Cutaneous Adverse Reactions to Psychotropic Drugs: Data From a Multicenter Surveillance Program

Christian Lange-Asschenfeldt, MD; Renate Grohmann, MD; Bernhard Lange-Asschenfeldt, MD; Rolf R. Engel, PhD; Eckart Rüther, MD; and Joachim Cordes, MD

Objective: Cutaneous adverse drug reactions (CADRs) in psychiatric pharmacotherapy are common, potentially harmful, and among the most frequent types of adverse events. To date, most of the data regarding CADRs to psychotropic medications are anecdotal, and systematic studies are lacking, particularly with respect to modern "second-generation" drugs.

Method: Data were drawn from a database of 208,401 psychiatric inpatients monitored by the multicenter drug safety surveillance project Drug Safety in Psychiatry (*Arzneimittelsicherheit in der Psychiatrie* [AMSP]) during the years 1993–2005. The project surveys clinically relevant adverse reactions to all marketed psychotropic drugs.

Results: Two hundred fourteen cases of clinically relevant CADRs with a "probable" or "definite" attribution to a single psychotropic compound were identified (0.1%), of which 7 were life threatening (3.3% of CADR cases). Eruptions occurred irrespective of age and mainly in women. The gender effect was significant only for mood-stabilizing antiepileptic drugs (AEDs; $P = .001$). Substances with the highest and statistically significant CADR risk were AEDs ($P < .0001$), particularly lamotrigine and carbamazepine. For the most part, the incidence in antidepressants did not differ from the mean CADR rate of the monitored drugs in this survey (0.103%). However, CADRs were seen significantly less often with modern antidepressants (such as selective serotonin reuptake inhibitors and dual-mechanism or other second-generation antidepressants) than with classical tricyclic and tetracyclic antidepressants ($P = .048$). Conventional and atypical antipsychotics alike had the lowest rates of dermatologic side effects.

Conclusions: Although serious complications are rare, clinicians should be aware of CADRs, particularly with AED mood stabilizers. Modern second-generation drugs appear to be associated with a rather low CADR risk.

J Clin Psychiatry 2009;70(9):1258–1265

Submitted: *July 23, 2008; accepted September 26, 2008.*
Online ahead of print: *June 16, 2009 (doi:10.4088/JCP.08m04563).*
Corresponding author: *Christian Lange-Asschenfeldt, MD, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Heinrich-Heine-Universität, Bergische Landstr. 2, D-40629, Düsseldorf, Germany (christian.lange-asschenfeldt@lvr.de).*

Cutaneous adverse drug reactions (CADRs) are among the most frequent types of pharmacologic adverse events.[1] Symptoms may range from mildly discomforting to life threatening, eg, anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. The morphological spectrum of less severe conditions mainly entails exanthematous manifestations. Other skin reactions to psychotropic drugs may occur as urticaria; lichenoid, seborrheic, and psoriasiform eruptions; vasculitis; fixed drug eruptions; phototoxic or photoallergic contact dermatitis; pigmentary disorders; and alopecia.[2] Mechanisms include the hypersensitivity types I (immunoglobulin E–mediated), II (cytotoxic antibody–related), III (immunoglobulin G– or M–mediated), and IV (delayed-type, T cell–mediated).

The estimated incidence of CADRs to psychotropic drugs is 2%–5% among psychiatric inpatients and is believed to range somewhat high compared to other drugs.[2] However, since CADRs are so common and predominantly of benign nature, they are rarely and inconsistently reported, and rates are difficult to assess. In contrast to an abundance of case reports dealing with this type of adverse reaction to psychotropic drugs in the literature, there is a scarcity of valid data from clinical trials. Moreover, it is largely unknown to what extent CADRs contribute to drug discontinuation in controlled trials since such trials often fail to provide details on how adverse drug reactions were defined or recorded.[3] During the past 2 decades, the advent of modern "second-generation" drugs, such as atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs), has induced a paradigm shift in psychiatric pharmacotherapy. Improvement of drug safety, such as cardiovascular and neurologic tolerability, has been the driving force for the development of such compounds. It appears all the more remarkable that large-scale studies analyzing dermatologic side effects to these drugs are still lacking.

A promising approach to such extensive evaluation of adverse reactions to groups or classes of drugs is through surveillance databases. Examples for such comprehensive systems are the United Kingdom General Practice Research Database and the Boston Collaborative Drug Surveillance Program, which have greatly enhanced our understanding of adverse drug reactions over many years from a pharmacoepidemiologic point of view.[4] Another large-scale surveillance database specialized in monitoring

of psychopharmacotherapy is provided by the Drug Safety in Psychiatry (*Arzneimittelsicherheit in der Psychiatrie* [AMSP]) program. The AMSP program yields a continued database of clinically significant adverse drug reactions monitored at 70 psychiatric hospitals in Germany, Austria, and Switzerland since 1993. The program has resulted in several publications[5–11] and, consequently, has already contributed greatly to psychiatric drug safety research. In this article, we analyze CADR reports regarding all marketed psychotropic drugs to date within this framework. Emphasis is placed upon frequency, type, and possible risk factors of single compounds and drug classes, as well as differences in classical versus second-generation or atypical medications.

