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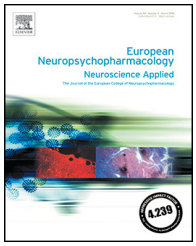

Cutaneous adverse drug reactions to psychotropic drugs and their risk factors – a case-control study

Waldemar Greil[a,b,*], Xueqiong Zhang[a,b], Hans Stassen[b,c], Renate Grohmann[a], René Bridler[b], Gregor Hasler[d], Sermin Toto[e], Stefan Bleich[e], Siegfried Kasper[f]

[a] *Department of Psychiatry, Ludwig-Maximilian University, Nussbaumstr. 7, Munich D-80331, Germany*
[b] *Psychiatric Hospital, Kilchberg, Zurich, Switzerland*
[c] *Institute for Response-Genetics, Psychiatric University Hospital (KPPP), Zurich, Switzerland*
[d] *Division of Molecular Psychiatry, University Psychiatry Department (UPD), University of Bern, Bern, Switzerland*
[e] *Department of Psychiatry, Socialpsychiatry & Psychotherapy, Hannover Medical School, Hannover, Germany*
[f] *Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria*

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Risk factors

Abstract
Cutaneous adverse drug reactions (CADRs) in patients with psychotropic drugs are common. Large studies on the relevant drugs and other risk factors are still scarce.
594 cases of severe CADRs ("cases") were compared with 8085 cases of other adverse drug reactions ("non-cases") documented in a pharmacovigilance program in psychiatry (AMSP) from 1993 to 2014. Logistic regression was carried out to determine risk factors and between-drug differences.
CADRs were relatively more prevalent in patients treated with clomipramine, maprotiline, carbamazepine, lamotrigine, acamprosate, clomethiazole and disulfiram as well as with antidepressants and anticonvulsants as drug classes ($p < 0.01$). For these drugs, significantly more women were found in patients using maprotiline, lamotrigine (not carbamazepine) and in the groups of antidepressants, tricyclics and anticonvulsants ($p < 0.01$). Women were more vulnerable to CADRs (67% in cases and 56% in non-cases, $p < 0.01$). The significantly higher rate of CADRs in women was mainly observed under age of 50 years, i.e. during female reproductive

* Corresponding author at: Department of Psychiatry, Ludwig-Maximilian University, Nussbaumstr. 7, Munich D-80331, Germany.
E-mail address: waldemar.greil@med.uni-muenchen.de (W. Greil).

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years. In a multivariate logistic regression, female sex, the diagnostic group ICD F1 (substance abuse), maprotiline, carbamazepine, lamotrigine and clomethiazole were identified as risk factors of CADRs.
The case/non-case approach allowed to identify risk factors based on empirical data rather than experts' evaluations. The new findings of substance abuse and clomethiazole as risk factors for CADRs have to be confirmed in further studies. Since CADRs can be life-threatening, it is important to be aware of risk factors, especially women during their reproductive period and with lamotrigine treatment.

1. Introduction

Although the true incidence of adverse drug reactions (ADRs) is difficult to determine, there is evidence that cutaneous adverse drug reactions (CADRs) are among the most frequently observed adverse reactions to drugs (Svensson et al., 2001). CADRs account for 10–20% of all reported ADRs (Faich et al., 1987; van der Linden et al., 1998). These reactions may range from mildly discomforting exanthematous skin rashes to severe, life-threatening event like toxic epidermal necrolysis (TEN). The most severe and life-threatening types of CADRs consist of erythema multiforme, urticaria, drug-induced hypersensitivity syndrome (DIHS) also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), and epidermal necrolysis - including Stevens-Johnson syndrome (SJS) and TEN (Mitkov et al., 2014).

In hospitalized patients, the incidence of CADRs ranges from 1% to 3% (Arndt and Jick, 1976; Bigby et al., 1986), whereas the incidence of CADRs in patients taking psychotropic medications has been estimated as being approximately 2–5% (Kimyai-Asadi et al., 1999). Due to possibly higher incidence of CADRs to psychotropic medications and potentially life-threatening reactions, it is clinically important to investigate cause and risk factors of CADRs to psychotropic medications.

The causality assessment varies among reported studies and is limited by the ethical constraints of re-challenging patients with a drug that may evoke a life-threatening or seriously disabling reaction (Svensson et al., 2001). Some risk factors, including female sex (Bigby et al., 1986; Naldi et al., 1999; Fattinger et al., 2000; Alvestad et al., 2007; Wang et al., 2012), greater age (Naldi et al., 1999; Warnock and Morris, 2002) and HLA-B*5801 and HLA-A*3101 subtype (McCormack et al., 2011) have been identified to be associated with CADRs. Despite of the high clinical relevance of CADRs, large scale studies identifying drugs prone to such effects, along with predictive risk factors are still rare.

In this paper we analyzed the ADR data provided by the international Drug Safety Program in Psychiatry (Arzneimittelsicherheit in der Psychiatrie, AMSP). The previous study of Lange-Asschenfeldt et al. (2009) with AMSP data from 1993–2005 about CADRs had its focus on the reported incidence rates of severe CADRs to psychiatric drugs and was based on probability ratings of causality by experts (Lange-Asschenfeldt et al., 2009). In this previous study, there were 214 cases of severe CADRs of psychotropic drugs including mood stabilizing anticonvulsants. Exanthems constituted the majority of the recorded severe CADRs. The most common symptom was pruritus (50%), followed by edema (12%). The median clinical latency was below 10 days for all subtypes. Life-threatening CADRs amounted to 3% of the CADR cases. Immediate drug discontinuation was the direct measure in the vast majority of cases (about 95%). Drug treatment involved antihistamine (about 50%) and steroids (35.0%).

