

Identification of risk factors for carbamazepine-induced serious mucocutaneous adverse reactions: A case-control study using data from spontaneous adverse drug reaction reports

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ABSTRACT

Objectives: To identify risk factors other than genetic for severe carbamazepine-induced mucocutaneous reactions, that is, SJS, TEN, and exfoliative dermatitis (ED). **Materials and Methods:** We did a case-control study using data from the Swedish national database of spontaneously reported adverse drug reactions (ADRs). We selected all patients who had been reported from January 1, 1965 to March 31, 2010 as having experienced SJS ($n = 78$), TEN ($n = 6$), or ED ($n = 8$), and assessed as at least possibly related to carbamazepine. We also included diagnoses possibly representative of early signs of these serious conditions, that is, erythema multiforme (EM, $n = 34$) and scaly rash ($n = 13$). We compared data on demographics, drug treatment, and clinical features for these patients (cases, $n = 139$) with those from patients who had experienced any other type of ADR from carbamazepine during the same time period (controls, $n = 887$). **Results:** After adjustment for multiple comparisons, alcohol abuse was statistically significantly more common among cases than controls (34.5% vs 8.7%, odds ratio 5.5 [95% confidence interval 3.6-8.4], $P = 3.14 \times 10^{-14}$). The same was seen for SJS and EM individually. **Conclusion:** Alcohol abuse is a possible risk factor for serious carbamazepine-induced mucocutaneous reactions.

Key words: Alcohol, exfoliative dermatitis, pharmacovigilance, Stevens–Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Adverse drug reactions (ADRs) are among the leading causes of morbidity and mortality.^[1] Most are dose-dependent and pharmacologically predictable (type A reactions).^[2] Some, however, have no known pharmacological cause (type B reactions). This latter type of ADRs are nonpredictable, commonly serious and lead more frequently than type A reactions to withdrawal of drugs from the market.^[3] Notable examples include the severe mucocutaneous eruptions Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN),

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exfoliative dermatitis (ED), and erythema multiforme (EM) majus.

SJS and TEN typically develop due to specific medications, although other triggers such as infections with *Mycoplasma pneumoniae* and *Herpes simplex* virus are also possible.^[4] SJS and TEN commonly present with fever and malaise, developing into cutaneous erythema with blister formation of various extent and hemorrhagic erosions of mucous membranes, for example, stomatitis, balanitis, colpitis, severe conjunctivitis, and blepharitis.^[5] There is still some debate whether SJS and TEN represent different diseases, but most experts consider them a single disease of different severity,^[1,5] with TEN being the more severe with epidermal detachment of >30% of the body surface area and SJS the less severe defined as <10% detachment.^[6] SJS and TEN are extremely rare, with incidence rates of 1-6 and 0.4-1.2 cases/million persons, respectively, and are associated with mortality rates of up to 5% and 40%, respectively.^[1]

SJS and TEN have long been considered to be variants of EM majus, but are nowadays considered as separate conditions due to differences in clinical presentation and potential causes.^[5,7] Virtually no patient with EM majus dies as a consequence of the condition. Although rarely drug-induced, ED, characterized by erythema and moderate to extensive scaling with involvement of total, or near total, body surface, share many of the clinical features of SJS and TEN.^[8] Whether or not ED is part of the same spectrum as SJS and TEN is unclear. It has been estimated to occur among 1-2/100,000 persons.^[8]

Pharmacovigilance studies have shown that SJS, TEN, and ED can be induced by up to 200 different drugs, although certain drugs including carbamazepine, phenytoin, and allopurinol are the most common ones.^[1,8] Whereas very little is known about the pathogenesis of ED, the mechanism by which SJS and TEN are induced is likely to be immune-mediated,^[4,9] although not fully understood. Candidate gene studies have shown that susceptibility to SJS/TEN has a significant genetic basis, while ED has not been studied in this respect. In genetic association studies of alleles within the HLA class I region, HLA-B*1502 has been shown to be strongly associated with carbamazepine-induced SJS/TEN in Han Chinese individuals.^[10] In Caucasians, HLA-B*1502 is rare and a similar association in this population has not been found. Instead, HLA-A*3101 has been identified as a predictor of carbamazepine-induced cutaneous ADRs such as SJS and TEN.^[11] However, the presence of the HLA-A*3101 allele is neither necessary nor sufficient for their development.

The rarity of the HLA-B*1502 allele in Europeans, coupled with the fact that the association with HLA-A*3101 is not sufficient to explain the pathogenesis of carbamazepine-induced serious cutaneous ADRs highlights the need for further studies. We

therefore aimed to identify possible risk factors other than genetic for severe mucocutaneous eruptions, that is, SJS, TEN, and ED, associated with carbamazepine in a predominantly Caucasian population. We also present a new approach for using databases of spontaneous ADR reports for the detection of possible risk factors for ADRs.

MATERIALS AND METHODS

We did a case-control study using data from the Swedish database of spontaneously reported ADRs (Swedish Drug Information System, SWEDIS).^[12] This database contains reports sent by Swedish physicians to the Swedish Medical Products Agency (MPA) since 1965. As of March 31, 2010, there were in total 103,235 reports in the database. In SWEDIS, a Swedish dictionary is used for coding ADRs, built on a three-level hierarchical structure developed by the MPA (Swedish adverse reaction terminology, SWE-ART). The first level is the system organ class, followed by group terms and finally preferred terms. The dictionary holds a little over 1000 preferred terms. The information in a report consists of patient demographics, reported ADRs, medication, and a case narrative, often accompanied by copies of medical records. All reports are reviewed by clinical assessors at the MPA and a causality assessment is made. All drugs, both suspected and concomitant, are coded using the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology International Anatomical Therapeutic Chemical (ATC) classification.^[13]

For the present study, we selected all patients who had been reported from January 1, 1965 to March 31, 2010 as having experienced reactions coded in SWE-ART as SJS ($n = 78$), TEN ($n = 6$), or ED ($n = 8$), assessed as at least possibly related to carbamazepine treatment (cases, $n = 92$). We also included SWE-ART terms of reactions, which can be difficult to differentiate from early signs of these serious conditions, that is, EM ($n = 34$) and scaly rash ($n = 13$). We compared data on demographics, drug treatment and clinical features for these patients (cases) with those from patients who had experienced any other type of ADR during the same time period (controls). From the initial complete sample of 910 controls, we excluded reports of congenital malformations and miscarriage ($n = 23$) as these are reflective of adverse effects on the fetus and not primarily the patient, arriving at a number of 887 controls. Otherwise there were no restrictions for inclusion.

For each patient, we entered data (age, sex, dose of carbamazepine, time to onset of the ADR, concomitant drugs and their ATC-codes, indication for treatment with carbamazepine and comorbidities) into an Excel spreadsheet (Microsoft Corporation, USA, v14.0). Diseases, that is, indication for treatment and comorbidities, were

coded according to their closest matching ICD-code (ICD 10).^[14] We also grouped diseases of similar type [Table 1] and drugs belonging to the same class [Tables 2 and 3]. Drugs/drug-classes and diseases, which were assessed as unlikely to be associated with SJS/TEN/ED, as well as diseases that

were too poorly defined to be categorized accurately, were excluded [Table 4]. We further excluded drugs/drug-classes and diseases occurring among less than six patients in the complete data-set [Table 3], thereby arriving at a final number of 144 variables for analysis [Table 2].

Table 1: Grouping of diseases of similar type

ICD-10 code	Diagnosis (ICD-10)	Disease group
F31	Bipolar affective disorder	Affective disorder
F32	Depressive episode	Affective disorder
F39	Unspecified mood [affective] disorder	Affective disorder
J30	Vasomotor and allergic rhinitis	Allergy
L23	Allergic contact dermatitis	Allergy
T78.4	Allergy, unspecified	Allergy
F41	Other anxiety disorders	Anxiety disorder
F42	Obsessive-compulsive disorder	Anxiety disorder
M16	Coxarthrosis (arthrosis of hip)	Arthrosis
M17	Gonarthrosis (arthrosis of knee)	Arthrosis
M19	Other arthrosis	Arthrosis
I44	Atrioventricular and left bundle-branch block	Cardiac conduction disorder
I45	Other conduction disorders	Cardiac conduction disorder
I45.9	Stokes-Adams syndrome	Cardiac conduction disorder
I48	Atrial fibrillation and flutter	Cardiac conduction disorder
Z95.0	Presence of cardiac pacemaker	Cardiac conduction disorder
G45	Transient cerebral ischemic attacks and related syndromes	Cerebrovascular disease
I61	Intracerebral hemorrhage	Cerebrovascular disease
I63	Cerebral infarction	Cerebrovascular disease
I64	Stroke, not specified as hemorrhage or infarction	Cerebrovascular disease
I67	Other cerebrovascular diseases	Cerebrovascular disease
R47.0	Dysphasia and aphasia	Cerebrovascular disease
Q90	Down's syndrome	Chromosomal abnormality
Q96	Turner's syndrome	Chromosomal abnormality
Q99.2	Fragile X chromosome	Chromosomal abnormality
D68	Other coagulation defects	Coagulative disorder
D69.1	Qualitative platelet defects	Coagulative disorder
F00	Dementia in Alzheimer's disease	Dementia
F01	Vascular dementia	Dementia
F03	Unspecified dementia	Dementia
F80.1	Expressive language disorder	Developmental disorder
F79	Unspecified mental retardation	Developmental disorder
F82	Specific developmental disorder of motor function	Developmental disorder
A15	Respiratory tuberculosis, bacteriologically and histologically confirmed	Infectious disease
A41.9	Sepsis, unspecified	Infectious disease
A80	Acute poliomyelitis	Infectious disease
B01	Varicella (chickenpox)	Infectious disease
B02	Zoster (herpes zoster)	Infectious disease
B18	Chronic viral hepatitis	Infectious disease
B24	Unspecified human immunodeficiency virus disease	Infectious disease
B34	Viral infection of unspecified site	Infectious disease

Contd...

Table 1: Contd...

ICD-10 code	Diagnosis (ICD-10)	Disease group
B49	Unspecified mycosis	Infectious disease
B58	Toxoplasmosis	Infectious disease
B89	Unspecified parasitic disease	Infectious disease
G04	Encephalitis, myelitis, and encephalomyelitis	Infectious disease
G06	Intracranial and intraspinal abscess and granuloma	Infectious disease
H66	Suppurative and unspecified otitis media	Infectious disease
I38	Endocarditis, valve unspecified	Infectious disease
J01	Acute sinusitis	Infectious disease
J06	Acute upper respiratory infections of multiple and unspecified sites	Infectious disease
J15	Bacterial pneumonia, not elsewhere classified	Infectious disease
J18	Pneumonia, organism unspecified	Infectious disease
J20	Acute bronchitis	Infectious disease
J32	Chronic sinusitis	Infectious disease
J69	Pneumonitis due to solids and liquids	Infectious disease
K81	Cholecystitis	Infectious disease
L04	Acute lymphadenitis	Infectious disease
M46	Other inflammatory spondylopathies	Infectious disease
N39.0	Urinary tract infection, site not specified	Infectious disease
N41	Inflammatory diseases of prostate	Infectious disease
N45	Orchitis and epididymitis	Infectious disease
K50	Crohn's disease (regional enteritis)	Inflammatory bowel disease
K51	Ulcerative colitis	Inflammatory bowel disease
I20	Angina pectoris	Ischemic heart disease
I21	Acute myocardial infarction	Ischemic heart disease
I24	Other acute ischemic heart diseases	Ischemic heart disease
I25	Chronic ischemic heart disease	Ischemic heart disease
G50.0	Trigeminal neuralgia	Neuropathy
G54	Nerve root and plexus disorders	Neuropathy
G58	Other mononeuropathies	Neuropathy
G62	Other polyneuropathy	Neuropathy
G63	Polyneuropathy in diseases classified elsewhere	Neuropathy
J44	Other chronic obstructive pulmonary disease	Obstructive airway disease
J45	Asthma	Obstructive airway disease
F20	Schizophrenia	Psychotic disorder
F23	Acute and transient psychotic disorders	Psychotic disorder
F29	Unspecified nonorganic psychosis	Psychotic disorder
N19	Unspecified kidney failure	Renal failure
Z49	Care involving dialysis	Renal failure
F10	Mental and behavioral disorders due to use of alcohol	Substance/alcohol abuse
F19	Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	Substance/alcohol abuse
D86	Sarcoidosis	Systemic disease
M06	Other rheumatoid arthritis	Systemic disease
M32	Systemic lupus erythematosus	Systemic disease
M35	Other systemic involvement of connective tissue	Systemic disease

Contd...

Table 1: Contd...

ICD-10 code	Diagnosis (ICD-10)	Disease group
M45	Ankylosing spondylitis	Systemic disease
C18	Malignant neoplasm of colon	Tumors
C34	Malignant neoplasm of bronchus and lung	Tumors
C50	Malignant neoplasm of breast	Tumors
C61	Malignant neoplasm of prostate	Tumors
C64	Malignant neoplasm of kidney, except renal pelvis	Tumors
C71	Malignant neoplasm of brain	Tumors
C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	Tumors
C73	Malignant neoplasm of thyroid and other endocrine glands	Tumors
C79	Secondary malignant neoplasm of other and unspecified sites	Tumors
C80	Malignant neoplasm, without specification of site	Tumors
C81	Hodgkin's disease	Tumors
C90	Multiple myeloma and malignant plasma cell neoplasms	Tumors
D30	Benign neoplasm of urinary organs	Tumors
D43	Neoplasm of uncertain or unknown behavior of brain and central nervous system	Tumors
D48	Neoplasm of uncertain or unknown behavior of other and unspecified sites	Tumors
I26	Pulmonary embolism	Venous embolism
I82	Other venous embolism and thrombosis	Venous embolism

ICD=International statistical classification of diseases and related health problems, HIV=Human immunodeficiency virus

Table 2: Variables included in the analyses. ATC-codes N02AA59 (codeine/acetylsalicylic acid/caffeine), M03BB53 (acetylsalicylic acid/dextropropoxyphene/chlorzoxazone) and M01AE51 (ibuprofen/codeine) were placed in both of the drug groups M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51 and N02A+M03BB53+M01AE51. ATC-code B01AC06 (acetylsalicylic acid) was also placed in two groups, B01AC and M01A+N02BA+B01AC06+N02AA59+M03BB53

Drug groups (ATC-code)	<i>n</i>	
N05CD+N05BA+N05CF-Benzodiazepine derivatives+benzodiazepine related drugs	105	Included
N03-Antiepileptics	104	Included
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-Anti-inflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+codeine, combinations with acetylsalicylic acid+ibuprofen, combinations	89	Included
N06A-Antidepressants	89	Included
N05A-Antipsychotics	84	Included
C03-Diuretics	72	Included
C07-Beta blocking agents	71	Included
J01+A07AA-Antibacterials for systemic use+antibiotics	61	Included
B01AC-Platelet aggregation inhibitors excl. heparin	60	Included
N02A+R05DA04+M03BB53+M01AE51-Opioids+codeine+dextropropoxyphene, combination+codeine, combination	56	Included
C09-Agents acting on the renin-angiotensin system	46	Included
C08-Calcium channel blockers	46	Included
A02B-Drugs for peptic ulcer and gastro-esophageal reflux disease	41	Included
R06-Antihistamines for systemic use	38	Included
H02-Corticosteroids for systemic use	34	Included
G03-Sex hormones and modulators of the genital system	29	Included
C10-Lipid modifying agents	22	Included
B01AA-Vitamin K antagonists	21	Included

Contd...

Table 2: Contd...

