilities for combating diseases and improving the overall health of our population, has brought about various medical risks in the form of adverse drug reactions (ADRs). In 1961 a public controversy over ADRs was sparked off after 'in-utero' exposure with thalidomide, a mild hypnotic marketed despite no obvious advantages over other similar drugs, was discovered to cause phocomelia in new-borns.[1] The growing impact and awareness of such ADRs, the rising number of product liability suits against drug manufacturers, and the realization that many ADRs are unlikely to be detected in pre-marketing randomized controlled trials (RCT; Table 1.1-1) called for new methods of post-marketing drug surveillance in large populations.[2–4]

Table 1.1-1: Adverse drug reactions that are unlikely to be detected in randomized controlled trials.

Undetected ADRs in RCTs	Advantages of pharmacoepidemiology over RCTs	Example
Rare ADRs	Due to restricted patient numbers of RCTs (500-3000 patients), rare ADRs often remain undetected.	With an incidence of 20 SJS cases/100'000 patients exposed to carbamazepine, SJS (adverse reaction to carbamazepine) likely remains undetected during RCTs.[5]
Long-latency ADRs	ADRs with a long latency-period only manifest after a prolonged period of drug exposure and are therefore unlikely to occur during RCTs.	Sclerosing peritonitis caused by practolol occurred on average 4 years after initiation of drug therapy.[6]
ADRs that mainly occur in specific patient groups	Although drug effects can vary with sex, ethnicity, age, and genetic differences, RCTs are often conducted in homogenous patient groups often excluding children, older patients, or pregnant women.	The incidence of major haemorrhage after exposure to warfarin is higher in patients aged ≥80 years compared to younger patients.[7] However, elderly patients are often excluded from premarketing studies.[8]

ARD=Adverse drug reaction; RCT=Randomized controlled trial; SJS=Stevens-Johnson syndrome.

The first steps towards a better understanding and prevention of ADRs were taken in 1952, when the first monograph of ADRs called 'Side Effects of Drugs' was published by L. Meyler,[9] and the first official registry of ADRs was established to collect cases of drug-induced blood dyscrasia (a morbid general state resulting from the presence of abnormal material in the blood).[10] In 1960, the Food and Drug Administration (FDA) began to collect reports of ADRs and sponsored new hospital-based drug monitoring programs.[2] Although spontaneous reports of ADRs have led to market withdrawal of several drugs (e.g. flosequinan due to increased mortality in 1993) the spontaneous reporting system has a number of shortcomings that are listed in Table 1.1-2.[11,12]

Table 1.1-2: Shortcomings of spontaneous ADR reporting systems.

Problem	Implication
Under-reporting	Reporting varies with the reporter's skill and experience to detect ADRs, as well as with the character of ADRs (see bias), and some ADRs might therefore remain unreported.
Bias	Trivial ADRs (e.g. mild headaches), ADRs perceived to already be well-known, and ADRs with a long latency period are less likely to be reported, and might therefore be overlooked.
Unknown population-at-risk	The risk associated with a drug cannot be quantified accurately because information on the underlying population that is exposed to the drug is lacking.
No control group	Patients who are exposed to a drug are often not comparable to patients who were not exposed to the same drug.

ADR=Adverse drug reaction.

These limitations prompted the demand for a more systematic and effective approach for post-marketing drug surveillance in large human populations, and thus led to the emergence of the science of pharmacoepidemiology in the mid 1960's. In the following years, the first pharmacoepidemiologic studies were conducted by the Boston Collaborative Drug Surveillance Program (BCDSP) and the Johns Hopkins Hospital after they started monitoring in-hospital drug use.[2]

The significance of pharmacoepidemiology for the assessment of ADRs that are difficult to detect in pre-marketing RCTs are well recognized today. But besides identifying adverse or unexpected effects of drugs, pharmacoepidemiology has further proven to be valuable for assessing benefit-to-risk relationships and cost-effectiveness of drug

therapies, which are issues of growing importance within the health-care system due to the increasing costs of medications. As a consequence the relatively young discipline has become an integral part of the drug development process over the past decades and is frequently used in academia, by health care providers, drug regulatory agencies, and the pharmaceutical industry to study patterns of drug use, drug safety, effectiveness of drugs, and economic evaluations of drug use.[2,3]

1.1.2 Observational research and particularities of pharmacoepidemiology

Clinical observational research is an area of non-experimental research in which a researcher observes usual clinical practice. Contrary to experimental clinical research (i.e. randomized or non-randomized clinical trials), the independent variable (e.g. patient's exposure status) is not actively assigned to in observational studies. Observational research can further be divided into two categories; descriptive studies (i.e. case reports and case series) and analytical studies (i.e. case-control studies, cohort studies, and cross-sectional studies; Figure 1.1-1). The main difference between the two categories is that while the latter only describes clinical observations in patients affected with an exposure or outcome of interest, analytical studies feature a control group allowing quantification of associations between an exposure and an outcome. Pharmacoepidemiology is comprised of analytical observational studies.[2]

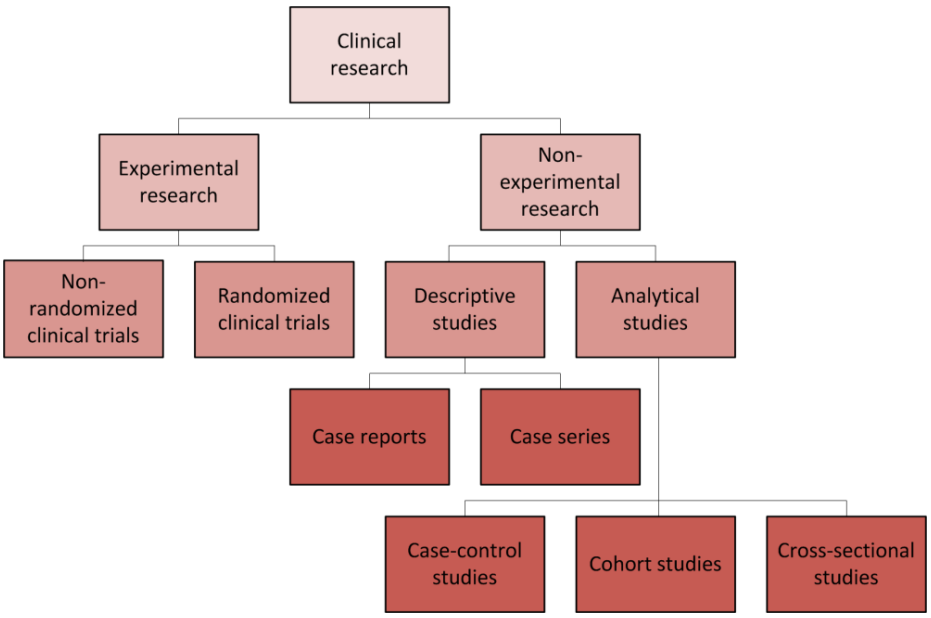

Figure 1.1-1: Classification of clinical research study designs.

Evidence-based medicine categorizes different types of clinical evidence and rates or grades them according to the strength of their absence of the various biases that beset medical research. In terms of evidence-based medicine, the classification presented in Table 1.1-3 has been suggested for clinical research studies regarding the quality of evidence (irrespective of internal validity).[13]

Table 1.1-3: Classification of clinical evidence according to the US Preventive Services Task Force.[14]

Grade of quality	Source of evidence
Level I	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort studies or case-control studies, preferably from more than one centre or research group.
Level II-3	Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The role of observational research in medicine

The existence of bias and confounding in observational studies due to the lack of randomization, previous examples of poorly designed observational studies (partly due to the lack of methodologic possibilities in the past), as well as the fact that causal inference cannot be drawn from observational studies due to their empirical nature have long undermined the significance of observational studies in medical research.[2,13,15] However, more recently studies have demonstrated that results from observational studies were congruent with results from RCTs if the study designs were aligned and data analysis was performed similarly.[16,17]

With growing data availability and advancements in the methodology, observational studies have become an invaluable tool in medical research and the method of choice whenever RCTs are not applicable due to practical or ethical restraints. Under the following conditions observational studies are of particular significance. Firstly, under circumstances where severe and potentially fatal outcomes are to be expected,

deliberately bringing patients into these circumstances is unethical (e.g.: exposing patients with a genetic predisposition for carbamazepine-induced SJS/TEN to carbamazepine; testing the effects of benzodiazepines on the ability to drive a car). Second, results from observational studies are more representative for the general population due to the restrictive eligibility criteria in RCTs (Table 1.1-1). Third, studying outcomes with a long latency-period or rare outcomes is impractical in RCTs (Table 1.1-1). Fourth, besides descriptive studies (e.g. case reports) observational studies are often the first to generate or assess hypotheses for previously unknown drug effects (e.g. the discovery that aspirin prevents myocardial infarction), which are only later analysed in RCTs. Finally, observational studies can be conducted in a more cost and time efficient manner.[2,3,18]

Particularities of drugs as an exposure variable

In epidemiology, an exposure variable can roughly be defined as a factor that may be associated with an outcome of interest. Researchers often rely on readily available (existing) data elements to identify a patient's exposure status, and the definition of the exposure variable is a key factor in observational studies. In pharmacoepidemiologic studies, the definition and assessment of exposure status requires unique methodologic considerations, as exposures to drugs, which depict the exposures of interest in pharmacoepidemiology, imply specific challenges.[18] First, comparisons between patients exposed and patients unexposed to a certain drug are often prone to confounding by indication and selection bias due to the underlying indication of the respective drug that is only present in the exposed patients or for contraindication for the respective drug that is only present in unexposed patients. Second, a patient's drug use and therefore exposure status may change over time in terms of changes in dosages, intermittent drug use, non-compliance, or limited duration of drug use. Third, knowledge of the pharmacokinetic and pharmacodynamic properties of drugs as well as the relationship between a potential culprit drug and the outcome of interest (e.g. dose-response relationship, relevant time period between exposure and outcome) have to be taken into consideration when defining drug exposure. Finally, poor drug compliance (i.e. patients do not follow medical instructions) might lead to differences between the assessed and

actual exposure status. To assure the internal validity of a pharmacoepidemiologic study (i.e. avoiding or minimising confounding and biases), the features listed above should be addressed with meticulous attention during the collection of data and the choice of a study design and methodology (see Chapter 1.1.4).[4,18]

1.1.3 Causality

Pharmacoepidemiology is an empirical science which mainly aims to identify the causes of certain outcomes in association with drug exposure. While the study designs and statistical methods used in pharmacoepidemiology allow determining the existence of associations between exposures and outcomes as well as measuring their strength, determining whether these associations are a consequence of a causal relationship is more complex. Besides complex study designs and statistical analyses, checklists with criteria that might infer causality, such as the 'Hill criteria' (Table 1.1-4), have been proposed as useful tools for assessing causality in epidemiologic research.[19] Checklists have furthermore been designed to assess causality between an exposure and a specific outcome only, such as the algorithm of drug causality in epidermal necrolysis (ALDEN), which is a clinical score used to assess causality between drug exposure and SJS/TEN.[20] However, due to its empirical nature pharmacoepidemiologic research will always fail to deliver a clear verdict for a proposed causal association irrespective of methodological approaches. Despite these limitations, observations from pharmacoepidemiologic research are nevertheless of great importance, if the available tools used to evaluate causal inference are used as effectively as possible, and resulting observations are analysed and interpreted with adequate critical scrutiny.[15]

Table 1.1-4: 'Hill criteria' on causal inference in medical research and their limitations.

Criterion	Reasoning	Problem

Strength of association	A strong association is more likely to have a causal component than a modest association.	• Strength can depend on confounders/other causes • Absence of a strong association does not rule out a causal effect
Consistency	Associations that are observed repeatedly in different populations, places etc. are more likely to be causal.	Shared flaws in different studies would tend to replicate the same wrong conclusion.
Specificity	An association observed specifically for a particular outcome or in a particular population is more likely to be causal.	A factor might be the cause for several outcomes.
Temporal relationship	The outcome has to occur after the alleged cause.	Temporality might be difficult to establish (e.g.: diseases that develop slowly).
Biological gradient	Evidence of a dose-response relationship indicates causality.	• Prone to confounding • Dose-response thresholds exist for some associations
Plausibility	A plausible mechanism underlying an association between a proposed cause and effect increases the likelihood of causality.	Novel observations might be wrongfully dismissed.
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge.	See consistency and plausibility.
Experiment	Causation is more likely if evidence is based on randomised experiments.	Not always available and applicable.
Analogy	If an association for analogous exposures and outcomes has already been shown, causality is more likely.	False analogies may be considered and mislead.

1.1.4 Study designs, bias, and confounding

Aside from estimating epidemiologic measures such as incidence rates (IRs), cumulative incidences, or prevalences (i.e. absolute risk measures), methodologically more elaborate pharmacoepidemiologic studies aim to compare such measures with the aim of predicting certain events, learning about the causes of these events, or evaluating the impact of these events on a population by calculating relative risk measures. The continuous advancements in data availability, as well as statistical methods and software have increased the methodological possibilities in pharmacoepidemiology. Some of the most important study designs and methodologic aspects are described below.

Case-control studies

In a case-control study patients are selected on the basis of whether they do (cases) or do not (controls) have a particular outcome (e.g. disease) of interest. The proportion of cases and controls which have experienced a certain exposure before this particular outcome of interest are then compared. This approach allows the calculation of an odds ratio (OR), which is a relative measure of effect size used to describe the strength of an association between two binary variables. An OR greater than 1 for example indicates that having an exposure of interest is associated with having an outcome of interest. Case-control studies are especially effective for the study of diseases with a long latency period, rare diseases, and multiple exposures of interest. However, because both the exposure and outcome have already occurred at the time the patients enter into a case-control study, this design is particularly prone to bias and confounding. Two major methodological measures to prevent such bias or confounding are ensuring comparability between cases and controls (i.e. despite not having the outcome of interest they should represent the population at risk of becoming cases as closely as possible), and ensuring that exposure information is reported/recorded similarly in cases and controls.[21]

Cohort studies

In a cohort study two groups of patients are defined on the basis of whether or not they are exposed to a particular factor of interest (e.g. antidiabetic drug treatment). Both groups are then followed over a period of time to assess and compare the occurrence or incidence of an outcome of interest in the two groups. All potential subjects must be free from the outcome of interest at the time that the exposure status is defined. Relative risk estimates in cohort studies are risk ratios, incidence rate ratios, and hazard ratios. Based on the point of time of data collection, cohort studies can be separated in prospective or retrospective studies. A prospective cohort study is initiated before the outcome of interest occurred and participants are followed into the future to assess the incidence of the outcomes of interest. In a retrospective cohort study all relevant events (i.e. exposure, outcomes of interest) have already occurred at the time the study is initiated. Advantages of cohort studies are that they allow analysing rare exposures as well as multiple effects

of a single exposure. Major sources of bias which have to be considered in cohort studies are differential losses to follow-up between exposed and unexposed subjects or potential changes in exposure status in subjects over time (e.g. a previously unexposed patient starts therapy with a drug under study during the study period).[21]

Nested case-control studies

Nested case-control studies are case-control studies embedded within a cohort. Analogously to a cohort study, a cohort of study participants is assembled and followed forward in time to assess the occurrence of an outcome of interest. However, the analysis of data is conducted as a case-control study, whereby subjects from the initial cohort who developed an outcome of interest are defined as cases and a number of subjects from the initial cohort who did not developed an outcome of interest are defined as controls (usually 4-10 controls for each case). If risk set sampling is applied, a future case is eligible to be a control for a prior case and that subject might be selected as a control more than once to prevent the occurrence of bias. The method of analysis is identical to that of a conventional matched case-control study. Nested case-control studies are often used when the exposure of interest is difficult or expensive to obtain and when the outcome is rare. Because data previously collected from a large cohort study can be used, the time and cost of initiating a new case-control study is avoided. Nested-case control studies furthermore allow calculating IRs of the outcome of interest and controlling for potential bias from time-dependent changes of risks for an event or of drug exposure through matching on the date of the outcome.[21]

Bias

Biases are systematic errors in epidemiologic studies that result in an incorrect estimate of the true association between an exposure and an outcome of interest.[22] Some examples of common types of biases in epidemiology are listed below.

Selection bias

Selection bias occurs when a systematic difference is present between subjects in the case and control or exposed and unexposed population, respectively. Common examples for selection bias are the 'healthy worker bias' which may occur when a subgroup of study participants are recruited in a specific occupational setting, or the 'health care access bias' which occurs when a subgroup of patients with access to health care is compared to patients without access to health care. Besides cautious selection of the study population, appropriate matching in the study population is an important measure to prevent selection bias.[22]

Information bias

Information bias arises from systematic errors that occur during the collection of data. Misclassification, where study subjects are assigned to the wrong category, is a common source of information bias. Misclassification is divided into differential misclassification (i.e. misclassification differs in the groups being compared), and non-differential misclassification (i.e. misclassification is similar across the groups being compared). Differential misclassification can result in both an exaggeration and underestimation of an effect, whereas non-differential misclassification of a dichotomous exposure always biases an effect towards the null. Common causes of misclassification are recall bias (i.e. differences in the accuracy or completeness of retrieved recollections of past events), detection bias (i.e. an event/variable is more likely to be observed for a particular set of study subjects), observer bias (i.e. researcher subconsciously influences the experiment), or reporting bias (i.e. observations of a certain kind are more likely to be reported).[22]

Protopathic bias

Protopathic bias is another type of information bias that is relevant in pharmacoepidemiology. It occurs when a drug is inadvertently administered for an early symptom of an outcome that has yet not been detected or recorded. When the outcome is later detected or recorded a causal association between the drug and the outcome may be incorrectly inferred.[23]

Confounding

Confounding occurs when a third variable influences both the dependent variable (outcome) and independent variable (exposure), without being an intermediate step in the causal pathway and without being a collider (i.e. a consequence of the exposure and the outcome; Figure 1.1-2).[24] Confounding can substantially distort risk estimates, and is a major issue in analytical observational studies. In observational studies, confounding can be controlled or prevented at the design stage of a study by matching or restriction of the study population. At the stage of data analysis confounding can be controlled by conditioning on potential confounders, given that sufficient and accurate information on potential confounders has been measured or assembled.[25]

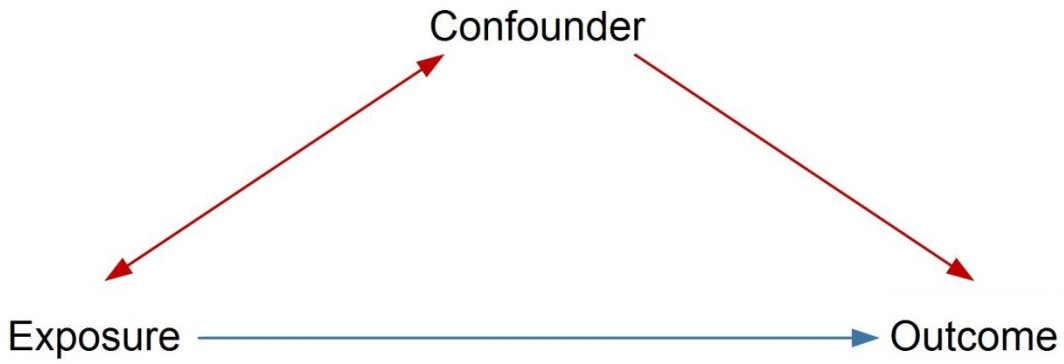

Figure 1.1-2: Schematic depiction of confounding.

Confounding by indication

A special type of confounding, which frequently has to be taken into consideration in pharmacoepidemiologic studies, is 'confounding by indication'. This type of confounding bias arises if the indication for the prescription of a drug of interest is related to the outcome of interest. Confounding by indication could for example underlie an observed association between antidepressant drug use and infertility, because depression itself (and therefore the indication for antidepressant drugs) is associated with infertility and is therefore a confounder. Confounding by indication may lead to false assumptions regarding the effectiveness of a drug under study, if exposed patients reveal a higher/lower incidence of the outcome of interest which should be prevented by the drug under study than unexposed patients. In other cases, a direct association between the drug under study and an outcome of interest might wrongfully be assumed.

Confounding by indication is often difficult to control, and is best prevented by implementing appropriate eligibility restrictions at the design stage of a study.[25]

Propensity scores in pharmacoepidemiology

In observational studies, systematic differences in covariate distributions between treated and untreated subjects remain a major challenge due to the lack of randomization. This may distort the estimates of measured treatment effects unless adequate statistical adjustments are made. Propensity scores are a meanwhile established method used to correct for such confounding by balancing the probability to receive a certain drug between patients in different treatment groups based on prognostic patient characteristics. Using logistic regression a single variable representing the likelihood of each patient to receive a treatment is calculated based on several patient characteristics. Study subjects are then matched, stratified, or weighted on their propensity scores, or scores can be integrated into a multivariate regression analysis. Propensity scores are particularly useful for studies conducted in smaller study populations that do not allow conventional matching or adjusting. However, propensity scores cannot rule out unmeasured confounding and further potential limitations arise from errors made during the selection of propensity score variables.[26]

1.1.5 Data sources in Pharmacoepidemiology

Before the 1980's, the data used for pharmacoepidemiologic studies was mainly hospital-based. While the validity of diagnoses is easily assessable, most information on exposures is retrieved by patient interviews and therefore specific information is only available if included in the questionnaire. Furthermore, this approach is prone to recall bias and only allows recruiting a limited number of patients for a study.[27] Other sources of data were multipurpose cohorts in which a defined population is followed over time. A famous example is the US Nurses' Health Study, in which questionnaires inquiring about different exposures, life-style factors, and chronic conditions are periodically sent to female nurses across the US. With the emergence of large health-care databases over the past decades the possibilities of conducting pharmacoepidemiologic observational

studies have substantially increased. However, in order to conduct high-quality pharmacoepidemiologic studies, researchers have to consider the strengths and weaknesses of such databases for observational research (Table 1.1-5).[27]

Table 1.1-5: Strengths and weaknesses of health-care databases for pharmacoepidemiologic studies.

Strengths of health-care databases for pharmacoepidemiologic studies	Weaknesses of health-care databases for pharmacoepidemiologic studies
• Potential for large sample sizes • Relatively inexpensive to use (by-product of existing administrative systems) • Data can be representative of a population • Include a broad range of medical information • Missing information can potentially be collected via linkages to other data sources • No recall or interviewer bias • Data is collected longitudinally	• Uncertainty regarding the validity of recorded information • Databases do not included all health-related information (e.g. inpatient information in primary-care databases; diagnoses in some claims databases) • Instability of the population (disenrollment of patients from the database) • Mainly include information about illnesses severe enough to come to medical attention • A database population may not representative for a general population

Claims or administrative databases

Claims data arises from a patient's use of the health-care system and consists of claims codes for medical billing events such as dispenses of drugs, medical procedures, or hospitalizations. Claims of medical expenses are subject to various controls and claims data is generally of very high quality. However, diagnoses are recorded with less reliability, because the ICD-9-CM codes used for diagnoses are not always of high accuracy and because reimbursement does not usually depend on the actual diagnosis.[27]

Medical record databases

Over the past decades, medical record databases started to emerge when informatics gained currency in the health care system and electronic patient records replaced paper patient records. Examples for such databases are the UK-based Clinical Practice Research Datalink (CPRD),[28] and 'The Health Improvement Network' (THIN), which primarily include primary-care outpatient data. Medical record databases have advantages over claims databases mainly regarding the validity of recorded diagnoses.

However, medical records often lack information about a patient's medical history depending on the source of the data (inpatient or outpatient databases).[27]

Clinical Practice Research Datalink

The CPRD is a UK-based primary care database which was established in 1987 as the small Value Added Medical Products (VAMP), then became the GPRD in 1993 and the CPRD in 2012. Participating general practitioners (GPs), who act as the first point of contact for any non-emergency health-related issues in the UK (i.e. GPs are the gatekeepers of the UK health-care system), were requested to record health-related information about their patients in anonymized electronic patient files. Secondary care teams also forward information to GPs about their patients, including key diagnoses. A subset of secondary practices has further consented to participate in the CPRD linkage scheme including for example Hospital Episode Statistics (HES data) or the Office for National Statistics (mortality data including causes of death). With 13 million participating patients, the CPRD is one of the largest databases of longitudinal medical records from primary care in the world, and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. Data are collected on demographic information, drug prescriptions, symptoms, diagnoses, preventive care, tests, vaccinations, specialist and hospital referrals, and details relating to death. Until 2015, additional information for certain events was furthermore accessible in the form of free texts (GP notes).[28] The data in the CPRD have been repeatedly demonstrated to be of high quality, and the database has been used for numerous epidemiological studies published in peer-reviewed journals.[29] Studies require approval by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

1.2 Stevens-Johnson syndrome and toxic epidermal necrolysis

1.2.1 History

The first report of SJS dates back to the year 1922, when the American paediatricians Albert Mason Stevens and Frank Chambliss Johnson described two patients with 'unusual conditions, entirely unlike anything previously observed'.[30] The condition, which was later named after the authors of this first case report, was therein characterized as 'generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis' (Figure 1.2-1).

A NEW ERUPTIVE FEVER ASSOCIATED WITH STOMATITIS AND OPHTHALMIA

REPORT OF TWO CASES IN CHILDREN *

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During a period of three months we had the opportunity of observing two cases of an extraordinary, generalized, eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis. The first patient was seen on the tenth day of illness and followed to recovery. The second patient did not come under observation until the twenty-second day after onset of the illness; but the skin lesions at that time corresponded exactly with those of the first case at the same stage of the disease, and a careful description of the eruption as seen in the first week establishes its identity with that in Case 1.

The condition was so unusual and so entirely unlike anything previously observed, that pains were taken to get as many expert opinions as possible from men of wide clinical experience. At the same time, a search was made in the literature of eruptive fevers and allied dermatologic conditions. No diagnosis could be made to correspond with the symptoms and course of the eruption in these two cases and no description was found of a skin condition in any degree comparable.

Figure 1.2-1: Extract from the first case report of SJS published in 1922.[30]

The term 'toxic epidermal necrolysis (TEN)' first appeared in 1956, when the Scottish dermatologist Alan Lyell described a severe skin disease which was later also referred to as Lyell's syndrome.[31] In his report, Lyell reported four cases of acute onset of a skin eruption with widespread areas of epidermal detachment, which he believed to be a consequence of a systemic upset caused by a toxin or an infection. As more patients with TEN were reported in the following years, it became clear that TEN is a consequence of exposure to a variety of drugs, of which sulphonamides and antiepileptic drugs (AEDs) were the most frequently alleged triggers.

Today, SJS and TEN are considered to be distinct disease entities within the same mucocutaneous disease spectrum, differing only by the severity of the disease.[32] Affected patients are classified into three groups according to the proportion of body surface area (BSA) affected by skin detachment: <10% defined as SJS, 10–30% defined as SJS/TEN overlap, and >30% defined as TEN.[33] However, before this classification was reached there has long been discordance regarding the terminology and classification of SJS/TEN and erythema multiforme majus (EMM), another cutaneous reaction with mucosal involvement. Although different in clinical pattern, prognosis, and etiology, EMM was widely considered to be part of the SJS/TEN spectrum, until a consensus definition suggesting the differentiation of EMM and SJS/TEN was reached in the mid 1990's.[33,34] This consensus classification has since been used in numerous observational studies.