METHOD

Study Design

The AMSP program is designed as a continuous open-end study. Severe adverse drug reactions (according to the project's definition, see below) to all marketed psychotropic drugs are assessed in the naturalistic setting of routine clinical inpatient treatment at, so far, 70 university, state, or municipal hospitals or departments.[12] Monitoring is performed by trained psychiatrists who contact the ward psychiatrist on a regular basis (ie, at least every 2 weeks), collect data on emerging adverse drug reactions, and document cases using standardized questionnaires. An in-depth description of adverse events is provided along with basic demographic patient data (age, sex, somatic and psychiatric diagnoses, etc) and psychiatric and somatic drug data (dosage, time course, and concurrent medication). Potential risk factors, alternative explanations, measures taken, course of the adverse reaction, and possible previous exposure to the drug in question are also documented in detail. The cases are reviewed by a senior member of the hospital and discussed thereafter at central case conferences held every 3 months. These conferences are attended by the drug monitors from all participating sites, representatives of the German Federal Institute for Drugs and Medicine Products as the national drug regulating authority, the Drug Commission of the German Medical Association, and drug safety experts of the pharmaceutical industry. When a consensus is reached and a probability rating is given to the adverse drug reaction, the completed case descriptions are sent to the various authorities and to the concerned pharmaceutical companies and saved in the central surveillance database for further analysis. The probability is graded as follows[12]:

- *Possible*: Adverse drug reaction not known or alternative explanation more likely.
- *Probable*: Adverse drug reaction known for drug in question and time course and dosage in accord with previous experience; alternative explanation less likely.
- *Definite*: "Probable" plus reappearance after rechallenge with the drug.
- Questionable or not sufficiently documented.

Data on drug use at the participating hospitals are derived from 2 reference days per year. On these reference days, all administered drugs are recorded along with basic demographic and diagnostic data, as well as detailed drug treatment data, for all patients. Moreover, the participating hospitals provide the number of inpatients and the mean treatment duration for all patients under surveillance; both variables are broken down according to diagnostic groups.

Data presented here refer solely to CADR cases judged "probable" and "definite." Moreover, only severe CADRs, according to the project's definition, were considered. An adverse drug reaction is rated as *severe* in the AMSP if it (1) significantly impacts on the course of treatment (eg, if life threatening or seriously endangering the patient's health), (2) considerably impairs everyday functioning, or (3) requires the patient's transfer to another department or ward providing more intensive or specialized care. In addition, a CADR may be rated as severe if it affects the whole body or more than 1 body part (eg, limb, face), if it is associated with fever or malaise, or if it results in significant systemic treatment.[12] However, in the dermatologic literature, the term *severe* frequently refers to life-threatening CADRs such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Thus, to avoid confusion, we use the term "clinically relevant CADR" throughout this text when the AMSP's severe rating applies.

Identification of the causative agent may be challenging in the case of a CADR emerging during combination therapy, which is common in psychiatric inpatient treatment. However, when dosage, time sequence, and potential risk are taken into account, a reliable statement can be made in the vast majority of the cases. In the rare cases in which this is not possible, the drugs used in combination therapy are given a "possible" rating and were thus not included in this analysis.

Statistics

Incidence rates are provided in percent of exposed patients to a given compound, drug class, or subclass and presented together with their 95% confidence intervals. With regard to the low actual CADR incidence rates and the high number of individuals exposed, the confidence interval (CI) was calculated according to the exact method and not one of the approximate methods.[13] For comparison of CADR rates regarding gender and age (cutoff age of 65 years) and those between tricyclic/tetracyclic versus other antidepressive drugs, the χ^2 test with Yates correction was used. Significance was set at $P < .05$. Statistical analysis was performed with the Statistical Product and Service Solutions software (SPSS), version 12.0 (SPSS Inc, Chicago, Illinois).

Table 1. Basic Demographic and Diagnostic Characteristics of Patients With Cutaneous Adverse Drug Reactions (CADR)[a]

Grouping Variable	Patients Monitored	Patients With Clinically Relevant CADR	Patients With CADR per 1000 Patients Monitored
Total	208,401	214	1.03
Age, mean ± SD, y	47.7 ± 16.8	48.0 ± 17.7	…
Age < 65 y	169,832	178	1.08
Age ≥ 65 y	38,569	36	1.14
Male	92,569	66	0.77
Female	115,832	148	1.35
Male:female	1:1.25	1:2.3	…
Diagnosis			
Schizophrenia/ schizoaffective disorders	81,528	59	0.72
Depressive disorders	59,988	80	1.33
Manic episode	5,748	15	2.61
Organic disorders	25,935	14	0.54
Substance use disorders	6,990	27	3.86
Others, such as personality or somatoform disorders	23,116	20	0.87

[a]Values expressed as N except where noted.
Symbol: … = not applicable.