	<i>n</i>	
C01A-Cardiac glycosides	18	Included
C01D-Vasodilators used in cardiac diseases	16	Included
N07BB-Drugs used in alcohol dependence	15	Included
N04AA+N04AB-Anticholinergic agents, tertiary amines+anticholinergic agents, ethers chemically close to antihistamines	11	Included
N02C-Antimigraine preparations	10	Included
A10B-Blood glucose lowering drugs, excl. insulins	10	Included
M03-Muscle relaxants	9	Included
G04C-Drugs used in benign prostatic hypertrophy	6	Included
J05-Antivirals for systemic use	6	Included
L02A-Hormones and related agents	6	Included
Individual drugs (ATC-code)		
N02BE01-Paracetamol	58	Included
B01AC06-Acetylsalicylic acid	56	Included
C03CA01-Furosemide	37	Included
N03AB02-Phenytoin	35	Included
C07AB02-Metoprolol	32	Included
N02AC04-Dextropropoxyphene	30	Included
N06AB04-Citalopram	30	Included
N05BA04-Oxazepam	29	Included
N05CM06-Propiomazine	28	Included
N05BA01-Diazepam	26	Included
C07AB03-Atenolol	25	Included
N05CF01-Zopiclone	24	Included
C09AA02-Enalapril	23	Included
H02AB01-Betamethasone	20	Included
R06AD01-Alimemazine	19	Included
B01AA03-Warfarin	18	Included
C01AA05-Digoxin	18	Included
N05CD02-Nitrazepam	18	Included
A02BC01-Omeprazole	17	Included
C08CA02-Felodipine	17	Included
N03AG01-Valproic acid	17	Included
N05CM02-Chlometiazole	17	Included
C10AA01-Simvastatin	15	Included
N03AX09-Lamotrigine	15	Included
N06AA09-Amitriptyline	15	Included
C03DB01-Amiloride	14	Included
N03AE01-Clonazepam	14	Included
N05AB01-Dixyrazine	14	Included
H02AB06-Prednisolone	13	Included
N07BB01-Disulfiram	13	Included
C03AA01-Bendroflumethiazide	12	Included
C08CA01-Amlodipine	12	Included
N05CF02-Zolpidem	12	Included
N02AA59-Acetylsalicylic acid/codeine/caffeine	11	Included
J01CE02-Phenoxyethylpenicilline	10	Included

Contd...

Table 2: Contd...

	<i>n</i>	
N05AA02-Levomepromazine	10	Included
C01DA02-Glyceryl trinitrate	9	Included
N02AX02-Tramadol	9	Included
N05AC02-Thioridazine	9	Included
C01DA14-Isosorbide mononitrate	8	Included
C08DA01-Verapamil	8	Included
N03AA02-Phenobarbital	8	Included
N03AX12-Gabapentin	8	Included
N05AA01-Chlorpromazine	8	Included
N05AD03-Melperone	8	Included
N05AF05-Zuclopentixole	8	Included
N05AN01-Lithium	8	Included
N05BA12-Alprazolam	8	Included
N05BB01-Hydroxyzine	8	Included
A02BA02-Ranitidine	7	Included
A02BC03-Lansoprazol	7	Included
A10BB01-Glibenclamide	7	Included
C03EA01-Amiloride/hydrochlorothiazide	7	Included
C08DB01-Diltiazem	7	Included
J01EE01-Sulfamethoxazole/trimethoprim	7	Included
J01FF01-Clindamycine	7	Included
N05AD01-Haloperidol	7	Included
N06AX11-Mirtazapine	7	Included
C07AA05-Propranolol	6	Included
C09CA06-Candesartan	6	Included
J01DC02-Cefuroxime	6	Included
M04AA01-Allopurinol	6	Included
N02BA01-Acetylsalicylic acid	6	Included
N03AA03-Primidone	6	Included
N05AH03-Olanzapine	6	Included
N05AX08-Risperidone	6	Included
N06AA04-Clomipramine	6	Included
R05CB01-Acetylcysteine	6	Included
R06AA04-Clemastine	6	Included
Disease groups*		
Diagnosis group-Neuropathy	162	Included
Diagnosis group-Substance/alcohol abuse	139	Included
Diagnosis group-Infectious disease	73	Included
Diagnosis group-Tumor	62	Included
Diagnosis group-Cerebrovascular disease	58	Included
Diagnosis group-Affective disorder	45	Included
Diagnosis group-Psychotic disorder	33	Included
Diagnosis group-Ischemic heart disease	17	Included
Diagnosis group-Obstructive airway disease	15	Included
Diagnosis group-Cardiac conduction disorder	14	Included
Diagnosis group-Dementia	9	Included

Contd...

Table 2: Contd...

	<i>n</i>	
Diagnosis group-Systemic disease	8	Included
Diagnosis group-Anxiety disorder	6	Included
Diagnosis group-Venous embolism	6	Included
Individual diseases (ICD-10)		
G40-Epilepsy	510	Included
G50.0-Trigeminal neuralgia	128	Included
F10-Mental and behavioral disorders due to use of alcohol	125	Included
I10-Essential (primary) hypertension	46	Included
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	44	Included
F39-Unspecified mood (affective) disorder	39	Included
G62-Other polyneuropathy	35	Included
I64-Stroke, not specified as hemorrhage or infarction	30	Included
B02-Zoster (herpes zoster)	27	Included
E14-Unspecified diabetes mellitus	19	Included
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	18	Included
I61-Intracerebral hemorrhage	18	Included
F23-Acute and transient psychotic disorders	17	Included
F20-Schizophrenia	16	Included
E03-Other hypothyroidism	13	Included
I48-Atrial fibrillation and flutter	11	Included
I21-Acute myocardial infarction	10	Included
J45-Asthma	10	Included
G44-Other headache syndromes	8	Included
I50-Heart failure	8	Included
M79-Other soft tissue disorders, not elsewhere classified	8	Included
G43-Migraine	7	Included
G80-Cerebral palsy	7	Included
I20-Angina pectoris	7	Included
N39.0-Urinary tract infection, site not specified	7	Included
F03-Unspecified dementia	6	Included
F41-Other anxiety disorders	6	Included
I67-Other cerebrovascular diseases	6	Included
J44-Other chronic obstructive pulmonary disease	6	Included

ATC=Anatomical therapeutic chemical, GERD=Gastro-esophageal reflux disease, ICD=International statistical classification of diseases and related health problems, *Disease groups are defined in Table 1

Table 3: Variables excluded from analyses (occurring among less than six patients)

	<i>n</i>	
Drug groups (ATC-code)		
A03F-Propulsives	5	Excluded
L01-Antineoplastic agents	5	Excluded
B01AB-Heparin group	4	Excluded
D02-Emollients and protectives	4	Excluded
L03AB-Interferons	4	Excluded
R03DA-Xanthines	4	Excluded
D07-Glucocorticoids, dopaminergic preparations	3	Excluded
G04BD-Urinary antispasmodics	3	Excluded
N04B-Dopaminergic agents	3	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
P01B-Antimalarials	3	Excluded
B03XA-Other antianemic preparations	2	Excluded
C01B-Antiarrhythmics, class I and III	2	Excluded
D01AC-Imidazole and triazole derivatives	2	Excluded
N06BA-Centrally acting sympathomimetics	2	Excluded
G03A-Hormonal contraceptives for systemic use	1	Excluded
Individual drugs (ATC-code)		
B01AC07-Dipyridamole	5	Excluded
C03DA01-Spironolactone	5	Excluded
C09AA05-Ramipril	5	Excluded
G03CA04-Estriol	5	Excluded

Contd...

Table 3: Contd...		<i>n</i>
J01MA06-Norfloxacin	5	Excluded
M01AB05-Diclofenac	5	Excluded
M01AE01-Ibuprofen	5	Excluded
M01AE01-Ibuprofen	5	Excluded
M03BX01-Baclophene	5	Excluded
N02AB01-Ketobemidone	5	Excluded
N04AA02-Biperidone	5	Excluded
N04AB02-Orphenadrine	5	Excluded
N05AB03-Perfenazine	5	Excluded
N06AB06-Sertraline	5	Excluded
N06AX16-Venlafaxine	5	Excluded
A10BA02-Metformin	4	Excluded
C07AA07-Sotalol	4	Excluded
C09CA04-Irbesartan	4	Excluded
G03AC03-Levonorgestrel	4	Excluded
G04CB01-Finasteride	4	Excluded
J01CA08-Pivmecillinam	4	Excluded
J01DB05-Cefadroxil	4	Excluded
J01FA01-Erythromycin	4	Excluded
J01MA02-Ciprofloxacin	4	Excluded
J02AC01-Fluconazole	4	Excluded
J05AB01-Aciclovir	4	Excluded
L02AB02-Medroxyprogesterone	4	Excluded
N02AA01-Morphine	4	Excluded
N03AG04-Vigabatrin	4	Excluded
N03AX11-Topiramate	4	Excluded
N05AF03-Chlorprothixene	4	Excluded
N05AH02-Clozapine	4	Excluded
N05BA06-Lorazepam	4	Excluded
N05CD03-Flunitrazepam	4	Excluded
N06AX03-Mianserin	4	Excluded
R06AD02 Promethazine	4	Excluded
R06AX13-Loratadin	4	Excluded
A02BC05-Esomeprazole	3	Excluded
A02BX02-Sucralphate	3	Excluded
A03AX13-Dimeticone	3	Excluded
A03FA02-Cisapride	3	Excluded
A07AA02-Nystatin	3	Excluded
A07DA03-Loperamide	3	Excluded
B01AA01-Dicoumarol	3	Excluded
B02AA02-Tranexamic acid	3	Excluded
C09CA01-Losartan	3	Excluded
D02AE01-Carbamide	3	Excluded
G03AA07-Ethinylestradiol/levonorgestrel	3	Excluded
G03DC03-Lynestrenol	3	Excluded
G03FA01-Estradiol/norethisterone	3	Excluded
J01AA02-Doxycycline	3	Excluded
J01CE01-Benzylpenicillin	3	Excluded
J01CF05-Flucloxacillin	3	Excluded
J01EA01-Trimethoprim	3	Excluded
J01XX05-Metenammine	3	Excluded
M01AE02-Naproxen	3	Excluded
N02CA72-Ergotamine/chlorcyclizine/caffeine	3	Excluded
N02CC01-Sumatriptan	3	Excluded
N03AX14-Levetiracetam	3	Excluded
N03AX16-Pregabalin	3	Excluded

Contd...