In the present study we analyzed a larger dataset from 1993–2014. Specifically, we aimed to identify new possible causes and risk factors through a case control design and multivariate regression. Thus we applied an empirical approach that allows us to be as independent of experts' decision as possible. A previous report in the literature has suggested that women in their reproductive years have a higher incidence rate of CADRs than men because of their more reactive immune system (Alvestad et al., 2007). Therefore, our study addressed the questions of (1) the extent to which the relative CADR rates differ between males and females; (2) the influence of age; (3) potential between-drug differences; and (4) risk factors that may predict CADRs.

2. Experimental procedures

2.1. Data source

The adverse drug reaction (ADR) dataset in the present study was collected through AMSP since 1993. AMSP is an ongoing international multicenter drug safety surveillance program that systematically collects data on psychopharmacotherapy and ADRs from more than 100 psychiatric hospitals in the German speaking countries (Germany, Austria and Switzerland). The underlying method of the project has been described in detail by various previous publications (Engel et al., 2004; Grohmann et al., 2004; Lange-Asschenfeldt et al., 2009; Friedrich et al., 2016): data on severe ADRs due to psychopharmacological treatment are systematically assessed by the participating hospitals. ADRs are regarded as "severe" when causing significant impact on the course of treatment (e.g., life-threatening or seriously endangering health) or on the patients' everyday functioning. The AMSP protocol provides specific guidelines for the assessment of ADRs in relation to respective organ system, for example, CADRs is classified as severe when the whole

body or more than one body part is affected (Grohmann et al., 2014). For each adverse event, a detailed description is documented along with the basic demographic, psychiatric and somatic data (including all diagnoses). All cases are reviewed by a senior psychiatrist of each hospital and discussed thereafter at case conferences. The probability for the ADR to be caused by a specific drug is rated as follows (Grohmann et al., 2004).

Possible: ADR unknown or alternative explanation more likely.

Probable: ADR known for drug in question and time-course and dosage in accordance with previous experience; alternative explanation less likely.

Definite: the same as "*probable*" together with reappearance after re-exposure with drug in question.

Questionable: questionable or not sufficiently documented.

In addition, drug use was collected by all participating hospitals on two pre-specified reference days every year for all inpatients. This prescription dataset was not used in this study.

Our study included all ADR cases from 1993 to 2014 with a probability rating of "definite", "probable", or "possible" with focus being laid on all concomitant drugs. By applying this method, our case control study is not limited by expert evaluations.

The AMSP drug surveillance program was approved by the leading boards of each participating institute prior to implementation, and the Ethics Committee of the University of Munich formally approved evaluations based on the AMSP databank.

2.2. Study design

A nested case control design, i.e. case/non-case approach (Moore et al., 1997) was used to identify new possible causes and risk factors of CADRs. CADRs were defined as cases, and all other ADRs were regarded as non-cases. Cases and non-cases were both derived from the ADR dataset of AMSP as described above. Reports were only included when data were complete and patients were 18 years or older. The ADR dataset under investigation was comprised of 9592 ADR reports. Of these, 474 cases were excluded because of incomplete information, and 439 cases because of skin related ADRs - like edema, acne and hair loss - which were not classified as CADRs for the purpose of this study. Hence, our study was conducted with 8679 ADR reports, representing 90.48% of the total available ADR reports. We identified 594 (6.84%) CADR cases and 8085 non-cases (93.16%). Reporting odds ratio (ROR) of ADR is the ratio of the reporting odd of the association between the CADR and the exposure of the interest. ROR is a measure of disproportionality in case/non-case approach (van Puijenbroek et al., 2002; Rothman et al., 2004). The ROR and its confidence intervals were computed as described in Moore et al. (1997). RORs whose confidence interval did not include 1 were considered as significantly different from 1.

If the ROR is greater than 1 as defined above, then it can be interpreted as indicating an association between the exposure and reporting of the reaction of interest. This method can be regarded as a variant of the database nested case-control method (Kramer et al., 1988; Strom et al., 1994). Exposure to a certain drug or drug class was defined as the presence of the drug or drug class of interest in a report, independently of whether or not the drug or drug class was suspected of causing the reaction. In addition, diagnostic groups and gender were investigated by means of the same method.

In the next step, we calculated and compared the ratios of female to male among different age groups for cases and non-cases.

2.3. Data analysis/statistics

In case/non-case approach, Student's t test was performed to assess the significance of differences in the mean of continuous variables between cases and non-cases. Differences in the proportions of the characteristics between cases and non-cases were tested for significance with χ^2 test or Fisher's exact test where appropriate. The strength of association between the exposure of interest and CADR was expressed as ROR with 95% confidence intervals. First, we conducted standard univariate analysis of ROR for several factors. Subsequently, these RORs were adjusted for age, reporting time period, hospital, number of diagnoses and number of concomitant drugs by means of multivariate logistic regression analysis. Finally, 95% confidence intervals of the resulting female-male ratios (by age groups) were calculated and compared between cases and non-cases.

All statistical calculations were performed using SAS software (Statistical Analysis System, version 9.3).

3. Results

The sample under investigation was comprised of 594 CADR cases and 8085 non-cases exhibiting other ADRs. Table 1 shows the basic characteristics of cases versus non-cases. There were significantly more female patients ($p < 0.001$) among the cases compared to the non-cases. Despite the differences in the sample composition, there was no significant difference in terms of mean age or mean number of concomitant medication between cases and non-cases. Moreover, no significant difference showed up between cases and non-cases regarding monotherapy, combination therapy and polypharmacy. To determine if the reporting period might play a role, we divided the observation interval into three periods: 1993–2000, 2001–2007 and 2008–2014. Interestingly, there were significantly fewer cases reported than non-cases during the most recent time period ($p < 0.001$).