1.2.2 Epidemiology of SJS/TEN

The epidemiology of SJS/TEN is under-investigated, primarily because many health-care databases, which are an important tool in epidemiologic research, have been shown to be ineligible for the study of SJS/TEN for different reasons. First, most databases are too small to allow the assembly of a sufficient number of SJS/TEN patients due to the rare nature of the disease. Second, studies have reported a rather low validity for SJS/TEN diagnoses in some databases, which they attributed to the complexity of correctly diagnosing SJS/TEN as well as to the long unclear differentiation from EMM.[35–37] Finally, up until 2008, the ICD-9 coding system which is used in many databases did not differentiate between erythema multiforme (EM) and SJS/TEN.[38]

Due to this absence of previous database studies, existing evidence on SJS/TEN is mainly based on hospital-based studies, which lack information on the underlying population at risk since only patients who develop the disease are captures. Consequently reported IRs of SJS/TEN vary greatly and range from 1.0 to 12.7 cases per million person-years (py).[39–42] Schöpf et al. conducted one of the earliest epidemiologic studies on SJS/TEN in West Germany between 1981 and 1985, and reported an annual risk of 1.1 cases and 0.93 cases per million patients for SJS and TEN,

respectively. The 574 SJS/TEN patients included in the study were recruited by sending questionnaires to all medical centres that were considered likely to treat severe skin reactions.[39] A more recent Europe-based study conducted in a Spanish primary care database between 2001 and 2011 reported an IR of 3.21 SJS/TEN cases/million py.[40] One large cross-sectional study including 3657 SJS/TEN patients investigated the epidemiology of SJS/TEN in the United States (US) between 2009 and 2012, using data from the Nationwide Inpatient Sample, and observed an overall IR of 12.7 SJS/TEN cases/million py (adults only), which is higher than most previously reported IRs for SJS/TEN.[42] Another large observational study (n=1167 SJS/TEN patients) based on insurance claims data from Korea with a coverage of 97% of the population calculated an IR of 5.9 SJS/TEN cases/million py between 2010 and 2013.[41]

1.2.3 Clinical manifestation

Acute phase

Initial symptoms of SJS/TEN usually present within 4 weeks after drug intake and include unspecific, flu-like symptoms such as fever, stinging eyes, rhinitis, and dysphagia. Mucocutaneous and cutaneous lesions typically develop 1-3 days after the onset of these prodromal symptoms. Lesions of mucous membranes occur in more than 80% of cases, predominantly involving the buccal, genital and/or ocular mucosa (by definition at least 2 sites are involved), and are characterized by erythema, hemorrhagic erosions, and painful bullae.[32] Ocular involvement is frequent (50-90% of SJS/TEN cases), and mainly affects the conjunctivas. Symptoms include acute conjunctivitis as well as conjunctival and corneal ulceration.[43]

Cutaneous lesions predominantly affect the trunk and face, and involve erythematous and purpuric macules, which manifest as atypical targets. The macules have a tendency to coalescence and evolve to the formation of tense bullae. In a second phase, large areas of epidermal detachment develop. In the absence of spontaneous epidermal detachment, checking for a positive Nikolsky sign can help asserting a SJS/TEN diagnosis.[32] A positive Nikolsky sign is present if tangential pressure induces epidermal detachment, but is not specific for SJS/TEN, as it can also be present in some other bullous skin

diseases.[32,44] The BSA of necrotic and detachable skin is a major prognostic factor for the outcome of SJS/TEN.[45]

In some cases of SJS/TEN the respiratory and gastrointestinal tracts are also affected. Pulmonary dysfunctions affect approximately 40% of SJS/TEN patients and include breathing difficulties, cough, pulmonary oedema, and bronchial obstruction,[46] whereas gastrointestinal involvement includes diarrhoea, bloating of the abdomen, and rarely bowel perforation.[47] Renal disturbances (e.g. acute renal failure, acute tubular necrosis, haematuria) have also been observed in the acute stage of SJS/TEN.[48]

Long term sequelae

Cutaneous sequelae

Cutaneous sequelae are the most commonly observed long-term complications of SJS/TEN. Case series have suggested that 44-81% of SJS/TEN survivors suffer from dermatological complications after SJS/TEN,[49–51] and reported a significantly decreased Dermatology Life Quality Index in affected patients.[52] The most common dermatological complications are hyper-/hypopigmentation, hypertrophic and keloid scars, eruptive naevi, chronic pruritus, hyperhidrosis, photosensitivity, and heterotopic ossification.[49,50,52–54] Furthermore, nail changes, such as onychomadesis (shedding of the nails) or permanent nail loss, have been observed to occur in approximately 50% of SJS/TEN survivors.[50,52,53]

Ocular sequelae

Chronic ocular complications affect 20–75% of SJS/TEN survivors and are associated with a substantially lower overall health-related quality of life.[49–53,55,56] Chronic ophthalmic complications result from multiple pathogenic processes during the acute phase of SJS/TEN.[56,57] Impaired tear production due to obstructed lacrimal glands lead to chronic dryness of the eyes.[57,58] Symblepharon or ankyloblepharon can cause inadequate blinking/closure of eyes and limited ocular mobility in SJS/TEN patients.[59] While cicatricial changes in both the conjunctiva and lid margins perpetuate ongoing damage,[59] the loss of limbal corneal stem cells further impairs reparative processes in the eye.[60] On the exterior of the eye, scarring of the lid margins leads to ectropion,

entropion and trichiasis/districhiasis.[60] The combination of these processes eventually results in recurrent corneal erosions, ulcerations, neovascularization, stromal scarring, and conjunctivalization of the corneal surface, and ultimately in decline of vision or even blindness.[61]

Oral sequelae

Although lesions of oral mucous membranes occur in most SJS/TEN patients during the acute phase, complete oral mucosal healing within 1 year has been reported in the majority of SJS/TEN patients.[55,62] However, studies have found that 10–20% of SJS/TEN survivors suffer from chronic oronasopharyngeal mucosal lesions, whereby the severity of acute oral mucosal involvement seems to be a predictor for such chronic complications.[49] Long-term oral complications include adhesions on lips, gingiva, and under the tongue, oral ulcers, depapillation of the tongue, Sjögren-like sicca syndrome, and reduced or acidic saliva production.[49,55,63] Such changes can affect mouth mobility,[64] and promote caries, gingival inflammation and periodontitis by encouraging the growth of bacteria.[65] Dental growth abnormalities as a consequence of disordered root development have been reported in children who suffered from SJS/TEN, and may cause eating difficulties.[66]

Pulmonary sequelae

Reported late pulmonary complications of SJS/TEN are interstitial lung disease, respiratory tract obstruction, bronchiectasis, bronchitis and bronchiolitis obliterans.[61] Bronchiolitis obliterans is a consequence of airway epithelial injury/scarring resulting in ciliary dysfunction, which predisposes to infections of the lungs, dyspnoea, and airway obstruction.[67] Bronchiolitis obliterans after SJS/TEN has predominantly been observed in paediatric SJS/TEN cases and has frequently been linked with concomitant mycoplasma infections, and it is not entirely clear if bronchiolitis obliterans is a direct consequence of pulmonary complications in SJS/TEN or the high incidence of mycoplasma infections in SJS/TEN patients.[61] Duong et al. observed that 18 out of 32 SJS/TEN survivors had abnormal pulmonary function tests two months after SJS/TEN, and that severity of SJS/TEN seems to correlate with decreased pulmonary function.[68]

Urogenital/gynaecological sequelae

Chronic gynaecological sequelae are observed in approximately 28% of patients,[69] and mainly involve adhesions. Female SJS/TEN survivors have been reported to suffer from vaginal adenosis, vulvovaginal endometriosis, persistent genital ulcerations, dyspareunia, haematocolpos due to complete fusion of the vulvar vestibule, and birth canal stenosis which may require delivery by caesarean section.[69–75] Vaginal adhesions and stenosis might be treated by nymphoplasty, (vulvo-) perineotomy, dissection with subsequent insertion of vaginal moulds, and menstrual suppression.[69] During the acute phase of SJS/TEN possible preventive measures for vulvovaginal sequelae include insertion of a mould into the vagina and using topical corticosteroids to prevent vaginal adhesion/stenosis, or postponing menstruation to prevent vaginal adenosis and endometriosis.[69,76] In men, chronic urogenital sequelae after SJS/TEN has to date not been described in detail.

Gastrointestinal and hepatic sequelae

Reported chronic gastrointestinal complications are oesophageal strictures, hypopharyngeal stenosis causing dysphagia and recurrent aspiration, inflammatory pancolitis with ulceration and persistent discharge, and intestinal ulceration causing diarrhoea and malabsorption.[47,77,78] Patients with chronic small intestinal complications may require parenteral nutrition or even ileal resection.[79] Few patients with SJS/TEN have also been reported to suffer from a chronic cholestasis known as vanishing bile duct syndrome after the acute stage of SJS/TEN.[80]

Renal sequelae

Although renal involvement in SJS/TEN is rather rare in the acute phase (20% of cases),[48] follow-up studies of SJS/TEN survivors showed that approximately 23% of SJS/TEN survivors developed renal issues including chronic renal insufficiency, and that 5% of SJS/TEN patients with renal complications during the acute phase of SJS/TEN require long-term dialysis.[49]

Psychiatric and psychosocial sequelae

The long-term psychiatric morbidity in SJS/TEN survivors has not been studied sufficiently as of to date. A study by Dodiuk-Gad et al. including 17 SJS/TEN survivors reported that 65% of the survivors showed symptoms of post-traumatic stress, 71%

suffered from significant psychological distress, and that only 29% were employed following SJS/TEN.[81]

Mortality

A longitudinal analysis in 460 SJS/TEN patients reported mortality rates after SJS/TEN of 23% at 42 days, 28% at 90 days, and 34% at 1 year, which suggests that the risk of death continues to be increased after the acute phase of SJS/TEN. The study further showed that risk of dying within 42 days after SJS/TEN was 7.7-times higher for patients with TEN when compared to patients with SJS, and 2.6-times higher for patients with SJS/TEN overlap when compared to SJS.[82] Old age, delayed admission to a specialist, and presence of comorbidities are other reported risk factors for death after SJS/TEN.[42,49,82]

1.2.4 Diagnosis

The tentative diagnosis of SJS/TEN is typically based on clinical signs, as to date no specific laboratory parameters which would allow diagnostic tests have been identified. Typical clinical signs of SJS/TEN are initial unspecific systemic symptoms with fever, flat targetoid skin lesions (i.e. circular, concentric lesions) with central necrosis mainly on the trunk and face, and mucosal involvement in at least 2 sites (mostly eyes and mouth).[83] Erythema multiforme can also present with mucocutaneous involvement, but the presence of typical target lesions and lesions on extremities suggests EM rather than SJS/TEN.[84] Further important indications to the diagnosis of SJS/TEN are non-blanchable (i.e. lesions do not lose redness upon application of pressure), non-transient, and often painful skin lesions, as well as a positive Nikolsky sign (i.e. affected skin exfoliates upon tangential pressure).[85] Aside from clinical signs, histological workup of a skin biopsy are used to rule out differential diagnoses such as generalized fixed drug eruption, acute generalized exanthematous pustulosis, drug-induced linear IgA bullous dermatosis, paraneoplastic pemphigus, disseminated fixed bullous drug eruption, and staphylococcal scalded skin syndrome.

1.2.5 Etiology

SJS/TEN is mostly triggered by drugs. SJS/TEN typically occurs 4-28 days after initiation of a new drug therapy, but cases with a latency period of up to 8 weeks have been observed. Current knowledge of the pathogenesis of SJS/TEN suggests that, aside from exposure to certain drugs, a patient's genetic predisposition (alleles of the human leukocyte antigen [HLA], drug metabolism by cytochrome P450 [CYP], and T-cell clonotypes) may play a role in a patient's susceptibility to SJS/TEN (Figure 1.2-2). Proposed triggers of SJS/TEN other than drugs are infections (e.g. mycoplasma pneumoniae, herpes virus) and radiotherapy.[86]

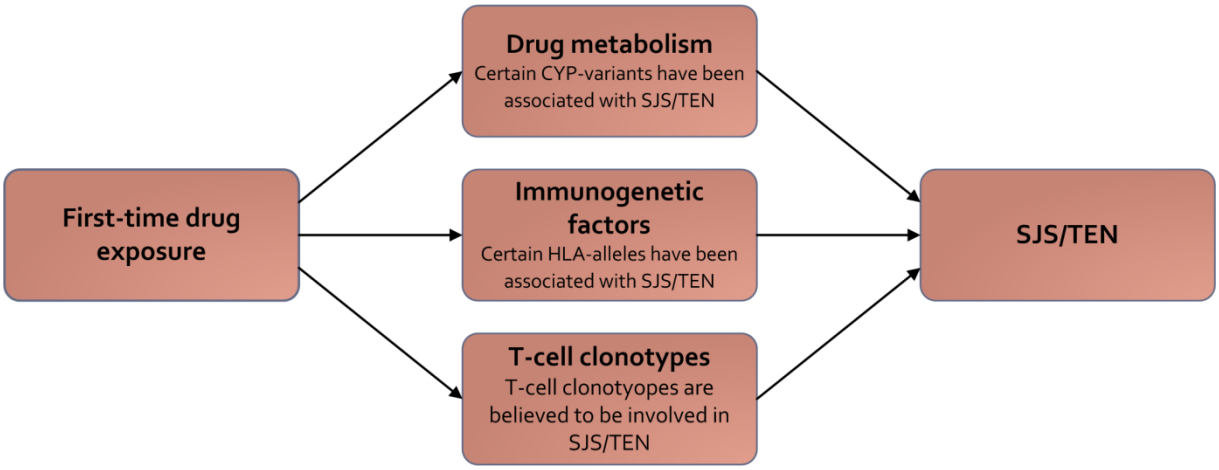

Figure 1.2-2: Etiologic factors involved in the pathomechanism of SJS/TEN.
CYP=Cytochrome P450, HLA=Human leukocyte antigen.

Culprit drugs

In the absence of effective pharmacotherapy for acute SJS/TEN, early identification and discontinuation of the culprit drug is essential to minimize complications of SJS/TEN. Despite the importance of knowledge of culprit drugs of SJS/TEN, Haddad et al. reported in a study where they assessed the accuracy and completeness of SJS/TEN warnings in drug dictionaries that the quality of information on the risk of SJS/TEN is rather low and needs improvement.[87] The lack of knowledge of culprit drugs can mainly be attributed to the rare nature of SJS/TEN, which requires a huge data source to identify a sufficiently large study population, previous issues with SJS/TEN diagnoses in healthcare databases (see Chapter 1.2.2.; multi-diagnostic coding of ICD-9 codes), and

the impracticability of conducting clinical studies on this subject due to ethical and practical considerations. Two previous multi-national case-control studies based in Europe have identified sulphonamide antibiotics, allopurinol, carbamazepine, phenobarbital, phenytoin, lamotrigine, nevirapine, and oxicam analgesics as the main culprit drugs of SJS/TEN.[88,89] Various other drugs have been linked to SJS/TEN albeit based on weak evidence from observational studies,[89,90] or from case reports (Table 1.2-1).[91–139]

Potential tests for the identification of the causative agents in SJS/TEN (e.g. patch testing, pin prick, intradermal injection, lymphocyte transformation test, basophil activation test) have not been proven to be reliable in predicting SJS/TEN and lack sensitivity.[140]

Table 1.2-1: Drug previously associated with SJS/TEN in observational studies or case reports.

Suspected culprit drugs for SJS/TEN with strong evidence from observational studies[88,89]	**Suspected culprit drugs for SJS/TEN with conflicting or few evidence from observational studies**[88,89]	**Suspected culprit drugs for SJS/TEN suggested in case reports only**[91–139]		
Carbamazepine	Valproate	Coxibs	Itraconazole	Amlodipine
Phenobarbital	Penicillins	Nimesulide	Fluconazole	Losartan
Phenytoin	Quinolones	Tetracepam	Voriconazole	Indapamide
Lamotrigine	Cephalosporins	Clobazam	Terbinafine	Dipyridamole
Allopurinol	Tetracyclines	Gabapentin	Metronidazole	Hydralazine
Oxicam-analgesics	Macrolides	Zonisamide	Vancomycin	Acetazolamide
Cotrimoxazole	Acetic-acid NSAIDs	Fluoxetine	Rifaximin	Methotrimeprazine
Sulfasalazine	Ibuprofen	Fluvoxamine	Oseltamivir	Bezafibrate
Nevirapine	Diclofenac	Paroxetine	Adefovir	Strontium ranelate
	Acetaminophen	Mirtazapine	Abacavir	Danazol
	Pyrazolones	Duloxetine	Efavirenz	Mesalamine
	Corticosteroids	Venlafaxine	Afatinib	Bendamustine
	Imidazole antimycotics	Bupropion	Sorafenib	Febuxostat
	Pantoprazole	Paliperidone	Etanercept	Hydroxychloroquine
	Sertraline	Omeprazole	Methotrexate	Ethambutol
		Esomeprazole	Metolazone	Modafinil
		Lansoprazole	Furosemide	Phosphodiesterease-5 inhibitors

Genetic predispositions of SJS/TEN

First reports of potential genetic susceptibility to SJS/TEN emerged in 1987, when associations between the presence of certain HLA alleles and sulphonamide-induced TEN (HLA-B*12, HLA-A*29, and HLA-DR*7), and oxicam-induced TEN (HLA-B*12 and HLA-A*2) were observed in Europeans.[141] Over the course of the following years many other associations between genetic predispositions and SJS/TEN have been discovered (Table 1.2-2).

Table 1.2-2: Drug previously associated with SJS/TEN in observational studies or case reports.

HLA **allele or CYP**	**Culprit drug**	**Ethnicity**	**References**
HLA alleles			
*HLA-B*15:02*	Carbamazepine Oxcarbazepine Lamotrigine Phenytoin	Asian	142–145
*HLA-B*15:11*	Carbamazepine	Asian	146,147
*HLA-B*59:01*	Carbamazepine	Asian	148
*HLA-A*31:01*	Carbamazepine	Asian, European	149,150
*HLA-B*38*	Sulfamethoxazole	European	151
*HLA-C*04:01*	Nevirapine	African	152
*HLA-B*73*	Oxicam	European	151
*HLA-B*58:01*	Allopurinol	Asian, European	151,153,154
CYP alleles			
*CYP2C9*3*	Phenytoin	Asian	155
CYP2B6	Nevirapine	African	156

CYP=Cytochrome P450; HLA=Human leukocyte antigen.

An association between the presence of HLA-B*15:02 and carbamazepine-induced SJS/TEN has been reported in Asians but so far not in Europeans, in whom the HLA-B*15:02 allele has a low prevalence (<1%).[142–145,157] The same association was also observed in Europeans with Asian ancestry.[157] This observation suggests that the risk of SJS/TEN might vary by ethnicity. Chen et al. reported a significant reduction of SJS/TEN-incidence in patients from Taiwan who were screened for HLA-B*15:02 prior to onset of carbamazepine treatment.[158] The results of this study suggested that routine screenings for the presence of a HLA-B*15:02 allele should be considered in Asian patients before starting carbamazepine treatment. The association between HLA-

B*58:01 and allopurinol-induced SJS/TEN on the other hand has been found in both Asian and European patients.[151,153]

Besides HLA alleles, altered drug metabolism or clearance may also play a role in the pathogenesis of SJS/TEN.[32] Two studies reported associations between phenytoin-related SJS/TEN and genetic variants of CYP2C, namely CYP2C9*3.[155,159] CYP2C9*3 has a reduced catalytic activity compared to wild-type CYP2C*1, resulting in delayed clearance of plasma phenytoin and increased phenytoin toxicity in patients carrying this CYP2C variant.[160] The results from a further study suggest that polymorphisms of CYP2B6 may influence the risk of developing SJS/TEN after exposure to nevirapine.[156]

1.2.6 Pathomechanism

Mechanism of Cell Death

The current understanding of the pathogenesis of SJS/TEN is mainly based on studies that found increased numbers of CD8 T-lymphocytes and Natural Killer (NK) cells in the blister fluid of patients with SJS/TEN.[161,162] These findings implicate, that the widespread keratinocyte cell death seen in SJS/TEN can be attributed to apoptosis (programmed cell death) rather than to necrosis (cell death triggered by external factors or diseases). The activated CD8 T-cells and NK cells in SJS/TEN induce keratinocyte death in a drug-specific, major histocompatibility complex-I (MHC-I)-restricted manner.[163]

Aside from drug-specific cytotoxic T-cells and NK cells multiple other cell-death mediators, as well as altered anti-apoptotic pathways, and altered or defective regulation of drug-specific immune reactions are suggested to play a role in the apoptosis of keratinocytes.[164] Granulysin, Fas–Fas ligand interaction, tumour necrosis factor-α (TNF-α), TNF-related apoptosis-inducing ligand, and perforin-granzyme B have all been implicated as mediators of apoptosis in SJS/TEN.[32,165]

Chung et al. identified granulysin, a cytolytic protein produced and secreted by cytotoxic T-lymphocytes and NK cells, as a key cell death mediator in SJS/TEN.[166] The study identified granulysin as the most highly expressed cytotoxic molecule in five patients

with SJS/TEN, and found that the concentration of granulysin in blister fluid of SJS/TEN patients correlated with clinical severity of the reaction. Dose-dependent blistering and cell death was further observed when injecting granulysin from SJS/TEN patient blisters into mice skin.[166]

The Fas–Fas ligand pathway is another proposed pathway for the widespread apoptosis of keratinocytes in SJS/TEN. Viard et al. found that TEN patients had elevated levels of soluble Fas ligands (sFasL) in keratinocytes which activate apoptosis by binding to Fas receptors.[167] However, a subsequent study by Abe et al. could only find elevated levels of sFasL in the serum, but not in keratinocytes.[168] They concluded that the elevated levels of sFasL stem from peripheral blood mononuclear cells rather than keratinocytes and that sFasL may thus not be the primary mediators of apoptosis. In a further study conducted in 35 SJS/TEN patients, they found that sFasL levels were significantly increased in the serum of affected patients before development of skin detachment or mucosal lesions, and proposed that sFasL may play a role as a marker of disease at initial presentation.[169]

Other 'death receptors' such as TNF-receptor 1, death receptors 4 and 5, and their ligands TNF-α and TNF-related apoptosis-inducing ligand may also be involved in the pathogenesis of SJS/TEN.[32,165]

Initiation of Apoptosis

The exact mechanism of cytotoxic T-cell activation in SJS/TEN is an issue that has not yet been sufficiently clarified. One proposed concept is that metabolites of culprit drugs interact with the T-cell receptors (TCR) after covalently binding to a peptide (hapten-concept). Another proposed concept is that culprit drugs non-covalently bind directly to MHC-I and TCR without being metabolized first (pharmacologic interaction concept).[32] The results of a study by Wei et al. support this proposed mechanism for carbamazepine-induced SJS/TEN, by showing that carbamazepine is able to directly bind to HLA-B*15:02 and activate T-cells.[170] However, the results of a further study suggest that the hapten-concept is more likely to underlie cytotoxic T-cell activation in SJS/TEN induced by abacavir.[171]

1.2.7 Management

Supportive care

If SJS/TEN is suspected, the culprit drug should be identified and discontinued as soon as possible. Early discontinuation of the culprit drug is crucial and often decisive for the outcome of SJS/TEN. Patients should then be referred to specialised clinicians or, in case of TEN, a burn intensive care unit to receive further supportive care, which mainly involves wound care with focus on preventing infections, and management of airways, renal function, fluid and electrolyte balance, nutrition, ocular complications, and pain.[172] The different analgesic regimens for pain management in SJS/TEN have to date not been investigated in studies. Existing guidelines suggest that patients with mild pain should be treated with acetaminophen and if required with oral codeine or tramadol. Because of the potential for renal and gastric injury, NSAIDs should be avoided. Patients with moderate or severe pain should receive opiate-based analgesia (e.g. morphine, fentanyl) enterally or via infusion.[172] Systemic antibiotics should only be administered if there are clinical signs of infections and not preventively.[172] When evaluating therapeutic actions caretakers should also consider assessing SCORTEN (severity-of-illness score for TEN), which is a score that was designed to predict the severity and risk of death in SJS/TEN patients based on age, affected BSA, presence of malignancy, heart rate, serum urea, serum bicarbonate, and serum glucose.[45]

Ophthalmologists play an important role in the management of SJS/TEN and should be consulted as soon as possible to prevent long-term ocular complications. Preventive measures include lubrication, use of topical antibiotics and corticosteroids, lysis of adhesion, and amniotic membrane transplantation. In patients with urogenital complications during the acute phase of SJS/TEN consultation with an urologist or gynaecologist is recommended to prevent urogenital sequelae.[172]

Pharmacological therapy

The pharmacologic treatment of SJS/TEN is a subject of discussion and evidence on various potentially effective drugs is conflicting and based on low patient numbers. To

date systemic corticosteroids, intravenous immunoglobulin (IVIG), TNF inhibitors, and cyclosporine A are discussed as potential adjunctive acute therapy options.

Systemic corticosteroids are regularly used to treat SJS/TEN despite conflicting evidence on their effectiveness. Previous observational studies reported that systemic corticosteroids successfully alleviate symptoms in SJS/TEN patients during the acute phase.[173,174] However, previous reports on the effects of systemic corticosteroids on mortality are contradictory. While some early studies found an increased risk for infections and death in patients treated with systemic corticosteroids,[175] more recent studies suggested a similar or a slightly better chance of survival when compared to supportive therapy alone.[82,176,177] Due to equivocal evidence and the lack of controlled clinical trials, guidelines do not give specific recommendations regarding the use of systemic corticosteroids in SJS/TEN.[172]

Intravenous immunoglobulins are commonly used in SJS/TEN. Although positive effects of IVIG in SJS/TEN patients have been described in case reports and series,[140] the results of a systematic review and meta-analysis including 221 SJS/TEN patients treated with IVIG suggested no significant advantage of IVIG over supportive care only regarding patient survival.[178] Due to the conflicting results on the efficacy of IVIG for the treatment of SJS/TEN and potential side effects, the use of IVIG should be carefully considered in SJS/TEN patients.[140,172]

Studies observed increased serum TNF-alpha levels in SJS/TEN patients suggesting that TNF-alpha inhibitors might be effective in the treatment of SJS/TEN.[179] However, to date only little evidence exists on the effectiveness of TNF inhibitors in SJS/TEN. Several case reports found that infliximab and etanercept impede skin detachment, promote re-epithelialization, and increase survival probability in SJS/TEN.[180–182]

An increased mortality in patients with TEN was observed in association with thalidomide in the only existing randomized placebo-controlled trial conducted to assess the effectiveness of adjunctive therapy in SJS/TEN. The study was terminated after 10 out of 12 TEN patients treated with thalidomide died, while only 3 deaths were observed in 10 TEN patients in the placebo group.[183]

Cyclosporine A has also been reported to slow progression of SJS/TEN in the acute phase in various case reports.[184] A retrospective analysis conducted in a cohort of 44 SJS/TEN patients further reported that cyclosporine A successfully decreased the number of deaths in 24 SJS/TEN patients when compared to the number of deaths predicted by SCORTEN.[185]

Chapter 2

Aims of the thesis

2 Aims of the thesis

The aim of this thesis was to contribute to the understanding of the epidemiology and culprit drugs of SJS/TEN by conducting comprehensive observational studies using data from the CPRD, a large, UK-based primary-care database. Despite the severe impact of SJS/TEN on affected patients, the current scientific understanding of SJS/TEN is insufficient, particularly regarding its epidemiology, aetiology, pathophysiology, treatment, and long-term sequelae.

SJS/TEN has not been studied in the CPRD before, and numerous previous attempts of studying these reactions in medical claims databases have failed due to issues with the multi-diagnostic coding of the ICD-9 coding system.[35–38] Study 3.1 is the basis of the project and aims to evaluate the eligibility of studying SJS/TEN in the CPRD by assessing the validity of SJS/TEN diagnoses recorded in the CPRD, and to establish a valid population of SJS/TEN patients from the CPRD for observational studies (i.e. Studies 3.2 to 3.5).

Study 3.2 aimed at comprehensively analysing the epidemiology of SJS/TEN by calculating IRs of SJS/TEN in the UK for the first time. We further aimed to identify risk groups of SJS/TEN by assessing associations between SJS/TEN and demographic factors, life-style characteristics, ethnicity, and pre-existing comorbidities.

Studies 3.3 to 3.5 analyse associations between SJS/TEN and potential culprit drugs as well as absolute risks of SJS/TEN in association with each of the drugs to provide a better understanding of the safety/risk of these drugs regarding SJS/TEN. Absolute risks of SJS/TEN have previously only been reported for some AEDs. Study 3.3 encompasses all AEDs in clinical use in the UK of which some have previously been associated with SJS/TEN with strong evidence (e.g. carbamazepine, lamotrigine, phenytoin, phenobarbital) or little evidence (e.g. valproate, gabapentin). Study 3.4 encompasses various antibiotic drugs among which cotrimoxazole in particular has repeatedly been linked to SJS/TEN. Numerous other drugs which have been associated with SJS/TEN in observational studies (e.g. allopurinol) or case reports (e.g. coxibs) as well as drugs of common use are included in Study 3.5.

Chapter 3

Stevens-Johnson and toxic epidermal necrolysis project

3 Stevens-Johnson syndrome and toxic epidermal necrolysis project

3.1 Validation of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis Diagnoses in the Clinical Practice Research Datalink (Study 3.1)

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3.1.1 Abstract

Purpose: To evaluate the validity of recorded diagnoses of Stevens–Johnson syndrome (SJS) and TEN in the CPRD.

Methods: We identified patients with a diagnosis of SJS or TEN between 1995 and 2013 in the CPRD. We reviewed information from patient records, free text, and HES data, and excluded patients with no indication of a secondary care referral. Remaining patients were classified as probable, possible, or unlikely cases of SJS/TEN by two specialised clinicians or based on pre-defined classification criteria. We quantified positive predictive values (PPV) for all SJS/TEN patients and for patients categorised as 'probable/possible' cases of SJS/TEN, based on a representative subsample of 118 patients for whom we had unequivocal information (original discharge letters or HES data).

Results: We identified 1324 patients with a diagnosis of SJS/TEN, among whom 638 had a secondary care referral recorded. Of those, 565 were classified as probable or possible cases after expert review. We calculated a PPV of 0.79 (95% CI, 0.71–0.86) for all SJS/TEN patients with a recorded secondary care referral, and a PPV of 0.87 (95% CI, 0.81–0.93) for probable/possible cases. After excluding 14 false positive patients, our study population consisted of 551 SJS/TEN patients.

Conclusions: Diagnoses of SJS/TEN are recorded with moderate diagnostic accuracy in the CPRD, which was substantially improved by additional expert review of all available information. We established a large population-based SJS/TEN study population of high diagnostic validity from the CPRD.

3.1.2 Introduction

SJS/TEN are life-threatening skin reactions, which predominantly occur as a complication of newly administered drug therapy. These reactions are rare, with estimated IRs of SJS/TEN ranging from 1 to 12.7 per million py.[40,42,186,187] Current evidence suggests that SJS and TEN are one disease entity, which differ by the proportion of BSA affected by skin detachment.[83,86,188] Epidemiologic data on SJS/TEN is limited; previous studies have focused primarily on identifying drugs that cause these skin reactions using hospital based case–control studies.[88,89,189] Large electronic databases are an important tool in epidemiologic research and can be particularly useful in conducting population-based studies on rare outcomes. However, studies on SJS/TEN using these data sources are scarce for several reasons. Some databases are too small to quantify such a rare disease, and up until 2008, data from large databases that used the ICD-9 coding system were not ideal for research because of the non-specific coding of the outcome, which did not differentiate between EM and SJS/TEN.[36,37,190] Thus, more evidence on IRs of SJS/TEN and characteristics of patients with the outcome from population-based data are needed. Previously reported IRs of SJS/TEN vary greatly presumably because of difficulties in defining the population at risk. Lack of longitudinal follow-up studies on SJS/TEN patients also limits knowledge about long-term complications in SJS/TEN survivors.[165,187,189,191]

The Clinical Practice Research Datalink is a large UK-based primary care database, and a potentially suitable resource to study the epidemiology of SJS/TEN, because its Read-coding system allows differentiation between EM, SJS, and TEN. Furthermore, anonymised original secondary care documentation is available. Moreover, the large size, the virtually complete drug prescription history, the long mean patient follow-up (9.4 years for currently enrolled patients), and the population-based nature of the database make it an attractive resource for studying rare diseases using a longitudinal approach. Diagnostic accuracy in the CPRD has been demonstrated to be high for many diseases, but the validity of recorded SJS or TEN diagnoses has not yet been evaluated. We therefore sought to (i) assess the feasibility of studying SJS/TEN in the CPRD, and to (ii) assemble a study population of validated incident SJS/TEN cases.

3.1.3 Patients and Methods

Data sources

CPRD

This study was conducted in the CPRD, a large (around 11 million patients) computerised primary care database that is representative of the UK population with regard to age and sex. Since 1987, participating GPs have recorded patient characteristics, symptoms, diagnoses, laboratory test results, drug prescriptions, and referrals, including the primary diagnoses made in secondary care (defined as hospitalisations and visits to outpatient consultants).[28] The data in the CPRD have been repeatedly demonstrated to be of high quality,[29] and the database has been used for numerous epidemiological studies published in peer-reviewed journals. This study was approved by the ISAC for MHRA database research (ISAC protocol 14_009R).

