

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

| | <i>n</i> | |
|--|----------|----------|
| Drug groups (ATC-code) | | |
| N05CD+N05BA+N05CF-Benzodiazepine derivatives+benzodiazepine related drugs | 105 | Included |
| N03-Antiepileptics | 104 | Included |
| M01A+N02BA+B01AC06+N02AA59+M03BB53+M01AE51-Antiinflammatory 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/cafeine | 11 | Included |
| J01CE02-Phenoxymethylpenicilline | 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-Estril | 5 | Excluded |

Contd...

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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-Metamphetamine | 3 | Excluded |
| M01AE02-Naproxen | 3 | Excluded |
| N02CA72-Ergotamine/chlorcyclizine/cafeine | 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-Paroxetine | 3 | Excluded |
| P01AB01-Metronidazole | 3 | Excluded |
| R06AE07-Cetirizine | 3 | Excluded |
| S01XA20-Artificial tears and other indifferent preparations | 3 | Excluded |
| A01AA01-Sodium fluoride | 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-Terazosin | 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/cafeine | 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-Calciumcarbimide/carbonic acid barium salt | 2 | Excluded |
| N07BB03-Acamprosate | 2 | Excluded |
| R03DA02-Choline theophyllinate | 2 | Excluded |
| R03DA04-Theophylline | 2 | Excluded |
| R06AX12-Terfenadine | 2 | Excluded |

Contd...

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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-Ursodeoxycholic 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-Gemeprost | 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...

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Table 3: Contd...

| | n | |
|--|---|----------|
| 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...

| | n | |
|---|---|----------|
| 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 |
| ln 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-glyceryl 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-lamotrigine | 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-hydroxyzine | 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 |
| ln 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 (n=78), mean | Other ADRs (n=887), mean | Difference | Lower 95% CI | Upper 95% CI | P |
|--|------------------------|--------------------------------|------------|-----------------|-----------------|--------|
| 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 (n=78), mean | Other ADRs (n=887), mean | Difference | Lower 95% CI | Upper 95% CI | P |
|---|------------------------|--------------------------------|------------|-----------------|-----------------|-------------------------|
| 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-glyceril 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-lamotrigine | 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-glyceryl 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] chlorithromycin 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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