Table 2 shows the diagnostic groups (according to ICD 10) for cases and non-cases. Mental and behavioral disorders due to psychoactive substance use (ROR 2.64; 95% CI 2.21–3.15), mood [affective] disorders (ROR 1.43; 95% CI 1.21–1.69) and disorders of adult personality and behavior (ROR 1.47; 95% CI 1.11–1.94) were the diagnostic groups significantly more involved in cases.

Table 3 shows the drug classes for cases and non-cases. We found a significant increase of RORs under antidepressants (AD: ROR 1.25; 95% CI 1.04–1.49), tricyclic antidepressants (TCA: ROR 1.43; 95% CI 1.14–1.79), antiepileptic

Table 1 Characteristics of cases and non-cases.

	Cases $N = 594$	Non-cases $N = 8085$	P value
Mean age (± S.D.)	47.12 (± 16.19)	48.45 (± 18.89)	NS
Female**	395 (66.50%)	4,521 (55.92%)	<0.001
Mean No. of medication (± S.D.)	3.88 (± 2.23)	3.97 (± 2.50)	NS
Medication			
Monotherapy	135 (22.73%)	1634 (20.21%)	NS
Combination therapy	177 (29.80%)	2426 (30.01%)	NS
Polypharmacy	282 (47.47%)	4025 (49.78%)	NS
Reporting year			
1993-2000	138 (23.23%)	1462 (18.08%)	NS
2001-2007	286 (48.15%)	3478 (43.02%)	NS
2008-2014**	170 (28.62%)	3145 (38.90%)	<0.001

Monotherapy: one psychotropic drug; Combination therapy: two psychotropic drugs; Polypharmacy: three or more psychotropic drugs.
* p value < 0.05, NS: not significant.
** p value < 0.01.

Table 2 Cases and non-cases per diagnosis group.

Diagnosis group ICD10*: definition	Cases $N = 594$	Non-cases $N = 8085$	ROR (95% CI)
F00-F09: organic, including symptomatic, mental disorders	46 (7.74%)	1045 (12.93%)	0.57 (0.42-0.77)
F10-F19**: mental and behavioral disorders due to psychoactive substance use	212 (35.69%)	1406 (17.39%)	2.64 (2.21-3.15)
F20-F29: schizophrenia, schizotypal and delusional disorders	137 (23.06%)	3351 (41.45%)	0.42 (0.35-0.52)
F30-F39**: mood [affective] disorders	300 (50.51%)	3372 (41.71%)	1.43 (1.21-1.69)
F40-F48: neurotic, stress-related and somatoform disorders	73 (12.29%)	818 (10.12%)	1.25 (0.96-1.61)
F50-F59: behavioral syndromes associated with physiological disturbances and physical factors	6 (1.01%)	114 (1.41%)	0.71 (0.31-1.63)
F60-F69**: disorders of adult personality and behavior	60 (10.10%)	575 (7.11%)	1.47 (1.11-1.94)
F70-F79: mental retardation	11 (1.85%)	208 (2.57%)	0.72 (0.39-1.32)

The total is higher than 100% since there could be multiple diagnoses per patient.
* With minimum of three cases of CADR.
** ROR significantly greater than 1.

drugs (AEP: ROR 3.30; 95% CI 2.79-3.90) and other psychotropic drugs (including acamprosate, clomethiazole and disulfiram; ROR 6.13; 95% CI 3.99-9.42).

Table 4 compares cases and non-cases for single drugs. Comparing CADRs to the other ADRs, clomipramine (ROR 1.86; 95% CI 1.15-3.03), maprotiline (ROR 1.22; 95% CI 2.26-4.19), carbamazepine (ROR 6.83; 95% CI 5.52-8.44), lamotrigine (ROR 4.14; 95% CI 3.01-5.68), clomethiazole (ROR 6.77 95% CI 4.13-11.09), acamprosate (ROR 4.56; 95% CI 1.23-16.87; only three CADRs) and disulfiram (ROR 4.10; 95% CI 1.13-14.94; only three CADRs) showed significantly more cases than non-cases.

Table 5 shows the percentage of females for relevant drug classes and for those drugs that were related to increased numbers of cases (Table 4). AD, TCA, AEP, maprotiline and lamotrigine were significantly more often prescribed in females among cases than among non-cases.

Our multivariate logistic regression model included the following variables: gender, age, time period, reporting hospital, number of diagnoses and number of concomitant drugs along with variables for diagnostic groups and medications. This model identified female sex, diagnoses F10-19 (substance abuse), maprotiline, carbamazepine, lamotrigine and clomethiazole as significant risk factors of CADRs (Table 6).

The time-to-onset (Fig. 1) had a median value of 6 days in cases and 10 days in non-cases. The mean value was 17 (± S.D. 127.4) days in the cases and 59 (± S.D. 301.8) days in the non-cases (not significant).

Fig. 2 shows the female-male ratios in CADRs stratified by age groups compared with non-cases. For the age groups 18-30, 31-40 and 41-50 years, female-male ratios were significantly higher in CADRs than in non-cases. This significant difference was not present in the higher age groups 51-60 and 61-70. The mean relative female-male ratio was 1.7 in the age group 18-50 and 1.24 in the age group 51-70.

4. Discussion

In this case-control study, 594 patients suffering from severe CADRs (cases) were compared with 8085 patients suffering from other severe ADRs (non-cases) as documented in a large pharmacovigilance program. The CADR cases were

Table 3 Cases and non-cases per drug class.