Free text

Free text can be added to the coded patient records by the GP and can contain important details of medical encounters, and often contains relevant information regarding diagnoses from secondary care, procedures, symptoms, referrals, or any other information the GP considered important.[190,192] Of note, free text is only available up to June 2013 because of new regulations of privacy protection within the UK.

Hospital episode statistics data

HES data are computerised details of hospitalisations in NHS hospitals in England (a subset of CPRD patients) available since 1989. These linked data include information on primary and secondary discharge diagnoses, procedures performed during a hospital stay, length of stay, and methods of admission and discharge.

Original discharge letters

We further ordered discharge letters for 50 randomly selected patients with an incident SJS/TEN diagnosis who were referred to a secondary care institution (hospital or dermatology/ophthalmology unit). Discharge letters were available from participating

GPs who copy and send, in anonymised manner, clinical records to the CPRD for validation purposes.

Study population

We identified all patients of any age in the CPRD who had a READ-code for SJS or TEN between January 1995 and December 2013 (Table 3.1-1). We then requested all available free text and HES data for these patients. Using all available information, we identified patients who had some indication, from one of the data sources, that they had been seen in secondary care within 30 days before or after the first SJS/TEN diagnosis code. We defined referrals to secondary care as a Read-code for a referral to a secondary care institution or a specialist (dermatologist or ophthalmologist), a hospitalisation recorded in HES data, receipt of letters from a specialist, or a recorded entry for a hospital discharge (or receipt of a discharge letter). Those with no information to suggest a secondary care visit were excluded from further study, because patients with true SJS/TEN inevitably require hospitalisation or consultation with a specialist.

Validation of SJS and TEN diagnoses

Researchers reviewed and abstracted all relevant information from CPRD electronic patient records (not including drug prescriptions), free text, and HES data of SJS/TEN patients with an identified secondary care referral. All information from free text or HES data with regard to drug prescriptions or any information that confirmed or refuted an SJS/TEN diagnosis (SJS/TEN diagnoses and differential diagnoses) was manually blinded before it was linked to the respective patient, because this information was later used to evaluate the PPV of the recorded SJS/TEN diagnoses. Patients were then allocated to either group A or group B. Group A included patients whose electronic record contained sufficient clinical information (≥3 different codes for symptoms, diagnoses, or patient management for skin disease or had free text with clinical information from secondary care or the GP). These were then evaluated by two clinicians, a dermatologist who is specialised in allergology, and an internist with specialisation in emergency and intensive care medicine. Based on their clinical knowledge, the two clinicians independently classified each potential SJS/TEN case as

probable, possible, or unlikely. We considered expert review the most accurate way to classify patients, because SJS/TEN is usually diagnosed in secondary care based on clinical presentation. Because there are no accepted universal clinical guidelines for SJS/TEN, implementation of an unequivocal pre-specified clinical validation algorithm was not feasible. Group B contained patients with an evident secondary care referral but whose records did not contain sufficient clinical information to be allocated in group A. Because we could not classify these patients based on clinical information, patients in group B were categorised as probable, possible, or unlikely strictly according to pre-specified criteria (Table 3.1-2), which were previously developed by two epidemiologists based on the number of SJS/TEN codes and other supporting codes such as procedures and patient management codes, recorded differential diagnoses, and hospital and emergency visits.

True diagnoses

We considered patients who had diagnoses of SJS/TEN found in secondary care discharge letters, HES data, or free text to be true cases of SJS/TEN if the letter explicitly confirmed the SJS/TEN diagnosis. We determined that when another differential skin diagnosis was present the SJS/TEN was not a true case. When there was ambiguity, letters were reviewed by an allergist (n=5; 3 considered true cases, and in 2 instances we were not able to confirm or refute the recorded SJS/TEN diagnosis based on the content of the letter). We accepted diagnoses recorded in free text as valid if they referred to a discharge letter and to the recorded diagnosis of interest, or to a diagnosis which was made by a specialist. Diagnoses from HES data were considered to validate cases if the primary discharge diagnosis explicitly confirmed the SJS/TEN diagnosis (bullous EM [ICD-10 L51.1]) or to refute the SJS/TEN diagnosis (another explicit differential diagnosis of SJS/TEN involving the skin or mucous membranes was recorded).

Statistical analysis

We calculated PPVs with 95% confidence intervals (CI) for (i) all SJS/TEN patients with a secondary care referral prior to expert classification (n=638), and for (ii) patients classified as possible or probable SJS/TEN patients after expert classification (n=565), based on a representative sample of SJS/TEN patients for whom true diagnoses from secondary care discharge letters, HES data, or free text were available. The PPV was calculated based on a representative subset of the 118 patients for whom information from HES data, free text, or discharge letters unequivocally confirmed or refuted the SJS/TEN diagnosis (93 cases confirmed and 25 refuted). Because the likelihood of having unequivocal information available was independent of the validity of the diagnosis, this proportion was then extrapolated to (i) the full set of all 638 SJS/TEN cases with secondary care referrals and separately to (ii) all 565 SJS/TEN patients classified as 'probable/possible' SJS/TEN cases to estimate the proportion of true cases in the study population.

To evaluate whether 'true' cases and unconfirmed 'probable/possible' SJS/TEN cases differed in specific characteristics from patients classified as unlikely (confirmed or unconfirmed) SJS/TEN cases, we compared the 2 groups with respect to sex and age distribution, the year of the first recorded SJS/TEN diagnosis, and whether or not patients had recorded diagnoses for EM within 2 weeks before or after the first SJS/TEN diagnosis. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Incidence rate

We calculated a population-based overall IR of SJS/TEN for the years 1995 through 2013, by dividing 551 probable/possible SJS/TEN cases by the total number of py at risk in patients without a previous diagnosis for SJS/TEN in the CPRD population. We adjusted the overall IR for type I error (false positive cases) and for type II error (false negative cases) by multiplying the numerator by the overall PPV (i.e. 0.87) and by the proportion of patients that was erroneously excluded because of a non-evident but true hospitalisation (proportion based on HES data 1.24).

3.1.4 Results

We identified 1324 patients with a recorded SJS/TEN diagnosis in the CPRD during the study period, of whom 638 had an ascertainable secondary care referral within 30 days before or after the first SJS/TEN diagnosis.

Based on the initial review, we allocated 284 patients into group A (for review by clinicians) and 354 patients into group B (for review by epidemiologists). In group A, 81 patients with SJS/TEN diagnoses were classified as probable, 151 as possible, and 52 as unlikely cases of SJS/TEN. Patients in group B were classified according to the criteria listed in Table 3.1-2, which resulted in 172 patients being classified as probable, 161 as possible, and 21 as unlikely SJS/TEN patients (Figure 3.1-1).

Of 959 patients with a recorded SJS/TEN diagnosis during the study period and an existing flag for available free text in the patient profile around the time of diagnosis, we received free text for 474 patients (49.4%; Table 3.1-5). Free text of 39 potential SJS/TEN patients contained extracts of discharge letters which explicitly confirmed (n=36) or refuted (n=3) the SJS/TEN diagnosis (Table 3.1-3).

A total of 176 patients had HES data recorded between 1995 and December 2013, of whom 70 patients had a hospitalisation recorded in HES data within one month prior to or after the first CPRD SJS/TEN diagnosis. Seventeen (24.3%) of those 70 secondary care referrals indicated in HES data were not otherwise coded as referrals in the CPRD patient profiles. The HES data confirmed the SJS/TEN diagnosis recorded in the CPRD patient profile in 39 patients. An additional 10 cases were refuted based on the information in the HES data (Table 3.1-3).

We received 35 of 50 requested discharge letters (70%; Table 3.1-5). Of these, 16 confirmed and 12 refuted the SJS/TEN diagnosis recorded in the CPRD patient profile. The remaining 7 discharge letters (14.0%) were not helpful as they either were not legible, contained too little information, or they referred to a diagnosis/symptom other than the SJS/TEN diagnosis (Table 3.1-3).

We identified 118 patients for whom we had unequivocal (true) diagnoses from HES data, free text, or discharge letters. Of these, 93 confirmed and 25 refuted the SJS/TEN

diagnoses. We estimated PPV based on the 118 cases for whom we had unequivocal diagnostic information, and applied the results to all SJS/TEN patients with a secondary care referral and to all SJS/TEN patients classified as probable/possible, respectively.

Among the 638 patients who had an incident SJS/TEN diagnosis in the CPRD between January 1995 and December 2013 accompanied by a coded secondary care referral we estimated, based on the sample, a PPV of 0.79 (95% CI, 0.71–0.86, Table 3.1-4). The 565 SJS/TEN cases who were classified as probable or possible yielded an overall PPV of 0.87 (95% CI, 0.81–0.93). The PPV in group A (53 true cases) was 0.89 (95% CI, 0.80–0.97), and the PPV in group B (54 true cases) was 0.85 (95% CI, 0.76–0.95, Table 3.1-4). Of these, 13.6% of patients were explicitly diagnosed with TEN. We combined patients classified as probable and possible into one group, because we observed no statistically significant differences between the PPVs (p-value =0.699, Pearson chi-square test) calculated separately in patients classified as probable versus unlikely (PPV=0.88) and possible versus unlikely (PPV=0.86; Table 3.1-4).

Based on the 551 probable/possible cases, we calculated an overall SJS/TEN IR of 6.52 cases/million py in the CPRD population between 1995 and 2013. Furthermore, cases of SJS/TEN classified as unlikely cases were more likely to have had a diagnosis of EM recorded within 2 weeks before or after the first SJS/TEN diagnosis (Table 3.1-6). Patient demographics were comparable across all groups.

3.1.5 Discussion

Our findings suggest that SJS and TEN diagnoses accompanied by secondary care referrals are recorded with moderate reliability in the CPRD (PPV 0.79, 95% CI, 0.71–0.86, i.e. 116 false positives out of 638 potential cases). However, additional evaluation of the available information by clinicians/epidemiologists improved the PPV (0.87, 95% CI 0.81–0.93) within our final SJS/TEN study population (i.e. 72 false positives out of 551 validated cases).

We restricted this study to SJS/TEN diagnoses with known secondary care referrals because most patients with SJS/TEN require inpatient or even intensive care treatment.

A recent study by Davis et al. validated SJS/TEN diagnoses recorded in US-based HMO data after the specific ICD-9-CM coding was introduced in 2008, and reported a PPV of 15% among 'not-hospitalised' patients with a specific SJS/TEN or EMM diagnosis.[193] Note that we did not look at EMM in our study so these results are not strictly comparable. The authors further quantified a PPV of 50% among hospitalised patients overall, which however was only based on secondary care record review of 10 potential SJS/TEN cases, including an unknown number of patients diagnosed with EMM. Because the final diagnosis is typically based on clinical presentation to a dermatologist in specialised secondary care, we used a large and representative sample of approximately 20% of all diagnoses documented in secondary care records to establish true cases. Consequently, we have no information on the validity of SJS/TEN diagnoses in the CPRD among patients for whom no secondary care referral was identified. Based on hospitalisations recorded in HES data, we estimated that approximately 24% of all patients with a recorded SJS/TEN diagnosis that were excluded because of absence of a secondary care referral, were actually hospitalised. We therefore adjusted the overall IR calculated from this study population accordingly. On the other hand, given the large size of the CPRD and the low rate of SJS/TEN, we can assume an overall high specificity of SJS/TEN diagnoses in the CPRD, and relative risk estimates derived from our study population will thus be of high precision.[28]

We were not able to assess the negative predictive value (NPV) of SJS/TEN diagnoses in the CPRD because we only evaluated patients with a recorded SJS/TEN diagnosis. While we were able to estimate the number of SJS/TEN cases missed because no hospitalisation was recorded, it was not feasible to evaluate whether some SJS/TEN cases were missed because the patient did not receive a SJS/TEN code at all or the patient for some reason had no contact with a primary care institution. However, because symptoms of SJS/TEN are serious and generally compel patients to seek medical attention (usually from a secondary care specialist), and because GPs participating in the CPRD are obliged to add all secondary care diagnoses to the patient's medical history,[28] the proportion of missed SJS/TEN episodes in the CPRD is likely to be small.

Of 25 patients determined not to have SJS/TEN based on HES data, free text, or discharge letters, 14 were incorrectly classified as possible or probable cases based on

electronic record review; 8 of these were in group B. Of the 11 patients correctly classified as unlikely cases (the final diagnosis refuted SJS/TEN diagnosis), 3 were in group B. However, because the resulting PPVs were similarly high in groups A and B, we plan to include cases from both in future research. Furthermore, clinically unequivocal SJS/TEN cases may not have as much clinical information recorded as compared to patients where the physician is insecure about the diagnosis.

Our calculated overall IR of 6.52 cases/million py is consistent with previously reported IRs for SJS/TEN, which ranged between 1 and 12.7 cases/million py.[40,42,186] This further corroborates the validity of our final study population, although the range of previously reported IRs is wide, likely because of difficulties in defining patients at risk, different case definition, or because of absence of certain triggering drugs on the market during earlier study periods.

There are several additional points that should be considered when interpreting the results of this validation study. First, we cannot guarantee the accuracy of all diagnoses, which were made in secondary care. Besides skin biopsy, which is routinely performed but is not diagnostic or specific, there are no diagnostic tests for SJS/TEN, and differential diagnoses, such as EM major, linear IgA dermatosis, generalised bullous fixed drug eruption, and exfoliative dermatitis can lead to misdiagnosis or diagnostic uncertainty even in specialised secondary care.[83,194] Second, although preferable, we were not able to order all available discharge letters, as this would have been too costly. However, in combination with information from HES data and free text, we were able to calculate the final PPV based on a relatively large and representative sample of 118 patients (approx. 20% of all patients) for whom we had unequivocal clinical information to validate the case of interest (likelihood of available secondary care referral was independent of the validity of the diagnosis in question). Third, we were not able to differentiate between SJS and TEN unless explicitly diagnosed. In our study population, only around 15% of patients had a specific TEN diagnosis recorded within 2 months after the index date (four of these were after a SJS diagnosis). We identified the most serious diagnosis recorded to capture the most severe form of disease to occur at any point in the disease progression. Previous estimates of the ratio of SJS and TEN are sparse, but have been reported to be between approximately 3:1 and 5:1.[86] In our study

the ratio of SJS to TEN was approximately 7:1, which may indicate that some TEN cases were mistakenly recorded as SJS, but it is also possible that previous studies overestimated the proportion of TEN events relative to SJS. We were further not able to capture SJS/TEN overlap syndrome (defined by the degree of affected BSA of 10–30%).[83] Finally, we cannot rule out the possibility that some patients had an episode of SJS/TEN prior to entering the CPRD.

Free text as well as original discharge letters was essential for the validation of these SJS/TEN cases, as a source of additional clinical information. Free text ceased to be available to CPRD researchers in July 2013 because of concerns about patient confidentiality. For the same reason, original discharge letters are no longer available to researchers. While it is important to safeguard patient confidentiality in observational research, the increasing constraints on data availability may severely hamper the conduct of observational studies, especially of rare diseases such as SJS/TEN, where the diagnosis is difficult to make and clinical details are critical to the case validation process, and where there will always be relatively few cases. While this limitation does not apply to the presented study, it will be a major impediment for future research.

In conclusion, the CPRD provides a valuable resource to perform population-based longitudinal epidemiologic research on SJS/TEN. However, exert validation of potential SJS/TEN cases is highly recommended. Because of the specific Read-coding system used in the CPRD and the ability to validate a large proportion of cases, we were able to establish the first well-validated SJS/TEN study population from a large electronic database. This large SJS/TEN study population (n=551) will allow population-based and longitudinal studies into SJS/TEN, which remains an under-investigated but clinically important disease.

Table 3.1-1: Distribution of index READ-codes based on which patients were identified.

Diagnosis	READ code	All identified patients (n=1324)
Stevens-Johnson syndrome	RM151700	1152 (87.0%)
Toxic epidermal necrolysis	RM151.12	134 (10.1%)
	RM151800	14 (1.1%)
Lyell's syndrome	RM151812	19 (1.4%)

	RM151.11	5 (0.4%)
Dermonecrolysis	RM151811	-

Table 3.1-2: Classification criteria used by epidemiologists to evaluate patients.

Probable: No recorded differential diagnosis ≤30 days after the diagnosis and ≥1 of the following:

- Recorded discharge from secondary care ≤7 days prior to the first SJS/TEN diagnosis.
- >1 recorded SJS/TEN diagnoses (≥2 days between diagnoses).
- Recorded (emergency) hospitalisation or dermatology referral ≤7 days prior to the first SJS/TEN diagnosis.
- Mentioning of ventilation, tracheostomy, parenteral nutrition, septicaemia, or intensive care treatment ≤7 days prior to or after the first SJS/TEN diagnosis.

Possible:	• No relevant information (differential diagnoses, treatment, additional SJS/TEN diagnoses, etc.) recorded besides the SJS/TEN diagnosis. • Recorded (emergency) hospitalisation or dermatology referral ≤14days after the first SJS/TEN diagnosis, and no recorded differential diagnosis ≤30 days after the first SJS/TEN diagnosis. • >1 recorded SJS/TEN diagnosis with a differential diagnosis recorded ≤30 days after the first SJS/TEN diagnosis. • Recorded discharge together with a recorded SJS/TEN and a recorded differential diagnosis (≤7 days prior to the index date).
Unlikely:	• A record for a discharge letter ≤2 days prior to or after a recorded differential diagnosis. No evident discharge recorded ≤2 days prior to or after the first recorded SJS/TEN diagnosis. • Multiple records for differential diagnoses with ≥1 differential diagnosis recorded ≤30 days after the first recorded SJS/TEN diagnosis. No additional information for SJS/TEN besides the recorded diagnosis.

Table 3.1-3: Response rates and information extracted from free text, HES data, and discharge letters.

	Available for N patients	Unequivocally confirmed/refuted diagnoses‡	Unequivocally confirmed SJS/TEN cases†	Unequivocally refuted SJS/TEN cases†
Free text	474	39 (4.4%)	36 (92.3%)	3 (7.7%)
HES data	176	51 (29.0%)	41 (80.4%)	10 (19.6%)
Discharge letters	35	28 (80.0%)	16 (57.1%)	12 (42.9%)

‡Diagnoses from secondary care used to confirm/refute SJS/TEN diagnoses.
†Percentages apply to the number of unequivocally confirmed/refuted diagnoses available from each data source.

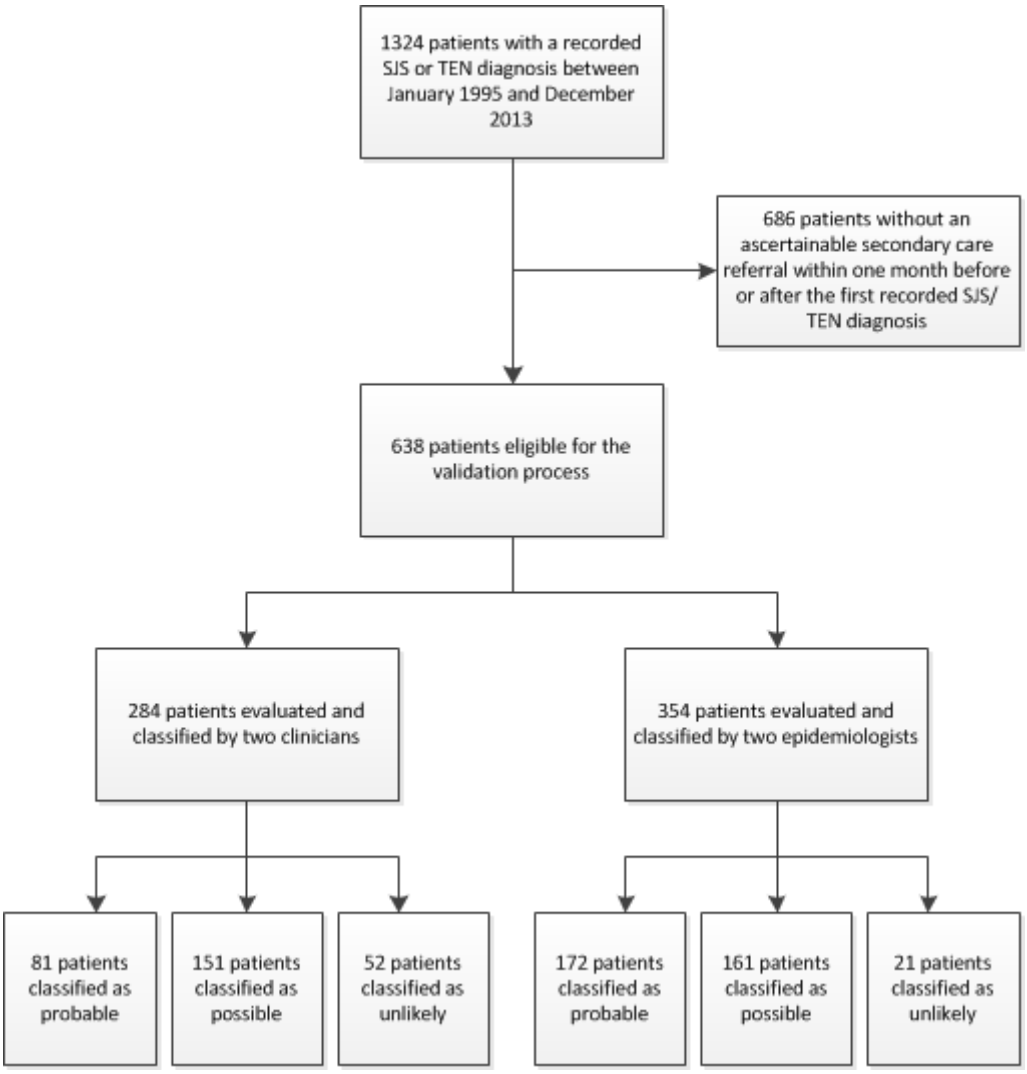

Figure 3.1-1: Patient selection and evaluation process.

Table 3.1-4: PPV for SJS/TEN with a secondary care referral on the CPRD before and after expert review.

	Sample size	True diagnoses			PPV	95% CIs
		Confirmed	**Refuted**	**Total**		
SJS/TEN diagnosis with secondary care referral	638	93	25	118	0.79	(0.71-0.86)
Total of patients classified as possible/probable cases of SJS/TEN	565	93	14	107	0.87	(0.81-0.93)
Total of patients classified as probable cases of SJS/TEN	253	45	6	51	0.88	(0.79-0.97)
Total of patients classified as possible cases of SJS/TEN	312	48	8	56	0.86	(0.77-0.95)
Classified as probable/possible according to predefined criteria (Table 2)	333	46	8	54	0.85	(0.76-0.95)
Classified as probable according to predefined criteria (Table 2)	172	26	4	30	0.87	(0.68-0.98)
Classified as possible according to predefined criteria (Table 2)	161	20	4	24	0.83	(0.75-0.99)
Classified as probable/possible by clinicians	232	47	6	53	0.89	(0.80-0.97)
Classified as probable by clinicians	81	19	2	21	0.91	(0.78-1.00)
Classified as possible by clinicians	151	28	4	32	0.88	(0.76-0.99)
Final study population	551	93	0	93	N/A	

Table 3.1-5: Response rates for ordered free text, HES data, and discharge letters.

	Requested for N patients	Received for N patients
Free text	959*	474 (49.4%)
HES data	176♦	176 (100%)
Discharge letters	50	35 (70%)

*FT were ordered for all patients with a recorded SJS/TEN diagnosis and an indication for available free text at any time during the study period (indicated in CPRD patient profiles).
♦HES data was ordered for all patients with a recorded SJS/TEN diagnosis who have a HES linkage (indicated in CPRD patient profiles).

Table 3.1-6: Comparison of characteristics between confirmed true, unconfirmed positively classified, confirmed false, and unconfirmed unlikely classified cases of SJS/TEN.

	Confirmed true cases of SJS/TEN (n=93)	**Unconfirmed cases of SJS/TEN classified possible/probable (n=458*)**	**Confirmed false cases of SJS/TEN (n=25)**	**Unconfirmed cases of SJS/TEN classified unlikely (n=62†)**
Mean age (years)	34.4	38.2	43.5	34.2
≤10 years	18.3%	17.7%	16.0%	23.3%
Gender (% male)	55.9%	48.9%	56.0%	42.5%
Year of first recorded SJS/TEN diagnosis				
1995-1999	13 (14.0%)	105 (22.9%)	4 (16.0%)	9 (14.5%)
2000-2004	32 (34.4%)	108 (23.6%)	9 (36.0%)	26 (41.9%)
2005-2009	28 (30.1%)	152 (33.2%)	7 (28.0%)	21 (33.9%)
After 2009	20 (21.5%)	93 (20.3%)	5 (20.0%)	6 (9.8%)
Diagnosis of EM recorded within 2 weeks before or after the first SJS/TEN diagnosis				
Total	3 (3.2%)	20 (4.4%)	4 (16.0%)	7 (11.3%)
1995-1999	-	5 (4.8%)	-	2 (22.2%)
2000-2004	2 (6.3%)	6 (5.6%)	1 (11.1%)	1 (3.9%)
2005-2009	1 (3.6%)	8 (5.3%)	1 (14.2%)	3 (14.3%)
2010 and after	-	1 (1.1%)	2 (40.0%)	1 (16.7%)

*N=All 565 patients classified as probable or possible minus 93 confirmed true and 14 confirmed false cases of SJS/TEN.
†N=All 73 patients classified as unlikely minus 11 confirmed false cases of SJS/TEN.

3.2 The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK (Study 3.2)

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3.2.1 Abstract

SJS/TEN are rare but life-threatening mucocutaneous diseases. SJS/TEN mostly manifest as a reaction to new drug use, but little is known about their incidence and epidemiology. We conducted a large observational study on the epidemiology of SJS/TEN using data from the UK-based CPRD. Among 551 validated SJS/TEN patients, we calculated an IR of 5.76 SJS/TEN cases per million py between 1995 and 2013, which was consistent throughout the study period and was highest in patients aged 1-10 years and 80 years or older. Within a 1:4 matched case-control analysis, black and Asian patients were at a 2-fold risk of SJS/TEN when compared with white patients. Among patients with epilepsy and gout, ORs for SJS/TEN were significantly increased only in the presence of recent new drug treatment with AEDs or allopurinol, respectively. We observed statistically significant associations between SJS/TEN and pre-existing depression, lupus erythematosus, recent pneumonia, chronic kidney disease (CKD), and active cancer, but confounding by drug use needs to be followed up. This large and longitudinal observational study on the epidemiology of SJS/TEN contributes to the understanding of this still underinvestigated severe skin disease in a European and largely white study population.

3.2.2 Introduction

SJS/TEN are rare but life-threatening mucocutaneous diseases that predominantly occur as adverse reactions to newly administered drugs. Several previous observational studies identified AEDs, allopurinol, and certain antibiotics (mostly sulphonamide antibiotics) as those drugs with the highest risk of SJS/TEN, although other drugs have been associated with less evidence (e.g., oxicam analgesics, sertraline [a selective serotonin reuptake inhibitor, or SSRI], coxibs).[88,89] SJS and TEN manifest with epidermal and mucosal necrosis and differ by the proportion of relative skin detachment.[83,86] Previously reported IRs of SJS/TEN range from 1.4 to 12.7 cases per million py.[42,186,195]

Large electronic databases are an important tool in epidemiologic research of rare diseases, but evidence on SJS/TEN from large observational databases is scarce. One large cross-sectional study investigated the epidemiology of SJS/TEN in the US between 2009 and 2012, using data from the Nationwide Inpatient Sample, focusing on inpatient cost, short-term mortality, and comorbidities.[42] The authors observed an overall IR of 12.7 cases/million py (adults only), which is higher than most previously reported IRs for SJS/TEN,[42] as well as increased ORs for SJS/TEN in association with non-white ethnicity, systemic lupus, epilepsy, cancer (mainly hematologic cancer), infections, and renal failure.[42] However, the non-longitudinal nature of the data precluded assessment of disease temporality and the role of outpatient drug therapies. Another large observational study based on insurance claims data from Korea (coverage of 97% of the population) calculated an IR of 5.9 SJS/TEN cases/million py between 2010 and 2013.[41]

We conducted a large longitudinal observational study to quantify IRs of SJS/TEN in a largely white European population (from the UK) using data from the population-based CPRD. In a case-control analysis we assessed the association of SJS/TEN with demographic and lifestyle factors, as well as with previously associated comorbidities, accounting for the temporality of disease occurrence and the role of recently initiated drug therapy wherever possible.

3.2.3 Patients and Methods

Data sources

This study was conducted using data from the CPRD, a large (13.3 million patients) primary care database that is representative of the UK population with regard to age and sex. Since 1987, participating GPs have recorded patient characteristics, symptoms, diagnoses, drug prescriptions, and referrals, including primary diagnoses made in secondary care.[28] High data quality has repeatedly been demonstrated, and the database has been used for numerous epidemiological studies.[29] This study was approved by the ISAC for Medicines and Healthcare products Regulatory Agency database research (ISAC protocol 14_009R). We previously validated diagnoses of SJS/TEN recorded in the CPRD that led to secondary care referral between 1995 and 2013. In short, two specialized clinicians classified all potential SJS/TEN patients with a recorded secondary care referral for which we had recorded clinical information into probable/possible or unlikely cases of SJS/TEN. Patients without recorded clinical information were classified according to pre-specified criteria. We then compared our classification against a representative subgroup of patients for whom we had unequivocal diagnoses from secondary care extracted from hospital discharge letters and HES data. We established a case population of 551 validated SJS/TEN patients, for which we calculated a PPV of 0.87. The validation and composition of our case population is described in detail elsewhere.[196]

Incidence rates

Incidence rates were calculated by dividing the number of new SJS/ TEN cases by the total number of py at risk. Person-years at risk were quantified by adding up person-time of SJS/TEN free patients in the CPRD (excluding those with non-validated SJS/TEN diagnoses) between January 1995 and the end of follow-up, which was the earliest of an SJS/TEN diagnosis (with or without subsequent secondary care referral, only counting validated cases into the numerator), death, disenrollment, or December 2013. Person time in the CPRD is representative of the UK population with regard to age and sex and reflects the demographic distribution of the population over time (Office for National Statistics UK, 2014). We further calculated IRs in categories of sex, age

(<1, 1-3, 4-6, 7-9 years, and in decades of age if ≥10 years), year of diagnosis, and season (spring ([March-May], summer [June-August], autumn [September-November], winter [December-February]).