Table 2. CADR Incidence Among Drug Classes

Drug Class/Subclass	Patients Monitored, N	Patients With Clinically Relevant CADR, N	CADR Incidence, %
Total	208,401	214	0.103
Mood stabilizers (antiepileptic drugs)	39,625	90	0.227
Antidepressants	109,412	59	0.054
TCA	34,453	25	0.073
SSRI	36,981	19	0.051
Other	37,978	15	0.039
Antipsychotics	137,281	40	0.029
Conventional	57,099	16	0.028
Atypical	80,182	24	0.030

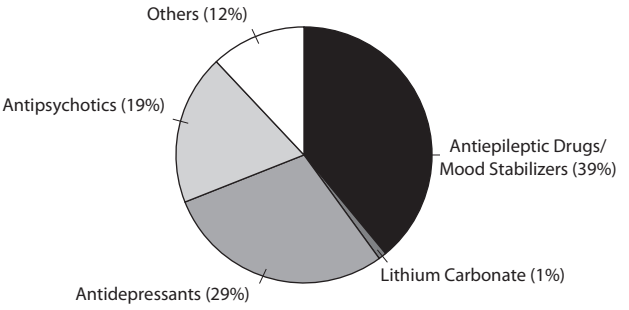
Abbreviations: CADR = cutaneous adverse drug reaction, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Gender-Specific Risk of CADRs Among Drug Classes (female vs male patients)

Drug Class/Subclass	χ^2	*P* Value	Odds Ratio (95% CI)
Total	15.45	< .0001	1.79 (1.34 to 2.40)
Mood stabilizers (antiepileptic drugs)	9.30	.001	2.03 (1.30 to 3.17)
Antidepressants	1.99	.07	1.57 (0.88 to 2.78)
TCA	1.11	.15	1.79 (0.71 to 4.49)
SSRI	1.70	.096	2.32 (0.77 to 6.99)
Other	0.004	.47	0.88 (0.30 to 2.35)
Antipsychotics	0.53	.23	1.33 (0.71 to 2.49)
Conventional	0.53	.23	1.69 (0.59 to 4.85)
Atypical	0.04	.42	1.17 (0.53 to 2.59)

Abbreviations: CADR = cutaneous adverse drug reaction, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 1. Causative Drug Groups in Identified Clinically Relevant Cutaneous Adverse Drug Reactions (N = 214)



RESULTS

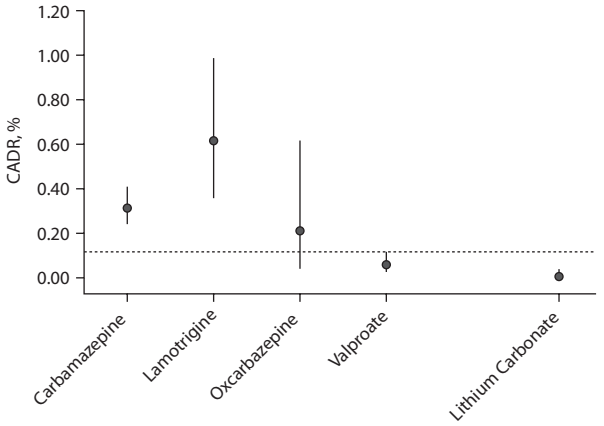
Epidemiology

From 1993 to 2005, a total of 208,401 inpatients receiving psychopharmacologic treatment were surveyed within the AMSP program, monitored in 55 institutions. During this period, skin eruptions were the second most frequently reported adverse drug reactions, following liver enzyme elevation. Clinically relevant CADRs were attributed to 49 of 172 psychotropic drugs used during the observation period and were documented in 214 cases (0.103% = graded "probable" and "definite"). Not included were 42 cases in which a skin reaction could not be attributed to a specific drug due to multiple medications. Seven cases have been classified as life threatening (3.3% of assessed CADRs). Among these, 1 case each of Stevens-Johnson syndrome and toxic epidermal necrolysis occurred, both during treatment with carbamazepine. In the remaining 5 cases, anaphylaxis with dyspnea was recorded. However, fatal outcomes were not reported.

An overview of all cases with respect to age, sex, and diagnoses is provided in Table 1. The highest CADR incidence was observed in patients diagnosed with substance use disorders, manic episode, and depressive disorders. The CADR rates of the different drug classes and subclasses and absolute values for CADR and monitored patients are given in Table 2. A significantly higher overall incidence of clinically relevant CADRs was recorded among female compared to male patients. However, as shown in Table 3, this effect was highly significant only for antiepileptic drugs (AEDs), whereas it was just a trend for antidepressants, particularly SSRI. No gender influence was seen with antipsychotics. There was no influence of age on CADR incidence in any drug class or subclass (data not shown).

Figure 1 provides an overview of the distribution of causative psychotropic drug groups underlying the reported CADR cases (N = 214). Antiepileptic drugs, applied, for example, as mood stabilizers and antimanic drugs, as well as for seizure prophylaxis in alcohol withdrawal and in comorbid epilepsy, accounted for the highest proportion of

Figure 2. Incidence Rates (95% CIs) of CADRs to Mood Stabilizers[a]



[a]Dotted line indicates mean incidence of all monitored drugs.
Abbreviation: CADR = cutaneous adverse drug reaction.