Drug class*	Cases $N = 594$	Non-cases $N = 8085$	ROR (95% CI)
AD**	411 (69.19%)	5,197 (64.28%)	1.25 (1.04-1.49)
TCAs**	98 (16.50%)	980 (12.12%)	1.43 (1.14-1.79)
SSRIs	132 (22.22%)	1658 (20.51%)	1.11 (0.91-1.35)
SNRIs	67 (11.28%)	995 (12.31%)	0.91 (0.70-1.18)
NaSSAs	67 (11.28%)	1015 (12.55%)	0.89 (0.68-1.15)
MAOIs	13 (2.19%)	116 (1.43%)	1.54 (0.86-2.74)
OADs	34 (5.72%)	442 (5.47%)	1.05 (0.73-1.50)
AEP**	285 (47.98%)	1766 (21.84%)	3.30 (2.79-3.90)
Lithium	47 (7.91%)	656 (8.11%)	0.97 (0.72-1.33)
Anti-parkinson drugs	43 (7.24%)	690 (8.53%)	0.84 (0.61-1.15)
Hypnotics	74 (12.46%)	889 (11.00%)	1.15 (0.89-1.48)
BZDs	200 (33.67%)	2867 (35.46%)	0.92 (0.78-1.10)
Z-drugs	43 (7.24%)	641 (7.93%)	0.91 (0.66-1.25)
Antipsychotics	458 (77.10%)	9385 (116.08%)	0.66 (0.59-0.75)
Typical antipsychotics	102 (17.17%)	2126 (26.30%)	0.76 (0.66-0.89)
Atypical antipsychotics	234 (39.39%)	5603 (69.30%)	0.29 (0.24-0.34)
Antidementia drugs	14 (2.36%)	252 (3.12%)	0.75 (0.44-1.29)
Tranquillizers	185 (31.14%)	2666 (32.97%)	0.92 (0.77-1.10)
Others**	31 (5.22%)	72 (0.89%)	6.13 (3.99-9.42)

AEP: antiepileptic; AD: antidepressant; TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors; SNRIs: selective Serotonin-norepinephrine reuptake inhibitors; NaSSAs: noradrenergic and specific serotonergic antidepressants; MAOIs: monoamine oxidase inhibitors; OADs: other ADs, including agomelatin, bupoprion, nefazodone, reboxetine, tianeptine and trazodone; BZDs: benzodiazepine derivatives; Z-drugs: zopiclone, zopidem and zaleplon; others: acamprosate, clomethiazole, disulfiram.

* With a minimum of three cases of CADR,

** ROR significantly greater than 1.

Table 4 Cases and non-cases per relevant single drug.

Medication*	Cases (%) $N = 594$	Non-cases (%) $N = 8085$	ROR (95% CI)
TCA			
Amitriptyline	15 (2.53%)	248 (3.07%)	0.82 (0.48-1.39)
Clomipramine**	19 (3.20%)	141 (1.74%)	1.86 (1.15-3.03)
Dibenzepine	3 (0.51%)	21 (0.26%)	1.95 (0.58-6.56)
Doxepine	15 (2.53%)	154 (1.90%)	1.34 (0.78-2.28)
Maprotiline**	12 (2.02%)	73 (0.90%)	1.22 (2.26-4.19)
Nortriptyline	6 (1.01%)	66 (0.82%)	1.24 (0.54-2.87)
Trimipramine	24 (4.04%)	224 (2.77%)	1.48 (0.96-2.27)
AEP			
Carbamazepine**	149 (25.08%)	378 (4.68%)	6.83 (5.52-8.44)
Clonazepam	5 (0.84%)	99 (1.22%)	0.69 (0.28-1.69)
Gabapentin	7 (1.18%)	47 (0.58%)	2.04 (0.92-4.53)
Lamotrigine**	53 (8.92%)	187 (2.31%)	4.14 (3.01-5.68)
Oxcarbazepine	10 (1.68%)	93 (1.15%)	1.47 (0.76-2.84)
Pregabalin	7 (1.18%)	168 (2.08%)	0.56 (0.26-1.20)
Valproate	47 (7.91%)	674 (8.34%)	0.95 (0.69-1.29)
Others			
Acamprosate**	3 (0.51%)	9 (0.11%)	4.56 (1.23-16.87)
Clomethiazole**	24 (4.04%)	50 (0.62%)	6.77 (4.13-11.09)
Disulfiram**	3 (0.51%)	10 (0.12%)	4.10 (1.13-14.94)

TCAs: tricyclic antidepressants; AEP: antiepileptic; Others: acamprosate, clomethiazole, disulfiram.

* With a minimum of three cases of CADRs from significant drug groups in Table 4, maprotiline is classified here as TCA.

** ROR significantly greater than 1.

Table 5 Percentage of females in cases and non-cases per relevant prescribed drug class and single drug.

	Cases (%) $N = 594$	Non-cases (%) $N = 8085$	*P* value
Female (%)**	395 (66.50%)	4521 (55.92%)	<0.001
AD**	74.94%	67.73%	0.0025
TCA**	79.59%	60.39%	0.0078
Clomipramine	73.68%	61.41%	NS
Maprotiline**	75.00%	66.22%	0.0055
AEP**	64.91%	53.79%	<0.001
Carbamazepine	54.36%	55.82%	NS
Lamotrigine**	88.68%	64.71%	<0.001
Others	22.58%	34.29%	NS
Acamprosate	33.33%	33.33%	NS
Clomethiazole	16.67%	30.00%	NS
Disulfiram	33.33%	20.00%	NS

AD: antidepressants; TCAs: tricyclic antidepressants; AEP: antiepileptics; Others: acamprosate, clomethiazole, disulfiram.

* p value < 0.05.

** p value < 0.01.

Table 6 Factors correlated with CADRs according to logistic regression.