We adjusted all IRs for false positive cases by multiplying the numerator by the previously calculated PPV (0.87) and for patients erroneously excluded because of a non-evident but true hospitalization by multiplying all patients in the numerator who did not have recorded HES data by 1.24. Based on such HES data (available for approx. 30% of CPRD patients), we previously estimated that 24% of patients with a recorded SJS/TEN diagnosis in the CPRD and no available HES data were hospitalized, although the hospitalization was not recorded.

Case-control study

For the case-control analysis, we included only those 480 validated SJS/TEN patients with at least 180 days of recorded active history in the CPRD before the index date. We randomly matched four SJS/ TEN-free control participants to each patient based on year of birth, sex, and years of active history in the CPRD.

Demographics, lifestyle factors, and comorbidities

We captured patients' age (0-19, 20-39, 40-59, 60-79, and ≥80 years), sex, body mass index (12-18.4, 18.5-24.9, 25.0-29.9, and 30.0-60.0 kg/m^2, or unknown), smoking status (non-smoker, current smoker, ex-smoker, or unknown), alcohol consumption (in units per week: none, 1-9, 10-19, ≥20, or unknown), ethnicity (white, black, Asian, mixed, or unknown), and records for alcohol or other substance abuse. We further captured whether patients had a recorded Read code for the following comorbidities before the index date: allergies (hay fever/rhinoconjunctivitis, asthma), autoimmune diseases (psoriasis, polymyalgia rheumatica, rheumatoid arthritis), diseases previously associated with SJS/TEN (lupus erythematosus, other collagen vascular diseases, pneumonia <120 days before the index date, CKD [Read code for CKD or ≥two recorded glomerular filtration rate values <60 ml/minute within 365 days, >90 days apart], and acute renal disease (last Read code <365 days before the index date). We assessed whether patients had previously been diagnosed with cancer and

subcategorized them by type of cancer (i.e., hematologic, central nervous system, breast, ovarian, bone, prostate, colon, respiratory tract, skin, uterus, pancreatic). We also subdivided all cancer patients into those with active cancer (a recorded cancer diagnosis or a record for radiotherapy, chemotherapy, or consultation with an oncologist <365 days before the index date) and those with presumably cured cancer. We further captured whether patients had a recorded Read code for diseases that are usually treated with one of the drugs associated with increased risk of SJS/TEN (i.e., epilepsy, gout, depression, or other affective disorders), and categorized patients into those with or without new drug therapy with the suspected drug within 84 days before index date (i.e., AEDs [carbamazepine, phenobarbital, phenytoin, lamotrigine, valproate], allopurinol, SSRIs). As a negative control, we identified patients who had previously been diagnosed with other common diseases not previously associated with SJS/TEN (i.e., chronic obstructive pulmonary disease, type 2 diabetes mellitus, hypertension, hyperlipidaemia, myocardial infarction).

Statistical analysis

We conducted conditional logistic regression analyses using SAS 9.4 (SAS Institute, Cary, NC) to calculate ORs with 95% CIs for the association between SJS/TEN and potential risk factors.

For all risk factors significantly associated with SJS/TEN (a-level of 0.05, i.e., lupus erythematosus, recent pneumonia, CKD, hematologic cancer), we reviewed the electronic CPRD patient records to capture patterns of clinical information or specific events that may have led to unrecorded drug intake (e.g., hospitalizations) before the index date. Small sample size precluded systematic analysis within subgroups of comorbidities. Because of confidentiality regulations, however, we are not able to share detailed patient information, and we therefore summarized some key findings observed during record review in the Results and Discussion sections.

3.2.4 Results

Among 551 previously validated SJS/TEN patients, 50.1% were male, and the mean age was 37.5 years. We calculated an overall IR of 5.76 cases/million py (95% CI = 5.31-6.30), with comparable IRs in men and women. The IRs were highest in children aged 1-10 years (7.63-8.97 cases/million py) and in elderly patients aged 80 years or older (8.75 cases/million py, 95% CI = 6.29-12.17). Although IRs remained stable across the entire duration of the study period, we observed higher IRs in winter months (7.21 cases/million py, 95% CI = 6.18-8.41; Table 3.2-1).

Lifestyle factors

We did not observe an association between SJS/TEN and smoking status, alcohol consumption, or body mass index. Black or Asian patients had 2-fold increased ORs for SJS/TEN when compared with white patients, but sample size was small because of missing information on race for 59.5% of patients and a largely white study population (93.4% of those with known ethnicity, Table 3.2-2).

Comorbidities

ORs for SJS/TEN were significantly increased in patients with epilepsy and new AED treatment for 84 days or fewer before the index date (date of the first recorded SJS/TEN diagnosis) (OR = 4.65, 95% CI = 2.67-8.10). The same was true for patients with gout and new allopurinol treatment (OR = 20.48, 95% CI = 2.39-175.19). ORs remained around unity for patients with either of those diseases in the absence of such new drug treatment. In contrast, ORs were increased in patients with depression or other affective disorders overall (OR = 1.48, 95% CI = 1.10-1.99) but not in those who initiated treatment with SSRIs 84 days or fewer before the index date (OR = 0.88, 95% CI = 0.10-7.53). We further observed significantly increased ORs for SJS/TEN in association with lupus erythematosus (cutaneous or systemic, OR = 16.00, 95% CI = 1.79-143.15), pneumonia within 120 days before the index date (OR = 1.80, 95% CI = 1.06-3.04), CKD (OR = 2.12, 95% CI = 1.14-3.96), and active cancer (OR = 2.01, 95% CI = 1.27-3.18). Subcategorization of cancer patients showed that the increased ORs were mainly driven by hematologic cancer (Table 3.3-3).

3.2.5 Discussion

In this UK-based observational study, we calculated an overall IR of 5.76 SJS/TEN cases/million py in the UK between 1995 and 2013, which is substantially lower than the IR of 12.7 SJS/TEN cases/million py among adults reported in a previous US-based observational study.[42] This discrepancy may be ascribed to greater overall drug use in the US compared with the UK.[197] A greater proportion of black or Asian patients in the US (16.8% reported) compared with the UK (4.9% in our study population) may further account for some of the observed difference. Both studies observed a 2-fold increased risk of SJS/TEN among black and Asian patients compared with white patients. Genetic variations, for instance of the allele HLA-B*1502, may explain the different susceptibility to SJS/TEN by ethnicity.[142] We recalculated our IRs (among adults only), applying the ethnic distribution observed in the US study, and observed an IR of 6.4 cases/million py. On the other hand, IRs of SJS/TEN from the prior Korea-based observational study (5.9 cases/million py, largely Asian patients) were very similar to those observed in our study.[41] Two hospital-based European observational studies previously reported IRs of 1.53 SJS/TEN cases/million py in Germany between 1990 and 1992,[186] and of 1.4 cases/million py in Italy between 2009 and 2014.[195] Methodologic, geographic, and temporal heterogeneity of the previous studies preclude an exact comparison with our results. Rigorous clinical case validation was a strength of the two hospital-based studies, whereas the strength of our CPRD-based study is that SJS/TEN cases and person-time at risk were captured from the same base population. This was not possible in hospital-based studies, where person-time at risk was extrapolated from national census statistics. Furthermore, with 76 SJS/TEN patients, the sample size in the Italian study was small.[195]

Incidence rates in our study were increased during winter months, which may be due to increased use of antibiotics in winter,[198] or to higher rates of viral infections, which has previously been discussed as an independent risk factor for SJS/TEN, although based on a small body of evidence.[42] Although IRs did not vary by sex, we observed slightly higher IRs in patients aged 1-10 years and in patients aged 80 years or older, which was also reported in the Korean study.[41] The higher incidence of epilepsy and subsequent new use of AEDs in children and elderly patients may partly explain these

observations.[199,200] Furthermore, first-time contact with antibiotics or certain viral infections is more frequent in early life, whereas polypharmacy may increase susceptibility to SJS/TEN among the elderly.[201] The IRs in children younger than 1 year have to be interpreted cautiously, because person-time was extrapolated from patients aged 1 year, because of a 30% proportion of missing person-time in this subgroup. Newborns likely do not register with a GP until after they are discharged from the care of the hospital paediatrician. GPs are generally advised to record such major disease events once a patient registers, but we cannot rule out that some SJS/TEN patients may have been missed.

Similar to other previous studies, we did not observe an association between SJS/TEN and alcohol consumption, smoking status, or body mass index. We observed increased ORs for SJS/TEN among patients with pre-existing gout or epilepsy and those who had recent new drug therapy with allopurinol or AEDs (carbamazepine, phenobarbital, phenytoin, lamotrigine, valproate), but not in the absence of such new drug treatment. These results are consistent with prior findings,[88,89] and indicate a rather complete capture of drug prescriptions among patients with epilepsy and gout in the CPRD. The observed small increase in risk of SJS/TEN in patients with a recorded diagnosis of depression or affective disorder was not present in the subset of patients with newly initiated SSRI treatment. Sertraline was previously associated with SJS/TEN,[89] but it was used by one patient out of four who were newly exposed to SSRIs 84 days or fewer before the index date among SJS/TEN patients in our study population. Sertraline was the fourth most frequently used SSRI in the UK in 2003 after fluoxetine, citalopram, and paroxetine,[202] and this study is likely underpowered to detect a potential association of SJS/TEN with sertraline. The observed association between SJS/TEN and depression/affective disorder in the absence of new-onset SSRI treatment may reflect confounding by polymorbidity or increased use of certain drugs that have not previously been strongly associated with SJS/TEN.

Patients with a pneumonia diagnosis within 120 days before the index date had an increased risk of SJS/TEN, which most likely reflects exposure to antibiotics.[88,89] All patients with recent pneumonia either had a recorded outpatient prescription for an antibiotic or a recorded hospitalization, which likely involved intravenous antibiotic

treatment. However, pneumonia might also be associated with SJS/TEN via viral infections.[42] Furthermore, a previous systematic review including 202 SJS/TEN patients with pneumonia suggested that Mycoplasma pneumoniae-associated mucocutaneous disease may be misdiagnosed as SJS/TEN in some patients.[203]

We observed a 16-fold increased risk of SJS/TEN among patients with lupus erythematosus, an association which has been reported repeatedly.[204] However, lupus erythematosus can manifest with bullous exanthema and epidermal necrosis, and we cannot rule out misclassification of SJS/TEN in some patients.[205] All SJS/TEN patients with lupus erythematosus were female, and 50% of patients initiated therapy with a drug known to increase the risk of SJS/TEN within 3 months before the index date (carbamazepine, sulphonamide antibiotics). Furthermore, all patients received their first lupus diagnosis at least 1 year before the index date and were receiving ongoing oral prednisolone treatment, which they had initiated between 5 months and 37 years before the index date. Corticosteroids have previously been considered as potential triggers of SJS/TEN, but given the previous duration of prednisolone treatment they were likely not the cause of SJS/TEN in this subgroup of lupus patients.[88,89] No association was found between other collagen vascular diseases and SJS/TEN.

The increased risk of SJS/TEN in patients with CKD was also reported in the US-based study.[42] A review of patient records from our study population showed that 11 of 17 SJS/TEN patients with CKD also had a recorded first-time prescription for a high-risk drug within 3 months before SJS/TEN diagnosis (allopurinol, coxibs, SSRI, penicillin, sulphonamide antibiotic), which suggests that CKD is a proxy for polymorbidity and polypharmacy rather than an independent risk factor of SJS/TEN.

The significantly increased risk of SJS/TEN among patients with active cancer is consistent with results from the US-based study and was mainly driven by patients with hematologic malignancies in both studies.[42] Numerous case reports have suggested different chemotherapeutic agents as causes of SJS/TEN,[135–137,206–208] but actual causation has not been established. Like CKD patients, cancer patients are usually exposed to a broad range of drugs, often including AEDs for pain management,[209] and allopurinol for the prevention of tumor lysis syndrome after a cycle of chemotherapy.[210]

However, in contrast to CKD patients, cancer patients are usually treated at specialized oncology clinics and see their GPs less frequently. Electronic record review showed little clinical information, except that almost all patients had recorded referrals to oncology clinics or hospital stays.

Despite several strengths of this large population-based observational study, some limitations must be considered. First, although we extensively validated our case population and adjusted IRs for type 1 error, some misclassification among SJS/TEN patients is more likely to be present among our study population than in previous hospital-based studies in which researchers had access to more clinical patient records, such as the EuroSCAR study.[89] Differentiation between EMM and SJS/TEN is difficult, and we have to assume that some misclassified EMM patients are included in our study population, which may introduce a slight null bias and somewhat overestimated IRs.[211] Second, we observed decreased ORs for SJS/TEN among patients with missing information on lifestyle factors. SJS/TEN often occurs in patients who are treated with potential culprit drugs for an underlying chronic disease. Patients with chronic diseases see a GP more frequently and thus may have a more complete CPRD history (information bias). However, we did not observe increased ORs for patients with chronic diseases, which have previously not been associated with SJS/TEN (e.g., type 2 diabetes, hypertension). This null result among the negative control patients suggests that such potential information bias does not play a major role. Third, the CPRD does not record over-the-counter or inpatient drug use, such as chemotherapy or inpatient antibiotic use, which is why we were not able to assess the role of specific drugs in the observed association between SJS/TEN and active cancer or pneumonia. We were also not able to assess the association between SJS/TEN and HIV, because HIV is usually treated in specialized clinics in the UK. Fourth, we were not in the position to quantify valid IRs for SJS and TEN separately because we could not validate the two disease entities separately, given that neither the Read code system nor HES data coding include a code for SJS/TEN overlap syndrome. Fifth, given the rare occurrence of SJS/TEN, low statistical power is an inherent problem of studies analysing risk factors of this disease, even when using large data sources such as electronic databases. Therefore, results have to be interpreted carefully, within the context of previously published evidence and

biologic plausibility, and conclusions should not be drawn from one single study. Finally, in-depth analyses of the association between all potentially triggering drugs and the risk of SJS/TEN exceed the scope of this epidemiological study and will be followed up in future studies. We did not present adjusted ORs because the numbers of exposed patients were low in most categories and because of potentially unrecorded confounders (ethnicity, inpatient drugs). However, we accounted for potential confounders by performing patient record reviews and subgroup stratification wherever possible.

In summary, in this large population-based observational study, we analysed the epidemiology of SJS/TEN in a European and largely white population using a large and longitudinal database. Our results confirm that SJS/TEN is a rare disease, with IRs being highest in children aged 1-10 years and in patients aged 80 years or older. We further observed that black or Asian patients were at increased risk of SJS/TEN and report associations between SJS/TEN and epilepsy or gout in the presence of new drug therapy with AEDs or allopurinol, respectively. Risk estimates for SJS/TEN were increased among patients with depression, lupus erythematosus, recent pneumonia, CKD, or active cancer (mainly hematologic malignancies), but the role of acute triggers, such as drug exposure, within these associations remains to be followed up.

Table 3.2-1: Incidence rates of SJS/TEN in the CPRD.

	Number of person-years at risk	**Number of SJS/TEN cases**	**Incidence rate* (95% confidence interval)**

Overall	91,128,351	551	5.76 (5.31-6.30)
By Sex			
Men	43,865,640	277	6.07 (5.38-6.85)
Women	47,262,711	274	5.51 (4.88-6.22)
By age			
<1	1,076,385†	5	4.82 (2.04-11.39)
1-3	3,297,232	27	7.69 (5.21-11.35
4-6	3,324,133	27	7.63 (5.17-11.26)
7-9	3,332,842	31	8.97 (6.27-12.84)
10-19	11,699,687	80	6.66 (5.34-8.32)
20-29	12,061,859	61	4.82 (3.72-6.23)
30-39	13,111,956	81	5.87 (4.69-7.34)
40-49	12,699,991	63	4.65 (3.60-6.00)
50-59	11,145,453	48	4.18 (3.14-5.57)
60-69	9,041,774	49	5.25 (3.95-6.97)
70-79	6,615,097	43	6.00 (4.40-8.20)
≥80	4,034,375	36	8.75 (6.29-12.17)
By year of diagnosis			
1995-1999	21,434,665	120	5.41 (4.51-6.49)
2000-2004	25,726,652	138	5.09 (4.29-6.04)
2005-2009	26,755,978	182	6.46 (5.57-7.50)
2010-2013	17,236,298	111	6.21 (5.14-7.50)
By season			
Spring	23,110,659	138	5.69 (4.80-6.75)
Summer	23,017,075	140	5.85 (4.95-6.93)
Autumn	22,514,328	105	4.37 (3.59-5.33)
Winter	22,486,288	168	7.21 (6.18-8.41)

*In SJS/TEN cases per million person-years

†Person-time was extrapolated from patients aged 1 year due to missing values.

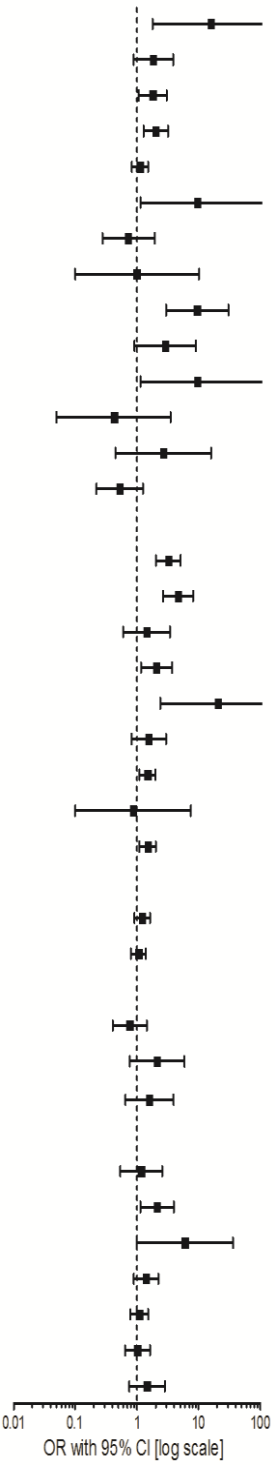
Table 3.2-2: Demographics and life-style factors of SJS/TEN cases and controls within the CPRD.

	Number of cases (%) (n=480)	**Number of controls (%) (n=1920)**	**OR crude (95% CI)**

Age (years)						
0-19	146	(30.4)	584	(30.4)	NA	
20-39	114	(23.8)	457	(23.8)	NA	
40-59	102	(21.3)	402	(21.0)	NA	
60-79	87	(18.1)	354	(18.4)	NA	
≥80	31	(6.5)	123	(6.4)	NA	
Sex						
Male	232	(48.3)	928	(48.3)	NA	
Female	248	(51.7)	992	(51.7)	NA	
BMI (kg m^{-2})						
12.0-18.4	10	(2.1)	27	(1.4)	1.43	(0.67-3.06)
18.5-24.9	114	(23.8)	441	(23.0)	1.00	(reference)
25.0-29.9	102	(21.3)	390	(20.3)	1.01	(0.74-1.37)
30.0-60.0	54	(11.3)	233	(12.1)	0.90	(0.62-1.30)
Unknown	200	(41.7)	829	(43.2)	0.84	(0.58-1.22)
By ethnicity						
Caucasian	211	(44.0)	697	(36.3)	1.00	(reference)
Black	9	(1.9)	16	(0.8)	2.20	(0.89-5.44)
Asian	8	(1.7)	15	(0.8)	2.09	(0.85-5.12)
Mixed	6	(1.2)	10	(0.5)	2.06	(0.73-5.79)
Unknown	246	(51.3)	1182	(61.6)	0.49	(0.37-0.65)
Smoking status						
Non	191	(39.8)	706	(36.8)	1.00	(reference)
Current	80	(16.7)	292	(15.2)	1.02	(0.75-1.39)
Ex	67	(14.0)	300	(15.6)	0.83	(0.59–1.15)
Unknown	142	(29.6)	622	(32.4)	0.66	(0.44–0.98)
Non-abusive alcohol consumption (units per week)						
None/Ex	111	(23.1)	410	(21.4)	1.00	(reference)
1-9	115	(24.0)	466	(24.3)	0.99	(0.74-1.34)
10-19	29	(6.0)	117	(6.1)	1.00	(0.63-1.61)
≥20 (but no explicit record of abuse)	25	(5.2)	89	(4.6)	1.15	(0.69-1.92)
Unknown	200	(41.7)	838	(43.7)	0.78	(0.54-1.12)
Alcoholism or other substance abuse						
No	459	(95.6)	1853	(96.5)	1.00	(ref)
Yes	21	(4.4)	67	(3.5)	1.29	(0.77-2.17)

Table 3.2-3: Comorbidities of SJS/TEN cases and controls in the CPRD.

	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		Odds ratio
Diseases previously associated with SJS/TEN					
Lupus erythematosus	<5	(<1.0)	<5	(<0.3)	16.00
Other collagen vascular disease	11	(2.3)	25	(1.3)	1.83
Pneumonia diagnosed <120 days prior	<5	(<1.0)	<5	(<0.3)	1.80
Active cancer*	29	(6.0)	61	(3.2)	2.01
Non-active cancer┼	79	(16.5)	303	(15.8)	1.12
Bone cancer	<5	(<1.0)	<5	(<0.3)	9.66
Breast cancer	5	(1.0)	27	(1.4)	0.73
Colon cancer	<5	(<1.0)	<5	(<0.3)	1.00
Hematologic cancer	10	(2.1)	5	(0.3)	9.46
Cancer of the nervous system	5	(1.0)	7	(0.4)	2.86
Ovarian cancer	<5	(<1.0)	<5	(<0.3)	9.66
Prostate cancer	<5	(<1.0)	9	(0.5)	0.43
Cancer of the respiratory tract	<5	(<1.0)	<5	(<0.3)	2.67
Skin cancer	7	(1.5)	48	(2.5)	0.53
Diseases usually treated with high risk drug for SJS/TEN					
Epilepsy	35	(7.3)	47	(2.5)	3.22
New use of antiepileptic drug ≤84 days	28	(5.8)	26	(1.4)	4.65
No new use of antiepileptic drug ≤84 days	7	(1.5)	21	(1.1)	1.44
Gout	20	(4.2)	43	(2.2)	2.08
New use of allopurinol ≤84 days	5	(1.0)	<5	(<0.3)	20.48
No new use of allopurinol ≤84 days	15	(3.1)	42	(2.2)	1.55
Depression and other affective disorders	80	(16.7)	240	(12.5)	1.48
New use of SSRI ≤84 days	<5	(<1.0)	5	(0.3)	0.88
No new use of SSRI ≤84 days	79	(6.4)	235	(12.2)	1.49
Allergies					
Hay fever / Allergic rhinoconjunctivitis	77	(16.0)	266	(13.9)	1.21
Asthma	83	(17.3)	318	(16.6)	1.06
Autoimmune diseases					
Psoriasis	12	(2.5)	62	(3.2)	0.77
Polymyalgia rheumatic	6	(1.3)	12	(0.6)	2.11
Rheumatoid arthritis	7	(1.5)	18	(0.9)	1.59
Other common diseases					
COPD	9	(1.9)	31	(1.6)	1.18
Chronic kidney disease	17	(3.5)	35	(1.8)	2.12
Acute kidney disease (<365 days)	<5	(<1.0)	<5	(<0.3)	6.00
Diabetes mellitus type 2	28	(5.8)	83	(4.3)	1.40
Hypertension	77	(16.0)	294	(15.3)	1.09
Hyperlipidemia	29	(6.0)	110	(5.0)	1.02
Myocardial infarction	13	(2.7)	37	(1.9)	1.45



COPD=chronic obstructive pulmonary disease.
*Last cancer related record <1 year prior
┼ Last cancer related record ≥1 year prior

3.3 The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs (Study 3.3)

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3.3.1 Abstract

Objective: Older AEDs are known to cause SJS/TEN. However, evidence for newer AED is sparse. We quantified risks of SJS/TEN in association with use of all AEDs in the United Kingdom (UK).

Methods: In a matched case-control study of 480 previously validated SJS/TEN cases (1995–2013) we used conditional logistic regression to calculate ORs with 95% CIs, and calculated absolute risks of SJS/TEN within separate cohorts of new users of 28 AEDs. We assessed causality between drugs and SJS/TEN in each exposed case, using an adapted version of the ALDEN score.

Results: We observed a strong association between SJS/TEN and new use of carbamazepine (OR 92.57, 95% CI 19.89–∞), phenytoin (OR 49.96, 95% CI 10.13–∞), and lamotrigine (OR 26.90, 95% CI 4.88–∞), where causality, according to the ALDEN score, was very probable or probable for most exposed cases. Absolute risks for SJS/TEN were highest for phenytoin (45.86 cases/100,000 exposed), lamotrigine (44.17 cases/100,000 exposed), and carbamazepine (20.38 cases/100,000 exposed). Despite increased ORs for valproate (40,941 exposed), gabapentin (116,037 exposed), pregabalin (59,967 exposed), and clobazam (4,300 exposed), ALDEN suggested no causal association. There were no observed cases of SJS/TEN among new users of levetiracetam (n = 9677), clonazepam (n = 18,075), or topiramate (n = 11,307).

Significance: The results of our study are consistent with those of previous studies of SJS/TEN, which found increased risks of SJS/TEN in new use of carbamazepine, phenytoin, and lamotrigine. Despite frequent use, no ALDEN-score confirmed cases were observed in new users of valproate, gabapentin, pregabalin, levetiracetam, topiramate, or clonazepam.

3.3.2 Introduction

SJS/TEN are rare but life-threatening mucocutaneous diseases, characterized by epidermal and mucosal necrosis. The two conditions are considered one disease entity, which differ by the proportion of BSA affected by skin detachment, with TEN being the more severe. SJS/TEN is predominantly an adverse reaction to newly administered drugs, and is associated with 1–9% mortality in SJS and 30–50% mortality in TEN.[83,86] In the absence of a generally accepted pharmacotherapy, early identification and discontinuation of the culprit drug is a key measure.[83,86,194] Two previous relatively large (n = 245 and 513 SJS/TEN cases) hospital-based case-control studies identified AEDs as the alleged triggers of 25% of all hospitalized SJS/TEN cases.[88,89,212] Between 1989 and 1994, Roujeau et al. and Rzany et al. reported strongly increased ORs for SJS/TEN in patients newly exposed (≤56 days) to carbamazepine, phenytoin, or phenobarbital in France, Germany, Italy, and Portugal.[88,212] The more recently published EuroSCAR study conducted by Mockenhaupt et al. (a case-control study based in six European countries between 1997 and 2001) confirmed these findings and further observed a significantly increased risk of SJS/TEN after new exposure (≤56 days) to lamotrigine, a drug that became available between 1993 and 1994.[89] An association between SJS/TEN and valproate has been reported, but causality remains unconfirmed due to small sample size and frequent co-medication with other potentially causal drugs.[88,212,213] Case reports describe cases of SJS/TEN after exposure to gabapentin, clobazam, and zonisamide,[106,121,124,214] but evidence on the potential association between SJS/TEN and AEDs other than carbamazepine, phenytoin, and phenobarbital is sparse, especially for drugs that have become available more recently.

We analyzed the relative and absolute risk of SJS/TEN in association with new use of AED within one of the largest validated SJS/TEN study populations using data from the UK-based CPRD.[196]

3.3.3 Patients and Methods

Data source

The CPRD is a large (13.3 million patient) anonymized primary care database that is representative of the UK population with regard to age and sex. Since 1987, participating GPs have recorded information on patient demographics and characteristics, symptoms, diagnoses, laboratory test results, and referrals to consultants and secondary care. Drug prescriptions are issued electronically by the GP, and the CPRD thus holds a virtually complete outpatient drug prescription history.[28] The data in the CPRD have been repeatedly demonstrated to be of high quality, and have been used for numerous epidemiologic studies published in peer-reviewed journals.[29] This study was approved by the ISAC for MHRA database research (ISAC protocol 14_009R).

Study population

Case patients

We previously validated diagnoses of referred SJS/TEN cases recorded in the CPRD between 1995 and 2013, where we established a population of 551 validated SJS/TEN cases. The PPV for SJS/TEN diagnoses in the CPRD was 0.87. The validation process is described in detail elsewhere.[196] In short, two specialized clinicians classified all potential referred cases of SJS/TEN into probable/possible or unlikely cases according to prespecified criteria using available clinical details in the CPRD patient record. We then compared our classification against a representative sample of patients for whom we had unequivocal diagnoses extracted from hospital discharge letters and HES data. Of the validated 551 cases, we included 480 patients who had ≥180 days of recorded active history in the CPRD prior to the index date. The index date was defined as the date of the first recorded SJS/TEN diagnosis (n = 238), or the date of the first recorded SJS/TEN-related symptom where available (e.g., sore throat symptom, rash, pain in eye) prior to the first recorded SJS/TEN diagnosis (n = 242).

Control patients

For each case, we randomly identified four control patients with no READ-code for SJS or TEN at any time, matched to cases on year of birth, sex, general practice, and years of recorded history prior to the index date. The index date for each control was the index date of the matched case. Control patients were required to have a recorded GP visit ≤30 days prior to or after the index date.

Exposure

We defined drug exposure as a first recorded prescription for an AED ≤84 days prior to the index date. We chose ≤84 days rather than ≤56 days (EuroSCAR study),[89] because the date of the first SJS/TEN record in the CPRD may not reflect the exact date of disease onset in every case (potential delay between patient presentation to emergency care and notification to the GP). We captured prescriptions for all AEDs that were on the market between 1995 and 2013 in the UK (Table 3.3-1).

Statistical analysis

Case-control

We conducted conditional logistic regression analyses using SAS statistical software version 9.4 (SAS Institute, Cary, NC, U.S.A.), and calculated ORs with 95% CIs. Where there were no exposed cases/controls, we used exact methods to estimate the ORs and 95% CIs.

Because of the small number of exposed patients in each drug class, we did not perform multivariable adjustment, but presented concomitant new use of at least one other high-risk drug within 84 days before the index date (Table 3.3-2).

Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included fewer than five patients.