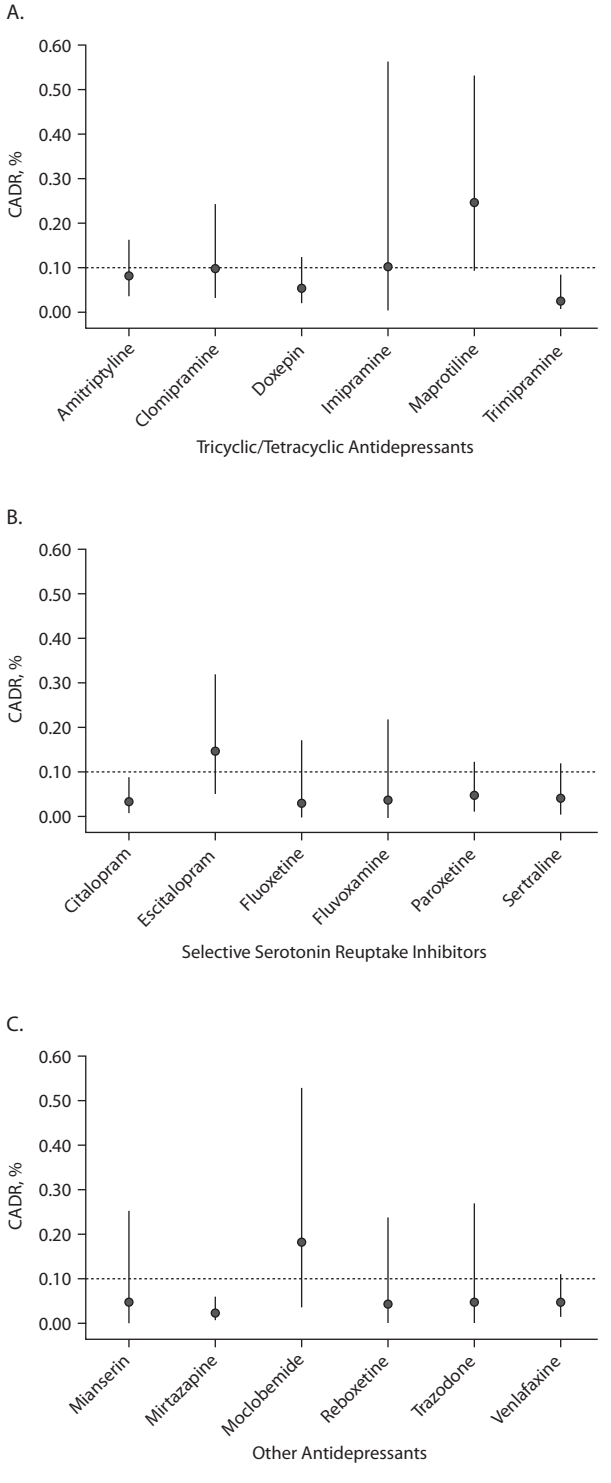
recorded CADRs, followed by antidepressants and antipsychotics. The remaining cases fell upon other, heterogeneous psychotropic drugs, such as hypnotics and drug withdrawal and antidementia drugs.

Cutaneous Adverse Drug Reactions in Different Drug Groups

With a pooled incidence of 0.23%, AED mood stabilizers accounted for the highest CADR rate as a drug group (Table 2 and Figure 2), with high statistical significance compared to the mean CADR rate ($P<.0001$). Within this group, lamotrigine (0.62%) and carbamazepine (0.32%) had the highest rates in the sample, followed by oxcarbazepine (0.21%) and valproate (0.06%). Lithium carbonate had a lower rate than the AEDs (0.01%). Lamotrigine, carbamazepine, and oxcarbazepine had incidence rates above the mean of all offending drugs. However, a wide CI was observed for lamotrigine and oxcarbazepine due to the small number of exposed patients (n = 2,748 and n = 1,412, respectively) as compared to carbamazepine (exposed n = 18,766) or valproate (exposed n = 14,626). As for lamotrigine, in 29% of all CADR cases, the dosage was increased faster than recommended by the manufacturer.