	Cases (%) $N = 594$	Non-cases (%) $N = 8085$	Unadjusted ROR (95% CI)	Adjusted[a] ROR (95% CI)	*P* value
Female**	395 (66.50%)	4521 (55.92%)	1.57 (1.31-1.87)	1.75 (1.43-2.13)	<0.001
Diagnosis group					
F00-F09	46 (7.74%)	1045 (12.93%)	0.57 (0.42-0.77)	0.53 (0.32-0.87)	0.0127
F10-F19**	212 (35.69%)	1406 (17.39%)	2.64 (2.21-3.15)	1.68 (1.15-2.45)	0.0073
F20-F29	137 (23.06%)	3351 (41.45%)	0.42 (0.35-0.52)	0.38 (0.26-0.56)	<0.001
F30-F39	300 (50.51%)	3372 (41.71%)	1.43 (1.21-1.69)	0.80 (0.56-1.15)	NS
F40-F49	73 (12.29%)	818 (10.12%)	1.25 (0.96-1.61)	0.89 (0.60-1.33)	NS
F50-F59	6 (1.01%)	114 (1.41%)	0.71 (0.31-1.63)	0.48 (0.20-1.18)	NS
F60-F69	60 (10.10%)	575 (7.11%)	1.47 (1.11-1.94)	0.82 (0.54-1.25)	NS
F70-F79	11 (1.85%)	208 (2.57%)	0.72 (0.39-1.32)	0.60 (0.29-1.26)	NS
Medications					
Clomipramine	19 (3.20%)	141 (1.74%)	1.86 (1.15-3.03)	1.35 (0.79-2.32)	NS
Maprotiline*	12 (2.02%)	73 (0.90%)	1.22 (2.26-4.19)	2.11 (1.09-4.10)	0.0270
Carbamazepine**	149 (25.08%)	378 (4.68%)	6.83 (5.52-8.44)	5.72 (4.45-7.37)	<0.001
Lamotrigine**	53 (8.92%)	187 (2.31%)	4.14 (3.01-5.68)	6.05 (4.20-8.72)	<0.001
Acamprosate	3 (0.51%)	9 (0.11%)	4.56 (1.23-6.87)	2.70 (0.65-11.24)	NS
Clomethiazole**	24 (4.04%)	50 (0.62%)	6.77 (4.13-1.09)	2.34 (1.27-4.33)	0.0066
Disulfiram	3 (0.51%)	10 (0.12%)	4.10 (1.13-4.94)	3.32(0.81-13.59)	NS

[a] adjustment was made for age, reporting years, reporting hospital, number of diagnosis and number of concomitant drugs. Adjusted R^2 of the regression model was 20.81%.

* p value < 0.05 and ROR greater than 1.

** p value < 0.01 and ROR greater than 1.

6.8% of all ADR cases, suggesting that CADR was rather frequently associated with psychotropic drugs. In the most recent period from 2007 to 2014, the percentage of CADR cases was lower (5.1%). The case/non-case approach with a multivariate logistic regression analysis allowed us to identify influencing factors without limited by experts' opinions.

4.1. Age/sex difference

Greater age has been associated with CADRs in general (Naldi et al., 1999) or with CADRs to antidepressants (Warnock and Morris, 2002). In our case/non-case analysis, the result showed that there was no significant difference of mean age between CADRs and other ADRs. This could be due to the nature of case/non-case analysis, since the case/non-case method compares different ADRs within the same dataset. Therefore, a risk factor generally associated to all ADRs cannot be found by this approach.

The generally higher risk of women developing adverse drug reactions is described for various adverse drug reactions (Fattinger et al., 2000; Pirmohamed et al., 2004; Patel et al., 2007; Franconi and Campesi, 2014), but could not be found in all studies (D'Incau et al., 2014). Regarding

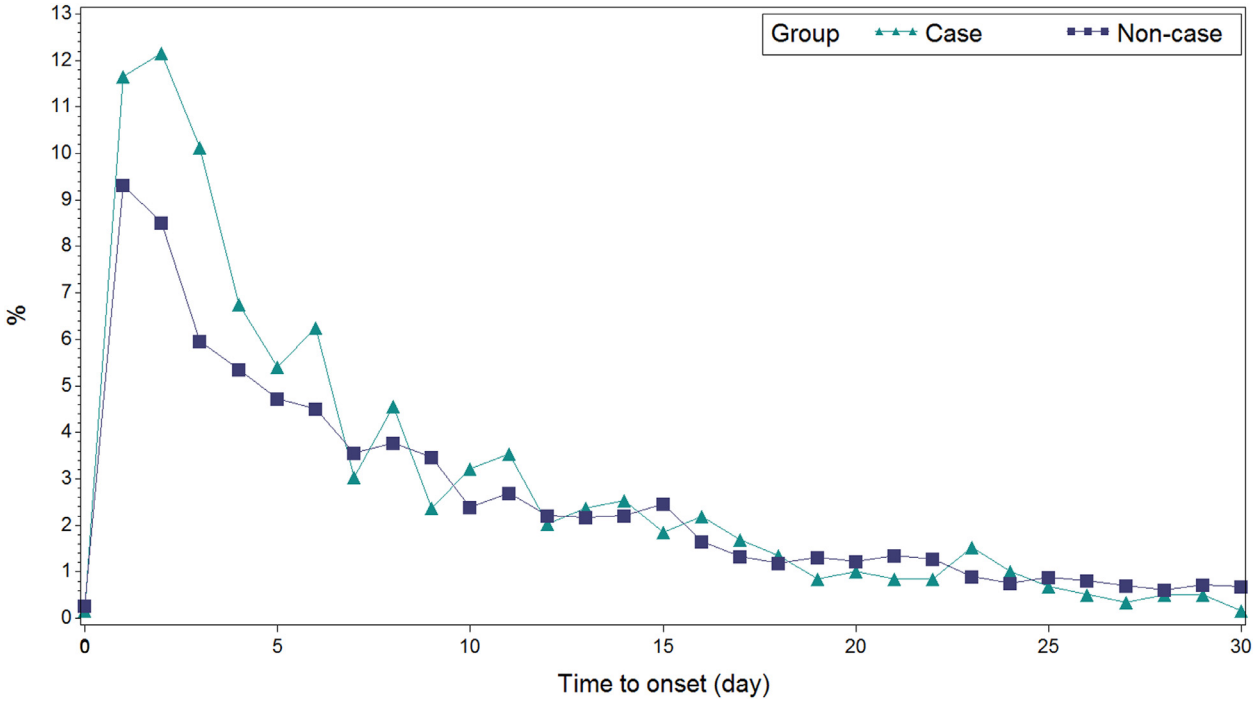

Figure 1 Frequency of time-to-onset of ADRs in case and non-case.