Table 3: Contd...		<i>n</i>
N05BA02-Chlordiazepoxide	3	Excluded
N05BE01-Buspiron	3	Excluded
N05CD08-Midazolam	3	Excluded
N06AA07-Lofepamine	3	Excluded
N06AB05-Paroxetin	3	Excluded
P01AB01-Metronidazole	3	Excluded
R06AE07-Cetirizine	3	Excluded
S01XA20-Artificial tears and other indifferent preparations	3	Excluded
A01AA01-Sodium flouride	2	Excluded
A02BC02-Pantoprazol	2	Excluded
A03FA01-Metoclopramide	2	Excluded
B01AB01-Heparin	2	Excluded
B02BA01-Phytomenadione	2	Excluded
C01DA08-Isosorbiddinitrate	2	Excluded
C03AA03-Hydrochlorothiazide	2	Excluded
C07AB07-Bisoprolol	2	Excluded
C08CA05-Nifedipine	2	Excluded
C09AA01-Captopril	2	Excluded
C10AA03-Pravastatin	2	Excluded
C10AA05-Atorvastatin	2	Excluded
C10AA07-Rosuvastatin	2	Excluded
D07AC01-Betamethasone	2	Excluded
G03AB03-Ethinylestradiol/Levonorgestrel	2	Excluded
G03AC08-Etonogestrel	2	Excluded
G03CA03-Estradiol	2	Excluded
G03CA57-Conjugated estrogens	2	Excluded
G04BD07-Tolterodine	2	Excluded
G04CA01-Alfuzosin	2	Excluded
G04CA03-Terazocin	2	Excluded
H01BA02-Desmopressin	2	Excluded
J01CA04-Amoxicillin	2	Excluded
J01DB01-Cefalexin	2	Excluded
J05AE06-Lopinavir/ritonavir	2	Excluded
L01AD02-Lomustine	2	Excluded
L01AX03-Temozolomide	2	Excluded
M01AB01-Indomethacine	2	Excluded
M02AA10-Ketoprofen	2	Excluded
M03BB53-Acetylsalicylic acid/dextropropoxyphene/chlorzoxazone	2	Excluded
N02CA52-Ergotamine/caffeine	2	Excluded
N02CC03-Zolmitriptan	2	Excluded
N03AB05-Fosphenytoin	2	Excluded
N03AD01-Ethosuximide	2	Excluded
N04BA02-Benserazide/levodopa	2	Excluded
N05AL04-Remoxipride	2	Excluded
N06AA10-Nortriptyline	2	Excluded
N06AB10-Escitalopram	2	Excluded
N06AX21-Duloxetine	2	Excluded
N06DA02-Donepezil	2	Excluded
N07BB02-Calciumcarbimidium/carbonic acid barium salt	2	Excluded
N07BB03-Acamprosate	2	Excluded
R03DA02-Choline theophyllinate	2	Excluded
R03DA04-Theophylline	2	Excluded
R06AX12-Terfenadine	2	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
S01EC01-Acetazolamide	2	Excluded
A02AD01-Ordinary salts, combinations	1	Excluded
A02BA01-Cimetidine	1	Excluded
A02BA03-Famotidine	1	Excluded
A02BC04-Rabeprazol	1	Excluded
A02BC04-Rabeprazole	1	Excluded
A03AB12-Mepenzolate	1	Excluded
A05AA02-Ursodeoxicholic acid	1	Excluded
A07AA09-Vancomycin	1	Excluded
A08AB01-Orlistat	1	Excluded
A10BB07-Glipizide	1	Excluded
A12CE-Selenium	1	Excluded
B01AB04-Dalteparin	1	Excluded
B01AB05-Enoxaparin	1	Excluded
B01AC04-Clopidogrel	1	Excluded
B01AC05-Ticlopidine	1	Excluded
B02BD02-Coagulation factor VIII	1	Excluded
B03XA01-Erythropoietin	1	Excluded
B03XA02-Darbepoetin alfa	1	Excluded
C01AA04-Digitoxin	1	Excluded
C01BA03-Disopyramide	1	Excluded
C01BC04-Flecainide	1	Excluded
C02AC01-Clonidine	1	Excluded
C02CA04-Doxazosin	1	Excluded
C03AB01-Bendroflumethiazide/potassium chloride	1	Excluded
C03AB03-Hydrochlorothiazide/potassium	1	Excluded
C03CA02-Bumetanide	1	Excluded
C03CA04-Torsemide	1	Excluded
C05AD01-Lidocaine	1	Excluded
C05BA01-Organo-heparinoid	1	Excluded
C07AA03-Pindolol	1	Excluded
C07AG02-Carvedilol	1	Excluded
C07FB02-Felodipin/metoprolol	1	Excluded
C09AA03-Lisinopril	1	Excluded
C09BA02-Enalapril/hydrochlorothiazide	1	Excluded
C09BA06-Hydrochlorothiazide/quinapril	1	Excluded
C09CA02-Eprosartan	1	Excluded
C09CA03-Valsartan	1	Excluded
C10AC02-Colestipol	1	Excluded
C10AD01-Niceritrol	1	Excluded
D01AC03-Econazole	1	Excluded
D01AC20-Econazole/triamcinolon	1	Excluded
D01BA02-Terbinafine	1	Excluded
D02AX-Other emollients and protectives	1	Excluded
D05AX02-Calcipotriol	1	Excluded
D07AC13-Mometasone	1	Excluded
G02AD03-Gemprost	1	Excluded
G03AA05-Norethisterone/estrogen	1	Excluded
G03AC06-Medroxyprogesterone	1	Excluded
G03CX01-Tibolone	1	Excluded
G04BD08-Solifenacin	1	Excluded
H02AB10-Cortisone	1	Excluded
J01CA01-Ampicillin	1	Excluded
J01CF01-Dicloxacillin	1	Excluded
J01CR05-Piperacillin/tazobactam	1	Excluded
J01DA08-Cefaclor	1	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
J01DD01-Cefotaxim	1	Excluded
J01DD14-Ceftibuten	1	Excluded
J01GB01-Tobramycin	1	Excluded
J01GB03-Gentamicin	1	Excluded
J01XE01-Nitrofurantoin	1	Excluded
J05AR01-Lamivudine/zidovudine	1	Excluded
L01CA02-Vincristine	1	Excluded
L01XB01-Procarbazine	1	Excluded
L01XX05-Hydroxycarbamide	1	Excluded
L02AE04-Triptorelin	1	Excluded
L02BB03-Bicalutamide	1	Excluded
L03AA02-Filgastrim	1	Excluded
L03AB01-Interferon alfa natural	1	Excluded
L03AB05-Interferon alfa-2b	1	Excluded
L03AB07-Interferon beta	1	Excluded
L03AB08-Interferon beta-1a	1	Excluded
L04AD01-Ciclosporin	1	Excluded
M01AB02-Sulindac	1	Excluded
M01AC01-Piroxicam	1	Excluded
M01AE51-Ibuprofen/codeine	1	Excluded
M01AH02-Rofecoxib	1	Excluded
M01AH05-Etoricoxib	1	Excluded
M01AX05-Glucosamine	1	Excluded
M03AX01-Botulinum toxin	1	Excluded
M03BA03-Methocarbamol	1	Excluded
M05BA04-Alendronic acid	1	Excluded
N01AH04-Phenoperidine	1	Excluded
N01BB52-Lidocaine, combinations	1	Excluded
N02CA01-Dihydroergotamine	1	Excluded
N03AF02-Oxcarbazepine	1	Excluded
N04AA01-Trihexyphenidyl	1	Excluded
N04BC05-Pramipexole	1	Excluded
N05AH04-Quetiapine	1	Excluded
N05AL01-Sulpiride	1	Excluded
N05AL02-Sulpiride	1	Excluded
N05BC01-Meprobamate	1	Excluded
N05CD05-Triazolam	1	Excluded
N06AA02-Imipramine	1	Excluded
N06AA06-Trimipramine	1	Excluded
N06AA21-Maprotilines	1	Excluded
N06AB02-Zimeldine	1	Excluded
N06AF01-Isocarboxacid	1	Excluded
N06AG02-Moclobemide	1	Excluded
N06AX06-Nefazodone	1	Excluded
N06AX18-Reboxetine	1	Excluded
N06BA04-Methylphenidate	1	Excluded
N06BA07-Modafinil	1	Excluded
N06BC01-Caffeine	1	Excluded
N07BA01-Nicotine	1	Excluded
P01BA01-Chloroquine phosphate	1	Excluded
P01BC01-Quinine	1	Excluded
P01BD01-Pyrimethamine	1	Excluded
R01BA01-Phenylpropanolamin	1	Excluded
R03DC03-Montelukast	1	Excluded
R05DA04-Codeine	1	Excluded
R06AE03-Cyclizine	1	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
S01ED51-Timolol, combinations	1	Excluded
S03CA04-Hydrocortisone/oxitetracycline/ polymyxine B	1	Excluded
V08AB02-lohexol	1	Excluded
Disease groups*		
Diagnosis group-Allergy	4	Excluded
Diagnosis group-Arthrosis	4	Excluded
Diagnosis group-Inflammatory bowel disease	4	Excluded
Diagnosis group-Chromosomal abnormality	3	Excluded
Diagnosis group-Coagulative disorder	3	Excluded
Diagnosis group-Renal failure	2	Excluded
Individual diseases (ICD-10)		
E78-Disorders of lipoprotein metabolism and other lipidemias	5	Excluded
F31-Bipolar affective disorder	5	Excluded
I26-Pulmonary embolism	5	Excluded
L40-Psoriasis	5	Excluded
B18-Chronic viral hepatitis	4	Excluded
F90-Hyperkinetic disorders	4	Excluded
G25-Other extrapyramidal and movement disorders	4	Excluded
G35-Multiple sclerosis	4	Excluded
G45-Transient cerebral ischemic attacks and related syndromes	4	Excluded
G54-Nerve root and plexus disorders	4	Excluded
G93-Other disorders of brain	4	Excluded
I25-Chronic ischemic heart disease	4	Excluded
I60-Subarachnoid hemorrhage	4	Excluded
K73-Chronic hepatitis, not elsewhere classified	4	Excluded
M25-Other joint disorders, not elsewhere classified	4	Excluded
M54-Dorsalgia	4	Excluded
R20-Disturbances of skin sensation	4	Excluded
R44-Other symptoms and signs involving general sensations and perceptions	4	Excluded
R94.0-Abnormal results of function studies of central nervous system	4	Excluded
B49-Unspecified mycosis	3	Excluded
C34-Malignant neoplasm of bronchus and lung	3	Excluded
C61-Malignant neoplasm of prostate	3	Excluded
C64-Malignant neoplasm of kidney, except renal pelvis	3	Excluded
E53-Deficiency of other B group vitamins	3	Excluded
F13-Mental and behavioral disorders due to use of sedatives or hypnotics	3	Excluded
F32-Depressive episode	3	Excluded
G47-Sleep disorders	3	Excluded
G81-Hemiplegia	3	Excluded
J01-Acute sinusitis	3	Excluded
J06-Acute upper respiratory infections of multiple and unspecified sites	3	Excluded
J18-Pneumonia, organism unspecified	3	Excluded
K29-Gastritis and duodenitis	3	Excluded
K51-Ulcerative colitis	3	Excluded
M10-Gout	3	Excluded
M35-Other systemic involvement of connective tissue	3	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
M51-Other intervertebral disc disorders	3	Excluded
N40-Hyperplasia of prostate	3	Excluded
R51-Headache	3	Excluded
A15-Respiratory tuberculosis, bacteriologically and histologically confirmed	2	Excluded
B01-Varicella (chickenpox)	2	Excluded
B89-Unspecified parasitic disease	2	Excluded
C18-Malignant neoplasm of colon	2	Excluded
C71-Malignant neoplasm of brain	2	Excluded
C73-Malignant neoplasm of thyroid and other endocrine glands	2	Excluded
D69.1-Hereditary thrombocyte disorder	2	Excluded
D86-Sarcoidosis	2	Excluded
E20-Hypoparathyroidism	2	Excluded
E66-Obesity	2	Excluded
F00-Dementia in Alzheimer's disease	2	Excluded
F17-Mental and behavioral disorders due to use of tobacco	2	Excluded
F60-Specific personality disorders	2	Excluded
F89-Unspecified disorder of psychological development	2	Excluded
G06-Intracranial and intraspinal abscess and granuloma	2	Excluded
G20-Parkinson's disease	2	Excluded
G63-Polyneuropathy in diseases classified elsewhere	2	Excluded
H36-Retinal disorders in diseases classified elsewhere	2	Excluded
H40-Glaucoma	2	Excluded
H93.1-Tinnitus	2	Excluded
I63-Cerebral infarction	2	Excluded
L30.9-Dermatitis, unspecified	2	Excluded
M06-Other rheumatoid arthritis	2	Excluded
M16-Coxarthrosis (arthrosis of hip)	2	Excluded
M32-Systemic lupus erythematosus	2	Excluded
M81-Osteoporosis without pathological fracture	2	Excluded
N19-Unspecified kidney failure	2	Excluded
Q03-Congenital hydrocephalus	2	Excluded
Q28-Other congenital malformations of circulatory system	2	Excluded
R41-Other symptoms and signs involving cognitive functions and awareness	2	Excluded
R42-Dizziness and giddiness	2	Excluded
R47.0-Dysphasia and aphasia	2	Excluded
R50-Fever of other and unknown origin	2	Excluded
R55-Syncope and collapse	2	Excluded
R62-Lack of expected normal physiological development	2	Excluded
T78.4-Allergy, unspecified	2	Excluded
Z95.0-Presence of cardiac and vascular implants and grafts	2	Excluded
A41.9-Sepsis, unspecified	1	Excluded
A80-Acute poliomyelitis	1	Excluded
B24-Unspecified human immunodeficiency virus disease	1	Excluded
B34-Viral infection of unspecified site	1	Excluded
B58-Toxoplasmosis	1	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
C50-Malignant neoplasm of breast	1	Excluded
C72-Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	1	Excluded
C79-Secondary malignant neoplasm of other and unspecified sites	1	Excluded
C80-Malignant neoplasm, without specification of site	1	Excluded
C81-Hodgkin's disease	1	Excluded
C90-Multiple myeloma and malignant plasma cell neoplasms	1	Excluded
D30-Benign neoplasm of urinary organs	1	Excluded
D48-Neoplasm of uncertain or unknown behavior of other and unspecified sites	1	Excluded
D64-Other anemias	1	Excluded
D68-Other coagulation defects	1	Excluded
D70-Agranulocytosis	1	Excluded
D84-Other immunodeficiencies	1	Excluded
D89-Other disorders involving the immune mechanism, not elsewhere classified	1	Excluded
E21-Hyperparathyroidism and other disorders of parathyroid gland	1	Excluded
E23.2-Diabetes insipidus	1	Excluded
E27.1-Primary adrenocortical insufficiency	1	Excluded
F01-Vascular dementia	1	Excluded
F05.9-Delirium, unspecified	1	Excluded
F11-Mental and behavioral disorders due to use of opioids	1	Excluded
F15-Mental and behavioral disorders due to use of other stimulants, including caffeine	1	Excluded
F29-Unspecified nonorganic psychosis	1	Excluded
F42-Obsessive-compulsive disorder	1	Excluded
F48.0-Neurasthenia	1	Excluded
F80.1-Expressive language disorder	1	Excluded
F84-Pervasive developmental disorders	1	Excluded
F95-Tic disorders	1	Excluded
G03-Meningitis due to other and unspecified causes	1	Excluded
G04-Encephalitis, myelitis and encephalomyelitis	1	Excluded
G31-Other degenerative diseases of nervous system, not elsewhere classified ("Progredierande hjärnatrofi")	1	Excluded
G58-Other mononeuropathies	1	Excluded
G64-Other disorders of peripheral nervous system	1	Excluded
G82-Paraplegia and tetraplegia	1	Excluded
G83-Other paralytic syndromes	1	Excluded
G93.0-Cerebral cysts	1	Excluded
G95-Other diseases of spinal cord	1	Excluded
H53-Visual disturbances	1	Excluded
H60-Otitis externa	1	Excluded
H66-Suppurative and unspecified otitis media	1	Excluded
I24-Other acute ischemic heart diseases	1	Excluded
I38-Endocarditis, valve unspecified	1	Excluded
I44-Atrioventricular and left bundle-branch block	1	Excluded
I45-Other conduction disorders	1	Excluded
I45.9-Conduction disorder, unspecified	1	Excluded
I71-Aortic aneurysm and dissection	1	Excluded
I72-Other aneurysm and dissection	1	Excluded
I82-Other venous embolism and thrombosis	1	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
J15-Bacterial pneumonia, not elsewhere classified	1	Excluded
J20-Acute bronchitis	1	Excluded
J30-Vasomotor and allergic rhinitis	1	Excluded
J32-Chronic sinusitis	1	Excluded
J69-Pneumonitis due to solids and liquids	1	Excluded
K11-Diseases of salivary glands	1	Excluded
K20-Esophagitis	1	Excluded
K21-Gastro-esophageal reflux disease	1	Excluded
K30-Dyspepsia	1	Excluded
K44-Diaphragmatic hernia	1	Excluded
K50-Crohn's disease (regional enteritis)	1	Excluded
K76-Other diseases of liver	1	Excluded
K81-Cholecystitis	1	Excluded
L02-Cutaneous abscess, furuncle and carbuncle	1	Excluded
L04-Acute lymphadenitis	1	Excluded
L23-Allergic contact dermatitis	1	Excluded
L68-Hirsutism	1	Excluded
L93-Lupus erythematosus	1	Excluded
L98-Other disorders of skin and subcutaneous tissue, not elsewhere classified	1	Excluded
M17-Gonarthrosis	1	Excluded
M19-Other arthrosis	1	Excluded
M25.5-Pain in joint	1	Excluded
M41-Scoliosis	1	Excluded
M45-Ankylosing spondylitis	1	Excluded
M46-Other inflammatory spondylopathies	1	Excluded
M47-Spondylosis deformans	1	Excluded
N14-Drug-and heavy-metal-induced tubulo-interstitial and tubular conditions	1	Excluded
N20.0-Calculus of kidney	1	Excluded
N25-Disorders resulting from impaired renal function	1	Excluded
N41-Inflammatory diseases of prostate	1	Excluded
N45-Orchitis and epididymitis	1	Excluded
N94-Pain and other conditions associated with female genital organs and menstrual cycle	1	Excluded
N95-Menopausal and other perimenopausal disorders	1	Excluded
O04-Medical abortion	1	Excluded
P54-Other neonatal hemorrhages	1	Excluded
P59-Neonatal jaundice from other and unspecified causes	1	Excluded
Q02-Microcephaly	1	Excluded
Q04-Other congenital malformations of brain	1	Excluded
Q05-Spina bifida	1	Excluded
Q07-Other congenital malformations of nervous system	1	Excluded
Q87.0-Congenital malformation syndromes predominantly affecting facial appearance	1	Excluded
Q90-Down's syndrome	1	Excluded
Q96-Turner's syndrome	1	Excluded
Q99.2-Fragile X chromosome	1	Excluded
R10-Abdominal and pelvic pain	1	Excluded
R20.2-Paraesthesia of skin	1	Excluded
R32-Unspecified urinary incontinence	1	Excluded
R79-Other abnormal findings of blood chemistry	1	Excluded
S02-Fracture of skull and facial bones	1	Excluded

Contd...

Table 3: Contd...

	<i>n</i>	
S06-Intracranial injury	1	Excluded
T85-Complications of other internal prosthetic devices, implants, and grafts	1	Excluded
X84-Intentional self-harm by unspecified means	1	Excluded
Z49-Care involving dialysis	1	Excluded
Z90-Acquired absence of organs, not elsewhere classified	1	Excluded
Z96-Presence of other functional implants	1	Excluded

*Disease groups are defined in Table 1. ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, HIV=Human immunodeficiency virus

Table 4: Excluded drugs/drug groups unlikely to be associated with SJS/TEN/ED, and excluded conditions too poorly defined

Drugs/drug groups (ATC-code)
A11-Vitamins
B03B-Vitamin B12 and folic acid
H03A-Thyroid preparations
A10A-Insulins and analogues
R03A-Adrenergics, inhalants
R03BA-Glucocorticoids, inhalants
R03BB-Anticholinergics
A06-Laxatives
A12B+B05XA01-Potassium+potassium chloride
A12A-Calcium
B05BB01-Sodium chloride
B03A-Iron preparations
V06DD-Amino acids, incl. combinations with polypeptides
Diagnoses (ICD-10) and disease groups*
R56-Convulsions, not elsewhere classified
R52-Pain, not elsewhere classified
Z92.4-Personal history of major surgery, not elsewhere classified
F99-Mental disorder, not otherwise specified
R94.0-Abnormal results of function studies of central nervous system
I51-Complications and ill-defined descriptions of heart disease
S33-Dislocation, sprain, and strain of joints and ligaments of lumbar spine and pelvis
S52-Fracture of forearm
Z29-Need for other prophylactic measures
Disease group-Developmental disorder

*Disease groups are defined in Table 1. ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems

Differences between cases and controls regarding age, sex, dose of carbamazepine, time to onset of the ADR, and for each variable in Table 2 were assessed for SJS, TEN, ED, EM, and scaly rash both separately and as a group. Fisher's exact test was used when comparing proportions and Student's *t*-test for mean values. We used Bonferroni's correction to adjust for the 864 comparisons that were made (144×6), which gave a two-tailed *P* value of 5.787×10^{-5} for statistical significance with 80% power. When comparing the mean daily dose of carbamazepine between groups, we excluded extreme outliers,

that is, cases of intentional self-intoxication with high doses ($n = 3$, doses ranging from 6000 to 20000 mg), young children below the age of 12 years ($n = 80$), and cases where information about the dose was likely to be erroneous ($n = 3$, daily doses ranging from 0.2 to 40 mg). For time to onset of the ADR, we similarly excluded extreme outliers ($n = 6$, time ranging from 7300 to 22,920 days). As the distribution of time to onset of the ADR was markedly skewed we ln-transformed this variable. All calculations were performed in JMP 7.0.1 (SAS Institute Inc., Cary, North Carolina, USA).

To test the validity of the data and the appropriateness of the study methodology, we also investigated whether known risk factors for carbamazepine-induced hyponatremia and SIADH, that is, high age, female gender, high dose, and concomitant treatment with antidepressants or diuretics (loop-diuretics and thiazides),^[15-19] would be more common among cases than controls, as expected. In the present dataset, there were 38 cases of hyponatremia and 14 of SIADH (terms according to SWE-ART).