ALDEN

The ALDEN score was developed in 2009 within the scope of the EuroSCAR study to assess drug causality for epidermal necrolysis,[20] by systematically grading potential causality between drug exposure and adverse epidermal necrolysis (very probable, probable, possible, unlikely, or very unlikely) in affected patients. Because the score

was developed for an inpatient setting, where more clinical information is available than in a study based on electronic databases, we assessed an adapted version of the ALDEN score for each case exposed to an AED ≤84 days prior to the index date, excluding information that is not available in the CPRD (Table 3.3-3).

Cohort studies to quantify absolute risks

We established 28 individual cohorts of new users of 28 AED. Patients were eligible if they had ≥180 days of active history in the CPRD prior to the first prescription, and ≥84 days of completed follow-up after the recorded first-time prescription in the database to allow for quantification of the absolute risk (cumulative incidence) in a population with complete follow-up. We excluded patients with any prior recorded diagnosis of SJS/TEN. We quantified absolute risks as the number of incident SJS/TEN diagnoses during follow-up, divided by the total number of new users of the same drug between 1995 and 2013. In a sensitivity analysis, we quantified absolute risks of SJS/TEN restricted to those exposed cases for which we assessed a very probable or probable ALDEN score for the respective drug.

Computer record review to assess reexposure to AED after SJS/TEN

We reviewed patient records of all SJS/TEN cases after initiation of a high-risk AED (significantly associated in the case control analysis) within ≤84 days prior to disease onset, to anecdotally capture AED use after the SJS/TEN diagnosis.

3.3.4 Results

Our case-control study population included 480 SJS/TEN cases and 1,920 controls, of whom 51.7% were women. The mean age at the index date was 38.5 years (±25.2). Of the 480 cases, 36 (7.5%) evidently started treatment with an AED within ≤84 days prior to the index date.

Case-control study

Table 3.3-2 presents the association between new use of AED and incident SJS/TEN in the case-control analysis. We observed substantially increased ORs for carbamazepine (OR 92.27, 95% CI 16.83–∞), lamotrigine (OR 49.96, 95% CI 10.13–∞), phenytoin (OR 26.90, 95% CI 4.88–∞), and valproate (OR 10.51, 95% CI 1.25–∞). The ALDEN score was very probable or probable for 87.5% of cases newly exposed to carbamazepine, 88.9% for lamotrigine, and 100% for phenytoin, whereas causality for valproate was possible according to ALDEN for all newly exposed cases (Figure 3.3-1; ALDEN score for cases newly exposed to an AED ≤84 days prior to the index date), mainly because the timing of first exposure was >28 or <5 days before the index date. We observed increased ORs for the association between SJS/ TEN and gabapentin (OR 6.35, 95% CI 1.06–38.22), pregabalin (OR 4.00, 95% CI 0.21–∞), and clobazam (OR 4.00, 95% CI 0.21–∞; Table 3.3-2), although statistically nonsignificant for pregabalin and clobazam; ALDEN-based causality was very unlikely, unlikely, or possible for all cases newly exposed to either of these drugs (Figure 3.3-1). This likely non-causality was due mainly to concomitant new exposure to other high-risk drugs and to the timing of first-time exposure. We did not identify any cases of SJS/TEN in association with new use of phenobarbital (Table 3.3-2), or with new use of primidone, ethosuximide, mesuximide, clonazepam, rufinamide, eslicarbazepine, oxcarbazepine, vigabatrin, tiagabine, sultiame, felbamate, topiramate, zonisamide, stiripentol, lacosamide, retigabine, perampanel, or beclamide (Table 3.3-4).

Cohort study

Within 28 individual cohorts of new AED users, we quantified the highest absolute risk of SJS/TEN for phenytoin (cumulative incidence of 45.86 cases/100,000 new users), followed by 44.17 cases/100,000 new users of lamotrigine and 20.38 cases/100,000 new users of carbamazepine (all cases were very probable or probable according to ALDEN; Table 3.3-5). We identified a total of 40,941 new users of valproate, 116,037 new users of gabapentin, 59,967 new users of pregabalin, and 4,300 new users of clobazam, which resulted in 0.27–4.89 cases/100,000 new users for valproate, gabapentin, and pregabalin. However, we only observed cases with very probable or probable (ALDEN scored) for phenytoin, lamotrigine and carbamazepine (Table 3.3-5). We did not observe any cases

of SJS/TEN among 18,075 new users of clonazepam, 11,307 new users of topiramate, or 9,677 new users of levetiracetam. We identified <5,000 new users and no cases of SJS/TEN in users of all other AEDs (Table 3.3-6).

3.3.5 Discussion

The results of this population-based observational study revealed a strong association between SJS/TEN and carbamazepine, lamotrigine, and phenytoin, with the highest absolute risk among new users of lamotrigine and phenytoin (both approximately 45 cases/100,000 new users), followed by carbamazepine (20 cases/100,000 new users). Despite similar numbers of new users of levetiracetam, topiramate, and clonazepam during the study period, we did not identify any cases of SJS/TEN among new users of these drugs. Despite increased ORs for valproate, gabapentin, pregabalin, and clobazam, cases did not meet the criteria for a causal association defined in ALDEN.

Two previous well-conducted hospital-based case-control studies reported increased risks of SJS/TEN in new users of aromatic AED (phenobarbital, phenytoin, and carbamazepine),[88,89,212] whereas a strong association between SJS/TEN and new lamotrigine use, also an aromatic AED, was reported in only the more recent EuroSCAR study, given that the drug has only been available in the UK since 1993.[89] Our results confirm these substantially increased risks of SJS/TEN among users of carbamazepine, phenytoin, and lamotrigine with very probable or probable ALDEN scores. Mockenhaupt et al. calculated a higher absolute risk of SJS/TEN in association with new use of phenytoin (83 cases/100,000 new users), but slightly lower in association with lamotrigine (25 cases/100,000 new users) and carbamazepine (14 cases/100,000 new users) when compared to our study.[191] However, given the registry nature of the data source (Registry of Serious Cutaneous reactions), they had to extrapolate the number of new users of AEDs in Germany based on the annual growth of daily doses dispensed, whereas in our study, new drug use and SJS/TEN cases were identified from the same base population. Exposure to phenobarbital, which was identified previously as one of the most common triggers of SJS/TEN, was low in our study (963 new users) due to decline in use since the 1980s. Previous evidence of a potential association between SJS/TEN and the nonaromatic AED valproate is equivocal. Roujeau et al. reported a

strongly increased risk in 10 cases exposed to valproate, but did not assess concomitant drug use,[88] whereas the EuroSCAR study observed no significant risk for SJS/TEN based on two cases newly exposed to valproate.[89] We observed a tenfold increased risk of SJS/TEN in fewer than five cases newly exposed to valproate, all of whom scored only as possible causal cases in ALDEN, mainly due to the timing of the first recorded prescription (>56 days prior to the index date). All cases newly exposed to valproate had diagnoses of brain tumors recorded shortly before the index date, and were likely treated in secondary care, and thus may have received unrecorded drugs or procedures/therapies.[215] Among AEDs that have not been associated with SJS/TEN in previous analytic studies (gabapentin, clobazam, and zonisamide were associated with SJS/TEN in case reports),[106,121,124,214] we observed increased ORs in new users of gabapentin, pregabalin, and clobazam, but ALDEN did not support causal associations. We observed <5 cases among a relatively high number of new users of drug gabapentin (116,037) and pregabalin (59,967), which were likely used at lower doses for the treatment of neuropathic pain in most cases. The ALDEN score for the 5 cases newly exposed to pregabalin and gabapentin further suggested no causality based on the timing of first exposure (>56 days prior to the index date) in 75%, and a concomitant lamotrigine prescription in the remaining 25%. All cases newly exposed to clobazam were concomitantly prescribed another high-risk AED, resulting in a "very unlikely" causality score in all cases (Table1, Figure 1).

There were no cases of SJS/TEN among new users of levetiracetam (9,677), topiramate (11,307), and clonazepam (18,075) where the number of new users was similar to that of phenytoin (10,902) and lamotrigine (18,112). For all other AEDs, we identified <3,000 new users during the study period, and thus information on the risk of SJS/TEN was limited.

It remains to be explained why many AEDs are among the most frequently reported triggers of SJS/TEN. Carbamazepine, lamotrigine, phenobarbital, and phenytoin are all metabolized to arene oxide metabolites, which have been hypothesized to cause these adverse reactions.[216] Valproate, gabapentin, and pregabalin are neither aromatic nor are they metabolized to arene oxides, which may explain a likely non-causal association between SJS/TEN and these drugs.

Computer record review revealed that cases who were newly exposed to phenytoin prior to the index date and who did not die or leave the practice shortly after the SJS/TEN diagnosis (60% of exposed cases), were exclusively treated with valproate thereafter. Levetiracetam was used to substitute lamotrigine in SJS/TEN survivors (44.4% of all exposed cases), whereas valproate, phenytoin, and carbamazepine were each prescribed in 11% of exposed cases, of whom none were diagnosed with a second SJS/TEN during the available follow-up. Of all SJS/TEN cases newly exposed to carbamazepine, 50% did not have a recorded diagnosis for epilepsy or seizure prior to or after the index date, and were likely treated for neurologic disorders, such as trigeminal neuralgia. Of the 50% of carbamazepine users with an epilepsy diagnosis, 37.5% were treated with valproate after the SJS/TEN diagnosis, 25% with lamotrigine, and 12.5% with phenytoin. Neither of these cases had a second SJS/TEN recorded in their patient records after the index date. Thus our results suggest that a number of newer AEDs (levetiracetam, topiramate, clonazepam, and so on) are likely a safer alternative for antiepileptic therapy in patients with previous SJS/TEN, but further data are required to confirm these results. Although an aromatic AED was apparently substituted with a different aromatic AED in six cases, we cannot conclude from a retrospective database study that such an approach is safe.

Despite several strengths of this large population-based observational study, some limitations must be considered. First, despite extensive validation of our case population, some misclassification of SJS/TEN cases cannot be ruled out. Misclassification was less likely to occur in the two previous hospital-based case-control studies due to the available in-depth clinical information.[88,89] In this database study, the well-known risk of SJS/TEN risk in association with AED may lead physician to overdiagnose SJS/TEN in AED users, which may have led to the inclusion of some false-positive cases, and thus to slightly overestimated ORs. However, our results were similar to prior results, which provides confidence in the validity of our cases.[217] Second, the proportion of cases who were recently exposed to AEDs was lower in our study (7.5%) than in the two previous studies (both 25%), which may partially be explained by the use of different AEDs over time and by the decreasing use of phenobarbital. However, it is also possible that we missed some AED exposures, given that over the

counter medication, in-hospital medication, and first-time prescriptions that are issued by specialists are not captured in the CPRD. In addition to underestimated ORs, this limitation could also have affected the assessment of concomitant use of other high-risk drugs for ALDEN in some cases. However, in a previous study based in the same study population, we observed increased risk of SJS/TEN only among patients with a diagnosis of epilepsy as well as a recent new prescription (≤84 days) of an AED, but not in epilepsy patients in the absence of such a prescription, suggesting that bias due to unobserved AED treatment is low in our study popyulation.[217] Third, because ALDEN automatically grades causality higher for drugs with previous evidence for an association with SJS/TEN, the assessed likelihood for a causal association could potentially be underestimated for newer AEDs that have not previously been associated with SJS/TEN. However, the criterion of causal attribution (existing evidence on a potential association between a drug and SJS/TEN; Table 3) was not the decisive factor to classify probability of causality in most of the assessed cases. Finally, due to very low numbers of use of oxcarbazepine and eslicarbazepine in the UK, we were not able to assess these drugs. Especially oxcarbazepine is extensively used as monotherapy and add-on therapy for focal epilepsy in the US and continental Europe, most particularly in cases of epilepsy of frontal and temporal origin.[218,219] Both compounds have been associated with various cutaneous adverse skin reactions.[220]

In summary, this population-based case-control study observed associations between SJS/TEN and new use of carbamazepine, lamotrigine, and phenytoin, with the highest absolute risk among users of phenytoin and lamotrigine. Despite a substantial number of users of levetiracetam, clonazepam, and topiramate, we did not identify any cases of SJS/TEN exposed to one of these drugs. This provides reassurance that these newer AEDs are not strongly associated with SJS/TEN.

Table 3.3-1: Antiepileptic drugs that were on the market between 1995 and 2013 in the UK.

Antiepileptic drugs of interest			
Carbamazepines	Clobazam	Levetiracetam	Rufinamide
Lamotrigine	Beclamide	Mesuximide	Stiripentol
Phenytoin	Clonazepam	Oxcarbazepine	Sultiame

Phenobarbital	Eslicarbazepine	Perampanel	Tiagabine
Valproate	Ethosuximide	Phenobarbital	Topiramate
Gabapentin	Felbamate	Primidone	Vigabatrin
Pregabalin	Lacosamide	Retigabine	Zonisamide

Table 3.3-2: Relative risk for SJS/TEN in patients with new antiepileptic drug treatment.

Antiepileptic drug	Number of cases (%) (n=480)	Number of controls (%) (n=1920)	OR crude (95% CI)	Cases (%) exposed to HRD
Previously associated antiepileptics:				
Carbamazepine				

≤84 days prior to the index date	16	(3.3)	0	(0.0)	92.57	(19.89-∞)	6.3%
>84 days prior to the index date	16	(3.3)	27	(1.4)	2.72	(1.39-5.30)	
Lamotrigine							
≤84 days prior to the index date	9	(1.9)	0	(0.0)	49.96	(10.13-∞)	9.1%
>84 days prior to the index date	5	(1.0)	5	(0.3)	4.00	(1.16-13.82)	
Phenytoin							
≤84 days prior to the index date	5	(1.0)	0	(0.0)	26.90	(4.88-∞)	20.0%
>84 days prior to the index date	7	(1.5)	7	(0.4)	4.36	(1.45-13.07)	
Valproate							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	10.61	(1.26-∞)	0.0%
>84 days prior to the index date	9	(1.9)	21	(1.1)	1.90	(0.86-4.19)	
Phenobarbital							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0
>84 days prior to the index date	<5	(<1.0)	<5	(<0.3)	2.00	(0.18-22.06)	
Previously not associated antiepileptics:							
Gabapentin							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.3)	6.35	(1.06-38.22)	33.3%
>84 days prior to the index date	7	(1.5)	19	(1.0)	1.61	(0.65-3.98)	
Pregabalin							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	0.0%
>84 days prior to the index date	<5	(<1.0)	10	(0.5)	0.40	(0.05-3.13)	
Clobazam							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	100%
>84 days prior to the index date	<5	(<1.0)	<5	(<0.3)	4.00	(0.56-28.40)	

OR=Odds ratio, CI=confidence interval, HRD=high-risk drugs.
HRD include: anti-infective sulfonamides, carbamazepine, allopurinol, phenytoin, lamotrigine, phenobarbital, nevirapine, and oxicam analgesics.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

Table 3.3-3: ALDEN score adapted to the information available in the CPRD.

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of SJS/TEN (index date)	Suggestive +3	5-28 days	-3 to +3
	Compatible +2	29-56 days	

	Likely +1 Unlikely -1 Excluded -3	1-4 days >56 days Drug started on or after the onset of SJS/TEN	
Drug present in the body on date of onset of SJS/TEN (index date)*	Likely 0 Doubtful -1 Excluded -3	Number of prescribed tablets and dose instructions suggest intake of drug up until the date of onset of SJS/TEN Number of prescribed tablets and dose instructions suggest intake of drug until 1-5 days prior the date of onset of SJS/TEN Number of prescribed tablets and dose instructions suggest intake of drug until >5 days prior the date of onset of SJS/TEN	-3 to 0
Rechallenge[†]	Positive specific for disease and drug +4 Positive specific for disease and drug +2 Positive unspecific +1 Negative -2	SJS/TEN after use of same drug SJS/TEN after use of similar drug[ǂ] or other reaction with same drug Other reaction after use of similar drug[ǂ] Re-exposure to same drug without any reaction	-2 to +4
Dechallenge	Neutral 0 Negative -2	Drug stopped Drug continued without harm	-2 to 0
Type of drug (notoriety)ⵏ	Strongly associated +3 Associated +2 Suspected +1 Unknown 0 Not suspected -1	Drug of high-risk according to previous case-control studies Drug with definite but lower risk according to previous case-control studies Previous case reports, ambiguous epidemiologic results Drugs with no reports or data from epidemiologic studies No evidence of an association in previous epidemiologic studies with sufficient number of exposed patients	-1 to +3
Other cause	Possible -1	Rank all drugs from highest to lowest intermediate score If at least one has an intermediate score of >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	≤0

* In the original ALDEN score, this criterion is assessed by taking into account the elimination half-life of each drug. Because the CPRD data does not allow determining the exact date that a patient was exposed to a tablet and because dose instructions are not available for all prescriptions we had to adjust this criterion.

[†] In the original ALDEN score, potential prechallenge to the suspected drug was also determined. Because we only included first-time prescriptions recorded ≤84 days prior to the index to assess potential culprit drugs, we did not need to assess potential prechallenge.

[ǂ] Same ATC code up to the forth level.

ⵏ Based on the EuroSCAR study, the case-control study by Roujeau et al., and previously published case reports.

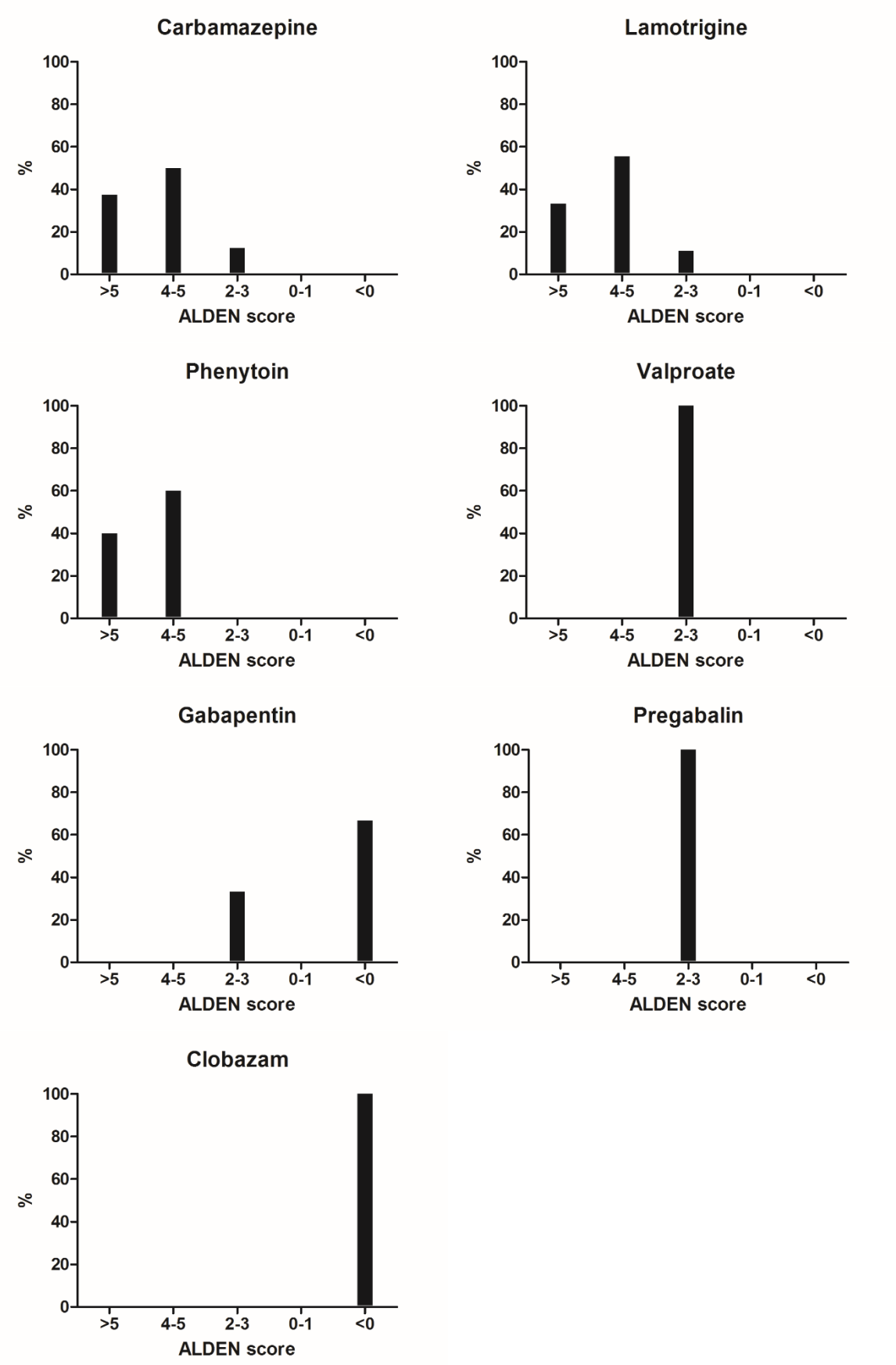

Figure 3.3-1: ALDEN score for cases newly exposed to carbamazepine, lamotrigine, phenytoin, valproate, gabapentin, pregabalin, clobazam.
<0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5 probable; >5, very probable.

Table 3.3-4: Number of SJS/TEN cases and controls with exposure to other new antiepileptic drug treatments.

Antiepileptic drug	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)		Cases (%) exposed to HRD
No newly exposed cases found:							
Barbiturates							
Primidone							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	<5	(<0.3)	4.00	(0.00-76.00)	
Succinimides							
Ethosuximide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	<5	(<0.3)	4.00	(0.00-76.00)	
Mesuximide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Benzodiazepines							
Clonazepam							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	<5	(<1.0)	<5	(<0.3)	2.00	(0.37-10.92)	
Carboxamide							
Rufinamide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Eslicarbazepine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Oxcarbazepine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	
Fatty acid derivatives							
Vigabatrine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	<5	(<0.3)	4.00	(0.00-76.00)	
Tiagabine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	
Other							
Sultiame							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Felbamate							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Topiramate							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	<5	(<1.0)	<5	(<0.3)	4.00	(0.81-19.82)	
Zonisamide							

≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	
Stiripentol							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Lacosamide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Retigabine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Perampanel							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Beclamide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		0.0%
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		

OR=Odds ratio, CI=confidence interval, HRD=high-risk drugs.
HRD include: anti-infective sulfonamides, carbamazepine, allopurinol, phenytoin, lamotrigine, phenobarbital, nevirapine, and oxicam analgesics.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

Table 3.3-5: Cumulative incidences of antiepileptic drugs associated with SJS/TEN.

Antiepileptic drug	Nr. of new users	Total number of SJS/TEN cases	Risk per 100'000 new users (95% CI)	Nr. of SJS/TEN cases with very probable or probable causality	Risk per 100'000 new users (95% CI)
Carbamazepines	68696	16	23.29 (14.27-38.02)	14	20.38 (12.07-34.41)
Lamotrigine	18112	9	49.69 (25.85-95.50)	8	44.17 (22.09-88.32)
Phenytoin	10902	5	45.86 (19.09-110.19)	5	45.86 (19.09-110.19)
Phenobarbital	963	0	0 (NA)	0	0 (NA)
Valproate	40941	<5	4.89 (1.22-19.55)	0	0 (NA)
Gabapentin	116037	<5	0.27 (0.09-0.84)	0	0 (NA)
Pregabalin	59967	<5	1.67 (0.24-11.86)	0	0 (NA)
Clobazam	4300	<5	23.26 (3.28-165.13)	0	0 (NA)

*Only cases with very probable or probable drug causality according to ALDEN.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

Table 3.3-6: Number of users of antiepileptic drugs with no observed cases of SJS/TEN* in this study.

Antiepileptic drug	Nr. of new users	Total number of SJS/TEN cases	Risk per 100'000 new users (95% CI)	Nr. of SJS/TEN cases with very probable or probable causality	Risk per 100'000 new users (95% CI)
Beclamide	<5	0	0 (NA)	0	0 (NA)
Clonazepam	18075	0	0 (NA)	0	0 (NA)
Eslicarbazepine	66	0	0 (NA)	0	0 (NA)
Ethosuximide	633	0	0 (NA)	0	0 (NA)
Felbamate	<5	0	0 (NA)	0	0 (NA)
Lacosamide	650	0	0 (NA)	0	0 (NA)
Levetiracetam	9677	0	0 (NA)	0	0 (NA)
Mesuximide	<5	0	0 (NA)	0	0 (NA)
Oxcarbazepine	1105	0	0 (NA)	0	0 (NA)
Perampanel	40	0	0 (NA)	0	0 (NA)
Phenobarbital	963	0	0 (NA)	0	0 (NA)
Primidone	2431	0	0 (NA)	0	0 (NA)
Retigabine	50	0	0 (NA)	0	0 (NA)
Rufinamide	79	0	0 (NA)	0	0 (NA)
Stiripentol	18	0	0 (NA)	0	0 (NA)
Sultiame	5	0	0 (NA)	0	0 (NA)
Tiagabine	216	0	0 (NA)	0	0 (NA)
Topiramate	11307	0	0 (NA)	0	0 (NA)
Vigabatrin	572	0	0 (NA)	0	0 (NA)
Zonisamide	800	0	0 (NA)	0	0 (NA)

*Only cases with very probable or probable drug causality according to ALDEN.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

3.4 Antibiotic drug use and the risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (Study 3.4)

A Population-Based Case-Control Study

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3.4.1 Abstract

SJS/TEN are rare, life-threatening mucocutaneous ADRs. Sulphonamide antibiotics are commonly accepted as one of the primary causes of SJS/TEN. This notion is based on results from two hospital-based case-control studies that identified the combined antibiotic cotrimoxazole (sulfamethoxazole and trimethoprim) as the cause of several SJS/TEN cases. Associations were also reported for penicillins, quinolones, cephalosporins, macrolides, tetracyclines, and metronidazole. Using data from the UK-based CPRD, we conducted a 1:4-matched case-control study including 480 previously validated SJS/TEN cases (1995-2013) to quantify the association between SJS/TEN and antibiotics. We further quantified absolute risks of SJS/TEN within separate cohorts of antibiotic users and assessed causality in each exposed case using an adapted version of ALDEN. We observed a strong association between SJS/TEN and trimethoprim alone (OR=9.44, 95% CI 3.83-23.25; absolute risk: 0.98 cases/100’000 users), which suggests that the previously reported association between cotrimoxazole and SJS/TEN is at least partly attributable to the non-sulphonamide antibiotic trimethoprim, which is frequently prescribed as a single agent in the UK. Our study further corroborates previously reported associations between SJS/TEN and use of penicillins, quinolones, cephalosporins, and macrolides.

3.4.2 Letter

Two hospital-based case-control studies found that 9% of cases with SJS/TEN had been exposed to sulphonamide antibiotics, of whom 59% and 69% received the combined antibiotic cotrimoxazole (trimethoprim/sulfamethoxazole). Other frequent exposures included allopurinol and AEDs. Associations were also reported for penicillins, quinolones, cephalosporines, tetracyclines, and macrolides.[88,89] Metronidazole was associated with SJS/TEN in a small case-control study.[134]

We conducted a population-based case-control study using data from the UK-based CPRD (Table 3.4-3) to quantify the association between antibiotic use and SJS/TEN.[28] The validated study population and detailed methods have been described in detail elsewhere.[196,217] In short, we identified 480 cases with a validated SJS/TEN diagnosis and a secondary care referral between 1995 and 2013, and matched four, randomly chosen controls (≥1 visit practice visit recorded ≤30 days before or after the index date) to each case on age, sex, general practice, and years of recorded history in the CPRD prior to the index date. We calculated ORs and 95% CI for incident SJS/TEN comparing users of various antibiotics (Table 1) to non-users of the respective antibiotic. Antibiotic use was defined as a first-time recorded prescription ≤84 days before the index date (date of SJS/TEN diagnosis or first recorded symptom). We evaluated potential causality using the score to assess drug causality for epidermal necrolysis (ALDEN; Table 3.4-4),[20] in nine cohorts of new antibiotic users to calculate absolute risks of SJS/TEN ≤84 days after treatment start.

We identified 15 cases exposed to trimethoprim alone; OR=9.44 (95% CI 3.83-23.25), and no cases exposed to cotrimoxazole or any other sulphonamide antibiotic. Compared to trimethoprim (n=1’168’741 users), use of cotrimoxazole (n=11’337) and other sulphonamide antibiotics (n=1’655) was low. ORs were also significantly increased for penicillins (OR 3.63, 95% CI 2.22-5.94), quinolones (OR 4.34, 95% CI 1.40-13.50), cephalosporins (OR 3.73, 95% CI 1.53-9.10), and macrolides (OR 4.83, 95% CI 2.47-9.47, Table 3.4-1). The proportion of exposed cases with very probable or probable ALDEN scores was 73.3% for trimethoprim, 72.7% for penicillins, 83.3% for quinolones, 44.4% for cephalosporins (due to timing of exposure [>56 days before the

index date] and exposure to other high-risk drugs), 22.2% for macrolides (due to timing of exposure [<4 days before the index date] and exposure to other high-risk drugs), and 0% for tetracyclines (due to timing of exposure [>56 days before the index date] and re-exposure after SJS/TEN; Figure 3.4-1). Results remained unchanged in a sensitivity analysis in which we shifted the index date by two weeks before the index date in the absence of recorded prodromal symptoms (Table 3.4-5).

The absolute risk of SJS/TEN was 0.93 cases/100'000 users of trimethoprim alone or cotrimoxazole (accounting for the 11 cases with probable/very probable ALDEN), and between 0.28-0.95 cases/100'000 in users of quinolones, penicillins, cephalosporins, macrolides, and metronidazole (Table 3.4-2).

Our results challenge the prevailing assumption that sulphonamide antibiotics are predominant triggers of SJS/TEN, and suggest that trimethoprim was at least partly responsible for the previously reported association between SJS/TEN and cotrimoxazole.[88,89] Due to infrequent use, we were not able to evaluate the potential contribution of sulfamethoxazole or other sulphonamide antibiotics (e.g. sulfadiazine, 5 of 13 cases in exposed to other sulphonamides in EuroSCAR). We further did not evaluate the non-antibiotic sulphonamide sulfasalazine, for which both previous case-control studies reported an association with SJS/TEN.[88,89] Despite the increased relative risk, the absolute risk of SJS/TEN in trimethoprim users was lower than for users of aromatic AEDs (20-45 cases/100'000 users) in the same study population.[5]

Our results corroborate previously reported associations between SJS/TEN and penicillins, cephalosporins, quinolones, and macrolides,[88,89] where the absolute risk for each antibiotic was comparable to the absolute risk in trimethoprim users. Conversely to the EuroSCAR study, which classified 6 of 7 cases exposed to tetracyclines with a probable/very probable ALDEN score,[20,89] we observed no probable/very probable ALDEN scores in cases exposed to tetracyclines despite a large number of users (877'889).