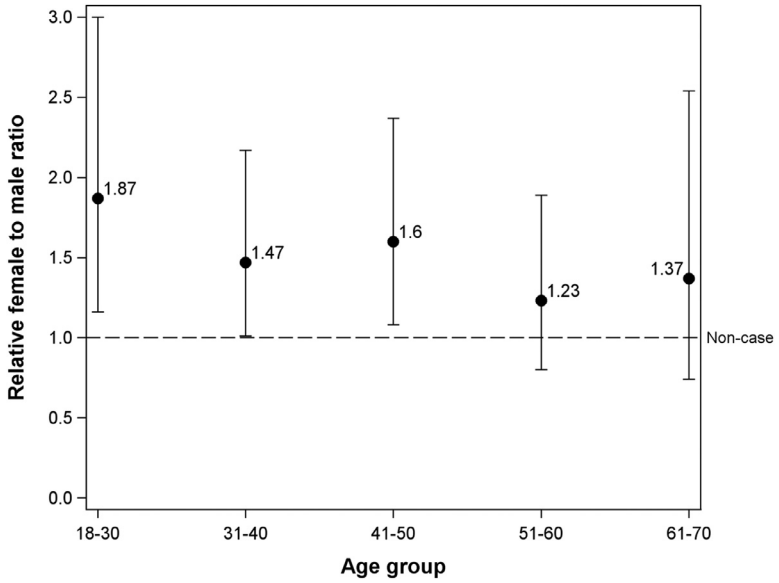

Figure 2 Female-male ratios of CADRs stratified by age groups.
* age groups with female-male ratio significantly greater than 1.

CADRs, a sex difference with higher incidence in women in general (Bigby et al., 1986; Naldi et al., 1999) or only for certain drug groups (Alvestad et al., 2007; Lange-Asschenfeldt et al., 2009; Wang et al., 2012) was found, but could not be shown in other studies (Li and Ma, 2006; Hirsch et al., 2006). Our results show that women (56%) predominated in non-cases, but the sex difference was more apparent in cases (67%). There were significantly more female patients ($p < 0.001$) in cases than non-cases, which clearly demonstrates that sex difference is particularly important for CADRs.

4.2. Polypharmacy

Between cases and non-cases, we did not find significant difference in terms of mean number of concomitant medication, proportion of monotherapy, combination therapy

and polypharmacy. In contrast, previous studies using different methods have identified polypharmacy as a risk factor for many clinically relevant ADRs (Fattinger et al., 2000). The discrepancy could be due to the nature of the approach, since case/non-case method compares different ADRs within one dataset. There are also contradicting findings whether polypharmacy is a risk factor of CADRs to psychotropic drugs. It has been identified as risk factor of CADRs to antidepressants (Warnock and Morris, 2002) and to mood stabilizers, especially the combination of lamotrigine and valproate (Warnock and Morris, 2003), whereas it was not found for antiepileptics in another study (Wang et al., 2012). Further research regarding polypharmacy of different drug classes and combinations as risk factor of CADRs is needed.

4.3. Reporting time period

We divided the reporting years into three groups: 1993–2000, 2001–2007 and 2008–2014. There was a significant difference between reporting of cases and non-cases during 2008–2014 ($p < 0.01$). During the latest time period, reports of CADRs dropped about 40% as compared to the second time period, while the reporting of other ADRs did not decrease. This indicates a decrease of CADR cases over time compared to other ADRs, presumably caused by different prescribing patterns with less frequent prescriptions of CADR related drugs (Tables 3 and 4), e.g. lower prescription rate of carbamazepine (Druschky et al., 2018) and tricyclic antidepressant drugs (Stübner et al., 2018) in the more recent years.

4.4. Time-to-onset

The time period between initiation of drug treatment and the onset of ADRs (time-to-onset) is clinically important. We found an average time-to-onset of 17 days in cases and 59 days in non-cases (not significant). The median time-to-onset was 6 days in cases and 10 days in non-cases. CADRs appeared to occur slightly earlier than the rest of the ADRs.

4.5. Medication

There have been several studies on CADRs to psychotropic drugs, especially regarding antiepileptic and antidepressant drugs (Warnock and Morris, 2002, 2003; Alvestad et al., 2007; Amsterdam et al., 2009; Wang et al., 2012). In the present study, we found clomipramine, maprotiline (tricyclic antidepressants and also the overall group of antidepressants), carbamazepine and lamotrigine (and antiepileptics in general) to be positively associated with CADRs. Our results are accordant with previous studies (Warnock and Morris, 2002, 2003; Alvestad et al., 2007; Wang et al., 2012). In addition, we found that acamprosate, clomethiazole and disulfiram (and thus also the group of “other psychotropic drugs”) were significantly more involved in CADR cases. It is remarkable that these three drugs prescribed preferably in alcohol abuse were associated with CADRs. These substances are not only structurally different, but also used for very different therapeutic purposes, e.g. for the treatment of delirium (clomethiazole), as an anti-craving substance (acamprosate) or as withdrawal / aversion therapy (disulfiram). This may indicate that the diagnosis itself (F1) could be the underlying risk factor.