Ethics approval

The study was approved by the local ethics committee (Sweden, Uppsala, 2012/200).

RESULTS

Patient characteristics in the complete data-set are shown in Table 5. The mean age was 48.9 years and there were slightly more women than men (51.3% vs 48.7%). The most common indication for treatment with carbamazepine was epilepsy, followed by trigeminal neuralgia and alcohol-related mental disorders. About 70% of all reports had been classified as serious. The most commonly involved system organ class was skin and subcutaneous tissue disorders (37.2%).

Differences between cases and controls for each studied variable are shown in Tables 6-11. When all investigated skin reactions (SJS, TEN, ED, EM, and scaly rash) were grouped [Table 6], alcohol-related mental and behavioral disorders were statistically significantly more common among cases than controls (34.5%, $n = 48$ vs 8.7%, $n = 77$; odds ratio (OR)=5.5 [95% confidence interval (CI) 3.6-8.4], $P = 3.14 \times 10^{-14}$), as was the disease group substance/alcohol abuse (37.4%, $n = 52$ vs 9.8%, $n = 87$; OR = 5.5 [3.7-8.3], $P = 5.99 \times 10^{-15}$). Mean time to onset was shorter among cases than controls (67 vs 127 days). The same pattern was evident for SJS [Table 7] and EM [Table 10] individually, although time to onset was not significantly different from the control group in the latter case. No statistically significant differences were seen for TEN [Table 8], ED [Table 9] and scaly rash [Table 11] individually, although for the latter, ORs similar to those for SJS and EM were seen regarding alcohol-related mental and behavioral disorders. For all of the

Table 5: Characteristics of the 1026 patients in the complete data-set

Variable	Mean	Median	Range
Age (years)	48.9	52	0-92
Gender (%)	48.7 male 51.3 female		
Dose carbamazepine (mg/day)	530	400	0.2-20000
After exclusion of extreme outliers	490.8	400	100-2000
Duration of treatment (days)	232.7	21	1-22920
After exclusion of extreme outliers	117.7	21	1-3650
In transformation	3	3	0-8.2
Indication for treatment with carbamazepine (ICD-10) (%)	G40-Epilepsy 56.8% G50-Trigeminal neuralgia 12.2% F10 2 Mental and behavioral disorders due to use of alcohol 9.2% B02-Zoster (herpes zoster) 3.1% G62-Other polyneuropathy 2.3% R56-Convulsions, not elsewhere classified 1.7% F23-Acute and transient psychotic disorders 1.5% F39-Unspecified mood (affective) disorder 1.4% D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system 1.2% Other 10.6%		
Reporter type (%)	Hospital physician 84.4% General practitioner 14.4% Other healthcare professional 1.2%		
Outcome (%)	Fatal 1.4% Not yet recovered 12.8% Recovered with sequelae 0.4% Recovered without sequelae 68.9% Unknown 16.5%		
Seriousness (%)	Serious 69.6% Nonserious 30.4%		
Route of administration of carbamazepine (%)	Per oral 99.3% Unknown 0.7%		
Adverse drug reaction-system organ classes (SWE-ART) (%)	Skin and subcutaneous tissue disorders 37.2% Blood and lymphatic system disorders 12.7% Investigations 10.3% General disorders and administration site conditions 9.6% Nervous system disorders 7.5% Gastrointestinal disorders 4.4% Metabolism and nutrition disorders 3.0% Hepatobiliary disorders 2.4% Respiratory, thoracic, and mediastinal disorders 2.0% Other 10.9%		
Adverse drug reactions-preferred terms (SWE-ART) (%)	Rash 14.3% Transaminases increased 8.1% Pyrexia 6.9% Stevens-Johnson syndrome 4.9% Thrombocytopenia 3.0% Rash erythematous 2.8%		

Contd...

Table 5: Contd...

Variable	Mean	Median	Range
	Leukopenia 2.7%		
	Urticaria 2.7%		
	Hyponatremia 2.4%		
	Other 52.2%		

SWE-ART=Swedish adverse reaction terminology

Table 6: Differences in patient demographics, daily dose of carbamazepine, time to onset of adverse reaction, medical history and concomitant drug treatment between cases and controls- all investigated skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme and scaly rash). Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	All investigated skin reactions (n=139), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	43.223	49.755	6.532	2.521	10.544	0.001
Daily dose (mg/day)	474.713	492.941	18.229	-36.108	72.565	0.510
Time to onset (days)	67.475	126.938	59.460	-19.100	138.030	0.138
In time to onset	2.236	3.141	0.904	0.575	1.234	9.459*10 ^{-8†}
	Proportion		Odds ratio			
Gender (male/female)	0.6231	0.4661	0.5280	0.3651	0.7634	0.0007
Individual drugs (exposed/nonexposed)						
A02BA02-ranitidine	0	0.0079	N/A			0.6027
A02BC01-omeprazole	0.0072	0.0180	0.3945	0.0519	2.9983	0.7169
A02BC03-lansoprazole	0.0072	0.0068	1.0640	0.1271	8.9052	1
A10BB01-glibenclamide	0.0072	0.0068	1.0640	0.1271	8.9052	1
B01AA03-warfarin	0.0144	0.0180	0.7947	0.1807	3.4945	1
B01AC06-acetylsalicylic acid	0.0072	0.0620	0.1096	0.0150	0.7986	0.0042
C01AA05-digoxin	0.0144	0.0180	0.7947	0.1807	3.4945	1
C01DA02-glyceril trinitrate	0.0072	0.0090	0.7962	0.0988	6.4152	1
C01DA14-isosorbide mononitrate	0	0.0090	N/A			0.6074
C03AA01-bendroflumethiazide	0.0072	0.0124	0.5771	0.0739	4.5050	1
C03CA01-furosemide	0.0360	0.0361	0.9970	0.3818	2.6036	1
C03DB01-amiloride	0.0144	0.0135	1.0645	0.2357	4.8077	1
C03EA01-amiloride+hydrochlorothiazide	0.0144	0.0056	2.5752	0.4947	13.4045	0.2429
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0.0216	0.0327	0.6526	0.1961	2.1720	0.6081
C07AB03-atenolol	0	0.0282	N/A			0.0383
C08CA01-amlodipine	0	0.0135	N/A			0.3871
C08CA02-felodipine	0	0.0192	N/A			0.1501
C08DA01-verapamil	0.0072	0.0079	0.9110	0.1112	7.4612	1
C08DB01-diltiazem	0.0072	0.0068	1.0640	0.1271	8.9052	1
C09AA02-enalapril	0.0072	0.0248	0.2849	0.0381	2.1308	0.3492
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			0.2443
H02AB01-betamethasone	0.0072	0.0214	0.3310	0.0440	2.4927	0.5037
H02AB06-prednisolone	0.0144	0.0124	1.1626	0.2549	5.3015	0.6925
J01CE02-phenoxymethylpenicillin	0.0288	0.0068	4.3506	1.2120	15.6172	0.0351

Contd...

Table 6: Contd...

Variable	All investigated skin reactions (n=139), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
J01DC02-cefuroxim	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
J01EE01-sulfamethoxazole and trimethoprim	0.0072	0.0068	1.0640	0.1271	8.9052	1
J01FF01-clindamycin	0	0.0079	N/A			0.6027
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0.0144	0.0101	1.4242	0.3045	6.6612	0.6514
N02AC04-dextropropoxyphene	0.0288	0.0293	0.9812	0.3372	2.8554	1
N02AX02-tramadol	0	0.0101	N/A			0.6182
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0.0360	0.0598	0.5872	0.2305	1.4955	0.3255
N03AA02-phenobarbital	0	0.0090	N/A			0.6074
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0.0216	0.0361	0.5894	0.1780	1.9513	0.6128
N03AE01-clonazepam	0.0072	0.0147	0.4872	0.0632	3.7537	0.7068
N03AG01-valproic acid	0	0.0192	N/A			0.1501
N03AX09-lamotrigin	0.0072	0.0158	0.4519	0.0590	3.4636	0.7075
N03AX12-gabapentin	0	0.0090	N/A			0.6074
N05AA01-chlorpromazine	0.0072	0.0079	0.9110	0.1112	7.4612	1
N05AA02-levomepromazine	0.0216	0.0079	2.7731	0.7085	10.8534	0.1427
N05AB01-dixyrazine	0.0144	0.0135	1.0645	0.2357	4.8077	1
N05AC02-thioridazine	0.0072	0.0090	0.7962	0.0988	6.4152	1
N05AD01-haloperidol	0.0072	0.0068	1.0640	0.1271	8.9052	1
N05AD03-melperon	0.0288	0.0045	6.5407	1.6167	26.4628	0.0146
N05AF05-zuclopenthixol	0.0144	0.0068	2.1436	0.4283	10.7280	0.2967
N05AH03-olanzapine	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
N05AN01-lithium	0	0.0090	N/A			0.6074
N05AX08-risperidone	0.0144	0.0045	3.2226	0.5847	17.7625	0.1896
N05BA01-diazepam	0.0216	0.0259	0.8286	0.2455	2.7973	1
N05BA04-oxazepam	0.0144	0.0304	0.4650	0.1093	1.9775	0.4120
N05BA12-alprazolam	0	0.0090	N/A			0.6074
N05BB01-hydroxizine	0.0216	0.0056	3.8912	0.9194	16.4679	0.0814
N05CD02-nitrazepam	0.0216	0.0169	1.2824	0.3664	4.4879	0.7247
N05CF01-zopiclone	0.0144	0.0248	0.5740	0.1335	2.4684	0.7608
N05CF02-zolpidem	0	0.0135	N/A			0.3871
N05CM02-clomethiazole	0.0360	0.0135	2.7208	0.9436	7.8453	0.0677
N05CM06-propiomazine	0.0360	0.0259	1.4017	0.5239	3.7500	0.5716
N06AA04-clomipramine	0	0.0068	N/A			1
N06AA09-amitriptyline	0.0144	0.0147	0.9815	0.2191	4.3967	1
N06AB04-citalopram	0.0288	0.0293	0.9812	0.3372	2.8554	1
N06AX11-mirtazapine	0.0072	0.0068	1.0640	0.1271	8.9052	1
N07BB01-disulfiram	0.0360	0.0090	4.0998	1.3217	12.7175	0.0221
R05CB01-acetylcysteine	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
R06AA04-clemastine	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
R06AD01-alimemazine	0.0576	0.0124	4.8633	1.9207	12.3142	0.0019
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0.0288	0.0417	0.6807	0.2388	1.9402	0.6418

Contd...

Table 6: Contd...

Variable	All investigated skin reactions (n=139), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
A10B-blood glucose lowering drugs, excl. insulins	0.0072	0.0101	0.7069	0.0889	5.6234	1
B01AA-vitamin K antagonists	0.0144	0.0214	0.6669	0.1536	2.8952	1
B01AC-platelet aggregation inhibitors excl. heparin	0.0216	0.0643	0.3212	0.0992	1.0402	0.0502
C01A-cardiac glycosides	0	0.0203	N/A			0.1550
C01D-vasodilators used in cardiac diseases	0.0072	0.0169	0.4213	0.0552	3.2145	0.7110
C03-diuretics	0.0576	0.0722	0.7853	0.3681	1.6754	0.7203
C07-beta blocking agents	0.0288	0.0755	0.3626	0.1301	1.0108	0.0467
C08-calcium channel blockers	0.0144	0.0496	0.2797	0.0670	1.1670	0.0750
C09-agents acting on the renin-angiotensin system	0.0144	0.0496	0.2797	0.0670	1.1670	0.0750
C10-lipid modifying agents	0.0072	0.0237	0.2988	0.0399	2.2394	0.3439
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			0.0246
G04C-drugs used in benign prostatic hypertrophy	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
H02-corticosteroids for systemic use	0.0216	0.0349	0.6091	0.1837	2.0199	0.6096
J01+A07AA-antibacterials for systemic use+antibiotics	0.0719	0.0575	1.2707	0.6293	2.5659	0.5612
J05-antivirals for systemic use	0.0144	0.0045	3.2226	0.5847	17.7625	0.1896
L02A-hormones and related agents	0	0.0068	N/A			1.0000
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0576	0.0913	0.6077	0.2872	1.2858	0.2550
M03-muscle relaxants	0.0288	0.0056	5.2267	1.3862	19.7071	0.0235
N02A+R05DA04+M03BB53+M01AE51-opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0504	0.0552	0.9069	0.4023	2.0447	1
N02C-antimigraine preparations	0	0.0113	N/A			0.3743
N03-antiepileptics	0.0360	0.1116	0.2970	0.1187	0.7429	0.0038
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			0.3775
N05A-antipsychotics	0.1007	0.0789	1.3072	0.7146	2.3912	0.4044
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine related drugs	0.0863	0.1048	0.8067	0.4298	1.5142	0.6511
N06A-antidepressants	0.0576	0.0913	0.6077	0.2872	1.2858	0.2550
N07BB-drugs used in alcohol dependence	0.0504	0.0090	5.8267	2.0786	16.3331	0.0018
R06-antihistamines for systemic use	0.0647	0.0327	2.0483	0.9481	4.4250	0.0855
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0.0288	0.0259	1.1130	0.3791	3.2683	0.7769
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0.0216	0.0462	0.4552	0.1390	1.4904	0.2585
E03-Other hypothyroidism	0	0.0147	N/A			0.2354
E14-Unspecified diabetes mellitus	0	0.0214	N/A			0.0946
F03-Unspecified dementia	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
F10-Mental and behavioral disorders due to use of alcohol	0.3453	0.0868	5.5487	3.6437	8.4497	3.14*10 ^{-14†}
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0.0576	0.0113	5.3557	2.0762	13.8158	0.0012
F20-Schizophrenia	0.0072	0.0169	0.4213	0.0552	3.2145	0.7110
F23-Acute and transient psychotic disorders	0.0216	0.0158	1.3755	0.3902	4.8492	0.4933
F39-Unspecified mood (affective) disorder	0.0072	0.0428	0.1619	0.0220	1.1888	0.0515

Contd...

Table 6: Contd...

Variable	All investigated skin reactions (n=139), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.3885	0.5141	0.6005	0.4166	0.8655	0.0062
G43-Migraine	0	0.0079	N/A			0.6027
G44-Other headache syndromes	0.0072	0.0079	0.9110	0.1112	7.4612	1
G50.0-Trigeminal neuralgia	0.0791	0.1319	0.5656	0.2965	1.0788	0.0966
G62-Other polyneuropathy	0.0144	0.0372	0.3778	0.0896	1.5924	0.2134
G80-Cerebral palsy	0.0144	0.0056	2.5752	0.4947	13.4045	0.2429
I10-Essential (primary) hypertension	0.0144	0.0496	0.2797	0.0670	1.1670	0.0750
I20-Angina pectoris	0	0.0079	N/A			0.6027
I21-Acute myocardial infarction	0	0.0113	N/A			0.3743
I48-Atrial fibrillation and flutter	0	0.0124	N/A			0.3775
I50-Heart failure	0.0144	0.0068	2.1436	0.4283	10.7280	0.2967
I61-Intracerebral hemorrhage	0	0.0203	N/A			0.1550
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			0.0255
I67-Other cerebrovascular diseases	0.0072	0.0056	1.2783	0.1482	11.0234	0.5835
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0.0144	0.0090	1.6040	0.3371	7.6325	0.6333
M79-Other soft tissue disorders not elsewhere classified	0.0072	0.0079	0.9110	0.1112	7.4612	1
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			0.6027
Disease groups* (exposed/nonexposed)						
Affective disorder	0.0144	0.0485	0.2865	0.0686	1.1964	0.0744
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			0.2373
Cerebrovascular disease	0.0072	0.0631	0.1075	0.0148	0.7832	0.0043
Dementia	0.0144	0.0079	1.8352	0.3774	8.9256	0.3499
Infectious disease	0.0935	0.0676	1.4221	0.7587	2.6654	0.2857
Ischemic heart disease	0	0.0192	N/A			0.1501
Neuropathy	0.0863	0.1691	0.4643	0.2504	0.8608	0.0120
Obstructive airway disease	0.0144	0.0147	0.9815	0.2191	4.3967	1
Psychotic disorder	0.0288	0.0327	0.8766	0.3034	2.5329	1
Substance/alcohol abuse	0.3741	0.0981	5.4961	3.6525	8.2704	5.99*10 ^{-15†}
Systemic disease	0	0.0090	N/A			0.6074
Tumor	0.0216	0.0665	0.3096	0.0957	1.0015	0.0352
Venous embolism	0	0.0068	N/A			1

†=Statistically significant difference ($P<0.00005747$). *Disease groups are defined in Table 2. GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

Table 7: Differences in patient demographics, daily dose of carbamazepine, time to onset of the adverse reaction, medical history and concomitant drug treatment between cases and controls-Stevens-Johnson syndrome. Toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme and scaly rash are excluded. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	SJS (n=78), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	41.487	49.755	8.268	3.094	13.443	0.002
Daily dose (mg/day)	498.000	492.941	-5.059	-75.876	65.758	0.889

Contd...