We observed an increased but non-significant OR for SJS/TEN in metronidazole users, and a low absolute risk (0.18 cases/100'000 users). Unlike in our study, all 40 cases exposed to metronidazole were concomitantly exposed to mebendazole in the previous

Taiwanese case-control study.[134] Other case-control studies did not report results for metronidazole.

Despite extensive case validation, we cannot rule out that other cutaneous reactions were incorrectly diagnosed as SJS/TEN in some cases. However, previously assessed associations were consistent with results from hospital-based observational studies with less potential for misclassification.[88,89,217] Furthermore, given that the CPRD is a primary care database, we were not able to evaluate antibiotics that are used in inpatient settings. Finally, protopathic bias or confounding by indication may play a role because antibiotics may be used to treat prodromal symptoms of SJS/TEN or as infection prophylaxis during the treatment of acute disease. To minimize the risk of protopathic bias, we defined the index date as the date of the first recorded symptom of SJS/TEN wherever possible and assessed ALDEN scores to quantify the likelihood of causality of observed associations.[20] Results from a sensitivity analysis in which we shifted the index date by two weeks before the date of the first recorded SJS/TEN diagnosis in all cases without recorded prodromal symptoms were virtually unchanged (Table 3.4-5). Further strengths and limitations of our study population and data source have been discussed elsewhere.[196,217]

In summary, our results suggest that the previously reported association between cotrimoxazole and SJS/TEN is at least partly attributable to the non-sulphonamide antibiotic trimethoprim, which is frequently given in combination with sulfamethoxazole. Our study further corroborates previously reported associations between SJS/TEN and penicillins, quinolones, cephalosporins, and macrolides.

Table 3.4-1: Relative risk for SJS/TEN in patients with new antibiotic drug treatment.

Drug exposure	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)	
Sulphonamide antibiotics:						
Cotrimoxazol[1] ≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A	
Sulfamethoxazole ≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A	
Non-sulphonamide antibiotics						
Trimethoprim only ≤84 days prior to the index date	15	(3.1)	7	(0.4)	9.44	(3.83-23.25)
Penicillins* ≤84 days prior to the index date	33	(6.9)	51	(2.7)	3.63	(2.22-5.94)
Quinolones+ ≤84 days prior to the index date	6	(1.2)	6	(0.3)	4.34	(1.40-13.50)
Cephalosporins‡ ≤84 days prior to the index date	9	(1.9)	12	(0.6)	3.73	(1.53-9.10)
Tetracyclines♦ ≤84 days prior to the index date	<5	(<1.0)	10	(0.5)	0.87	(0.19-3.95)
Macrolides□ ≤84 days prior to the index date	18	(3.8)	18	(0.9)	4.83	(2.47-9.47)
Metronidazole ≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	2.98	(0.50-17.93)

OR=Odds ratio, CI=confidence interval.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.
1 **S**ulfamethoxazole + trimethoprim.
* 16x floxacillin, 9x phenoxymethylpenicillin, 8x amoxicillin.
+ <5x ciprofloxacin, <5x norfloxacin.
‡ 7x cephalexin, <5x cephradine, <5x cefadroxil.
♦ <5x doxycycline, <5x lymecycline.
□ 12x erythromycin, 6x clarithromycin.

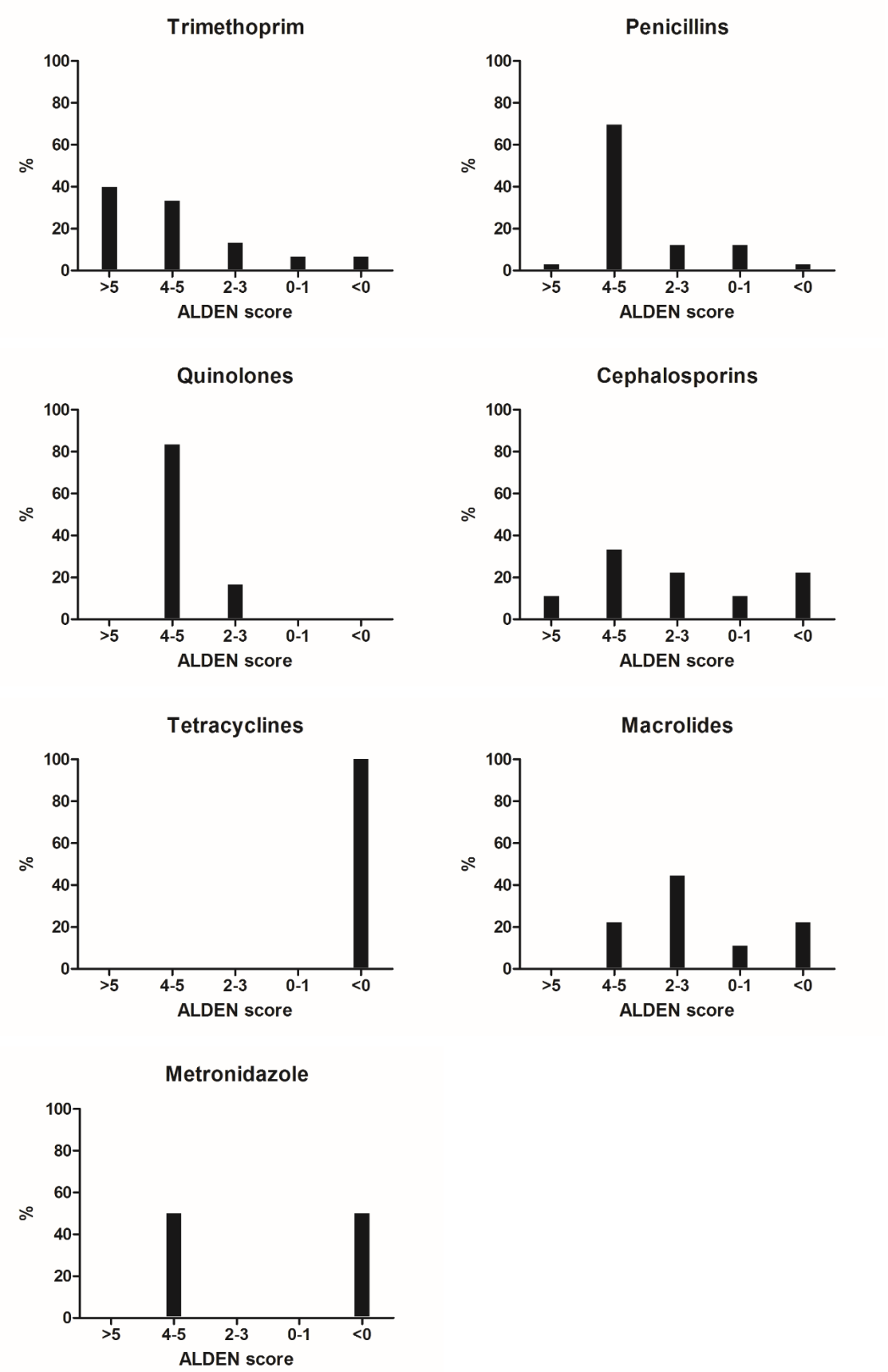

Figure 3.4-1: ALDEN score for cases newly exposed to trimethoprim, penicillins, quinolones, cephalosporins, tetracyclines, macrolides, and metronidazole.
<0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5 probable; >5, very probable.

Table 3.4-2: Cumulative incidences of SJS/TEN among new users of suspected antibiotic culprit drugs.

Antibiotic drug	Number of new users	Total number of SJS/TEN cases	Risk per 100'000 new users (95% CI)	Nr. of SJS/TEN cases with very probable or probable causality	Risk per 100'000 new users (95% CI)
All sulphonamide antibiotics without trimethoprim	1'655	0	0 (NA)	0	0 (NA)
Sulfamethoxazole	0	0	0 (NA)	0	0 (NA)
All trimethoprim	1'134'395	15	1.32 (0.80-2.19)	11	0.97 (0.54-1.75)
Cotrimoxazole	11'337	0	0 (NA)	0	0 (NA)
Trimethoprim only	1'123'041	15	1.34 (0.81-2.22)	11	0.98 (0.54-1.77)
Penicillins	2'519'811	33	1.31 (0.93-1.84)	24	0.95 (0.64-1.42)
Quinolones	521'707	6	1.15 (0.52-2.56)	5	0.96 (0.40-2.30)
Tetracyclines	877'889	<5	0.23 (0.06-0.91)	0	0 (NA)
Cephalosporins	923'648	9	0.97 (0.51-1.87)	<5	0.43 (0.16-1.15)
Macrolides	1'438'087	18	1.25 (0.79-1.99)	<5	0.28 (0.10-0.74)
Metronidazole	556'422	<5	0.36 (0.09-1.44)	<5	0.18 (0.03-1.28)

CI=Confidence interval.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

Table 3.4-3: Brief description of the Clinical Practice Research Datalink.

Clinical Practice Research Datalink
The Clinical Practice Research Datalink (CPRD) is an anonymised longitudinal primary care database. The data from the CPRD consists of medical patient records which are compiled by general practitioners, and covers approximately 13 million patients from more than 600 practices in the UK. With more than 4 million active patients, approximately 7% of the UK population are included and patients are representative of the UK general population in terms of age, sex and ethnicity. The CPRD primary care database is a valuable source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies (virtually complete outpatient drug prescription history), health-related behaviours and referrals to secondary care. For more than 50% of patients, linkage with datasets from secondary care, disease-specific cohorts and mortality records are available. The data in the CPRD has been repeatedly demonstrated to be of high quality, and has been used for numerous epidemiological studies published in peer-reviewed journals.

Table 3.4-4: ALDEN score adapted to the information available in the CPRD.

Criterion	Values	Rules to apply	Point range
Delay from initial drug component intake to onset of SJS/TEN (index date)	Suggestive +3	5-28 days	-3 to +3
	Compatible +2	29-56 days	
	Likely +1	1-4 days	
	Unlikely -1	>56 days	
	Excluded -3	Drug started on or after the onset of SJS/TEN	
Drug present in the body on date of onset of SJS/TEN (index date)*	Likely 0	Number of prescribed tablets and dose instructions suggest intake of drug up until the date of onset of SJS/TEN	-3 to 0
	Doubtful -1	Number of prescribed tablets and dose instructions suggest intake of drug until 1-5 days prior the date of onset of SJS/TEN	
	Excluded -3	Number of prescribed tablets and dose instructions suggest intake of drug until >5 days prior the date of onset of SJS/TEN	
Rechallenge[┼]	Positive specific for disease and drug +4	SJS/TEN after use of same drug	-2 to +4
	Positive specific for disease and drug +2	SJS/TEN after use of similar drug[╪] or other reaction with same drug	
	Positive unspecific +1	Other reaction after use of similar drug[╪]	
	Negative -2	Re-exposure to same drug without any reaction	
Dechallenge	Neutral 0	Drug stopped	-2 to 0
	Negative -2	Drug continued without harm	
Type of drug (notoriety)[┐]	Strongly associated +3	Drug of high-risk according to previous case-control studies	-1 to +3
	Associated +2	Drug with definite but lower risk according to previous case-control studies	
	Suspected +1	Previous case reports, ambiguous epidemiologic results	
	Unknown 0	Drugs with no reports or data from epidemiologic studies	
	Not suspected -1	No evidence of an association in previous epidemiologic studies with sufficient number of exposed patients	
Other cause	Possible -1	Rank all drugs from highest to lowest intermediate score If at least one has an intermediate score of >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	≤0

ALDEN=Algorithm of drug causality for epidermal necrosis.
* In the original ALDEN score, this criterion is assessed by taking into account the elimination half-life of each drug. Because the CPRD data does not allow determining the exact date that a patient was exposed to a tablet and because dose instructions are not available for all prescriptions we had to adjust this criterion.
┼ In the original ALDEN score, potential prechallenge to the suspected drug was also determined. Because we only included first-time prescriptions recorded ≤84 days prior to the index to assess potential culprit drugs, we did not need to assess potential prechallenge.
╪ Same ATC code up to the forth level.
┐ Based on the EuroSCAR study, the case-control study by Roujeau et al., and previously published case reports.

Table 3.4-5: Relative risk for SJS/TEN in patients with new antibiotic drug treatment with adjusted index date*.

Drug exposure	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)	
Sulphonamide antibiotics:						
Cotrimoxazol ≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A	
Sulfamethoxazole ≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A	
Non-sulphonamide antibiotics						
Trimethoprim only ≤84 days prior to the index date	11	(2.3)	6	(0.3)	7.94	(2.93-21.53)
Penicillins ≤84 days prior to the index date	24	(5.00)	48	(2.5)	2.70	(1.57-4.63)
Quinolones ≤84 days prior to the index date	6	(1.2)	6	(0.3)	4.76	(1.43-15.80)
Cephalosporins ≤84 days prior to the index date	9	(1.9)	11	(0.6)	4.05	(1.63-10.09)
Tetracyclines ≤84 days prior to the index date	<5	(<1.0)	10	(0.5)	1.73	(0.54-5.51)
Macrolides ≤84 days prior to the index date	14	(2.9)	15	(0.8)	4.36	(2.09-9.09)
Metronidazole ≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	2.20	(0.40-12.03)

*The index date was moved to two weeks before the date of the first recorded SJS/TEN diagnosis in all cases without a clear indication for disease onset.
OR=Odds ratio, CI=confidence interval.
Due to confidentiality regulations, we were not able to report the exact number of patients for categories that included <5 patients.

3.5 Stevens-Johnson syndrome and toxic epidermal necrolysis in association with commonly used drugs other than antiepileptics and antibiotics

A population-based case-control study

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3.5.1 Abstract

Background: SJS/TEN have been associated with use of various drugs, but evidence is scarce. We studied the association between new use of drugs other than AEDs and antibiotics and SJS/TEN.

Methods: We conducted a matched (1:4) case-control analysis in 480 previously validated SJS/TEN cases (1995-2013). We calculated ORs with 95% CI for SJS/TEN in new users of drugs compared to non-users. For cases of SJS/TEN diagnosed ≤84 days after first use of a drug we assessed causality between drug exposure and SJS/TEN using ALDEN. We calculated absolute risks by dividing the number of SJS/TEN cases ≤84 days after new drug exposure by the total number of new users of the drug.

Results: There was an association between SJS/TEN and use of allopurinol (OR 24.51, 95% CI 2.94-204.04) and coxibs (OR 24.19, 95% CI 2.91-200.92). Proton pump inhibitors (PPIs), fluoxetine, mirtazapine, and 5-aminosalicylates (sulfasalazine and mesalamine) were also associated with an increased risk of SJS/TEN, though with lower ORs. Causality was probable in most exposed cases according to ALDEN. Absolute risks of SJS/TEN were 1.9-6.0/100'000 users for allopurinol, coxibs, and 5-aminosalicylates, and 0.2-1.6/100’000 users for the remaining drugs. We found no association between SJS/TEN and oxicam analgesics, benzodiazepines, citalopram, sertraline, paroxetine, venlafaxine, and phosphodiesterase-5 inhibitors despite >100’000 new users.

Conclusions: In this observational study we observed likely associations between SJS/TEN and use of allopurinol, coxibs, and 5-aminosalicylates, and potential associations for PPIs, fluoxetine, and mirtazapine.

3.5.2 Introduction

SJS/TEN are rare muco-cutaneous ADRs with a previously reported mortality of 1-9% for SJS and 30-50% for TEN. In the absence of effective pharmacotherapy, identification and early discontinuation of the culprit drug is crucial.[83,86,194] Various AEDs, sulphonamide antibiotics, allopurinol, antiretroviral drugs, and oxicam analgesics have repeatedly been identified as key triggers of SJS/TEN.[88,89] Reports of potential associations between SJS/TEN and a variety of other drugs are abundant, albeit based on little evidence. Hospital-based case-control studies reported an association between SJS/TEN and new exposure to the SSRI sertraline and to the proton pump inhibitor (PPI) pantoprazole.[88,89] Case reports further anecdotally linked numerous other drugs to SJS/TEN, such as other SSRIs and PPIs, atypical antidepressants, benzodiazepines, and coxibs.[91,93,96–102,104,109–112,114–116,133] Additionally, official drug product labels and national formularies (e.g. British National Formulary) list SJS/TEN as a potential adverse reaction to a variety of other drugs such as sildenafil (phosphodiesterase-5 [PDE5] inhibitor), duloxetine, atorvastatin, or ACE-inhibitors.[87,221]

We conducted a case-control study using data from the CPRD to analyse the association between SJS/TEN and a variety of allegedly associated drugs as well as a selection of not previously associated but commonly used drugs. The association between AEDs or anti-infective drugs and SJS/TEN has been evaluated in separate studies.[5,222]

3.5.3 Patients and Methods

Data source

The CPRD is a large (13.3 million patients) anonymized primary care database that is representative of the UK population in terms of age and sex. Since 1987 participating GPs have recorded patient demographics and characteristics, symptoms, diagnoses, laboratory test results, and referrals to secondary or tertiary care. Drug prescriptions by the GP are issued electronically; thus, the CPRD holds a virtually complete outpatient drug prescription history.[28] High quality of CPRD data has been repeatedly demonstrated, and the database has been used for numerous epidemiological studies

published in peer-reviewed journals.[29] This study (including the use of HES data for the validation of the case population) was approved by the ISAC for MHRA database research (ISAC protocol 14_009R).

Study population

Case patients

We previously validated all SJS/TEN diagnoses recorded in the CPRD that led to secondary care referral between 1995 and 2013.[196] In short, two specialised clinicians classified all potential SJS/TEN cases with a recorded secondary care referral based on all available clinical information into probable/possible or unlikely cases of SJS/TEN. Patients without or little available clinical information were classified according to pre-specified criteria. We then compared our classification against a representative sub-group of patients for whom we had unequivocal diagnoses from secondary care extracted from hospital discharge letters and HES data. We established a case population of 551 validated SJS/TEN cases with a PPV of 0.87. The validation of our case population is described in detail elsewhere.[196]

Of those 551 patients, we included 480 patients with ≥180 days of recorded active history in the CPRD prior to the 'index date'. We defined the index date as the date of the first recorded SJS/TEN diagnosis (n=238), or the date of the first recorded SJS/TEN-related symptom, wherever available (e.g. sore throat, painful eyes) prior to the first recorded SJS/TEN diagnosis (n=242).

Control patients

For each case, we randomly identified four control patients with no recorded diagnosis of SJS/TEN at any time. We matched control patients to cases on age, sex, general practice and years of recorded history prior to the index date. The index date for each control patient was the date of the first recorded SJS/TEN diagnosis of the matched case. Control patients were required to have a recorded GP visit ≤30 days prior to or after the index date to ensure active patient status.

Exposure

We defined drug exposure as a first-time recorded prescription of a drug listed in Table 3.5-4 ≤84 days prior to the index date. The CPRD only rarely captures over the counter (OTC) drugs, and drugs prescribed in an inpatient setting or secondary care. Thus we did not assess potential associations for acetaminophen, ibuprofen, or diclofenac (typical OTC drugs), or various antineoplastic agents and intravenous corticosteroids (only administered in secondary care) despite previous reports of potential associations with SJS/TEN.[89,135–137] We chose to evaluate drugs prescribed ≤84 days prior to the recording of a SJS/TEN event rather than ≤56 days (EuroSCAR study),[89] because the recoding of the SJS/TEN diagnoses may have been delayed if patients initially presented for emergency secondary care.

Statistical analysis

Case-control study

We conducted conditional logistic regression analyses using SAS 9.4 (SAS Institute, Cary, NC, USA), to calculate ORs with 95% CIs to assess the association between various drugs and SJS/TEN. Where there was no exposed case or no exposed control for a given exposure, we used exact methods to estimate the ORs and 95% CIs.

Given the small number of exposed patients per drug, we were not able to adjust our models for concomitant drug use. Instead, we reported the percentage of exposed cases who started therapy with another high risk drug ≤84 days before the index date for each drug (Table 3.5-1, anti-infective sulphonamides, carbamazepine, allopurinol, phenytoin, lamotrigine, phenobarbital, nevirapine, and oxicam analgesics). Due to confidentiality regulations, we were not able to report the exact number of patients for cells with <5 patients.

ALDEN

A score to assess drug causality for epidermal necrolysis (ALDEN) was developed in 2009,[20] to systematically grade potential causality between drug exposure and SJS/TEN. The ALDEN score was developed for an inpatient setting where a lot of clinical information is available, rather than for studying data in electronic databases. We thus used an adapted version of ALDEN, excluding information that is not available in the

CPRD (Table 3.5-5) for each case who was considered exposed to a study drug. We plotted the proportion of cases by their likelihood of causality for each drug (Figure 3.5-1).

Cohorts to calculate absolute risk of SJS/TEN in new drug users

We established 32 cohorts of new study drug users listed in Table 3.5-4. Patients with a first prescription for a drug of interest between January 1995 and December 2013 were eligible if they had ≥180 days of prior active history in the CPRD and ≥84 days of completed follow up after the recorded first prescription to ensure complete follow-up. We excluded patients with a previous diagnosis of SJS/TEN (with or without secondary care referral). We quantified the absolute risk of SJS/TEN as the number of incident diagnoses during follow up (only cases with a very probable/probable ALDEN), divided by the total number of patients who initiated therapy with the drug of interest. In a sensitivity analysis, we quantified absolute risks of SJS/TEN in all cases irrespective of ALDEN.

3.5.4 Results

Study population

Among 480 SJS/TEN cases and 1,920 controls, 51.7% were women, and the mean age at the index date was 38.5 years (±25.2).

Highly suspected drugs

We observed 6 cases (1.3%) and <5 controls who were newly exposed to allopurinol, which resulted in an OR of 24.51 (95% CI 2.94-204.04). The ALDEN-based causality was probable in 66.7% of cases. We further observed an increased OR of SJS/TEN in association with new use of the sulphonamide sulfasalazine (OR 4.00, 95% CI 0.21-∞), based on <5 newly exposed cases, all of whom had a probable ALDEN score. Use of oxicam analgesics yielded an OR of 4.00 (95% CI 0.25-63.95; <5 exposed cases Table 3.5-1), although all cases had very unlikely ALDEN scores (Figure 3.5-1).

Coxibs

Use of coxibs yielded an OR of 24.19 (95% CI 2.91-200.92; Table 3.5-1) based on <5 exposed cases of whom 80% had probable/very probable ALDEN scores. Cases were exposed to rofecoxib, celecoxib, or etoricoxib (Figure 3.5-1).

Proton pump inhibitors

We observed increased ORs for omeprazole (OR 5.85, 95% CI 2.07-16.56; 9 cases), lansoprazole (OR 3.66, 95% CI 0.98-13.72; <5 cases), and rabeprazole (OR 9.66, 95% CI 0.21-∞; <5 cases; Table 3.5-1), with probable ALDEN scores in 20%, 50%, and 100% of cases, respectively (Figure 3.5-1). Due to small sample size, we were not able to assess the association between SJS/TEN and new use of pantoprazole (Table 3.5-6).

Antidepressants and benzodiazepines

Fluoxetine showed a slight association with SJS/TEN; OR of 1.36 (95% CI 0.28-6.75; <5 cases; Table 3.5-1) where 50% had a probable ALDEN score (Figure 3.5-1). There were fewer users of other antidepressants and thus few exposed cases. There were no very probable/probable ALDEN scored cases among citalopram exposed patients (<5 unlikely cases; mainly due to timing of use), and no cases exposed to sertraline, paroxetine, or duloxetine. Among other antidepressants, we observed <5 mirtazapine exposed cases (OR 4.00, 95% CI 0.56-28.40; 100% probable ALDEN score), and <5 venlafaxine exposed cases, all with ALDEN scores of unlikely or very unlikely. Finally there were <5 cases exposed to a benzodiazepines all of whom were concomitantly exposed to a high-risk drug; Table 3.5-6, Figure 3.5-2).

Other previously associated drugs

We identified <5 cases newly exposed to mesalamine (OR 4.00, 95% CI 0.25-63.95), all of whom had a probable ALDEN score. Alendronate was associated with an increased OR of 15.39 (95% CI 2.33-∞) based on <5 cases, with a probable ALDEN score in only 33.3% of the exposed cases. We observed some cases who were newly exposed to dipyridamole and tranexamic acid, but ALDEN suggested no causal

association in all cases (mainly concomitant exposure to other high-risk drugs; Table 3.5-6, Figure 3.5-2).

Commonly used drugs

We did not observe an association between SJS/TEN and new use of statins, beta blockers, calcium channel blockers (dihydropyridines, phenylalkylamines, and benzothiazepines separately), ACE inhibitors, angiotensin receptor blockers, metformin, sulfonylurea, or oral contraceptives (Table 2). Different diuretics yielded statistically significantly increased ORs but ALDEN suggested unlikely or very unlikely causality for all associations, mainly due to concomitant exposure to other high-risk drugs or treatment start <4 days or >56 days prior to SJS/TEN; furosemide (OR 5.46, 95% CI 1.46-20.43, n=5 cases), bendroflumethiazide (OR 8.00, 95% CI 1.46-43.70, n<5 cases), and spironolactone (OR 6.21, 95% CI 1.04-37.22, n<5 cases; Figure 3.5-2 and Table 3.5-2).

Absolute risks

Allopurinol yielded the highest absolute risk of SJS/TEN, with 6.0 cases/100'000 new users (n=5 cases [only including cases with very probable/probable ALDEN scores]), followed by sulfasalazine (4.3 cases/100’000 new users; n=<5 cases) and mesalamine (3.8 cases/100’000 new users; n=<5 cases). All other drugs with ≥1 exposed case with a very probable/probable ALDEN score conferred lower absolute risks between 0.2-1.9/100’000 new users (Table 3.5-3). We observed no cases or unlikely/very unlikely ALDEN scores among 153’172 new users of oxicam analgesics, 197’911 new users of sertraline, 181’962 new users of paroxetine, 113’977 new users of venlafaxine, 560’777 new users of citalopram, 934’941 new users of benzodiazepines, 149’344 new users of tranexamic acid, and 200’523 new users of PDE5 inhibitors. We identified <100’000 new users and no cases among users of all other evaluated drugs (Table 3.5-7).

3.5.5 Discussion

The results of this study corroborate the previously established association between allopurinol and SJS/TEN, with an absolute risk of 6 cases/100'000 new users.[88,89] Among all other evaluated drugs, mesalamine and sulfasalazine conferred the highest absolute risks of SJS/TEN, with approximately 4 cases/100'000 new users, whereas oxicam analgesics (mainly meloxicam and piroxicam) were not associated with SJS/TEN.

Several previous studies reported a strong association between new allopurinol use and SJS/TEN but provided no information on absolute risks. We estimated an absolute risk of 6 cases/100'000 new allopurinol users, which is higher than for most other culprit drugs of SJS/TEN (e.g.: 1 case/100'000 trimethoprim users),[222] but much lower than for aromatic AEDs (20-46 cases/100'000 new users).[5] In our study population, 1.3% of SJS/TEN cases were newly exposed to allopurinol, whereas previous hospital-based case-control studies reported allopurinol as alleged trigger of SJS/TEN in 15-20% of cases.[89,223] Bias by unrecorded allopurinol use in gout patients does not explain the low exposure in our study, since gout diagnoses were not associated with SJS/TEN in the absence of a new prescription for allopurinol in our study population.[217] However, allopurinol is frequently used at higher doses in cancer therapy, and is usually applied at specialized outpatient oncology-facilities in the UK, and these exposures are not captured by the CPRD.[210] It is thus possible that a large proportion of previously observed cases were treated with allopurinol for other indications and at doses higher than those used for gout-attack prevention. However, none of the previous studies reported the underlying indication of allopurinol treatment.[88,89]

Previous hospital-based case-control studies identified strong associations between new use of oxicam analgesics (meloxicam, piroxicam and tenoxicam) and SJS/TEN.[88,89] We observed <5 cases (all exposed to meloxicam) who were diagnosed with SJS/TEN among >150'000 oxicam initiators (piroxicam, meloxicam, and tenoxicam), all of whom had a very unlikely ALDEN score which, by definition, rules out a causal association with 99% probability. It is possible that use of oxicam analgesics is not captured completely in the CPRD, since these drugs are mainly used for the treatment of

rheumatic diseases and may be prescribed in secondary care. However, even if previous associations were causal, our results suggest that the absolute risk of SJS/TEN for oxicam analgesics is low.

Interestingly, both 5-aminosalicylates (sulfasalazine and mesalamine) were associated with a relatively high absolute risk (4 SJS/TEN cases/100'000 new users). Previous evidence on these drugs is scarce; sulfasalazine was evaluated in a case-control study, albeit in one drug class together with sulphonamide antibiotics, whereas mesalamine was only associated with SJS/TEN in a case report.[88,89] However, given the relatively small number of new users (23'195 for sulfasalazine, 26'496 for mesalamine), our results will have to be followed up in further research.

We observed a 24-fold increased risk of SJS/TEN in association with new exposure to coxibs (rofecoxib, celecoxib, and etoricoxib). The first coxibs (celecoxib and rofecoxib) were introduced to the European market in 2001, after the previous observational studies on SJS/TEN were initiated.[88,89] However, a US-based case series reported 63 cases of SJS/TEN after exposure to valdecoxib, celecoxib, and rofecoxib in 2005.[91] The absolute risk of SJS/TEN in new users of coxibs (1.9 cases/100'000 new users) is similar to the risk observed for trimethoprim,[222] but much lower than the absolute risk for SJS/TEN in association with aromatic AEDs or allopurinol.[5]

Unlike the EuroSCAR study,[20,89] we did not observe an association between sertraline and SJS/TEN. Despite high numbers of new users of SSRIs (n=197'911 for sertraline, n=560'777 for citalopram, n=181'962 for paroxetine), we only observed likely-causal SJS/TEN cases for new exposure with fluoxetine (0.24 cases/100'000 new users, n=425'732 new users). On the other hand, we report for the first time a slightly increased absolute risk of SJS/TEN of 1.5 cases/100'000 new users of mirtazapine, an association which has not been evaluated before and which will have to be followed up.