4.6. Diagnosis

Consecutively, we examined the relationship between diagnosis and CADRs. Interestingly, we found that F1 (mental and behavioral disorders due to psychoactive substance use), F3 (mood [affective] disorders) and F6 (disorders of adult personality and behavior) according to ICD 10 were more prevalent in patients with CADRs compared to other ADRs. To decide whether the diagnostic group or the respective medication was more relevant for CADRs, a logistic regression was performed (see below).

4.7. Relation of medication, sex and age

For drugs that were significantly more involved in cases than non-cases, sex differences were calculated. Our analyses found significant sex differences for tricyclic antidepressants, for antidepressant drugs generally, for antiepileptics generally and for lamotrigine (but not for carbamazepine). Consistently, previous studies from AMSP reported higher incidence of CADRs in woman using antiepileptic drugs (Lange-Asschenfeldt et al., 2009) and lamotrigine specifically (Druschky et al., 2018).

Remarkably, the relative rates of CADRs of female to male were larger than 1 in the age groups between 18 and 50. In contrast, there was no statistically significant sex difference in higher age groups. While in the reproductive age group there were 70% more women than men, in the higher age group there were only 24% more women. Female sex has been identified as a risk factor of CADR in many previous publications (Bigby et al., 1986; Naldi et al., 1999; Fattinger et al., 2000; Alvestad et al., 2007; Wang et al., 2012), but only one previous study also showed that females are at higher risk of CADRs only during reproductive years (Alvestad et al., 2007). This interaction between age and sex might be explained with sex hormones during reproductive years and their effects on the immune system.

There are several known pathomechanisms for CADRs. Some are the result of non-immunological causes such as cumulative toxicity, photosensitivity or interaction with other drugs, while others are immune-mediated reactions such as allergic reactions (Marzano et al., 2016). Women have been considered “immune-privileged” due to the sex hormones (Giefing-Kröll, 2015). The female sex steroid hormones enhance the innate immune responses in both physiological and pathological states, whereas androgens mainly suppress them (Da Silva, 1999; Giefing-Kröll, 2015). For example, responses to various types of vaccination are often higher in women (Cook, 2008) and a similar shift to female predominance is reported for asthma, atopic conditions and hay fever during reproductive years (Shamssain and Shamsian, 1999; Osman, 2003). It has been discussed that women lose their immunological “advantage” after menopause based

on epidemiological data, and hormone replacement therapy (HRT) shows beneficial effects on the immune system (Giefing-Kröll, 2015).

4.8. Factors according to the multivariate logistic regression

Our multivariate analysis demonstrated that sex (female), diagnostic group (F1 substance abuse), maprotiline, carbamazepine and lamotrigine as well as clomethiazole were independent risk factors in CADR cases with adjustment for age, reporting years, reporting hospital, diagnostic groups and medications. To our knowledge, we for the first time demonstrated that substance abuse and clomethiazole were associated with CADRs after controlling for possibly confounding factors. Previously, a report of toxic epidermal necrolysis as ADR of carbamazepine administration, heroin and alcohol abuse was published (Petter and Haustein, 1999). Furthermore, another case-control study identified alcohol abuse as the only risk factor for carbamazepine-induced serious mucocutaneous adverse reactions using multivariate regression (Bertulyte et al., 2014). Whether substance abuse (especially alcohol) alters immunity and subsequently increases susceptibility to CADRs needs to be further investigated. Consistently, a case of severe allergic reaction to clomethiazole has been reported (Khan, 1976). However, the case report was discussed briefly after that the allergic reaction might have been caused by the coloring agent tartrazine in the capsules of clomethiazole, not the drug itself (Weeks, 1977), but another reply added one case report of allergic skin reaction to clomethiazole (Halstead and Madden, 1976). Taken together, the new findings encourage to further explore the underlying mechanisms of CADRs possibly caused by substance abuse or by clomethiazole.

4.9. Strength and limitation

The method of case/non-case study has led to plausible and novel results. The ADRs with their prescriptions were compared without taking the experts' causality assessment ("imputation") into account. Prejudice, which is unavoidable in imputation, e.g. due to technical information/package insert and to the state of literature, is eliminated to some extent.

The ROR is identical to the odds ratio calculated from a case-control study that compares each drug to all other drugs (Rothman et al., 2004). An advantage of using ROR is that non-selective underreporting of a drug or ADR does not essentially influence the ROR. Underreporting is inevitable in spontaneous reporting ADR datasets. It has been suggested that underreporting is more or less of the same magnitude for all drugs and other exposures. Hence, it is possible to identify differences in adverse effects of drugs from comparison of their frequency within the same data source (Pierfitte et al., 1999).

One of the disadvantages of the approach is that the associations in case/non-case study can be biased in some ways. The association of a drug and a single ADR in the analysis of spontaneous reports can be lessened if another reaction specific to the drug is widely reported (Moore et al., 1997). In our study, antipsychotics were underrepresented in CADRs (Table 3). This could be due to the fact that antipsychotics have other ADRs in the foreground, such as extrapyramidal disorders or weight gain. On the other hand, very low incidence rates of CADRs of antipsychotics have also been reported previously (Lange-Asschenfeldt et al., 2009).

Another problem occurs in the selection of cases from a spontaneous reporting database. In the AMSP study, drug monitors collect data on ADRs in association with psychopharmacological treatment that occurred within these hospitals. The cases are then reviewed by a senior doctor of each hospital and discussed thereafter at central case conference. We cannot rule out that CADRs have been detected more often than some other ADRs such as clinically relevant changes in laboratory values. On the other hand, a few CADR cases may have been missed because of the selection criteria based on experts' decision that the CADR has to be related to the drug treatment. There could be uneven under-reporting among different drugs due to the possible unrecognition of the reaction as drug-related. To alleviate the issue, the present study included all the ADR cases with a probability rating of "*possible*" or higher and all the concomitant drugs of ADR cases were analyzed regardless of whether the drugs were imputed or not. Therefore, it is aligned with our goal of the evidence-based approach, since it is not limited only to the drugs imputed by experts. Nevertheless, in a spontaneous reporting system, the under- and selective reporting of ADRs is principally a serious problem in quantifying ADRs in relation to drugs and other risk factors.