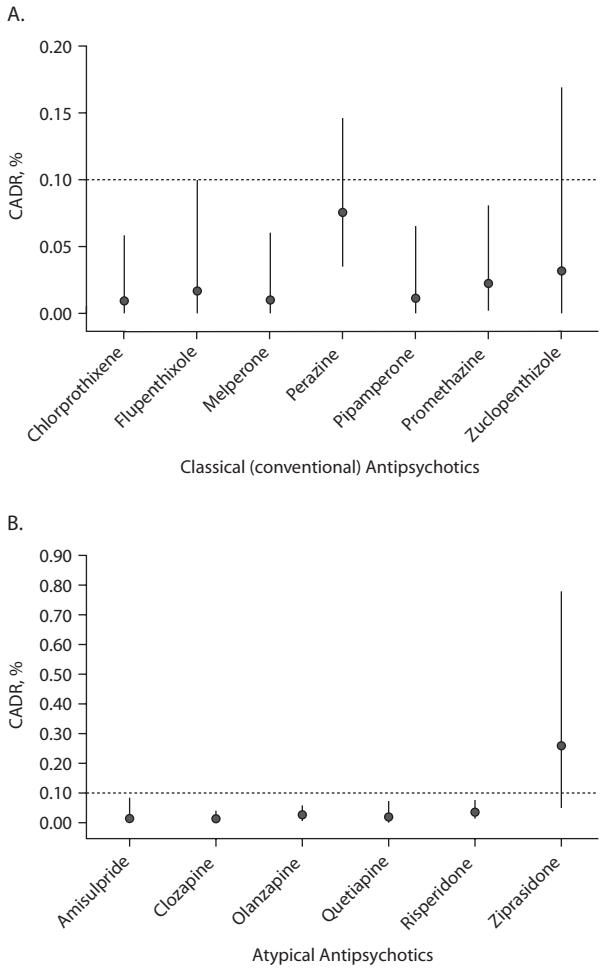
Antidepressants were the second most frequent psychotropic drug group to cause clinically relevant drug eruptions (0.054%, Table 2). Maprotiline (0.24%), escitalopram (0.15%), and moclobemide (0.18%) had CADR rates above the mean of all monitored drugs (Figure 3). Maprotiline, however, had a relatively low administration rate (CADR rate: 6/2452 = 0.24%) resulting in a wide confidence interval, but it has already shown a high CADR incidence in a precursor study of the AMSP.[14] Rates for tricyclic/tetracyclic antidepressants, SSRIs, and other compounds were 0.07%, 0.05%, and 0.04%, respectively. Rates for single compounds

Figure 3. Incidence Rates of CADRs to Antidepressants by Category: (A) Tricyclic/Tetracyclic Antidepressants, (B) Selective Serotonin Reuptake Inhibitors, and (C) Other Antidepressants[a]



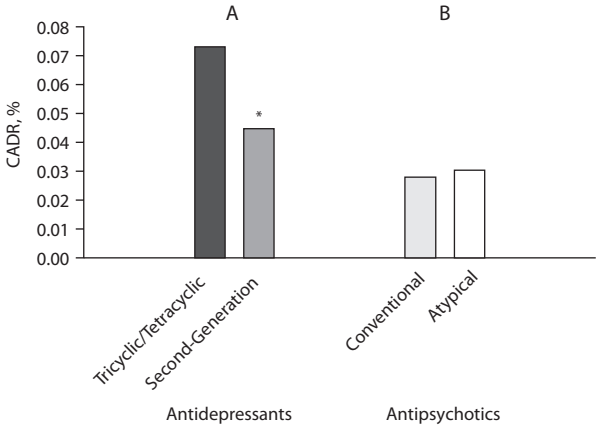
[a]Dotted line indicates mean incidence of all monitored drugs.
Abbreviation: CADR = cutaneous adverse drug reaction.

Figure 4. Incidence Rates of CADRs to Antipsychotics: (A) Classical (conventional) and (B) Atypical Antipsychotics[a]



[a]Dotted line indicates mean incidence of all monitored drugs.
Abbreviation: CADR = cutaneous adverse drug reaction.

Figure 5. Incidence of CADRs to Classical Versus Modern Second-Generation Drugs



*$P < .05$ (χ^2 test).
Abbreviation: CADR = cutaneous adverse drug reaction.

and CIs are depicted in Figure 3. As displayed in Figure 3, other antidepressants with a wide CI were the rarely used imipramine (CADR rate: 1/991 = 0.10%) and moclobemide (3/1680 = 0.18%).

As noted previously, antipsychotics were the drug group least commonly involved in CADRs (Table 2). All classes of antipsychotics—conventional (phenothiazines, thioxanthenes, butyrophenones) and atypical alike—had CADR rates below the mean of the other psychotropic drugs under surveillance. Rates for the different classes and single compounds are depicted in Figure 4. Ziprasidone was the only antipsychotic with a higher-than-mean CADR rate (3/1114 = 0.27%). However, it was also the least frequently applied drug of this group, resulting in a wide CI and limiting its validity for differentiation.

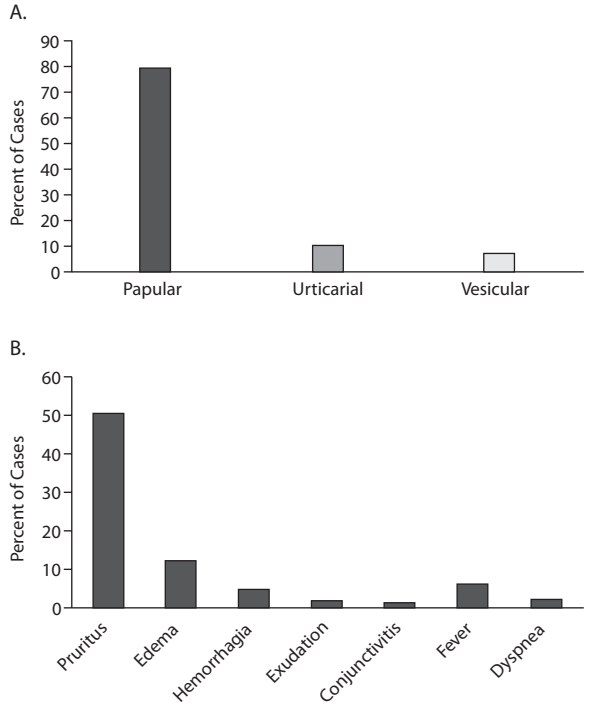
Of note, no CADRs were reported with benzodiazepine tranquilizers. Other single drugs associated with dermatologic side effects were the hypnotic substances zopiclone and chloral hydrate, the alcohol dependence–treatment drugs clomethiazole and disulfiram, and the antidementive agents donepezil, rivastigmine, and memantine. All of these compounds had a mean CADR rate comparable to the pooled incidence rates of all monitored drugs.