The EuroSCAR study reported a substantially increased risk of SJS/TEN among new users of pantoprazole.[89] We observed associations between omeprazole, lansoprazole, and rabeprazole and SJS/TEN, but found no cases exposed to pantoprazole. It should be noted however, that there were only 59'431 new pantoprazole users in these data, fewer than other PPIs (n=78'621-925'125). PPIs are associated with polypharmacy,[224] and

confounding by indication may also have played a role since PPIs may be used during acute SJS/TEN patients to prevent stress ulcers.[172] Absolute risks of SJS/TEN were similar for all PPIs and ranged between 0.60-1.27 cases/100'000 new users.

Although case reports suggested an association between benzodiazepines and SJS/TEN,[96,121,225] we did not see such an association, which is consistent with previously reported null-results from large hospital-based case-control studies.[88,89]

Despite high numbers of new users (>100'000) and case reports hypothesizing an association with SJS/TEN,[101,115,221] we did not observe any likely causal SJS/TEN cases among new users of venlafaxine, tranexamic acid, or PDE5 inhibitors.

Finally, we did not find evidence for an association between new use of metformin, sulfonylurea, statins, ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, or contraceptives and SJS /TEN. There is a suggestion of an increased risk of SJS/TEN in users of diuretics (i.e. furosemide, bendroflumethiazide, and potassium-sparing diuretics) but all potential cases were considered unlikely according to ALDEN. Chronic kidney disease has been associated with SJS/TEN in previous studies,[42,217] which could explain the finding with diuretics and could be biased by polypharmacy and polymorbidity in these patients.

Despite the strengths of this study, some limitations need to be considered. First, we had less clinical information available to validate SJS/TEN diagnoses than previous hospital-based case-control studies such as the EuroSCAR.[89] Thus, despite extensive outcome validation, misclassification might have led to some diminished risk estimates. Second, physicians might be more likely to diagnose SJS/TEN if patients are exposed to drugs which have previously been associated with SJS/TEN; this may have led to some overestimation of relative risks. Furthermore, we were not able to assess the association between nevirapine and SJS/TEN, because HIV patients are treated in specialized clinics in the UK; the same holds true for other drugs administered in secondary care or in specialised clinics (e.g. chemotherapy drugs) or typical OTC drugs (e.g. ibuprofen). This likely explains why we were only able to identify a likely culprit drug in approximately 25% of SJS/TEN cases, whereas previous hospital-based observational studies were able to identify a likely drug cause in 65% of SJS/TEN

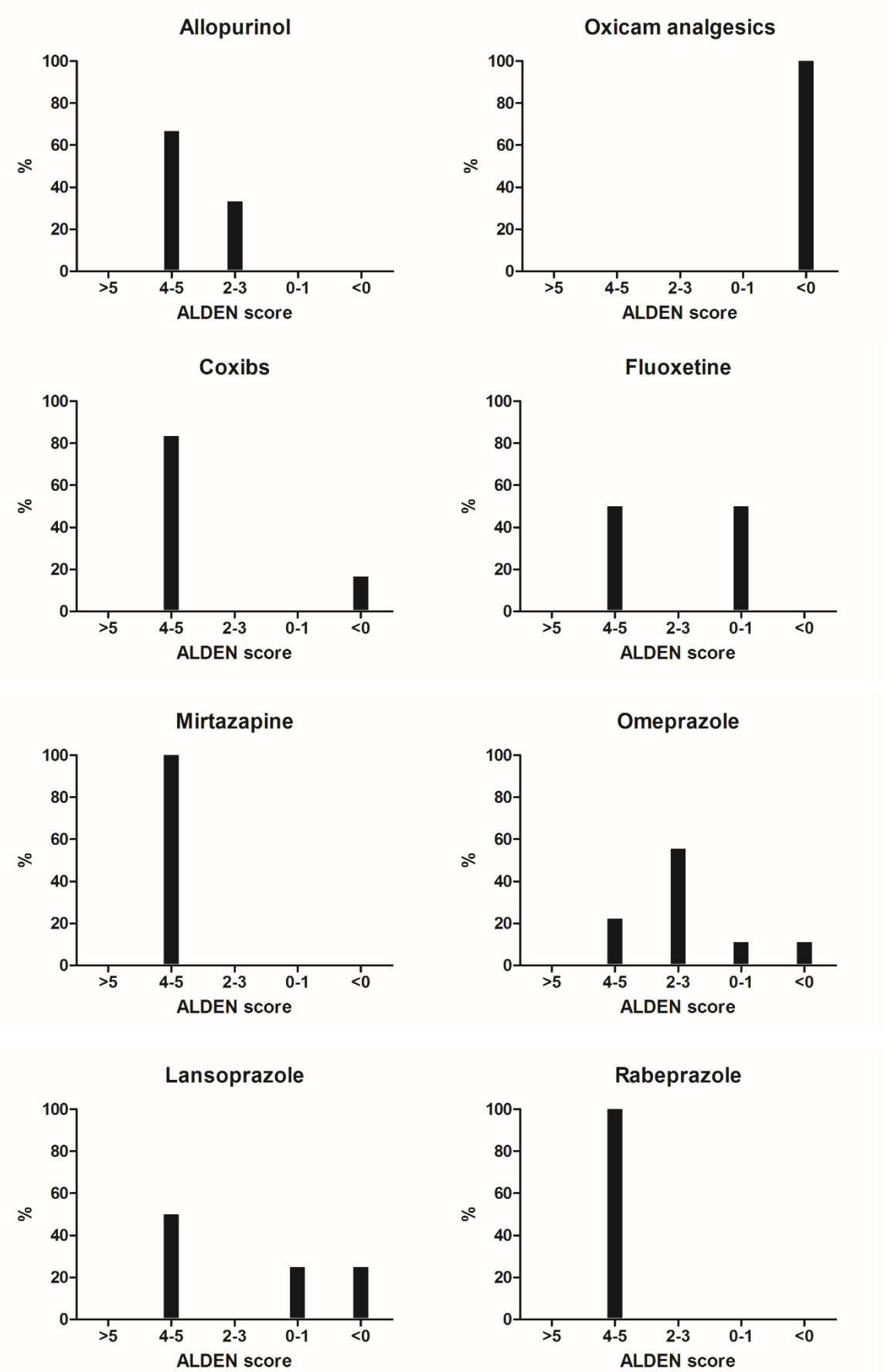
patients.[226] Use of unrecorded OTC-NSAIDs might be more likely in patients using coxibs, which could have led to biased risk estimates in these patients. Third, because ALDEN automatically grades causality higher for drugs with previous evidence for an association with SJS/TEN, the assessed likelihood for a causal association could potentially be underestimated for drugs that have not previously been associated with SJS/TEN.[20]

Despite these limitations, this retrospective study found an increased risk of SJS/TEN in new allopurinol users. The absolute risk was lower than those of high-risk AEDs.[88,89] 5-aminosalicylates (sulfasalazine and mesalamine) and coxibs further conferred increased risks of SJS/TEN. On the other hand, previously associated oxicam analgesics were not associated with an increased risk of SJS/TEN, and neither were commonly used drugs such as non-insulin antidiabetics, various antihypertensive drugs, statins, and contraceptives.

Table 3.5-1: Relative risk for SJS/TEN in association with suspected culprit drugs.

Drug exposure	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)		Cases (%) exposed to HSD
Highly suspected drugs:							
Allopurinol							
≤84 days prior to the index date	6	(1.3)	<5	(<0.2)	24.51	(2.94-204.04)	0
>84 days prior to the index date	11	(2.3)	28	(1.5)	1.61	(0.78-3.28)	
Oxicam derivatives							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	4.00	(0.25-63.95)	100%
>84 days prior to the index date	12	(2.5)	51	(2.7)	0.95	(0.48-1.90)	
Sulfasalazine							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	4.00	(0.21-∞)	0
>84 days prior to the index date	6	(1.2)	16	(0.8)	1.55	(0.58-4.15)	
Drugs with some evidence for an association previous observational studies:							
SSRI							
Sertraline							
≤84 days prior to the index date	0	(0.0)	<5	(<0.2)	4.00	(0.00-76.00)	N/A
>84 days prior to the index date	17	(3.5)	49	(2.6)	1.42	(0.80-2.51)	
Association suggested in case reports:							
COX-2 inhibitors							
All							
≤84 days prior to the index date	†6	(1.3)	<5	(<0.2)	24.19	(2.91-200.92)	16.7%
>84 days prior to the index date	21	(4.4)	72	(3.8)	1.22	(0.72-2.07)	
SSRI							
Fluoxetine							
≤84 days prior to the index date	<5	(<1.0)	6	(0.3)	1.36	(0.28-6.75)	0
>84 days prior to the index date	41	(8.5)	103	(5.4)	1.78	(1.18-2.67)	
Other antidepressants							
Mirtazapine							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	4.00	(0.56-28.40)	0
>84 days prior to the index date	6	(1.3)	14	(0.7)	1.74	(0.66-4.61)	
PPI							
All							
≤84 days prior to the index date	♦14	(2.9)	13	(0.7)	5.07	(2.32-11.04)	7.1%
>84 days prior to the index date	91	(19.0)	263	(13.7)	1.70	(1.26-2.30)	
Other							
Mesalamine/Mesalazine							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	4.00	(0.25-63.95)	0
>84 days prior to the index date	<5	(<1.0)	17	(0.9)	0.47	(0.11-2.04)	
Alendronate							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	15.39	(2.33-∞)	0
>84 days prior to the index date	5	(1.0)	27	(1.4)	0.71	(0.26-1.96)	

OR=Odds ratio, CI=confidence interval, HSD=high suspected drugs.
†Rofecoxib (2x), Celecoxib (3x), Etoricoxib (1x)
♦Omeprazole (9x), Lansoprazole (4x), Rabeprazole (1x)


Allopurinol
Oxicam analgesics
Coxibs
Fluoxetine
Mirtazapine
Omeprazole
Lansoprazole
Rabeprazole
%
100
80
60
40
20
0
>5
4-5
2-3
0-1
<0
ALDEN score

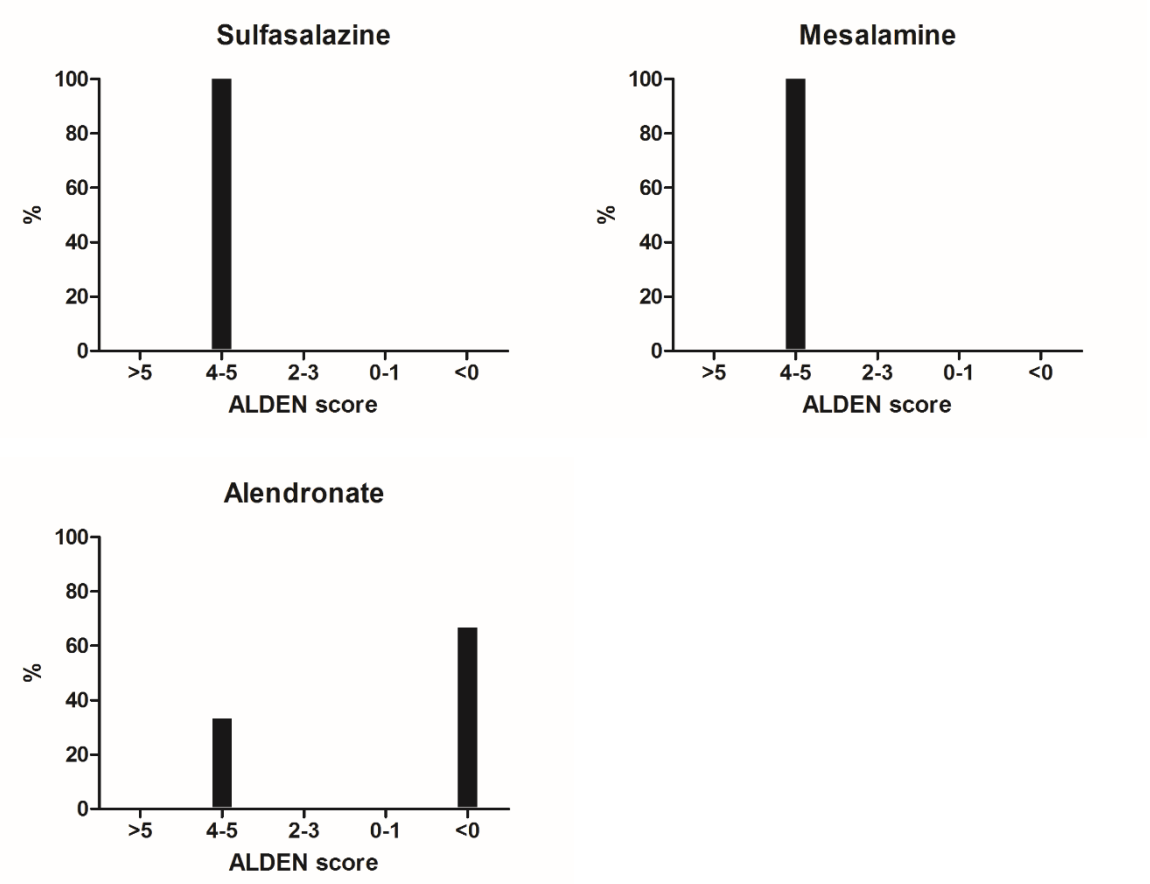


Figure 3.5-1: ALDEN score for SJS/TEN cases newly exposed to suspected culprit drugs.
<0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5 probable; >5, very probable.

Table 3.5-2: Relative risk for SJS/TEN in association with drugs of common use.

Drug exposure	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)		Cases (%) exposed to HSD
Drugs of common use:							
Antidiabetics							
Metformin							
≤84 days prior to the index date	0	(0.0)	<5	(<0.2)	<1.82	(0.00-15.26)	0
>84 days prior to the index date	20	(4.2)	45	(2.3)	1.89	(1.08-3.31)	
Sulfonylurea							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	NA		0
>84 days prior to the index date	21	(4.4)	44	(2.3)	1.97	(1.15-3.37)	
Oral contraceptives							
All							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	1.08	(0.12-9.75)	0
>84 days prior to the index date	66	(13.8)	244	(12.7)	1.24	(0.79-1.96)	
Calcium-channel blockers							
Dihydropyridine							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	1.31	(0.14-12.64)	0
>84 days prior to the index date	34	(7.1)	145	(7.6)	0.92	(0.60-1.41)	
Benzothiazepine							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	4.00	(0.25-63.95)	0
>84 days prior to the index date	10	(2.1)	29	(1.5)	1.43	(0.67-3.06)	
Phenalkylamine							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	>3.73	(0.20-∞)	0
>84 days prior to the index date	<5	(0.4)	11	(0.6)	0.80	(0.18-3.65)	
ACE inhibitors							
All							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	2.70	(0.45-16.18)	1 (50.0%)
>84 days prior to the index date	55	(11.5)	187	(9.7)	1.28	(0.88-1.86)	
B-blockers							
All							
≤84 days prior to the index date	<5	(<1.0)	6	(0.3)	2.16	(0.50-9.24)	0
>84 days prior to the index date	65	(13.5)	249	(13.0)	1.07	(0.78-1.48)	
ARBs							
All							
≤84 days prior to the index date	<5	(0.2)	0	(0.0)	>4.00	(0.21-∞)	0
>84 days prior to the index date	17	(3.5)	44	(2.1)	1.64	(0.90-2.99)	
Loop diuretics							
Furosemide							
≤84 days prior to the index date	5	(1.0)	<5	(<0.2)	5.46	(1.46-20.43)	0
>84 days prior to the index date	36	(7.5)	100	(5.2)	1.69	(1.07-2.65)	
Thiazide diuretics							
Bendroflumethiazide							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	8.00	(1.46-43.70)	2 (50.0%)
>84 days prior to the index date	41	(8.5)	166	(8.7)	1.00	(0.67-1.49)	
Other thiazides							
≤84 days prior to the index date	0	(0.0)	<5	(<0.2)	<4.00	(0.00-76.00)	0

>84 days prior to the index date	7	(1.5)	20	(1.0)	1.44	(0.59-3.56)	
Potassium sparing diuretics							
Spironolactone							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	6.21	(1.04-37.22)	0
>84 days prior to the index date	22	(4.6)	70	(3.7)	1.36	(0.79-2.33)	
Statins							
All							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	1.75	(0.18-17.09)	0
>84 days prior to the index date	50	(10.4)	157	(8.2)	1.57	(0.99-2.28)	

OR=Odds ratio, CI=confidence interval, HSD=high suspected drugs.

Table 3.5-3: Absolute risks of SJS/TEN among new users of suspected culprit drugs.

Antiepileptic drug	Number of new users	Nr. of SJS/TEN cases with very probable or probable causality	Risk per 100'000 new users (95% CI)	Total number of SJS/TEN cases	Risk per 100'000 new users (95% CI)
Allopurinol	66’527	<5	6.01 (2.26-16.02)	6	9.02 (4.05-20.08)
Oxicam analgesics	153’172	0	0 (NA)	<5	0.65 (0.92-4.64)
Coxibs	263’216	5	1.90 (0.79-4.56)	6	2.28 (1.02-5.07)
Omeprazole	925’125	<5	0.22 (0.06-0.88)	9	0.97 (0.51-1.86)
Lansoprazole	667’272	<5	0.30 (0.08-1.20)	<5	0.60 (0.23-1.60)
Rabeprazole	78’621	<5	1.27 (0.18-9.03)	<5	1.27 (0.18-9.03)
Fluoxetine	425’732	<5	0.24 (0.03-1.67)	<5	0.47 (0.12-1.88)
Mirtazapine	128’432	<5	1.56 (0.39-6.23)	<5	1.56 (0.39-6.23)
Mesalamine/mesalazine	26‘496	<5	3.77 (0.53-26.79)	<5	3.77 (0.53-26.79)
Sulfasalazine	23‘195	<5	4.31 (0.61-30.61)	<5	4.31 (0.61-30.61)
Alendronate	146‘010	<5	0.69 (0.10-4.86)	<5	2.06 (0.66-6.37)

CI=Confidence interval.

Table 3.5-4: List of suspected culprit drugs for SJS/TEN and drugs of common use included in this study.

Highly suspected culprit drugs for SJS/TEN	Suspected culprit drugs for SJS/TEN		Drugs of common use
Allopurinol	COX-2 inhibitors*	Methotrexate	Metformin
Oxicam-analgesics	Sertraline	Methotrimeprazine	Sulfonylurea
Sulfasalazine	Fluoxetine	Metolazone	Oral contraceptives
	Citalopram	Dipyridamole	Calcium-channel blockers
	Rabeprazole	Paliperidone	ACE inhibitors
	Benzodiazepines▪	Strontium ranelate	Beta-blockers
	Fluvoxamine	Febuxostat	Angiotensin receptor antagonists
	Paroxetine	Bupropione	Loop diuretics
	Mirtazapine	Tranexamic acid	Thiazide diuretics
	Duloxetine	Mesalamine	Potassium-sparing diuretics
	Venlafaxine	Modafinil	Statins
	Omeprazole	Alendronate	
	Esomeprazole	Phosphodiesterease-5 inhibitors†	
	Lansoprazole	Bezafibrate	
	Pantoprazole		

*Celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib.
▪Alprazolam, bromazepam, clobazam, clonazepam, clorazepam, lorazepam, medazepam, oxazepam.
†Avanafil, sildenafil, tadalafil, vardenafil.

Table 3.5-5: ALDEN score adapted to the information available in the CPRD.

Criterion	Values	Rules to apply	Point range
Delay from initial drug component intake to onset of SJS/TEN (index date)	Suggestive +3 Compatible +2 Likely +1 Unlikely -1 Excluded -3	5-28 days 29-56 days 1-4 days >56 days Drug started on or after the onset of SJS/TEN	-3 to +3
Drug present in the body on date of onset of SJS/TEN (index date)*	Likely 0 Doubtful -1 Excluded -3	Number of prescribed tablets and dose instructions suggest intake of drug up until the date of onset of SJS/TEN Number of prescribed tablets and dose instructions suggest intake of drug until 1-5 days prior the date of onset of SJS/TEN Number of prescribed tablets and dose instructions suggest intake of drug until >5 days prior the date of onset of SJS/TEN	-3 to 0
Rechallenge†	Positive specific for disease and drug +4 Positive specific for disease and drug +2 Positive unspecific +1 Negative -2	SJS/TEN after use of same drug SJS/TEN after use of similar drug‡ or other reaction with same drug Other reaction after use of similar drug‡ Re-exposure to same drug without any reaction	-2 to +4
Dechallenge	Neutral 0 Negative -2	Drug stopped Drug continued without harm	-2 to 0
Type of drug (notoriety)⁋	Strongly associated +3 Associated +2 Suspected +1 Unknown 0 Not suspected -1	Drug of high-risk according to previous case-control studies Drug with definite but lower risk according to previous case-control studies Previous case reports, ambiguous epidemiologic results Drugs with no reports or data from epidemiologic studies No evidence of an association in previous epidemiologic studies with sufficient number of exposed patients	-1 to +3
Other cause	Possible -1	Rank all drugs from highest to lowest intermediate score If at least one has an intermediate score of >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	≤0

ALDEN=Algorithm of drug causality for epidermal necrosis.
* In the original ALDEN score, this criterion is assessed by taking into account the elimination half-life of each drug. Because the CPRD data does not allow determining the exact date that a patient was exposed to a tablet and because dose instructions are not available for all prescriptions we had to adjust this criterion.
† In the original ALDEN score, potential prechallenge to the suspected drug was also determined. Because we only included first-time prescriptions recorded ≤84 days prior to the index to assess potential culprit drugs, we did not need to assess potential prechallenge.
‡ Same ATC code up to the forth level.
⁋ Based on the EuroSCAR study, the case-control study by Roujeau et al., and previously published case reports.

Table 3.5-6: Relative risk for SJS/TEN in association with suspected culprit drugs (no newly exposed cases with very probable or probable ALDEN scores).

Drug exposure	Number of cases (%) (n=480)		Number of controls (%) (n=1920)		OR crude (95% CI)		Cases (%) exposed to HSD
SSRI							
Citalopram							
≤84 days prior to the index date	<5	(<1.0)	11	(0.6)	0.38	(0.05-2.92)	0
>84 days prior to the index date	29	(6.0)	74	(3.9)	1.66	(1.04-2.64)	
Fluvoxamine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	4	(0.2)	<0.76	(0.00-4.46)	
Paroxetine							
≤84 days prior to the index date	0	(0.0)	<5	(<0.2)	1.66	(0.00-13.89)	N/A
>84 days prior to the index date	22	(4.6)	60	(3.1)	1.52	(0.91-2.54)	
Other antidepressants							
Venlafaxine							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	2.00	(0.18-22.06)	0
>84 days prior to the index date	13	(2.9)	20	(1.0)	2.93	(1.45-5.91)	
Duloxetine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	1	(0.1)	<4.00	(0.00-76.00)	
Benzodiazepines							
All							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	1.33	(0.14-12.82)	100%
>84 days prior to the index date	10	(2.1)	28	(1.5)	1.45	(0.69-3.11)	
Other							
Tranexamic acid							
≤84 days prior to the index date	<5	(<1.0)	<5	(<0.2)	2.12	(0.19-23.47)	100%
>84 days prior to the index date	13	(2.7)	32	(1.7)	1.79	(0.88-3.63)	
Dipyridamole							
≤84 days prior to the index date	<5	(<1.0)	0	(0.0)	>9.66	(0.21-∞)	0
>84 days prior to the index date	7	(1.5)	13	(0.7)	2.21	(0.87-5.64)	
Methotrimeprazine							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Metolazone							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	1	(0.1)	<4.00	(0.00-76.00)	
Paliperidone							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Strontium ranelate							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	3	(0.7)	<1.04	(0.00-6.86)	
Febuxostat							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		

Bupropione							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	4	(0.8)	7	(0.4)	2.41	(0.67-8.66)	
Leflunomide							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		
Methotrexate							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	4	(0.8)	11	(0.6)	1.46	(0.46-4.57)	
Modafinil							
≤84 days prior to the index date	0	(0.0)	0	(0.0)	N/A		N/A
>84 days prior to the index date	0	(0.0)	2	(<0.2)	1.66	(0.00-13.89)	
Phosphodiesterase-5 inhibitors							
≤84 days prior to the index date	0	(0.0)	1	(<0.2)	4.00	(0.00-76.00)	N/A
>84 days prior to the index date	5	(1.0)	22	(1.15)	0.90	(0.33-2.47)	
Bezafibrate							
≤84 days prior to the index date	0	(0.0)	1	(<0.2)	4.00	(0.00-76.00)	N/A
>84 days prior to the index date	1	(<1.0)	10	(0.5)	0.39	(0.05-3.10)	

OR=Odds ratio, CI=confidence interval, HSD=high suspected drugs.

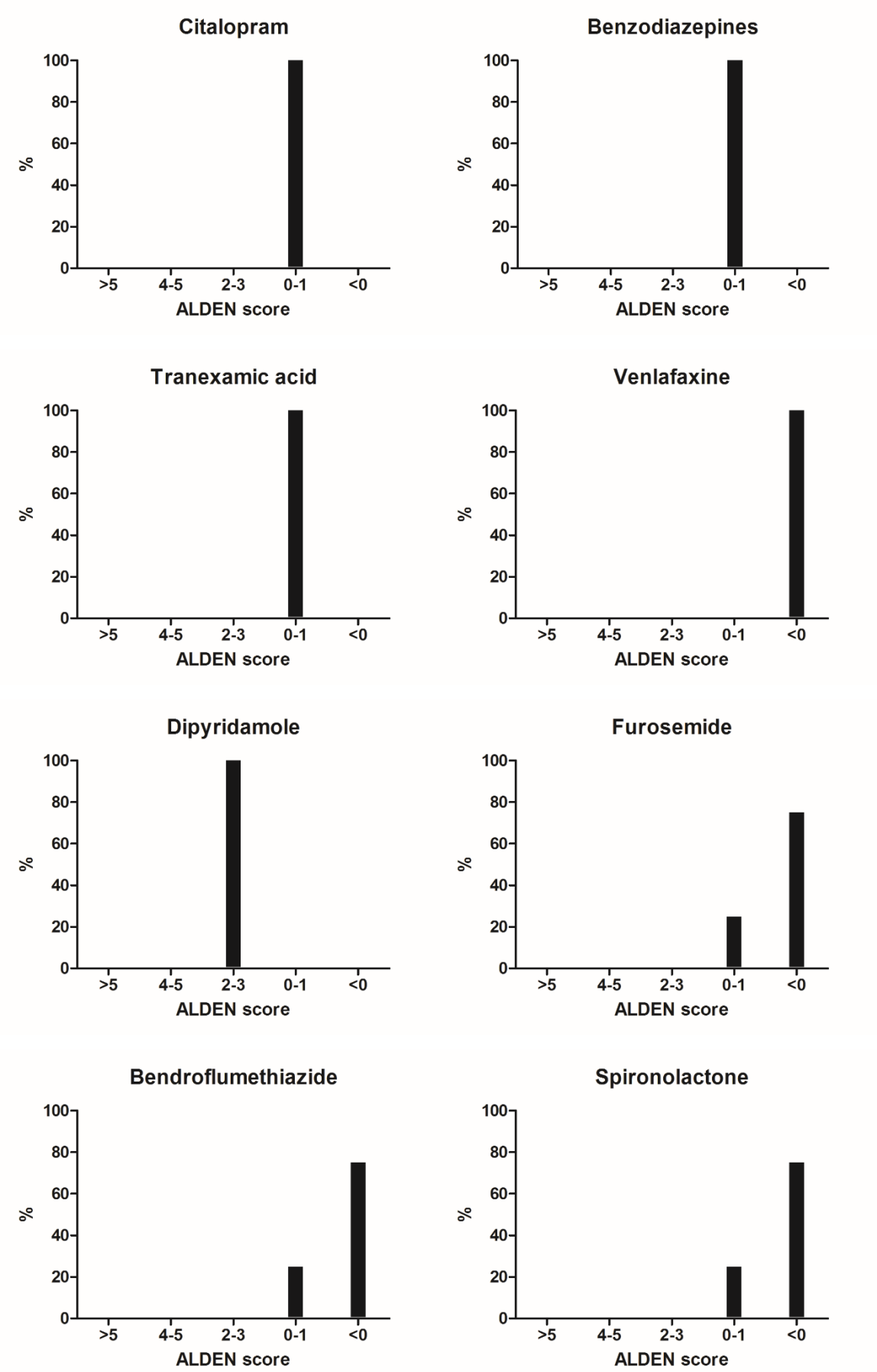


Figure 3.5-2: ALDEN score for SJS/TEN cases newly exposed to suspected culprit drugs.
<0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5 probable; >5, very probable.

Table 3.5-7: Absolute risks of SJS/TEN among new users of suspected culprit drugs (no newly exposed cases).

Antiepileptic drug	Number of new users	Nr. of SJS/TEN cases with very probable or probable causality	Risk per 100'000 new users (95% CI)	Total number of SJS/TEN cases	Risk per 100'000 new users (95% CI)
Citalopram	560’777	0	0 (NA)	<5	0.18 (0.03-1.27)
Venlafaxine	113’977	0	0 (NA)	<5	0.88 (0.12-6.23)
Benzodiazepines	934’941	0	0 (NA)	<5	0.11 (0.02-0.76)
Dipyridamole	47‘488	0	0 (NA)	<5	2.11 (0.30-14.95)
Tranexamic acid	149‘344	0	0 (NA)	<5	0.67 (0.09-4.75)
Pantoprazole	59’431	0	0 (NA)	0	0 (NA)
Esomeprazole	73’867	0	0 (NA)	0	0 (NA)
Sertraline	197’911	0	0 (NA)	0	0 (NA)
Fluvoxamine	2369	0	0 (NA)	0	0 (NA)
Paroxetine	181’962	0	0 (NA)	0	0 (NA)
Duloxetine	30’089	0	0 (NA)	0	0 (NA)
Methotrimeprazine	3985	0	0 (NA)	0	0 (NA)
Metolazone	6897	0	0 (NA)	0	0 (NA)
Paliperidone	69	0	0 (NA)	0	0 (NA)
Strontium ranelate	9679	0	0 (NA)	0	0 (NA)
Febuxostat	769	0	0 (NA)	0	0 (NA)
Bupropione	49‘129	0	0 (NA)	0	0 (NA)
Methotrexate	30‘994	0	0 (NA)	0	0 (NA)
Modafinil	1708	0	0 (NA)	0	0 (NA)
Phosphodiesterase-5 inhibitors	200‘523	0	0 (NA)	0	0 (NA)
Bezafibrate	20‘460	0	0 (NA)	0	0 (NA)

CI=Confidence interval.