4.10. Conclusion

Regarding time-to-onset, the CADRs seem to occur earlier than other ADRs covered by the AMSP project: median 6 days versus 10 days. Particularly at the beginning of the treatment, CADR should be considered.

Important risk factors of CADRs identified in this study are: female sex (especially during reproductive age period), diagnostic group F1 (substance abuse) and the drugs maprotiline, carbamazepine, lamotrigine and clomethiazole. Since CADRs can be threatening, it is important to be aware of these risk factors. In contrast to maprotiline, carbamazepine and clomethiazole, lamotrigine still plays a major role in psychiatric pharmacotherapy. Patients prescribed with lamotrigine, especially females, should be informed about CADRs and encouraged to observe themselves, and all recommended and widely followed precautionary measures should be strictly followed, e.g. slow increase in dosing. In addition, this study indicates that substance abuse is an important risk factor for CADRs. So far, little attention has been paid to substance abuse (diagnosis group F1), which apparently favors the likelihood of CADRs to different medications.

By the case/non-case study with all prescriptions and related ADRs, novel relationships could be found that need to be verified or falsified in further studies. In the present study, substance abuse and clomethiazole identified as risk factors of CADRs are such novel findings.

Role of funding sources

No funding was received for this study.

Conflict of interests

The AMSP Drug Safety Program is based on non-profit associations in the German- speaking countries Germany, Austria and Switzerland. In recent years, financial support has been contributed by almost all the pharmaceutical companies involved in CNS research. Since 1993 educational and research grants have been awarded by the following pharmaceutical companies to the three national non-profit associations of the AMSP.

Austrian companies: AstraZeneca Österreich GmbH, Boehringer Ingelheim Austria, Bristol-Myers Squibb GmbH, CSC Pharmaceuticals GmbH, Eli Lilly GmbH, Germania Pharma GmbH, GlaxoSmithKline Pharma GmbH, Janssen-Cilag Pharma GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Pfizer Med Inform, Servier Pharma Austria, Wyeth Lederle Pharma GmbH.

German companies: Abbott GmbH & Co. KG, AstraZeneca GmbH, Aventis Pharma Deutschland GmbH GEO/R/N, Bayer Vital GmbH & Co. KG, Boehringer Mannheim GmbH, Bristol-Myers-Squibb, Ciba Geigy GmbH, Desitin Arzneimittel GmbH, Duphar Pharma GmbH & Co. KG, Eisai GmbH, esparma GmbH Arzneimittel, GlaxoSmithKline Pharma GmbH & Co. KG, Hoffmann-La Roche AG Medical Affairs, Janssen-Cilag GmbH, Janssen Research Foundation, Knoll Deutschland GmbH, Lilly Deutschland GmbH Niederlassung Bad Homburg, Lundbeck GmbH & Co. KG, Nordmark Arzneimittel GmbH, Novartis Pharma GmbH, Organon GmbH, Otsuka-Pharma Frankfurt, Pfizer GmbH, Pharmacia & Upjohn GmbH, Promonta Lundbeck Arzneimittel, Rhone-Poulenc Rohrer, Sanofi-Synthelabo GmbH, Sanofi-Aventis Deutschland, Schering AG, Servier Pharma, SmithKlineBeecham Pharma GmbH, Solvay Arzneimittel GmbH, Synthelabo Arzneimittel GmbH, Dr Wilmar Schwabe GmbH & Co., Thiemann Arzneimittel GmbH, Trommsdorff GmbH & Co. KG Arzneimittel, Troponwerke GmbH & Co. KG, Upjohn GmbH, Wander Pharma GmbH, Wyeth-Pharma GmbH.

Swiss companies: AHP (Schweiz) AG, AstraZeneca AG, Bristol-Myers Squibb AG, Desitin Pharma GmbH, Eli Lilly (Suisse) S.A., Essex Chemie AG, GlaxoSmithKline AG, Janssen-Cilag AG, Lundbeck (Suisse) AG, Mepha Schweiz AG/Teva, MSD Merck Sharp & Dohme AG, Organon AG, Pfizer AG, Pharmacia, Sandoz Pharmaceuticals AG, Sanofi-Aventis (Suisse) S.A., Sanofi-Synthelabo SA, Servier SA, SmithKlineBeecham AG, Solvay Pharma AG, Vifor SA, Wyeth AHP (Suisse) AG, Wyeth Pharmaceuticals AG.

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S. Toto is a project manager of AMSP, has been a member of an advisory board for Otsouka and has received speakerś honoraria from Janssen Cilag, Lundbeck, Otsouka and Servier.
X. Zhang: no conflicts of interest to be declared.

Contributions

WG initiated the study, developed the concept and revised the various versions of the manuscript.

XZ extracted the data from the AMSP SAS databank, performed the statistical analyses and prepared the various versions of the manuscript.

HS created the AMSP SAS databank, gave important recommendations for the statistical analyses and revised the various versions of the manuscript.

RG supported the statistical analyses and revised the various versions of the manuscript.

RB gave relevant recommendations for evaluation and revised the various versions of the manuscript.

GH revised the various versions of the manuscript.

ST revised the various versions of the manuscript.

SB revised the various versions of the manuscript.

SK supported the developement of the concept and revised the various versions of the manuscript.

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