It was further analyzed whether modern, second-generation psychotropic drugs had different incidence rates compared to classical, first-generation substances. Antidepressants were divided into classical (tricyclic/tetracyclic drugs) versus the heterogenous subclass of second-generation compounds (SSRIs, venlafaxine as a selective norepinephrine and serotonin reuptake inhibitor, reboxetine as a selective norepinephrine reuptake inhibitor, moclobemide as a monoamine oxidase-A inhibitor, mirtazapine, mianserin, and trazodone). Accordingly, conventional antipsychotics were compared to modern atypical drugs. It was found that new antidepressants had a significantly lower rate of skin eruptions than classical antidepressants (0.073% vs 0.045%, $\chi^2 = 2.76$, $P = .048$, OR = 1.6) (Figure 5). However, CADR rates were not different between the conventional and atypical antipsychotics (0.28% vs 0.3%, $\chi^2 = 0.002$, $P = .97$, OR = 0.94).

Dermatologic Considerations

As expected, exanthems constituted the majority of the recorded CADRs. The proportion of papular (morbilliform) eruptions was 78.9% and that of urticaria and vesicular manifestations was 9.6% and 6.3%, respectively (Figure 6A). The median clinical latency for these subtypes was 9, 5, and 4 days, respectively (not significant, Mann-Whitney test). Independent of the dermatologic diagnosis, the most common symptom was pruritus (50.0%), followed by edema

Figure 6. (A) Morphology and (B) Symptomatology of Cutaneous Adverse Drug Reaction Cases



(12.0%), hemorrhagia (4.3%), and exudative lesions (1.4%). Concurrent conjunctivitis occurred in 1.0%, fever in 5.8%, and dyspnea in 1.9% (Figure 6B).

In the majority of cases, the body trunk was affected (65.1%) and large body areas were covered. Confinement of lesions to face, limbs, or trunk, without affecting other areas, was relatively rare, in part due to the definition of a clinically relevant CADR in AMSP. As mentioned previously, pruritus was the most common symptom, occurring with half of the reported CADRs and with all types. We did not find any significant differences regarding type, symptomatology, and distribution of CADRs when calculated separately for both sexes (data not shown).

As expected when considering the AMSP definition of a *severe* CADR (see Method section), immediate drug discontinuation was the direct consequence in the vast majority of cases (93.7%). In 11 cases (5.1%), transfer to a medical monitoring or intensive care unit became necessary. Drug treatment involved antihistamines—applied topically or systemically—in 106 cases (49.5%) and steroids in 75 cases (35.0%). Steroids were administered topically (29 cases, 39%), orally (28 cases, 37%), or intravenously (18 cases, 24%).

The highest rates of CADRs occurred during the winter months (35.9%). The remaining figures were roughly equally distributed among the other seasons (23.2% in both spring and summer and 17.7% in fall). This argues against a substantial contribution of photosensitive reactions, which are common with psychotropic drugs, since CADRs occurred predominantly in the winter months when skin exposure to the sun and intensity of sun light is usually lowest.

DISCUSSION

Whereas clinical trials detect adverse events in a limited and highly selected population and spontaneous reporting systems have the disadvantage of incompleteness and susceptibility to bias, surveillance systems are designed to assess large populations in a systematic way. To date, especially in psychopharmacology, research on dermatologic adverse events relies predominantly on anecdotal data, such as case reports and spontaneous reports, and their quantitative estimation still represents a methodological challenge.[15,16] However, systematic general drug safety surveillance studies of the kind mentioned here have already been conducted on CADRs for more than 30 years.[17–19] The goal of the present study was to provide large-scale comparative data on the incidence of CADRs to classical as well as modern psychotropic drugs from the well-established AMSP project.

Epidemiologic data in general pharmacotherapy suggest that, although any drug may provoke a CADR, the majority of the clinically relevant drug eruptions is caused by only a limited number of drugs.[20] In our study, we confirm this finding also for psychotropic drugs since, of the 172 drugs under surveillance, only 49 drugs were identified as offending agents, and only 7 had a CADR incidence above the mean.