Table 7: Contd...

Variable	SJS (n=78), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Time to onset (days)	97.470	126.938	29.470	-75.520	134.460	0.582
In time to onset	1.999	3.141	1.141	0.714	1.569	2.07*10 ^{-7†}
	Proportion		Odds ratio			
Gender (male/female)	0.649	0.466	0.472	0.290	0.767	0.003
Individual drugs (exposed/nonexposed)						
A02BA02-ranitidine	0	0.0079	N/A			1
A02BC01-omeprazole	0	0.0180	N/A			0.6325
A02BC03-lansoprazole	0	0.0068	N/A			1
A10BB01-glibenclamide	0.0128	0.0068	1.9069	0.2267	16.0430	0.4467
B01AA03-warfarin	0.0128	0.0180	0.7070	0.0925	5.4029	1
B01AC06-acetylsalicylic acid	0	0.0620	N/A			0.0181
C01AA05-digoxin	0.0128	0.0180	0.7070	0.0925	5.4029	1
C01DA02-glyceryl trinitrate	0.0128	0.0090	1.4269	0.1762	11.5583	0.5332
C01DA14-isosorbide mononitrate	0	0.0090	N/A			1
C03AA01-bendroflumethiazide	0	0.0124	N/A			1
C03CA01-furosemide	0.0128	0.0361	0.3470	0.0468	2.5742	0.5103
C03DB01-amiloride	0.0128	0.0135	0.9470	0.1215	7.3800	1
C03EA01-amiloride+hydrochlorothiazide	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0.0128	0.0327	0.3842	0.0516	2.8593	0.5044
C07AB03-atenolol	0	0.0282	N/A			0.2545
C08CA01-amlodipine	0	0.0135	N/A			0.6137
C08CA02-felodipine	0	0.0192	N/A			0.3878
C08DA01-verapamil	0.0128	0.0079	1.6327	0.1983	13.4423	0.4918
C08DB01-diltiazem	0.0128	0.0068	1.9069	0.2267	16.0430	0.4467
C09AA02-enalapril	0	0.0248	N/A			0.2478
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			0.6251
H02AB01-betamethasone	0	0.0214	N/A			0.3920
H02AB06-prednisolone	0	0.0124	N/A			1
J01CE02-phenoxymethylpenicillin	0.0385	0.0068	5.8733	1.4400	23.9564	0.0299
J01DC02-cefuroxim	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
J01EE01-sulfamethoxazole and trimethoprim	0	0.0068	N/A			1
J01FF01-clindamycin	0	0.0079	N/A			1
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0.0128	0.0101	1.2670	0.1584	10.1319	0.5713
N02AC04-dextropropoxyphene	0.0256	0.0293	0.8715	0.2029	3.7420	1
N02AX02-tramadol	0	0.0101	N/A			1
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0.0128	0.0598	0.2044	0.0279	1.4981	0.1176
N03AA02-phenobarbital	0	0.0090	N/A			1
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0.0256	0.0361	0.7031	0.1653	2.9906	1
N03AE01-clonazepam	0.0128	0.0147	0.8731	0.1127	6.7637	1
N03AG01-valproic acid	0	0.0192	N/A			0.3878

Contd...

Table 7: Contd...

Variable	SJS (<i>n</i> =78), mean	Other ADRs (<i>n</i> =887), mean	Difference	Lower 95% CI	Upper 95% CI	<i>P</i>
N03AX09-lamotrigin	0.0128	0.0158	0.8098	0.1051	6.2411	1
N03AX12-gabapentin	0	0.0090	N/A			1
N05AA01-chlorpromazine	0	0.0079	N/A			1
N05AA02-levomepromazine	0.0256	0.0079	3.3083	0.6754	16.2042	0.1604
N05AB01-dixyrazine	0.0256	0.0135	1.9189	0.4217	8.7313	0.3145
N05AC02-thioridazine	0.0128	0.0090	1.4269	0.1762	11.5583	0.5332
N05AD01-haloperidol	0	0.0068	N/A			1
N05AD03-melperon	0.0513	0.0045	11.9324	2.9247	48.6823	0.0022
N05AF05-zuclopenthixol	0	0.0068	N/A			1
N05AH03-olanzapine	0	0.0056	N/A			1
N05AN01-lithium	0	0.0090	N/A			1
N05AX08-risperidone	0.0256	0.0045	5.8092	1.0470	32.2306	0.0782
N05BA01-diazepam	0.0128	0.0259	0.4879	0.0650	3.6617	0.7140
N05BA04-oxazepam	0.0128	0.0304	0.4137	0.0555	3.0857	0.7205
N05BA12-alprazolam	0	0.0090	N/A			1
N05BB01-hydroxyzine	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
N05CD02-nitrazepam	0.0256	0.0169	1.5298	0.3434	6.8146	0.6412
N05CF01-zopiclone	0	0.0248	N/A			0.2478
N05CF02-zolpidem	0	0.0135	N/A			0.6137
N05CM02-clomethiazole	0.0385	0.0135	2.9167	0.8053	10.5633	0.1142
N05CM06-propiomazine	0.0513	0.0259	2.0306	0.6841	6.0273	0.2671
N06AA04-clomipramine	0	0.0068	N/A			1
N06AA09-amitriptyline	0	0.0147	N/A			0.6153
N06AB04-citalopram	0.0128	0.0293	0.4301	0.0576	3.2125	0.7176
N06AX11-mirtazapine	0.0128	0.0068	1.9069	0.2267	16.0430	0.4467
N07BB01-disulfiram	0.0513	0.0090	5.9392	1.7474	20.1867	0.0119
R05CB01-acetylcysteine	0	0.0056	N/A			1
R06AA04-clemastine	0	0.0056	N/A			1
R06AD01-alimemazine	0.0641	0.0124	5.4545	1.8454	16.1223	0.0065
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0	0.0417	N/A			0.0659
A10B-blood glucose lowering drugs, excl. insulins	0.0128	0.0101	1.2670	0.1584	10.1319	0.5713
B01AA-vitamin K antagonists	0.0128	0.0214	0.5933	0.0784	4.4920	1
B01AC-platelet aggregation inhibitors excl. heparin	0.0128	0.0643	0.1891	0.0258	1.3846	0.0789
C01A-cardiac glycosides	0	0.0203	N/A			0.3887
C01D-vasodilators used in cardiac diseases	0.0128	0.0169	0.7550	0.0984	5.7924	1
C03-diuretics	0.0385	0.0722	0.5144	0.1578	1.6768	0.3542
C07-beta blocking agents	0.0256	0.0755	0.3221	0.0774	1.3404	0.1117
C08-calcium channel blockers	0.0256	0.0496	0.5042	0.1199	2.1203	0.5754
C09-agents acting on the renin-angiotensin system	0	0.0496	N/A			0.0429
C10-lipid modifying agents	0	0.0237	N/A			0.4044
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			0.1609
G04C-drugs used in benign prostatic hypertrophy	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
H02-corticosteroids for systemic use	0	0.0349	N/A			0.1678
J01+A07AA-antibacterials for systemic use+antibiotics	0.0769	0.0575	1.3660	0.5669	3.2917	0.4522

Contd...

Table 7: Contd...

Variable	SJS (<i>n</i> =78), mean	Other ADRs (<i>n</i> =887), mean	Difference	Lower 95% CI	Upper 95% CI	<i>P</i>
J05-antivirals for systemic use	0	0.0045	N/A			1
L02A-hormones and related agents	0	0.0068	N/A			1
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0256	0.0913	0.2619	0.0631	1.0860	0.0549
M03-muscle relaxants	0.0256	0.0056	4.6421	0.8858	24.3285	0.1038
N02A+R05DA04+M03BB53+M01AE51-opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0513	0.0552	0.9244	0.3246	2.6326	1
N02C-antimigraine preparations	0	0.0113	N/A			1
N03-antiepileptics	0.0513	0.1116	0.4302	0.1540	1.2023	0.1242
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			1
N05A-antipsychotics	0.1154	0.0789	1.5224	0.7291	3.1789	0.2781
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine-related drugs	0.0641	0.1048	0.5848	0.2305	1.4838	0.3288
N06A-antidepressants	0.0256	0.0913	0.2619	0.0631	1.0860	0.0549
N07BB-drugs used in alcohol dependence	0.0641	0.0090	7.5257	2.4007	23.5916	0.0023
R06-antihistamines for systemic use	0.0641	0.0327	2.0265	0.7615	5.3924	0.1865
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0.0128	0.0259	0.4879	0.0650	3.6617	0.7140
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0	0.0462	N/A			0.0700
E03-Other hypothyroidism	0	0.0147	N/A			0.6153
E14-Unspecified diabetes mellitus	0	0.0214	N/A			0.3920
F03-Unspecified dementia	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
F10-Mental and behavioral disorders due to use of alcohol	0.3846	0.0868	6.5747	3.9380	10.9767	2.25*10 ^{-11†}
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0.0641	0.0113	6.0068	2.0000	18.0410	0.0048
F20-Schizophrenia	0	0.0169	N/A			0.6251
F23-Acute and transient psychotic disorders	0.0256	0.0158	1.6410	0.3661	7.3545	0.3758
F39-Unspecified mood (affective) disorder	0.0128	0.0428	0.2902	0.0393	2.1424	0.3607
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.3205	0.5141	0.4458	0.2722	0.7303	0.0013
G43-Migraine	0	0.0079	N/A			1
G44-Other headache syndromes	0.0128	0.0079	1.6327	0.1983	13.4423	0.4918
G50.0-Trigeminal neuralgia	0.0385	0.1319	0.2632	0.0817	0.8484	0.0119
G62-Other polyneuropathy	0	0.0372	N/A			0.1025
G80-Cerebral palsy	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977
I10-Essential (primary) hypertension	0.0128	0.0496	0.2488	0.0338	1.8308	0.2539
I20-Angina pectoris	0	0.0079	N/A			1
I21-Acute myocardial infarction	0	0.0113	N/A			1
I48-Atrial fibrillation and flutter	0	0.0124	N/A			1
I50-Heart failure	0	0.0068	N/A			1
I61-Intracerebral hemorrhage	0	0.0203	N/A			0.3887
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			0.1638
I67-Other cerebrovascular diseases	0.0128	0.0056	2.2909	0.2643	19.8574	0.3977

Contd...

Table 7: Contd...

Variable	SJS (n=78), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0	0.0090	N/A			1
M79-Other soft tissue disorders not elsewhere classified	0.0128	0.0079	1.6327	0.1983	13.4423	0.4918
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			1
Disease groups* (exposed/nonexposed)						
Affective disorder	0.0256	0.0485	0.5165	0.1227	2.1737	0.5730
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			0.6193
Cerebrovascular disease	0.0128	0.0631	0.1927	0.0263	1.4114	0.0784
Dementia	0.0256	0.0079	3.3083	0.6754	16.2042	0.1604
Infectious disease	0.0641	0.0676	0.9441	0.3676	2.4245	1
Ischemic heart disease	0	0.0192	N/A			0.3878
Neuropathy	0.0385	0.1691	0.1965	0.0612	0.6315	0.0010
Obstructive airway disease	0	0.0147	N/A			0.6153
Psychotic disorder	0.0256	0.0327	0.7786	0.1823	3.3257	1
Substance/alcohol abuse	0.4103	0.0981	6.3968	3.8701	10.5730	1.26*10 ^{-11†}
Systemic disease	0	0.0090	N/A			1
Tumor	0	0.0665	N/A			0.0113
Venous embolism	0	0.0068	N/A			1

†=Statistically significant difference ($P<0.00005747$). *Disease groups are defined in Table 2. GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

Table 8: Differences in patient demographics, daily dose of carbamazepine, time to onset of the adverse reaction, medical history and concomitant drug treatment between cases and controls-toxic epidermal necrolysis. Stevens-Johnson syndrome, exfoliative dermatitis, erythema multiforme, and exfoliative rash are excluded. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	TEN (n=6), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	58.833	49.755	-9.078	-27.250	9.094	0.327
Daily dose (mg/day)	400.000	492.941	92.940	-191.120	377.000	0.521
Time to onset (days)	16.500	126.938	110.440	-288.890	509.770	0.587
In time to onset	2.445	3.141	0.696	-0.952	2.344	0.407
	Proportion		Odds ratio			
Gender (male/female)	0.167	0.466	4.366	0.508	37.520	0.224
Individual drugs (exposed/nonexposed)						
A02BA02-ranitidine	0	0.0079	N/A			1
A02BC01-omeprazole	0	0.0180	N/A			1
A02BC03-lansoprazole	0	0.0068	N/A			1
A10BB01-glibenclamide	0	0.0068	N/A			1
B01AA03-warfarin	0.1667	0.0180	10.8875	1.2025	98.5784	0.1092
B01AC06-acetylsalicylic acid	0	0.0620	N/A			1
C01AA05-digoxin	0.1667	0.0180	10.8875	1.2025	98.5784	0.1092
C01DA02-glyceryl trinitrate	0	0.0090	N/A			1
C01DA14-isosorbide mononitrate	0	0.0090	N/A			1
C03AA01-bendroflumethiazide	0	0.0124	N/A			1

Contd...

Table 8: Contd...

Variable	TEN (n=6), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
C03CA01-furosemide	0.3333	0.0361	13.3594	2.3597	75.6331	0.0192
C03DB01-amiloride	0.1667	0.0135	14.5833	1.5818	134.4509	0.0845
C03EA01-amiloride+hydrochlorothiazide	0	0.0056	N/A			1
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0	0.0327	N/A			1
C07AB03-atenolol	0	0.0282	N/A			1
C08CA01-amlodipine	0	0.0135	N/A			1
C08CA02-felodipine	0	0.0192	N/A			1
C08DA01-verapamil	0	0.0079	N/A			1
C08DB01-diltiazem	0	0.0068	N/A			1
C09AA02-enalapril	0.1667	0.0248	7.8636	0.8815	70.1463	0.1453
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			1
H02AB01-betamethasone	0	0.0214	N/A			1
H02AB06-prednisolone	0	0.0124	N/A			1
J01CE02-phenoxymethylpenicillin	0	0.0068	N/A			1
J01DC02-cefuroxim	0	0.0056	N/A			1
J01EE01-sulfamethoxazole and trimethoprim	0	0.0068	N/A			1
J01FF01-clindamycin	0	0.0079	N/A			1
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0	0.0101	N/A			1
N02AC04-dextropropoxyphene	0.1667	0.0293	6.6231	0.7470	58.7183	0.1687
N02AX02-tramadol	0	0.0101	N/A			1
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0.1667	0.0598	3.1472	0.3612	27.4239	0.3129
N03AA02-phenobarbital	0	0.0090	N/A			1
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0	0.0361	N/A			1
N03AE01-clonazepam	0	0.0147	N/A			1
N03AG01-valproic acid	0	0.0192	N/A			1
N03AX09-lamotrigin	0	0.0158	N/A			1
N03AX12-gabapentin	0	0.0090	N/A			1
N05AA01-chlorpromazine	0	0.0079	N/A			1
N05AA02-levomepromazine	0.1667	0.0079	25.1429	2.5919	243.9039	0.0527
N05AB01-dixyrazine	0	0.0135	N/A			1
N05AC02-thioridazine	0	0.0090	N/A			1
N05AD01-haloperidol	0	0.0068	N/A			1
N05AD03-melperon	0	0.0045	N/A			1
N05AF05-zuclopenthixol	0	0.0068	N/A			1
N05AH03-olanzapine	0	0.0056	N/A			1
N05AN01-lithium	0	0.0090	N/A			1
N05AX08-risperidone	0	0.0045	N/A			1
N05BA01-diazepam	0	0.0259	N/A			1
N05BA04-oxazepam	0.1667	0.0304	6.3704	0.7194	56.4072	0.1744
N05BA12-alprazolam	0	0.0090	N/A			1

Contd...