Chapter 4

Discussion and Outlook

4 Discussion and Outlook

4.1 Discussion

Although the knowledge about SJS/TEN has substantially increased over the past years, many aspects of the disease, such as the exact pathophysiology, the main culprit drugs, long-term complications in survivors, and pharmacological treatment remain under-investigated. As a consequence, the quality of SJS/TEN warnings in drug dictionaries have been shown to be of low accuracy and the current guidelines for the management of SJS/TEN patients are mainly based on a consensus of expert opinions rather than scientific evidence.[87,172] Because of the rare nature of SJS/TEN, clinical trials are often too small to detect SJS/TEN as an ADR of the drug under study. Observational research therefore plays an important role for the future understanding of SJS/TEN. However, existing observational studies on SJS/TEN are scarce, mainly because large medical claims databases have been proven to be unsuitable for the study of SJS/TEN.[35–38] Consequently, the largest previously conducted observational studies on SJS/TEN have recruited case patients in hospitals via questionnaires.[88,89] While this approach allowed assessing the validity of SJS/TEN elaborately and with high accuracy, it is also accompanied by some limitations. Recruiting patients in hospitals is time-consuming and often costly, assessing the exposure status of patients is prone to recall bias, the exact population-at-risk is often unknown, and following-up on patients after the acute phase of SJS/TEN is difficult. Therefore, this thesis aimed to determine in a first step whether the CPRD allows conducting observational studies on SJS/TEN, by comprehensively assessing the validity of SJS/TEN diagnoses recorded in CPRD data. In Study 3.1 we elaborately describe and discuss the methodology of the validation and composition of our SJS/TEN case population.

In a further step, we aimed to contribute to the general understanding of SJS/TEN by conducting comprehensive observational studies in our SJS/TEN case population established from the CPRD. Pharmacoepidemiology is a multidisciplinary research that is applied in the assessment of disease burden, in the evaluation of undiscovered drug effects, in the analysis of drug utilization, and also in comparative effectiveness or cost-effectiveness analyses. The different studies presented in this SJS/TEN project

exemplify this versatility of pharmacoepidemiologic research. Study 3.2 describes the burden of SJS/TEN by presenting IRs of SJS/TEN in the UK for the first time. In the same study, demographics and characteristics of patients with SJS/TEN are elaborately analysed and described. Studies 3.3, 3.4, and 3.5 assessed potential associations between SJS/TEN and drugs, which have previously been associated with SJS/TEN in observational studies or case reports. In these studies, we further presented absolute risks of SJS/TEN associated with each of these drugs, which might contribute to future considerations of preventive measures in patients starting therapy with drugs carrying a relatively high risk of SJS/TEN. Calculating the cumulative incidence of SJS/TEN in new drug users further allowed us to show that a number of drugs that have previously been suggested as culprit drugs of SJS/TEN (e.g. benzodiazepines, citalopram), appear to be at least relatively safe in terms of SJS/TEN. Table 4.1-1 outlines the objectives, main findings, research area, and the novelty of the results of each of the studies included in this project. A thorough discussion of the results and limitations of the individual studies is presented in the discussion section of the respective studies. The most important findings and implications of these studies are discussed in the following sections.

A study assessing mortality and long term sequelae of SJS/TEN using our CPRD-based case population is planned in the future but is not included in this thesis.

Discussion

Table 4.1-1: Overview and summary of the five observational studies presented within this thesis.

Objectives	Main findings	Research area	Novelty of findings		
			New	Little existing evidence	Strong existing evidence
Study 3.1: • To assess the validity of SJS/TEN diagnoses recorded in the CPRD • To establish a relatively large and validated SJS/TEN case population	• The overall validity of SJS/TEN diagnoses recorded in the CPRD is rather low and requires comprehensive validation • We managed to establish a population of 551 SJS/TEN cases with a positive predictive value of 90%	Validation study	X		
		Case selection	X		
Study 3.2: • To calculate first-ever IRs of SJS/TEN in the UK • To describe demographics and characteristics of SJS/TEN patients • To assess associations between SJS/TEN and life-style factors as well as comorbidities	• Overall IR of SJS/TEN in the UK: 5.76 cases/1'000'000 py • IR highest in children and elderly • Patients of non-Caucasian ethnicity were at increased risk of SJS/TEN • Patients with pre-existing depression, lupus erythematosus, chronic kidney disease, recent pneumonia, or active cancer were at increased risk of SJS/TEN	Disease burden	X		
		Analysis of risk groups	X		
		Analysis of risk groups		X	
		Associated disease		X	
Study 3.3: • To assess potential associations between SJS/TEN and antiepileptics • To calculate absolute risks of SJS/TEN associated with each antiepileptic	• Strong association between SJS/TEN and new use of aromatic antiepileptics • Absolute risks of SJS/TEN between 20-46 cases/100'000 new users for carbamazepine, phenytoin, lamotrigine • Valproate, gabapentin, and pregabalin appear to relatively safe regarding SJS/TEN	Suspected drug effect			X
		Absolute risk assessment		X	
		Suspected drug effect		X	
Study 3.4: • To assess potential associations between SJS/TEN and antibiotics • To calculate absolute risks of SJS/TEN associated with each antibiotic	• Strong association between SJS/TEN and new use of trimethoprim • Likely association between SJS/TEN and new use of penicillins, quinolones, cephalosporins, and macrolides • Absolute risks of SJS/TEN between 0.3-1 cases/100'000 new users of antibiotics	Suspected drug effect	X		
		Suspected drug effect		X	
		Absolute risk assessment	X		
Study 3.5: • To assess potential associations between SJS/TEN and drugs other than antiepileptics and antibiotics • To calculate absolute risks of SJS/TEN associated with each drug included in the study	• Association between SJS/TEN and new use of allopurinol • Potential association for new use of 5-aminosalicylates, coxibs, proton pump inhibitors, fluoxetine, and mirtazapine • Absolute risks of SJS/TEN between 0.2-6 cases/100'000 new users for these dugs • No association between SJS/TEN and oxicams, benzodiazepines, citalopram, sertraline, paroxetine, venlafaxine, and phosphodiesterase-5 inhibitors	Suspected drug effect			X
		Suspected drug effect		X	
		Absolute risk assessment	X		
		Suspected drug effect		X	

CPRD=Clinical Practice Research Datalink, SJS/TEN=Stevens-Johnson syndrome and toxic epidermal necrolysis, IR=Incidence rate, py=person-years.

4.1.1 Study 3.1

Validation of Stevens-Johnson syndrome and toxic epidermal necrolysis in the Clinical Practice Research Datalink

- Together with two specialised clinicians, we evaluated the validity of the first-recorded SJS/TEN diagnosis in 1324 patients based on all information available in the CPRD (including additional notes made by GPs [free texts]). A total of 565 patients were classified as very probable or probable SJS/TEN cases.
- The validity of our classification of recorded SJS/TEN diagnoses was tested against our gold standard (i.e. available diagnoses from secondary care extracted from discharge letters, HES data, and free text).
- We established a final case population of 551 SJS/TEN patients requiring secondary care with a PPV of 90%.

Study 3.1 was pivotal for the feasibility of the further studies on SJS/TEN presented within this project. Observational studies are instrumental for the investigation of SJS/TEN, because this ADR is unlikely to be detected in controlled clinical trials due to its rare nature. Numerous early observational studies (conducted between 1980 and 1995) have not been able to establish SJS/TEN case populations from health-care databases due to issues with multi-diagnostic within the ICD-9 coding system.[35–38] Only recently, a few epidemiologic studies on SJS/TEN have successfully been conducted in medical claims databases.[41,42] In the majority of the existing large observational studies on SJS/TEN, case patients were recruited in hospitals, which allowed a better evaluation of potential SJS/TEN diagnoses, but makes defining a population-at-risk, which is a key variable for the calculation of absolute risk measures, difficult.[88,89]

The validation of our study population revealed that the CPRD is a valid resource to study SJS/TEN in a large longitudinal population-based study population. However, when composing our case population we excluded more than 50% of all patients with a recorded SJS/TEN diagnosis because they either have not reportedly been referred to secondary care or because the validity of the SJS/TEN diagnosis was deemed uncertain during expert review. This indicates that extensive validation of potential SJS/TEN patients in the CPRD is absolutely required.

Discussion

Free texts have furthermore proven to be an invaluable tool for the evaluation and validation of potential SJS/TEN diagnoses by providing more detailed clinical information in addition to the codes recorded in the CPRD and diagnoses from secondary care which we used as our gold standard (n=39). From the year 2013 on, free texts are no longer collected by the CPRD, which will complicate the validation of SJS/TEN diagnoses recorded in the CPRD after 2013. Due to concerns about patient confidentiality, original discharge letters are also no longer available to researchers. While it is important to safeguard patient confidentiality in observational research, the increasing constraints on data availability may severely hamper the conduct of observational studies, especially of rare diseases that are difficult to diagnose correctly such as SJS/TEN, where clinical details are critical to the case validation process, and where there will always be relatively few cases. While this limitation did not apply to this study, it might be a major impediment for future research.

4.1.2 Study 3.2

The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK

- The first ever calculated overall IR of SJS/TEN in the UK was 5.76 cases/1'000'000 py. Incidence rates were highest in patients aged <10 or ≥80 years and during the winter months, but did not significantly vary by sex or year of diagnosis.
- We found that patients of black, Asian, or mixed ethnicity were at a 2-fold increased risk of SJS/TEN when compared to Caucasians.
- We observed associations between SJS/TEN and pre-existing depression, lupus erythematosus, CKD, recent pneumonia, and active cancer, which may be caused by underlying drug therapy in most of these diseases.

Study 3.2 describes the case population in detail in terms of demographics, and frequency of life-style factors and comorbidities. We calculated IRs of SJS/TEN in the

UK population and assessed potential associations between SJS/TEN and life-style factors, demographics, and various comorbidities.

The calculated IRs (5.76 cases/1'000'000 py) and observed associations between SJS/TEN and non-white ethnicity, and various comorbidities were in line with previously reported results (1-12 cases/1'000'000 py) and further corroborate the validity of our case population.[39–42] The results are discussed in detail in the discussion section of Study 3.2. This study is of great significance as it is the first study to describe the disease burden of SJS/TEN within the UK. Other observational studies have reported a lower overall IR of SJS/TEN in other European countries (1-3 cases/1'000'000 py),[39] a higher overall IR of SJS/TEN in the US (12.7 cases/1'000'000 py),[42] and an overall IR of SJS/TEN comparable to the one we calculated for the UK in Korea (5.9 cases/1'000'000 py).[41] The IR of SJS/TEN is likely to vary across geographical regions, because the risk of SJS/TEN seems to depend on ethnicity (potentially associated with different HLA expression),[157] and because drug usage might vary in different countries. The reported associations between SJS/TEN and pre-existing depression, lupus erythematosus, CKD, recent pneumonia, and active cancer as well as increased IRs of SJS/TEN in some categories contribute to the understanding of at-risk-patients and might thus be useful for preventive considerations regarding SJS/TEN.

4.1.3 Study 3.3

The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs

- We observed a strong association between SJS/TEN and new use of carbamazepine (OR 92.57, 95% CI 19.89–∞), phenytoin (OR 49.96, 95% CI 10.13–∞), and lamotrigine (OR 26.90, 95% CI 4.88–∞). Causality, according to the ALDEN score, was very probable or probable for most exposed cases.
- Absolute risks for SJS/ TEN were highest for phenytoin (45.86 cases/100,000 exposed), lamotrigine (44.17 cases/100,000 exposed), and carbamazepine (20.38 cases/100,000 exposed).

Discussion

- Despite frequent use, no ALDEN-score confirmed cases were observed in new users of valproate (40,941 exposed), gabapentin (116,037 exposed), pregabalin (59,967 exposed), levetiracetam (9677 exposed), topiramate (11,307 exposed), or clonazepam (18,075 exposed).
- The results of our study are consistent with those of previous studies of SJS/TEN, which found increased risks of SJS/TEN in new users of the aromatic AEDs, carbamazepine, phenytoin, and lamotrigine.

Study 3.3 confirms the association between SJS/TEN and the aromatic AEDs carbamazepine, phenytoin, and lamotrigine, which have been reported in previous hospital-based observational studies.[88,89] However, conversely to the hospital-based studies, the CPRD allowed assessing the total number of new users for each drug (i.e. the population-at-risk) and thus the calculation of absolute risks of SJS/TEN in association with each AED. Knowledge of these absolute risks is important regarding cost effectiveness considerations of suggested routine pre-treatment screenings for previously discovered HLA alleles, which appear to increase susceptibility to SJS/TEN upon exposure to certain culprit drugs of SJS/TEN. Knowledge of the population-at-risk further enabled us to systematically show that some AEDs which have been suggested to cause SJS/TEN in case reports appear to be at least relatively save regarding SJS/TEN and may thus be considered as potential alternative drugs in epilepsy patients who developed SJS/TEN under treatment with a high-risk antiepileptic.

4.1.4 Study 3.4

Antibiotic drug use and the risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis - A Population-Based Case-Control Study.

- We observed a strong association between SJS/TEN and trimethoprim in the absence of sulfamethoxazole (OR=9.44, 95% CI 3.83-23.25; absolute risk: 0.98

SJS/TEN cases/100'000 users). This suggests that the previously reported association between cotrimoxazole and SJS/TEN is at least partly attributable to the non-sulphonamide antibiotic trimethoprim, which is frequently prescribed as a single agent in the UK, whereas trimethoprim is usually prescribed as a combined antibiotic with sulfamethoxazole (cotrimoxazole) in most other countries that have contributed data to SJS/TEN research.

- Our study further corroborated previously reported associations between SJS/TEN and use of penicillins, quinolones, cephalosporins, and macrolides, for which absolute risks were between 0.28-0.96 SJS/TEN cases/100'000 users.
- We further observed an association between SJS/TEN and metronidazole. However, more data on this association is required.

While previous case-control studies reported a strong association between SJS/TEN and cotrimoxazole (sulfamethoxazole+trimethoprim),[88,89] this study was the first to show an association between SJS/TEN and trimethoprim as a single agent. Although the synergistic effect of trimethoprim and sulfamethoxazole is in contestation,[227–229] the use of trimethoprim as a single agent in the UK is exceptional because cotrimoxazole is still the first choice in many countries. Previous studies were therefore not able to separately assess associations for trimethoprim and sulfamethoxazole as single agents. Interestingly, the sulphonamide sulfamethoxazole rather than trimethoprim was generally considered to be the causative agent of SJS/TEN.[89] Although previously reported associations between SJS/TEN and antibiotics other than sulphonamides are corroborated in Study 3.4,[88,89] further evidence on these associations is required. The results of this study further suggest that the absolute risk of SJS/TEN in association with antibiotics (including trimethoprim) is significantly lower than for aromatic AEDs or allopurinol.

4.1.5 Study 3.5

Stevens-Johnson syndrome and toxic epidermal necrolysis in association with commonly used drugs other than antiepileptics and antibiotics - A population-based case-control study.

Discussion

- The results of this study confirm an association between SJS/TEN and the use of allopurinol (OR 24.51, 95% CI 2.94-204.04).
- Coxibs (OR 24.19, 95% CI 2.91-200.92), PPIs (OR 5.07, 95% CI 2.32-11.04), fluoxetine (OR 1.36, 95% CI 0.28-6.75), mirtazapine (OR 4.00, 95% CI 0.56-28.40), sulfasalazine (OR 4.00, 95% CI 0.21-∞), and mesalamine (OR 4.00, 95% CI 0.25-63.95) were also associated with an increased risk of SJS/TEN.
- Absolute risks of SJS/TEN were 6 cases/100'000 new users of allopurinol, 1.9 cases/100'000 new users of coxibs, 4.3 cases/100'000 new users of sulfasalazine, 3.8 cases/100'000 new users of mesalamine, 1.6 cases/100'000 new users of mirtazapine, 0.2 cases/100'000 new users of fluoxetine, and 0.2-1.3 cases/100'000 new users of PPIs.
- We found no association between SJS/TEN and previously associated oxicam analgesics, benzodiazepines, citalopram, sertraline, paroxetine, venlafaxine, and phosphodiesterase-5 inhibitors despite >100'000 new users of each drug in the CPRD.

Study 3.5 confirms the previously reported association between SJS/TEN and allopurinol.[88,89] However, the absolute risk of SJS/TEN in our study was significantly lower for allopurinol when compared to aromatic AEDs (6 cases/100'000 new users vs. 20-46 cases/100'000 new users). However, it needs to be highlighted, that our absolute risks of SJS/TEN in allopurinol users pertain to gout patients only, since patients with chemotherapy and cancer (a frequent indication for allopurinol at higher dosages) are treated at specialized facilities and are not systematically captured in the CPRD. We further identified coxibs, PPIs, fluoxetine, mirtazapine, sulfasalazine, and mesalamine as likely culprit drugs of SJS/TEN, with absolute risks of SJS/TEN of 0.2-4.3 cases/100'000 new users. Because there is only little previous evidence suggesting these associations, more data is needed to confirm these observations.

Various other drugs have been suggested as culprit drugs of SJS/TEN in numerous case reports (Table 1.2-1). The great number of such reports as well as the lack of systematic observational research on such associations has led to much confusion regarding the risk of SJS/TEN and certain drugs.[87] In Study 3.5 we did not find any exposed SJS/TEN

cases despite a high number of new users (>100’000) for a number of drugs which have repeatedly been linked to SJS/TEN (oxicam analgesics, benzodiazepines, citalopram, sertraline, paroxetine, venlafaxine, and phosphodiesterase-5 inhibitors). Our results suggest that these drugs appear to be at least relatively safe in terms of SJS/TEN.

4.2 Limitations of this project

4.2.1 Case misclassification

Despite the many strengths of this project and of database research in general, disease misclassification is a challenge when using health-care databases for observational studies (Table 1.1-5). The validity of SJS/TEN diagnoses in the CPRD has not been assessed prior to this project, which is why we elaborately validated our SJS/TEN case population based on a profound understanding of the CPRD and of the clinical presentation of SJS/TEN. Although the results of our validation study suggest a rather high validity of our final case population (PPV of 87%), the inclusion of some false positive cases other than the 13% indicated by the PPV is possible. Correctly diagnosing SJS/TEN is difficult due to the lack of specific tests, various differential diagnoses, and the rare encounter with this type of reaction. Aside from the SJS/TEN diagnoses recorded in the CPRD, we therefore also cannot guarantee the accuracy of all the diagnoses made in secondary care, which we defined as our gold standard for the validation of SJS/TEN cases. Such potential case misclassification may have resulted in somewhat overestimated IRs (although we adjusted IRs for type 1 error) and may have introduced a slight null bias when assessing potential risk factors for SJS/TEN. On the other hand, reported ORs could potentially be overestimated for assessed associations between SJS/TEN and well-known culprit drugs of SJS/TEN (e.g. AED or allopurinol) because physicians may over-diagnose SJS/TEN in users of these drugs. However, our results were similar to results from previous hospital-based studies in which researchers had access to more clinical patient records (e.g. EuroSCAR study[89]) and case validity could be addressed more sufficiently, which generally corroborates the validity of our case population. We were furthermore not able to assess false negative SJS/TEN patients in the CPRD. However, owing to the severity of SJS/TEN, it can be assumed that the number of patients for whom a SJS/TEN diagnosis was erroneously not recorded is rather low in any health-care database.

4.2.2 Stevens-Johnson syndrome vs. toxic epidermal necrolysis

Although in the CPRD specific diagnostic codes to differentiate between SJS and TEN exist, we did not differentiate between SJS and TEN for any analyses of the presented project. Firstly, some clinical diagnoses from secondary care, which we used as gold standard for the validation of SJS/TEN diagnoses, did not allow validating SJS and TEN diagnoses separately, because they only consisted of e general code SJS/TEN. As a consequence we were not able to assess the accuracy of differentiation between SJS and TEN diagnoses in the CPRD. Second, neither Read codes nor HES data include a code for SJS/TEN overlap, which is why we assumed that separately calculated IRs would be somewhat overestimated for both SJS and TEN. Previous estimates of the ratio of SJS and TEN are sparse, but have been reported to be 3:1 and 5:1.[86] In our study the ratio of SJS to TEN was approximately 7:1, which may indicate that some TEN cases were recorded as SJS. However, it is also possible that previous studies overestimated the proportion of TEN events relative to SJS. However, given that the pathophysiology and presumed culprit drugs do not differ between SJS, SJS/TEN overlap, and TEN our comparative analyses are not affected by this limitation.

4.2.3 Missing information on drug exposures

Missing information about certain drug exposures is a further limitation of the presented project. The proportion of cases who were recently exposed to well-known culprit drugs of SJS/TEN was lower in our studies than in the hospital-based EuroSCAR study (e.g. 7.5% vs. 25% for AEDs, 1.3% vs. 14.8% for allopurinol).[89] This might indicate that information about drug exposures was missing in some cases. Besides underestimated ORs, this limitation could also have affected the assessment of concomitant use of other high-risk drugs for ALDEN in some cases. The CPRD does furthermore not record over-the-counter drugs (e.g. ibuprofen), inpatient drug use (e.g. chemotherapy or inpatient antibiotic use), or use of HIV drugs (e.g. nevirapine), which is why we were not able to assess associations between SJS/TEN and a number of drugs that have been suggested as culprit drugs of SJS/TEN. This potentially explains why we were only able to identify a likely culprit drug in approximately 25% of SJS/TEN cases, whereas previous

observational studies were able to identify drugs as likely etiologic factor in 65% of SJS/TEN patients.[226] We furthermore cannot guarantee that a patient with a recorded prescription of a certain drug in the CPRD has actually taken this drug, and was therefore correctly considered to be exposed to the respective drug, which is a general limitation of the CPRD.

4.2.4 ALDEN score

The ALDEN score was an invaluable tool for the assessment of potential causality between SJS/TEN and drug exposure in our cases, but might underestimate the causal association for drugs that have not previously been associated with SJS/TEN because it systematically grades causality higher for drugs with previous evidence for an association with SJS/TEN.[20] However, the criterion of causal attribution was not the decisive factor to classify probability of causality in almost all of the assessed cases in Studies 3.3, 3.4, and 3.5 (i.e. causality was likely or unlikely respectively regardless of this criterion in the majority of cases). Due to the available data in the CPRD we furthermore had to adapt some criteria from the original clinical ALDEN score. Among other criteria, the ALDEN score grades the likelihood for causality based on whether or not the drug is present in the patient's body on the day of the onset of SJS/TEN. Because information on the number of prescribed tablets and dose instructions is sometimes missing in the CPRD, and because we do not have information about a patient's adherence to the treatment instructions, we were not able to accurately assess this criterion.

4.2.5 Further limitations

First, although we were primarily interested in IRs and likely etiologic factors of the first recorded SJS/TEN diagnosis in each case patient, we cannot assure that none of the cases included in our studies had an episode of SJS/TEN prior to entering the CPRD. Second, given the rare occurrence of SJS/TEN, low statistical power is an inherent problem of studies analysing risk factors of SJS/TEN, even when using large data

sources such as the CPRD. Therefore, the results presented in our studies have to be interpreted carefully, within the context of previously published evidence and biologic plausibility, and conclusions should not be drawn from one single study. Third, protopathic bias or confounding by indication may play a role in a number of assessed associations between SJS/TEN and drugs. Antibiotics, for example, may be used to treat prodromal symptoms of SJS/TEN or as infection prophylaxis during the treatment of acute disease (although treatment guidelines advised against prophylactic antibiotics, as this might promote skin colonialization, particularly with *Candida albicans*).[172] To minimize the risk of protopathic bias, we defined the index date as the date of the first recorded symptom of SJS/TEN wherever possible, assessed ALDEN scores to quantify the likelihood of causality of observed associations, and performed sensitivity analyses in which we shifted the index date by 2 weeks before the date of the first recorded SJS/TEN diagnosis in all cases without recorded prodromal symptoms wherever applicable. Finally, general limitations of observational research in health-care databases that might not be included in the discussion above are presented in Table 1.1-5.

4.3 Outlook

Although the body of existing research of SJS/TEN is growing rapidly, many aspects of this disease remain unclear and subjects of speculation. This comprehensive SJS/TEN project contributes to the general understanding of this under-investigated disease, by revealing previously unreported findings and by confirming previous hypotheses with little existing evidence regarding the epidemiology and culprit drugs of SJS/TEN. It further provides evidence that similar diseases, such as acute generalized exanthematous pustulosis, can be successfully studied in the CPRD through extensive validation of recorded diagnoses. We hope that the results of our studies as well as future improvements of recorded information within health-care databases will encourage researchers to consider future observational studies on SJS/TEN or similar diseases using data from the CPRD or other similar health-care databases. However, as discussed in Study 3.1, the successful validation of SJS/TEN diagnoses recorded in the CPRD considerably relied on information extracted from free texts and discharge letters. The acquisition of these additional data sources has over the past years been compromised due to patient confidentiality concerns, which might to some extent jeopardize similar research in the future. While working with sensitive patient data inevitably requires regulations on patient confidentiality, this project also highlights the importance of being able to obtain a wide range of health-related patient data in order to be able to conduct observational studies of high-quality. In the light of this project, we would therefore like to point out that patient confidentiality was not at danger of being compromised during our analysis of free texts and discharge letters in any way due to prior anonymization of the patient details and censoring of critical information. Whilst we understand that patient confidentiality is a growing concern particularly with the growing impact and popularity of big data, we are not entirely convinced that halting the collection and access to these additional data sources is the best solution to address these concerns due to the potentially weighty impact on some future observational studies using CPRD data.

While we comprehensively studied the epidemiology of SJS/TEN as well as potential risk factors and culprit drugs of SJS/TEN in our case population, we have so far not studied the mortality and long-term complications in SJS/TEN patients. Analysing the

follow-up in SJS/TEN patients in hospital-based observational studies is challenging, as information about the time after the acute phase of SJS/TEN is difficult to collect. Therefore the various proposed long-term complications in SJS/TEN survivors have almost exclusively been described in case reports or case series.[61] The longitudinal nature of CPRD data, and the fact that death is recorded at high validity, our case population would allow assessing the mortality of SJS/TEN, to analyse the influence of other variables on the risk of dying from SJS/TEN, and to study potential long-term complications in survivors of SJS/TEN. The list of reported long-term complications of SJS/TEN is extensive and diverse.[61] Ocular complications are common in survivors of SJS/TEN but may not be recorded sufficiently in the CPRD, because ocular complications are likely treated by ophthalmologists rather than GPs. Similarly, urogenital/gynaecological complications (e.g. vaginal adenosis) might predominantly be treated in specialised clinics rather than by GPs and thus might not be eligible to be studied in the CPRD. On the other hand psychological complications (e.g. depression or anxiety disorders) and pulmonary complications (e.g. bronchiolitis obliterans) might be assessable via recorded diagnoses, or drug prescriptions and other therapeutic interventions used to manage these long-term complications. We therefore plan to analyse the mortality and, wherever possible, long-term complications of SJS/TEN in a propensity-score matched cohort study using the SJS/TEN case population established in Study 3.1 in the future.

The understanding of genetic factors predisposing for SJS/TEN is growing rapidly, and associations between some culprit drugs of SJS/TEN and predisposing genetic factors (e.g. HLA-B*15:02 for carbamazepine-induced SJS/TEN) have been established with strong evidence.[143] A previous study conducted by Chen et al. has already proven the effectiveness of screening patients for predisposing risk factors of SJS/TEN before initiating therapy with a known culprit drug of SJS/TEN.[158] The absolute risks of SJS/TEN associated with each drug presented within this project might further be useful for future economic considerations regarding such screening, as costs associated with SJS/TEN have been reported previously.[42]

Chapter 5

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Curriculum Vitae

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Date of birth	04.06.1989
Hometown	Erlinsbach (SO)
Nationality	Swiss
Marital status	Single, no children

Education

09/2014 – 03/2018	**PhD with Prof. Christoph R. Meier at the Basel Pharmacoepidemiology Unit (Division Clinical Pharmacy & Epidemiology, University of Basel, Switzerland)** The Epidemiology of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis
09/2016 – 12/2016	**Research stay as part of PhD thesis, Boston Collaborative Drug Surveillance Program, Boston University, USA**
09/2013 – 04/2014	**Master‘s thesis, Institute of Glycomics, Griffith University Gold Coast, Australia** Title: Elucidation of Structure-Function Relationship of the CMP-Sialic acid Transporter
04/2013 – 06/2013	**Internship, Development and validation of a new learning platform (Smartphone-App), University of Basel**
09/2012 – 08/2014	**Master in pharmaceutical sciences, University of Basel**
09/2009 – 08/2012	**Bachelor in pharmaceutical sciences, University of Basel**
08/2005 – 06/2009	**Academic Upper Secondary School Aarau** General qualification for university entrance Focus: biology & chemistry
1995 – 1997	**Johannes-Gutenberg School, Sydney, Australia**

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- Frey N, Bodmer M, Bircher A, Rüegg S, Jick SS, Meier CR, Spoendlin J. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs. Epilepsia. 2017 Dec;58(12):2178-2185. (Impact factor: 5.3)

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- Frey N, Hügle T, Jick SS, Meier CR, Spoendlin J. Hyperlipidaemia and incident osteoarthritis of the hand: a population-based case-control study. Osteoarthritis Cartilage. 2017 Jul;25(7):1040-1045. (Impact factor: 4.7)

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Working experience

09/2006 – 08/2012	Sub worker in the construction industry, F. Blattner Construction Company (holyday job)
06/2010 – 08/2012	Service staff, Boiler Club Aarau
01/2013 – 02/2013	Office employee, architect's office Josef Wettstein

Languages

German	Mother tongue
English	Fluent, spoken and written
French	Conversant, Level B1

Time spent abroad

2016	Boston, USA
2013 – 2014	Gold Coast, Australia
1995 – 1997	Sydney, Australia
1989 – 1991	New Jersey, USA