Also in line with findings in general pharmacotherapy, CADRs developed significantly more often in women in our survey.[17,18] This gender effect was particularly strong in AEDs and vanished when this drug class was not considered. The only other drug class with a considerably higher risk in female patients was antidepressants, and particularly SSRIs, in both of which a trend was observed. A recent retrospective study of 15 AEDs found a higher rash frequency in females compared to males during the reproductive years, suggesting hormonal influences.[21,22] Similar effects of other psychotropic drugs on levels of certain sex hormones have been demonstrated.[23] Third, in congruence with clinical experience and a vast body of evidence, the majority of cases in the current study displayed a papular exanthem,[1,2] and the time course of CADR manifestation determined in this study corresponded well to data in the literature.[1]

We found an overall CADR incidence of 0.1%. However, a somewhat higher actual rate must be assumed since large-scale drug surveillance studies typically underestimate adverse event rates due to the fact that reporting depends on the time and motivation of a multitude of drug monitors, reporting physicians, and participating centers. Moreover, this particular surveillance program considers only clinically relevant adverse events (see Method section). Less

severe or transient rashes are not assessed. Thus, conclusions drawn from our results apply only to CADRs with direct clinical consequences.

We found the highest rate of drug eruptions with AED mood stabilizers. Of the 49 drugs that caused CADRs during the surveillance period, the only 2 mood stabilizers with a significantly higher-than-mean incidence were lamotrigine and carbamazepine. The 2 histologically confirmed cases of Stevens-Johnson syndrome and toxic epidermal necrolysis were both seen with carbamazepine, which is in line with the literature.[24,25] The finding that CADRs occurred most frequently in patients with mania and addiction (Table 1) is most likely explained by the high AED administration rate in these conditions. Female gender, previous CADR, and—interestingly in view of our study—a history of psychiatric illness are known risk factors for drug eruptions with AEDs.[26] Given the potentially serious complications, there is agreement that the occurrence of any CADR should prompt immediate discontinuation of the offending AED.[27]

In contrast to AEDs, drug eruptions with antidepressants and antipsychotics have received much less attention, and systematic data are scant, especially for the expanding group of second-generation drugs emerging during the past 2 decades. An abundance of single case studies or case series, though, reports on various types of skin effects of newer antidepressants, particularly the SSRIs. However, reported CADRs to this drug subclass are mainly petechiae and bruises (which are rarely "severe" in the sense of this survey and, like edema, are covered in a different category in the AMSP program) due to cutaneous bleeding—probably caused by platelet dysfunction following blockade of serotonin reuptake in platelets—and distinct entities like pruritic leukocytoclastic vasculitis.[28] However, to date, the frequency of clinically relevant CADRs among antidepressants and their epidemiologic relation to drug eruptions with other psychotropic drugs has not been clarified. Our results from a large database with about 100,000 monitored patients receiving antidepressants suggest a significantly lower risk of relevant cutaneous effects of modern compared to classical antidepressants. The lowest rates of CADRs were seen with SSRIs, the most widely applied antidepressants, and other new compounds, above all mirtazapine. The validity of this conclusion is underscored by the fact that a potential bias would likely favor the conventional drugs since there is often a higher vigilance to adverse events to newer drugs in spontaneous reporting as well as surveillance systems. In addition, serious complications did not arise with antidepressant-related drug eruptions in our survey and have been less often reported than with AEDs.[29]

To our knowledge, CADRs with antipsychotics have also not yet been evaluated systematically. Existing data from case reports and case series point to a rather benign nature of antipsychotic-related cutaneous effects.[30] Accordingly, our data revealed the lowest CADR risk for antipsychotics, the most commonly used psychotropic drug group in our population, applying to conventional and atypical compounds alike.

It is still not clear if chemical structure determines the offending potential of different drugs. For example, among the drugs with the highest reported CADR rates are antimicrobial agents, specifically sulfonamides and penicillins,[31] which belong to completely different chemical classes. The 2 drugs with uniquely high rates of CADRs in this study, lamotrigine and carbamazepine, also belong to different classes. However, they are both polyaromatic compounds with ammonium residues. In contrast, citalopram and escitalopram, which—as enantiomers—are chemically almost identical, appear to differ considerably in their CADR rates. It could be concluded that a specific drug's potential to cause CADR seems not predictable from its chemical structure although we found a higher risk with tricyclic and tetracyclic antidepressants. More research is certainly needed to clarify this issue.

In sum, the AMSP as a large-scale drug safety surveillance program proved of value in estimating and comparing CADR frequencies in psychotropic drugs. The rate of skin reactions was considerable in this survey, particularly in female patients (AEDs and, to a certain extent, antidepressants) but independently of age. Drugs with the highest rate of skin eruptions were AEDs in contrast to antipsychotics, which had the lowest rate, irrespective of their classification as conventional or atypical. The CADR risk of antidepressants was within the average range. Drug eruptions occurred significantly less often in modern second-generation compared to classical tricyclic or tetracyclic antidepressants. Given the frequency and potential harmfulness, patients should be informed in detail about possible CADRs. Upon occurrence, clinicians should carefully weigh the potential risk of possible consequences against that of treatment cessation. Severe intensity, systemic symptoms such as fever or general malaise, and the need of systemic treatment should prompt immediate drug discontinuation.