Table 8: Contd...

Variable	TEN (n=6), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
N05BB01-hydroxyzine	0	0.0056	N/A			1
N05CD02-nitrazepam	0	0.0169	N/A			1
N05CF01-zopiclone	0	0.0248	N/A			1
N05CF02-zolpidem	0	0.0135	N/A			1
N05CM02-clomethiazole	0	0.0135	N/A			1
N05CM06-propiomazine	0.1667	0.0259	7.5130	0.8437	66.9027	0.1512
N06AA04-clomipramine	0	0.0068	N/A			1
N06AA09-amitriptyline	0	0.0147	N/A			1
N06AB04-citalopram	0.1667	0.0293	6.6231	0.7470	58.7183	0.1687
N06AX11-mirtazapine	0	0.0068	N/A			1
N07BB01-disulfiram	0	0.0090	N/A			1
R05CB01-acetylcysteine	0	0.0056	N/A			1
R06AA04-clemastine	0	0.0056	N/A			1
R06AD01-alimemazine	0	0.0124	N/A			1
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0.1667	0.0417	4.5946	0.5235	40.3261	0.2302
A10B-blood glucose lowering drugs, excl. insulins	0	0.0101	N/A			1
B01AA-vitamin K antagonists	0.1667	0.0214	9.1368	1.0179	82.0177	0.1274
B01AC-platelet aggregation inhibitors excl. heparin	0.1667	0.0643	2.9123	0.3346	25.3474	0.3324
C01A-cardiac glycosides	0	0.0203	N/A			1
C01D-vasodilators used in cardiac diseases	0	0.0169	N/A			1
C03-diuretics	0.3333	0.0722	6.4297	1.1556	35.7752	0.0665
C07-beta blocking agents	0	0.0755	N/A			1
C08-calcium channel blockers	0	0.0496	N/A			1
C09-agents acting on the renin-angiotensin system	0.1667	0.0496	3.8318	0.4382	33.5038	0.2674
C10-lipid modifying agents	0	0.0237	N/A			1
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			1
G04C-drugs used in benign prostatic hypertrophy	0	0.0056	N/A			1
H02-corticosteroids for systemic use	0	0.0349	N/A			1
J01+A07AA-antibacterials for systemic use+antibiotics	0.1667	0.0575	3.2784	0.3760	28.5863	0.3030
J05-antivirals for systemic use	0	0.0045	N/A			1
L02A-hormones and related agents	0	0.0068	N/A			1
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.3333	0.0913	4.9753	0.8975	27.5822	0.1001
M03-muscle relaxants	0.1667	0.0056	35.2800	3.4671	358.9976	0.0398
N02A+R05DA04+M03BB53+M01AE51-opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.1667	0.0552	3.4204	0.3920	29.8454	0.2930
N02C-antimigraine preparations	0	0.0113	N/A			1
N03-antiepileptics	0	0.1116	N/A			1
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			1
N05A-antipsychotics	0.1667	0.0789	2.3343	0.2690	20.2584	0.3926
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine-related drugs	0.1667	0.1048	1.7075	0.1974	14.7730	0.4880

Contd...

Table 8: Contd...

Variable	TEN (n=6), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
N06A-antidepressants	0.1667	0.0913	1.9901	0.2297	17.2420	0.4399
N07BB-drugs used in alcohol dependence	0	0.0090	N/A			1
R06-antihistamines for systemic use	0	0.0327	N/A			1
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0	0.0259	N/A			1
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0.3333	0.0462	10.3171	1.8363	57.9670	0.0300
E03-Other hypothyroidism	0	0.0147	N/A			1
E14-Unspecified diabetes mellitus	0	0.0214	N/A			1
F03-Unspecified dementia	0	0.0056	N/A			1
F10-Mental and behavioral disorders due to use of alcohol	0.1667	0.0868	2.1039	0.2427	18.2380	0.4231
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0	0.0113	N/A			1
F20-Schizophrenia	0	0.0169	N/A			1
F23-Acute and transient psychotic disorders	0	0.0158	N/A			1
F39-Unspecified mood (affective) disorder	0	0.0428	N/A			1
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.6667	0.5141	1.8904	0.3445	10.3734	0.6873
G43-Migraine	0	0.0079	N/A			1
G44-Other headache syndromes	0	0.0079	N/A			1
G50.0-Trigeminal neuralgia	0	0.1319	N/A			1
G62-Other polyneuropathy	0	0.0372	N/A			1
G80-Cerebral palsy	0	0.0056	N/A			1
I10-Essential (primary) hypertension	0	0.0496	N/A			1
I20-Angina pectoris	0	0.0079	N/A			1
I21-Acute myocardial infarction	0	0.0113	N/A			1
I48-Atrial fibrillation and flutter	0	0.0124	N/A			1
I50-Heart failure	0.3333	0.0068	73.4167	11.2286	480.0235	0.0010
I61-Intracerebral hemorrhage	0	0.0203	N/A			1
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			1
I67-Other cerebrovascular diseases	0	0.0056	N/A			1
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0.1667	0.0090	21.9750	2.2999	209.9694	0.0591
M79-Other soft tissue disorders not elsewhere classified	0	0.0079	N/A			1
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			1
Disease groups* (exposed/nonexposed)						
Affective disorder	0	0.0485	N/A			1
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			1
Cerebrovascular disease	0	0.0631	N/A			1
Dementia	0	0.0079	N/A			1
Infectious disease	0.1667	0.0676	2.7567	0.3170	23.9744	0.3467
Ischemic heart disease	0	0.0192	N/A			1
Neuropathy	0	0.1691	N/A			0.5968
Obstructive airway disease	0.1667	0.0147	13.4462	1.4666	123.2808	0.0907
Psychotic disorder	0	0.0327	N/A			1

Contd...

Table 8: Contd...

Variable	TEN (n=6), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Substance/alcohol abuse	0.1667	0.0981	1.8391	0.2124	15.9215	0.4644
Systemic disease	0	0.0090	N/A			1
Tumor	0.3333	0.0665	7.0169	1.2593	39.1003	0.0576
Venous embolism	0	0.0068	N/A			1

*Disease groups are defined in table 2. There are no statistically significant differences ($P < 0.00005747$). GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

Table 9: Differences in patient demographics, daily dose of carbamazepine, time to onset of the adverse reaction, medical history and concomitant drug treatment between cases and controls-exfoliative dermatitis. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative rash are excluded. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	Exfoliative dermatitis (n=8), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	40.750	49.755	9.005	-6.787	24.797	0.263
Daily dose (mg/day)	480.000	492.941	12.940	-207.440	233.320	0.908
Time to onset (days)	51.750	126.938	75.190	-324.140	474.520	0.712
In time to onset	3.937	3.141	-0.797	-2.443	0.849	0.342
	Proportion		Odds ratio			
Gender (male/female)	0.2500	0.4661	2.6195	0.5258	13.0489	0.2970
Individual drugs (exposed/nonexposed)						
A02BA02-ranitidine	0	0.0079	N/A			1
A02BC01-omeprazole	0.1250	0.0180	7.7768	0.9033	66.9528	0.1428
A02BC03-lansoprazole	0	0.0068	N/A			1
A10BB01-glibenclamide	0	0.0068	N/A			1
B01AA03-warfarin	0	0.0180	N/A			1
B01AC06-acetylsalicylic acid	0.1250	0.0620	2.1610	0.2612	17.8780	0.4049
C01AA05-digoxin	0	0.0180	N/A			1
C01DA02-glyceryl trinitrate	0	0.0090	N/A			1
C01DA14-isosorbide mononitrate	0	0.0090	N/A			1
C03AA01-bendroflumethiazide	0	0.0124	N/A			1
C03CA01-furosemide	0.1250	0.0361	3.8170	0.4560	31.9527	0.2605
C03DB01-amiloride	0	0.0135	N/A			1
C03EA01-amiloride+hydrochlorothiazide	0	0.0056	N/A			1
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0.1250	0.0327	4.2266	0.5034	35.4852	0.2396
C07AB03-atenolol	0	0.0282	N/A			1
C08CA01-amlodipine	0	0.0135	N/A			1
C08CA02-felodipine	0	0.0192	N/A			1
C08DA01-verapamil	0	0.0079	N/A			1
C08DB01-diltiazem	0	0.0068	N/A			1
C09AA02-enalapril	0	0.0248	N/A			1
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			1
H02AB01-betamethasone	0.1250	0.0214	6.5263	0.7648	55.6938	0.1660

Contd...

Table 9: Contd...

Variable	Exfoliative dermatitis (n=8), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
H02AB06-prednisolone	0	0.0124	N/A			1
J01CE02-phenoxymethylpenicillin	0	0.0068	N/A			1
J01DC02-cefuroxim	0	0.0056	N/A			1
J01EE01-sulfamethoxazole and trimethoprim	0	0.0068	N/A			1
J01FF01-clindamycin	0	0.0079	N/A			1
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0	0.0101	N/A			1
N02AC04-dextropropoxyphene	0	0.0293	N/A			1
N02AX02-tramadol	0	0.0101	N/A			1
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0	0.0598	N/A			1
N03AA02-phenobarbital	0	0.0090	N/A			1
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0	0.0361	N/A			1
N03AE01-clonazepam	0	0.0147	N/A			1
N03AG01-valproic acid	0	0.0192	N/A			1
N03AX09-lamotrigin	0	0.0158	N/A			1
N03AX12-gabapentin	0	0.0090	N/A			1
N05AA01-chlorpromazine	0	0.0079	N/A			1
N05AA02-levomepromazine	0	0.0079	N/A			1
N05AB01-dixyrazine	0	0.0135	N/A			1
N05AC02-thioridazine	0	0.0090	N/A			1
N05AD01-haloperidol	0	0.0068	N/A			1
N05AD03-melperon	0	0.0045	N/A			1
N05AF05-zuclopenthixol	0	0.0068	N/A			1
N05AH03-olanzapine	0	0.0056	N/A			1
N05AN01-lithium	0	0.0090	N/A			1
N05AX08-risperidone	0	0.0045	N/A			1
N05BA01-diazepam	0	0.0259	N/A			1
N05BA04-oxazepam	0	0.0304	N/A			1
N05BA12-alprazolam	0	0.0090	N/A			1
N05BB01-hydroxyzine	0	0.0056	N/A			1
N05CD02-nitrazepam	0	0.0169	N/A			1
N05CF01-zopiclone	0	0.0248	N/A			1
N05CF02-zolpidem	0	0.0135	N/A			1
N05CM02-clomethiazole	0	0.0135	N/A			1
N05CM06-propiomazine	0	0.0259	N/A			1
N06AA04-clomipramine	0	0.0068	N/A			1
N06AA09-amitriptyline	0	0.0147	N/A			1
N06AB04-citalopram	0	0.0293	N/A			1
N06AX11-mirtazapine	0	0.0068	N/A			1
N07BB01-disulfiram	0	0.0090	N/A			1
R05CB01-acetylcysteine	0	0.0056	N/A			1
R06AA04-clemastine	0	0.0056	N/A			1
R06AD01-alimemazine	0	0.0124	N/A			1

Contd...

Table 9: Contd...

Variable	Exfoliative dermatitis (n=8), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0.1250	0.0417	3.2819	0.3935	27.3685	0.2942
A10B-blood glucose lowering drugs, excl. insulins	0	0.0101	N/A			1
B01AA-vitamin K antagonists	0	0.0214	N/A			1
B01AC-platelet aggregation inhibitors excl. heparin	0.1250	0.0643	2.0802	0.2516	17.1993	0.4162
C01A-cardiac glycosides	0	0.0203	N/A			1
C01D-vasodilators used in cardiac diseases	0	0.0169	N/A			1
C03-diuretics	0.1250	0.0722	1.8371	0.2226	15.1626	0.4543
C07-beta blocking agents	0.1250	0.0755	1.7484	0.2120	14.4218	0.4699
C08-calcium channel blockers	0	0.0496	N/A			1
C09-agents acting on the renin-angiotensin system	0.1250	0.0496	2.7370	0.3295	22.7363	0.3392
C10-lipid modifying agents	0.1250	0.0237	5.8912	0.6934	50.0481	0.1812
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			1
G04C-drugs used in benign prostatic hypertrophy	0	0.0056	N/A			1
H02-corticosteroids for systemic use	0.1250	0.0349	3.9447	0.4708	33.0520	0.2536
J01+A07AA-antibacterials for systemic use+antibiotics	0	0.0575	N/A			1
J05-antivirals for systemic use	0	0.0045	N/A			1
L02A-hormones and related agents	0	0.0068	N/A			1
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.1250	0.0913	1.4215	0.1727	11.6982	0.5379
M03-muscle relaxants	0	0.0056	N/A			1
N02A+R05DA04+M03BB53+M01AE51-opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0	0.0552	N/A			1
N02C-antimigraine preparations	0	0.0113	N/A			1
N03-antiepileptics	0	0.1116	N/A			0.6086
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			1
N05A-antipsychotics	0	0.0789	N/A			1
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine related drugs	0	0.1048	N/A			1
N06A-antidepressants	0	0.0913	N/A			1
N07BB-drugs used in alcohol dependence	0	0.0090	N/A			1
R06-antihistamines for systemic use	0	0.0327	N/A			1
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0.1250	0.0259	5.3665	0.6340	45.4214	0.1961
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0.1250	0.0462	2.9477	0.3543	24.5237	0.3203
E03-Other hypothyroidism	0	0.0147	N/A			1
E14-Unspecified diabetes mellitus	0	0.0214	N/A			1
F03-Unspecified dementia	0	0.0056	N/A			1
F10-Mental and behavioral disorders due to use of alcohol	0	0.0868	N/A			1
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0	0.0113	N/A			1
F20-Schizophrenia	0	0.0169	N/A			1
F23-Acute and transient psychotic disorders	0	0.0158	N/A			1

Contd...

Table 9: Contd...

Variable	Exfoliative dermatitis (n=8), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
F39-Unspecified mood (affective) disorder	0	0.0428	N/A			1
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.6250	0.5141	1.5753	0.3742	6.6316	0.7263
G43-Migraine	0	0.0079	N/A			1
G44-Other headache syndromes	0	0.0079	N/A			1
G50.0-Trigeminal neuralgia	0.2500	0.1319	2.1937	0.4376	10.9977	0.2887
G62-Other polyneuropathy	0.1250	0.0372	3.6970	0.4420	30.9217	0.2673
G80-Cerebral palsy	0	0.0056	N/A			1
I10-Essential (primary) hypertension	0.1250	0.0496	2.7370	0.3295	22.7363	0.3392
I20-Angina pectoris	0	0.0079	N/A			1
I21-Acute myocardial infarction	0	0.0113	N/A			1
I48-Atrial fibrillation and flutter	0	0.0124	N/A			1
I50-Heart failure	0	0.0068	N/A			1
I61-Intracerebral hemorrhage	0	0.0203	N/A			1
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			1
I67-Other cerebrovascular diseases	0	0.0056	N/A			1
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0	0.0090	N/A			1
M79-Other soft tissue disorders not elsewhere classified	0	0.0079	N/A			1
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			1
Disease groups* (exposed/nonexposed)						
Affective disorder	0	0.0485	N/A			1
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			1
Cerebrovascular disease	0	0.0631	N/A			1
Dementia	0	0.0079	N/A			1
Infectious disease	0.1250	0.0676	1.9690	0.2383	16.2674	0.4328
Ischemic heart disease	0	0.0192	N/A			1
Neuropathy	0.2500	0.1691	1.6378	0.3274	8.1927	0.6297
Obstructive airway disease	0	0.0147	N/A			1
Psychotic disorder	0	0.0327	N/A			1
Substance/alcohol abuse	0	0.0981	N/A			1
Systemic disease	0	0.0090	N/A			1
Tumor	0.1250	0.0665	2.0048	0.2426	16.5673	0.4273
Venous embolism	0	0.0068	N/A			1

*Disease groups are defined in Table 2. There are no statistically significant differences ($P < 0.00005747$). GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

Table 10: Differences in patient demographics, daily dose of carbamazepine, time to onset of the adverse reaction, medical history and concomitant drug treatment between cases and controls-erythema multiforme. Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and exfoliative rash are excluded. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	Erythema multiforme (n=34), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	41.824	49.755	7.932	0.136	15.728	0.046
Daily dose (mg/day)	455.000	492.941	37.940	-72.670	148.560	0.501
Time to onset (days)	27.152	126.938	99.790	-39.260	238.830	0.159
In time to onset	2.256	3.141	0.885	0.298	1.471	0.003
	Proportion		Odds ratio			
Gender (male/female)	0.6765	0.4661	0.4176	0.2011	0.8670	0.0217
Individual drugs (exposed/nonexposed)						

Contd...

Table 10: Contd...

Variable	Erythema multiforme (n=34), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
A02BA02-ranitidine	0	0.0079	N/A			1
A02BC01-omeprazole	0	0.0180	N/A			1
A02BC03-lansoprazole	0	0.0068	N/A			1
A10BB01-glibenclamide	0	0.0068	N/A			1
B01AA03-warfarin	0	0.0180	N/A			1
B01AC06-acetylsalicylic acid	0	0.0620	N/A			0.2577
C01AA05-digoxin	0	0.0180	N/A			1
C01DA02-glyceril trinitrate	0	0.0090	N/A			1
C01DA14-isosorbide mononitrate	0	0.0090	N/A			1
C03AA01-bendroflumethiazide	0.0294	0.0124	2.4132	0.3026	19.2473	0.3650
C03CA01-furosemide	0.0294	0.0361	0.8097	0.1074	6.1065	1
C03DB01-amiloride	0	0.0135	N/A			1
C03EA01-amiloride+hydrochlorothiazide	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0	0.0327	N/A			0.6210
C07AB03-atenolol	0	0.0282	N/A			1
C08CA01-amlodipine	0	0.0135	N/A			1
C08CA02-felodipine	0	0.0192	N/A			1
C08DA01-verapamil	0	0.0079	N/A			1
C08DB01-diltiazem	0	0.0068	N/A			1
C09AA02-enalapril	0	0.0248	N/A			1
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			1
H02AB01-betamethasone	0	0.0214	N/A			1
H02AB06-prednisolone	0.0294	0.0124	2.4132	0.3026	19.2473	0.3650
J01CE02-phenoxymethylpenicillin	0.0294	0.0068	4.4495	0.5207	38.0206	0.2322
J01DC02-cefuroxim	0	0.0056	N/A			1
J01EE01-sulfamethoxazole and trimethoprim	0.0294	0.0068	4.4495	0.5207	38.0206	0.2322
J01FF01-clindamycin	0	0.0079	N/A			1
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0.0294	0.0101	2.9562	0.3638	24.0209	0.3148
N02AC04-dextropropoxyphene	0	0.0293	N/A			0.6196
N02AX02-tramadol	0	0.0101	N/A			1
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0.0588	0.0598	0.9835	0.2295	4.2150	1.0000
N03AA02-phenobarbital	0	0.0090	N/A			1
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0.0294	0.0361	0.8097	0.1074	6.1065	1
N03AE01-clonazepam	0	0.0147	N/A			1
N03AG01-valproic acid	0	0.0192	N/A			1
N03AX09-lamotrigin	0	0.0158	N/A			1
N03AX12-gabapentin	0	0.0090	N/A			1
N05AA01-chlorpromazine	0.0294	0.0079	3.8095	0.4555	31.8621	0.2607
N05AA02-levomepromazine	0	0.0079	N/A			1
N05AB01-dixyrazine	0	0.0135	N/A			1

Contd...

Table 10: Contd...

Variable	Erythema multiforme (n=34), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
N05AC02-thioridazine	0	0.0090	N/A			1
N05AD01-haloperidol	0.0294	0.0068	4.4495	0.5207	38.0206	0.2322
N05AD03-melperon	0	0.0045	N/A			1
N05AF05-zuclopenthixol	0.0294	0.0068	4.4495	0.5207	38.0206	0.2322
N05AH03-olanzapine	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
N05AN01-lithium	0	0.0090	N/A			1
N05AX08-risperidone	0	0.0045	N/A			1
N05BA01-diazepam	0.0588	0.0259	2.3478	0.5305	10.3901	0.2347
N05BA04-oxazepam	0	0.0304	N/A			0.6196
N05BA12-alprazolam	0	0.0090	N/A			1
N05BB01-hydroxyzine	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
N05CD02-nitrazepam	0.0294	0.0169	1.7616	0.2259	13.7371	0.4550
N05CF01-zopiclone	0.0294	0.0248	1.1915	0.1559	9.1077	0.5835
N05CF02-zolpidem	0	0.0135	N/A			1
N05CM02-clomethiazole	0.0294	0.0135	2.2096	0.2790	17.5000	0.3888
N05CM06-propiomazine	0	0.0259	N/A			1
N06AA04-clomipramine	0	0.0068	N/A			1
N06AA09-amitriptyline	0.0294	0.0147	2.0373	0.2588	16.0395	0.4117
N06AB04-citalopram	0.0294	0.0293	1.0035	0.1321	7.6204	1
N06AX11-mirtazapine	0	0.0068	N/A			1
N07BB01-disulfiram	0.0294	0.0090	3.3295	0.4046	27.3999	0.2883
R05CB01-acetylcysteine	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
R06AA04-clemastine	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
R06AD01-alimemazine	0.0588	0.0124	4.9773	1.0592	23.3889	0.0800
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0.0294	0.0417	0.6962	0.0927	5.2294	1
A10B-blood glucose lowering drugs, excl. insulins	0	0.0101	N/A			1
B01AA-vitamin K antagonists	0	0.0214	N/A			1
B01AC-platelet aggregation inhibitors excl. heparin	0	0.0643	N/A			0.2624
C01A-cardiac glycosides	0	0.0203	N/A			1
C01D-vasodilators used in cardiac diseases	0	0.0169	N/A			1
C03-diuretics	0.0588	0.0722	0.8037	0.1883	3.4298	1
C07-beta blocking agents	0	0.0755	N/A			0.1667
C08-calcium channel blockers	0	0.0496	N/A			0.4018
C09-agents acting on the renin-angiotensin system	0	0.0496	N/A			0.4018
C10-lipid modifying agents	0	0.0237	N/A			1
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			0.6210
G04C-drugs used in benign prostatic hypertrophy	0	0.0056	N/A			1
H02-corticosteroids for systemic use	0.0294	0.0349	0.8368	0.1108	6.3169	1
J01+A07AA-antibacterials for systemic use+antibiotics	0.0882	0.0575	1.5863	0.4691	5.3642	0.4443
J05-antivirals for systemic use	0	0.0045	N/A			1
L02A-hormones and related agents	0	0.0068	N/A			1
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0882	0.0913	0.9630	0.2880	3.2193	1

Contd...

Table 10: Contd...

Variable	Erythema multiforme (n=34), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
M03-muscle relaxants	0	0.0056	N/A			1
N02A+R05DA04+M03BB53+M01AE51- opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0294	0.0552	0.5182	0.0694	3.8685	1
N02C-antimigraine preparations	0	0.0113	N/A			1
N03-antiepileptics	0.0294	0.1116	0.2412	0.0326	1.7829	0.1646
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			1
N05A-antipsychotics	0.0882	0.0789	1.1295	0.3368	3.7876	0.7465
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine related drugs	0.1471	0.1048	1.4720	0.5563	3.8951	0.3963
N06A-antidepressants	0.0588	0.0913	0.6219	0.1464	2.6426	0.7612
N07BB-drugs used in alcohol dependence	0.0294	0.0090	3.3295	0.4046	27.3999	0.2883
R06-antihistamines for systemic use	0.0882	0.0327	2.8632	0.8273	9.9090	0.1099
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0	0.0259	N/A			1
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0	0.0462	N/A			0.3956
E03-Other hypothyroidism	0	0.0147	N/A			1
E14-Unspecified diabetes mellitus	0	0.0214	N/A			1
F03-Unspecified dementia	0	0.0056	N/A			1
F10-Mental and behavioral disorders due to use of alcohol	0.3824	0.0868	6.5121	3.1379	13.5145	5.33*10 ^{-6†}
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0.0588	0.0113	5.4813	1.1534	26.0484	0.0693
F20-Schizophrenia	0.0294	0.0169	1.7616	0.2259	13.7371	0.4550
F23-Acute and transient psychotic disorders	0.0294	0.0158	1.8896	0.2412	14.8009	0.4337
F39-Unspecified mood (affective) disorder	0	0.0428	N/A			0.3934
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.3824	0.5141	0.5851	0.2894	1.1831	0.1620
G43-Migraine	0	0.0079	N/A			1
G44-Other headache syndromes	0	0.0079	N/A			1
G50.0-Trigeminal neuralgia	0.1176	0.1319	0.8775	0.3036	2.5359	1
G62-Other polyneuropathy	0	0.0372	N/A			0.6292
G80-Cerebral palsy	0.0294	0.0056	5.3455	0.6073	47.0505	0.2025
I10-Essential (primary) hypertension	0	0.0496	N/A			0.4018
I20-Angina pectoris	0	0.0079	N/A			1
I21-Acute myocardial infarction	0	0.0113	N/A			1
I48-Atrial fibrillation and flutter	0	0.0124	N/A			1
I50-Heart failure	0	0.0068	N/A			1
I61-Intracerebral hemorrhage	0	0.0203	N/A			1
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			0.6224
I67-Other cerebrovascular diseases	0	0.0056	N/A			1
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0.0294	0.0090	3.3295	0.4046	27.3999	0.2883
M79-Other soft tissue disorders not elsewhere classified	0	0.0079	N/A			1
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			1
Disease groups* (exposed/nonexposed)						
Affective disorder	0	0.0485	N/A			0.3993

Contd...

Table 10: Contd...

Variable	Erythema multiforme (n=34), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			1
Cerebrovascular disease	0	0.0631	N/A			0.2599
Dementia	0	0.0079	N/A			1
Infectious disease	0.0882	0.0676	1.3339	0.3963	4.4897	0.5010
Ischemic heart disease	0	0.0192	N/A			1
Neuropathy	0.1176	0.1691	0.6551	0.2274	1.8870	0.6384
Obstructive airway disease	0.0294	0.0147	2.0373	0.2588	16.0395	0.4117
Psychotic disorder	0.0588	0.0327	1.8491	0.4227	8.0884	0.3188
Substance/alcohol abuse	0.4118	0.0981	6.4368	3.1396	13.1966	3.30*10 ^{-6†}
Systemic disease	0	0.0090	N/A			1
Tumor	0	0.0665	N/A			0.1610
Venous embolism	0	0.0068	N/A			1

†=Statistically significant difference ($P<0.00005747$). *Disease groups are defined in table. GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

Table 11: Differences in patient demographics, daily dose of carbamazepine, time to onset of the adverse reaction, medical history and concomitant drug treatment between cases and controls- scaly rash. Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme are excluded. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	Scaly rash (n=13), mean	Other ADRs (n=887), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	51.615	49.755	-1.860	-14.235	10.515	0.768
Daily dose (mg/day)	411.111	492.941	81.830	-82.270	245.930	0.328
Time to onset (days)	32.727	126.938	94.210	-146.590	335.010	0.443
ln time to onset	2.906	3.141	0.235	-0.763	1.232	0.644
	Proportion		Odds ratio			
Gender (male/female)	0.7692	0.4661	0.2619	0.0716	0.9582	0.0464
Individual drugs (exposed/nonexposed)						
A02BA02-ranitidine	0	0.0079	N/A			1
A02BC01-omeprazole	0	0.0180	N/A			1
A02BC03-lansoprazole	0.0769	0.0068	12.2361	1.3663	109.5841	0.0971
A10BB01-glibenclamide	0	0.0068	N/A			1
B01AA03-warfarin	0	0.0180	N/A			1
B01AC06-acetylsalicylic acid	0	0.0620	N/A			1
C01AA05-digoxin	0	0.0180	N/A			1
C01DA02-glyceryl trinitrate	0	0.0090	N/A			1
C01DA14-isosorbide mononitrate	0	0.0090	N/A			1
C03AA01-bendroflumethiazide	0	0.0124	N/A			1
C03CA01-furosemide	0	0.0361	N/A			1
C03DB01-amiloride	0	0.0135	N/A			1
C03EA01-amiloride+hydrochlorothiazide	0	0.0056	N/A			1
C07AA05-propranolol	0	0.0068	N/A			1
C07AB02-metoprolol	0.0769	0.0327	2.4655	0.3101	19.6031	0.3584
C07AB03-atenolol	0	0.0282	N/A			1

Contd...

Table 11: Contd...

Variable	Scaly rash, mean	Other ADRs, mean	Difference	Lower 95% CI	Upper 95% CI	P
C08CA01-amlodipine	0	0.0135	N/A			1
C08CA02-felodipine	0	0.0192	N/A			1
C08DA01-verapamil	0	0.0079	N/A			1
C08DB01-diltiazem	0	0.0068	N/A			1
C09AA02-enalapril	0	0.0248	N/A			1
C09CA06-candesartan	0	0.0068	N/A			1
C10AA01-simvastatin	0	0.0169	N/A			1
H02AB01-betamethasone	0	0.0214	N/A			1
H02AB06-prednisolone	0.0769	0.0124	6.6364	0.7927	55.5599	0.1611
J01CE02-phenoxymethylpenicillin	0	0.0068	N/A			1
J01DC02-cefuroxim	0	0.0056	N/A			1
J01EE01-sulfamethoxazole and trimethoprim	0	0.0068	N/A			1
J01FF01-clindamycin	0	0.0079	N/A			1
M04AA01-allopurinol	0	0.0068	N/A			1
N02AA59-acetylsalicylic acid+codeine+caffeine	0	0.0101	N/A			1
N02AC04-dextropropoxyphene	0.0769	0.0293	2.7596	0.3458	22.0224	0.3288
N02AX02-tramadol	0	0.0101	N/A			1
N02BA01-acetylsalicylic acid	0	0.0068	N/A			1
N02BE01-paracetamol	0.0769	0.0598	1.3113	0.1673	10.2763	0.5551
N03AA02-phenobarbital	0	0.0090	N/A			1
N03AA03-primidone	0	0.0068	N/A			1
N03AB02-phenytoin	0	0.0361	N/A			1
N03AE01-clonazepam	0	0.0147	N/A			1
N03AG01-valproic acid	0	0.0192	N/A			1
N03AX09-lamotrigin	0	0.0158	N/A			1
N03AX12-gabapentin	0	0.0090	N/A			1
N05AA01-chlorpromazine	0	0.0079	N/A			1
N05AA02-levomepromazine	0	0.0079	N/A			1
N05AB01-dixyrazine	0	0.0135	N/A			1
N05AC02-thioridazine	0	0.0090	N/A			1
N05AD01-haloperidol	0	0.0068	N/A			1
N05AD03-melperon	0	0.0045	N/A			1
N05AF05-zuclopenthixol	0.0769	0.0068	12.2361	1.3663	109.5841	0.0971
N05AH03-olanzapine	0	0.0056	N/A			1
N05AN01-lithium	0	0.0090	N/A			1
N05AX08-risperidone	0	0.0045	N/A			1
N05BA01-diazepam	0	0.0259	N/A			1
N05BA04-oxazepam	0	0.0304	N/A			1
N05BA12-alprazolam	0	0.0090	N/A			1
N05BB01-hydroxyzine	0.0769	0.0056	14.7000	1.5945	135.5255	0.0838
N05CD02-nitrazepam	0	0.0169	N/A			1
N05CF01-zopiclone	0.0769	0.0248	3.2765	0.4079	26.3166	0.2874
N05CF02-zolpidem	0	0.0135	N/A			1
N05CM02-clomethiazole	0.0769	0.0135	6.0764	0.7308	50.5241	0.1734
N05CM06-propiomazine	0	0.0259	N/A			1
N06AA04-clomipramine	0	0.0068	N/A			1

Contd...

Table 11: Contd...

Variable	Scaly rash, mean	Other ADRs, mean	Difference	Lower 95% CI	Upper 95% CI	P
N06AA09-amitriptyline	0.0769	0.0147	5.6026	0.6777	46.3140	0.1855
N06AB04-citalopram	0.0769	0.0293	2.7596	0.3458	22.0224	0.3288
N06AX11-mirtazapine	0	0.0068	N/A			1
N07BB01-disulfiram	0	0.0090	N/A			1
R05CB01-acetylcysteine	0	0.0056	N/A			1
R06AA04-clemastine	0	0.0056	N/A			1
R06AD01-alimemazine	0.0769	0.0124	6.6364	0.7927	55.5599	0.1611
Drug groups (exposed/nonexposed)						
A02B-drugs for peptic ulcer and gastro-esophageal reflux disease	0.0769	0.0417	1.9144	0.2424	15.1166	0.4315
A10B-blood glucose lowering drugs, excl. insulins	0	0.0101	N/A			1
B01AA-vitamin K antagonists	0	0.0214	N/A			1
B01AC-platelet aggregation inhibitors excl. heparin	0	0.0643	N/A			1
C01A-cardiac glycosides	0	0.0203	N/A			1
C01D-vasodilators used in cardiac diseases	0	0.0169	N/A			1
C03-diuretics	0	0.0722	N/A			0.6156
C07-beta blocking agents	0.0769	0.0755	1.0199	0.1306	7.9633	1
C08-calcium channel blockers	0	0.0496	N/A			1
C09-agents acting on the renin-angiotensin system	0	0.0496	N/A			1
C10-lipid modifying agents	0	0.0237	N/A			1
G03-sex hormones and modulators of the genital system	0	0.0327	N/A			1
G04C-drugs used in benign prostatic hypertrophy	0	0.0056	N/A			1
H02-corticosteroids for systemic use	0.0769	0.0349	2.3011	0.2900	18.2580	0.3774
J01+A07AA-antibacterials for systemic use+antibiotics	0	0.0575	N/A			1
J05-antivirals for systemic use	0.1538	0.0045	40.1364	6.6443	242.4513	0.0028
L02A-hormones and related agents	0	0.0068	N/A			1
M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-antiinflammatory and antirheumatic products, nonsteroids+salicylic acid and derivatives+acetylsalicylic acid+codeine, combinations excl. psycholeptics+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0	0.0913	N/A			0.6204
M03-muscle relaxants	0.0769	0.0056	14.7000	1.5945	135.5255	0.0838
N02A+R05DA04+M03BB53+M01AE51-opioids+codeine+chlorzoxazone, combinations excl. psycholeptics+ibuprofen, combinations	0.0769	0.0552	1.4252	0.1816	11.1845	0.5268
N02C-antimigraine preparations	0	0.0113	N/A			1
N03-antiepileptics	0	0.1116	N/A			0.3813
N04AA+N04AB-tertiary amines+ethers chemically close to antihistamines	0	0.0124	N/A			1
N05A-antipsychotics	0.0769	0.0789	0.9726	0.1246	7.5896	1
N05CD+N05BA+N05CF-benzodiazepine derivatives+benzodiazepine related drugs	0.0769	0.1048	0.7115	0.0915	5.5337	1
N06A-antidepressants	0.2308	0.0913	2.9852	0.8052	11.0667	0.1132
N07BB-drugs used in alcohol dependence	0.0769	0.0090	9.1563	1.0607	79.0378	0.1233
R06-antihistamines for systemic use	0.0769	0.0327	2.4655	0.3101	19.6031	0.3584
Individual diseases (exposed/nonexposed)						
B02-Zoster (herpes zoster)	0.1538	0.0259	6.8300	1.4316	32.5844	0.0479
D43-Neoplasm of uncertain or unknown behavior of brain and central nervous system	0	0.0462	N/A			1
E03-Other hypothyroidism	0	0.0147	N/A			1

Contd...

Table 11: Contd...

Variable	Scaly rash, mean	Other ADRs, mean	Difference	Lower 95% CI	Upper 95% CI	P
E14-Unspecified diabetes mellitus	0	0.0214	N/A			1
F03-Unspecified dementia	0	0.0056	N/A			1
F10-Mental and behavioral disorders due to use of alcohol	0.3077	0.0868	4.6753	1.4071	15.5344	0.0232
F19-Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	0.0769	0.0113	7.3083	0.8658	61.6895	0.1487
F20-Schizophrenia	0	0.0169	N/A			1
F23-Acute and transient psychotic disorders	0	0.0158	N/A			1
F39-Unspecified mood (affective) disorder	0	0.0428	N/A			1
F41-Other anxiety disorders	0	0.0068	N/A			1
G40-Epilepsy	0.5385	0.5141	1.1027	0.3677	3.3072	1
G43-Migraine	0	0.0079	N/A			1
G44-Other headache syndromes	0	0.0079	N/A			1
G50.0-Trigeminal neuralgia	0.1538	0.1319	1.1966	0.2619	5.4663	0.6859
G62-Other polyneuropathy	0.0769	0.0372	2.1566	0.2723	17.0804	0.3959
G80-Cerebral palsy	0	0.0056	N/A			1
I10-Essential (primary) hypertension	0	0.0496	N/A			1
I20-Angina pectoris	0	0.0079	N/A			1
I21-Acute myocardial infarction	0	0.0113	N/A			1
I48-Atrial fibrillation and flutter	0	0.0124	N/A			1
I50-Heart failure	0	0.0068	N/A			1
I61-Intracerebral hemorrhage	0	0.0203	N/A			1
I64-Stroke, not specified as hemorrhage or infarction	0	0.0338	N/A			1
I67-Other cerebrovascular diseases	0	0.0056	N/A			1
J44-Other chronic obstructive pulmonary disease	0	0.0068	N/A			1
J45-Asthma	0	0.0090	N/A			1
M79-Other soft tissue disorders not elsewhere classified	0	0.0079	N/A			1
N39.0-Urinary tract infection, site not specified	0	0.0079	N/A			1
Disease groups* (exposed/nonexposed)						
Affective disorder	0	0.0485	N/A			1
Anxiety disorder	0	0.0068	N/A			1
Cardiac conduction disorder	0	0.0158	N/A			1
Cerebrovascular disease	0	0.0631	N/A			1
Dementia	0	0.0079	N/A			1
Infectious disease	0.2308	0.0676	4.1350	1.1084	15.4257	0.0564
Ischemic heart disease	0	0.0192	N/A			1
Neuropathy	0.2308	0.1691	1.4740	0.4009	5.4199	0.4720
Obstructive airway disease	0	0.0147	N/A			1
Psychotic disorder	0	0.0327	N/A			1
Substance/alcohol abuse	0.3846	0.0981	5.7471	1.8398	17.9528	0.0066
Systemic disease	0	0.0090	N/A			1
Tumor	0	0.0665	N/A			1
Venous embolism	0	0.0068	N/A			1

*Disease groups are defined in Table 2. There are no statistically significant differences ($P < 0.00005747$). GERD=Gastro-esophageal reflux disease, ATC=Anatomical therapeutic chemical, ICD=International statistical classification of diseases and related health problems, CI=Confidence interval

48 cases with any of the investigated skin reactions and who were classified with the ICD-10 code alcohol-related mental and behavioral disorders, as well as for the corresponding

77 controls, this ICD-10 classification had been made due to alcoholism. According to the information contained within the 48 reports, the indication for treatment with carbamazepine

for 40 was alcoholism. The precise condition was not always stated but alcohol withdrawal was commonly described. In Sweden, alcohol withdrawal is the only approved indication related to alcoholism for carbamazepine.^[20] The indications for treatment among the remaining eight were Wernicke–Korsakoff syndrome in one case, epilepsy in four, and unspecified convulsions in three. Concomitant substance abuse was mentioned in the case narratives for 4 of the 48 cases (1 each of amphetamine and morphine, and 2 of unspecified drugs).

Table 12 shows differences in age, gender, daily dose of carbamazepine, and concomitant treatment with antidepressants or diuretics between patients with hyponatremia/SIADH and controls. Patients who had experienced hyponatremia or SIADH had a higher mean age than controls (64.0 vs 48.1 years, $P = 7.87 \times 10^{-7}$) were more often women (78.4% vs 49.9%, $P = 7.24 \times 10^{-5}$), and were more often on concomitant treatment with antidepressants (26.9% vs 7.7%, $P = 5.73 \times 10^{-5}$) or diuretics (23.1% vs 6.2%, $P = 1.23 \times 10^{-4}$). However, there was no difference in daily dose of carbamazepine.

DISCUSSION

In this case-control study of spontaneous ADR reports for carbamazepine sent from healthcare professionals to the Swedish drug regulatory authority, we identified alcohol abuse as well as substance/alcohol abuse as possible risk factors for serious mucocutaneous reactions. We have also shown that the study methodology can be used to identify possible risk factors for ADR in databases of spontaneous ADR reports. The identified associations were seen for SJS and EM but not for TEN, ED, and scaly rash. Whether this reflects a true difference between the reactions or simply a difference in sample size – SJS and EM made up 80% of all investigated skin reactions – is not possible to determine. The possibility of an association between alcohol and/or substance abuse and any type of skin reaction was assessed as unlikely as there were no statistically significant differences for these variables between

patients with dermatologic ADRs other than SJS, TEN, ED, EM and scaly rash, and patients with nondermatologic ADRs [Table 13].

Our study has limitations. One concerns the information contained within a report. Bias may have been introduced if the extent and detail of clinical data differed between cases and controls, that is, the reporter or the assessor handling the ADR report may have decided to include or retrieve more data for serious mucocutaneous reactions than less severe or nonserious and common ADRs. Such information may have included alcohol use. Indeed, in one of the case narratives for a report of SJS during 1986, the assessor at the MPA had made a comment that “these cases often involve a history of alcohol problems, then withdrawal, and then treatment with carbamazepine”. However, none of the other case narratives mentioned a suspected link with alcohol abuse. A second limitation is the known association between alcohol and other substance abuse. Because of this strong association, we grouped the individual ICD-10 codes mental and behavioral disorders due to use of alcohol with mental and behavioral disorders due to multiple drug use and use of other psychoactive substances, into the disease group substance/alcohol abuse. The association with serious mucocutaneous reactions was slightly stronger for the disease group than for the individual diseases, making it somewhat problematic to pinpoint the associated component. However, as there was no statistically significant association with mental and behavioral disorders due to multiple drug use and use of other psychoactive substances, and since this was co-present with alcohol abuse in only very few of the cases with serious mucocutaneous reactions, we believe that the component most likely to be associated with the studied ADRs is alcohol abuse. A third limitation is the lack of information for most cases whether alcohol abuse was ongoing, had occurred in the past, or if a patient was experiencing withdrawal symptoms. The last limitation is the inability of epidemiological studies to establish cause-effect relationships. Thus, alcohol abuse may simply be a marker of another or other, unknown risk factor (s). Such factors might include malnutrition or immunological effects due to overconsumption of alcohol.

Table 12: Differences in known risk factors for hyponatremia/SIADH (SWE-ART terms) during treatment with carbamazepine. Drugs/drug groups are classified by their ATC-codes

Variable	Hyponatremia or SIADH (n=52), mean	Other ADRs (n=974), mean	Difference	Lower 95% CI	Upper 95% CI	P
Age (years)	63.961	48.076	-15.885	-22.157	-9.612	7.868*10 ⁻⁷
Daily dose of carbamazepine (mg/day)	526.316	488.835	-37.480	-116.720	41.760	0.353
	Proportion		Odds ratio			
Gender (male/female)	0.2157	0.5015	3.6589	1.8555	7.2150	7.244*10 ⁻⁵
Drug groups (exposed/nonexposed)						
C03-diuretics	0.2308	0.0616	4.5700	2.2785	9.1659	1.229*10 ⁻⁴
N06A-antidepressants	0.2692	0.0770	4.4161	2.2905	8.5143	5.728*10 ⁻⁵

SWE-ART=Swedish adverse reaction terminology, ATC=Anatomical therapeutic chemical, SIADH=Syndrome of inappropriate secretion of antidiuretic hormone, ADRs=Adverse drug reactions, CI=Confidence interval

Table 13: Differences in variables reflective of alcohol/substance abuse between patients with skin reactions (SWE-ART system organ class skin and subcutaneous tissue disorders) other than Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme and scaly rash, and patients with nondermatologic ADRs. Drugs/drug groups are defined by their ATC-codes. Individual diseases are classified according to ICD-10

Variable	Skin reactions other than those investigated, proportion	Other ADRs, proportion	Odds ratio	Lower 95% CI	Upper 95% CI	P
Individual drugs (exposed/nonexposed)						
N07BB-drugs used in alcohol dependence	0.0099	0.0083	1.1975	0.2976	4.8186	1
Individual diseases (exposed/nonexposed)						
F10-Mental and behavioral disorders due to use of alcohol	0.1064	0.0704	1.5730	0.9825	2.5184	0.0720
Disease groups* (exposed/nonexposed)						
Substance/alcohol abuse	0.1188	0.0807	1.5350	0.9837	2.3952	0.0694

*Disease groups are defined in table 2. ADRs=Adverse drug reactions, CI=Confidence interval, ICD=International statistical classification of diseases and related health problems

To our knowledge, this is the first study to suggest alcohol abuse as a risk factor for carbamazepine-induced serious mucocutaneous reactions. Illing *et al.* recently showed that abacavir, a drug strongly associated with acute hypersensitivity syndrome among carriers of the HLA-B*5701 allele, binds to HLA-B*5701 and changes the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides that can bind HLA-B*5701.^[21] In this way, abacavir guides the selection of new endogenous peptides, inducing activation of abacavir-specific T-cells with driving of polyclonal CD8 T-cell activation and a systemic reaction manifesting as acute hypersensitivity syndrome. It was also shown that carbamazepine binds to HLA-B*1502, producing alterations in the repertoire of presented self peptides, and that this is the likely mechanism underlying reactions such as SJS. The same mechanism is therefore likely to be involved in the association between HLA-A*3101 and the risk of carbamazepine-induced serious cutaneous reactions in Europeans. However, as the presence of the HLA-A*3101 allele is not sufficient to explain the pathogenesis of these reactions, other mechanisms must also be involved. Such a factor might be alcohol. We have found two published case reports suggesting an association between alcohol abuse and serious cutaneous reactions to carbamazepine when given for treatment of withdrawal symptoms,^[22,23] although heroin was co-suspected in one case. Another case report also describes the onset of SJS in a patient with alcohol abuse following treatment of withdrawal symptoms with carbamazepine, although a possible link with alcohol abuse was not suspected.^[24] A further three reports of SJS in patients with alcohol abuse have been published for other drugs, that is, lamotrigine,^[25] clarithromycin and/or disulfiram,^[26] and phenytoin.^[27] One case report also describes recurrent EM in a patient on therapy with ciprofloxacin after ingestion of alcohol.^[28]

The underlying mechanism whereby alcohol abuse might increase the risk of carbamazepine-induced serious cutaneous

reactions will remain speculative. Like the majority of secreted, cell surface, and immune-related molecules, HLA proteins contain posttranslational glycan modifications that are initiated in the endoplasmic reticulum.^[29] Such glycans can stabilize the conformation of the protein structure both locally and at distant protein domains. In disease settings, however, these glycan structures can be altered significantly through factors such as altered expression patterns of glycosidases and glycosyltransferases in the golgi apparatus, altered availability of carbohydrate building blocks, and increased expression of cellular proteins that may overwhelm the limits of the secretory pathway. Inflammatory stimuli, for instance, can alter the glycan branching pattern and levels of sialylation of cell bound and secreted glycoproteins. Perhaps chronic alcohol ingestion modifies HLA protein dynamics as well as the structure–function relationship through such a mechanism.

CONCLUSION

In conclusion, we have identified alcohol abuse as a possible risk factor for carbamazepine-induced serious mucocutaneous reactions. This association needs confirmation in other data-sets. We have also shown that databases of spontaneous ADR reports may still be under-utilized, and that case-control studies as described within this report could be used for the detection of possible risk factors of ADRs.

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