Drug names: carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clozapine (FazaClo, Clozaril, and others), disulfiram (Antabuse), donepezil (Aricept and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium carbonate (Eskalith, Lithobid, and others), memantine (Namenda), mirtazapine (Remeron and others), norepinephrine (Levophed and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), promethazine (Promethegan, Promethacon, and others), quetiapine (Seroquel), risperidone (Risperdal and others), rivastigmine (Exelon and others), sertraline (Zoloft and others), trimipramine (Surmontil and others), valproate (Depacon and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Author affiliations: Department of Psychiatry and Psychotherapy, Heinrich-Heine University, Düsseldorf (Drs C. Lange-Asschenfeldt and Cordes); Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University, and the Arzneimittelsicherheit in der Psychiatrie (AMSP) Institute for Drug Safety in Psychiatry, Munich (Drs Grohmann, Engel, and Rüther); and Department of Dermatology, Venereology, and Allergy, Skin Cancer Center, Charité University Hospital, Berlin (Dr B. Lange-Asschenfeldt), Germany.

Financial disclosure: **Dr Rüther** has received grant/research support from Bristol-Myers Squibb, Organon, Janssen, AstraZeneca, Bayer, and Novartis and is a member of the speakers/advisory boards for Lundbeck, Sanofi, Wyeth, GlaxoSmithKline, and Esparma. **Dr Cordes** has received grant/research support from Janssen-Cilag, Eli Lilly, Pfizer, and AstraZeneca and is a member of the speakers/advisory boards for Eli Lilly, Servier, Bristol-Myers Squibb, and Pfizer. **Dr C. Lange-Asschenfeldt** has received grant/research support from Pfizer and is a member of the speakers boards of Pfizer and Novartis. **Drs Grohmann**, **B. Lange-Asschenfeldt**, and **Engel** report no financial affiliations or other relationships relevant to the subject of this article.
Funding/support: None reported.

REFERENCES

1. Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev.* 2001;53(3):357–379.
2. Kimyai-Asadi A, Harris JC, Nousari HC. Critical overview: adverse cutaneous reactions to psychotropic medications. *J Clin Psychiatry.* 1999;60(10):714–725.
3. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA.* 2001;285(4):437–443.
4. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy.* 2003;23(5):686–689.
5. Stübner S, Padberg F, Grohmann R, et al. Pisa syndrome (pleurothotonus): report of a multicenter drug safety surveillance project. *J Clin Psychiatry.* 2000;61(8):569–574.
6. Schmid C, Grohmann R, Engel RR, et al. Cardiac adverse effects associated with psychotropic drugs. *Pharmacopsychiatry.* 2004;37 (suppl 1):S65–S69.
7. Degner D, Grohmann R, Kropp S, et al. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. *Pharmacopsychiatry.* 2004;37(suppl 1):S39–S45.
8. Stubner S, Grohmann R, Engel R, et al. Blood dyscrasias induced by psychotropic drugs. *Pharmacopsychiatry.* 2004;37(suppl 1):S70–S78.
9. Stubner S, Rustenbeck E, Grohmann R, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. *Pharmacopsychiatry.* 2004;37(suppl 1):S54–S64.
10. Bender S, Grohmann R, Engel RR, et al. Severe adverse drug reactions in psychiatric inpatients treated with neuroleptics. *Pharmacopsychiatry.* 2004;37(suppl 1):S46–S53.
11. Kropp S, Grohmann R, Hauser U, et al. Hyperglycemia associated with antipsychotic treatment in a multicenter drug safety project. *Pharmacopsychiatry.* 2004;37(suppl 1):S79–S83.
12. Grohmann R, Engel RR, Ruther E, et al. The AMSP drug safety program: methods and global results. *Pharmacopsychiatry.* 2004;37 (suppl 1):S4–S11.
13. Vollset SE. Confidence intervals for a binomial proportion. *Stat Med.* 1993;12(9):809–824.
14. Schmidt LG, Grohmann R, Muller-Oerlinghausen B, et al. Adverse drug reactions to first- and second-generation antidepressants: a critical evaluation of drug surveillance data. *Br J Psychiatry.* 1986;148:38–43.
15. Swanbeck G, Dahlberg E. Cutaneous drug reactions. An attempt to quantitative estimation. *Arch Dermatol Res.* 1992;284(4):215–218.
16. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol.* 2001;137(6):765–770.
17. Bigby M, Jick S, Jick H, et al. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA.* 1986;256(24):3358–3363.
18. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. A report from the Boston Collaborative Drug Surveillance Program. *JAMA.* 1976;235(9):918–923.
19. Hunziker T, Kunzi UP, Braunschweig S, et al. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy.* 1997;52(4):388–393.
20. Stern RS, Steinberg LA. Epidemiology of adverse cutaneous reactions to drugs. *Dermatol Clin.* 1995;13(3):681–688.
21. Alvestad S, Lydersen S, Brodtkorb E. Rash from antiepileptic drugs: influence by gender, age, and learning disability. *Epilepsia.* 2007;48(7):1360–1365.
22. Herzog AG, Drislane FW, Schomer DL, et al. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. *Neurology.* 2005;65(7):1016–1020.
23. Bell S, Shipman M, Bystritsky A, et al. Fluoxetine treatment and testosterone levels. *Ann Clin Psychiatry.* 2006;18(1):19–22.
24. Rzany B, Correia O, Kelly JP, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet.* 1999;353(9171):2190–2194.
25. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Res.* 1996;23(2):149–155.
26. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology.* 2007;68(20):1701–1709.
27. Warnock JK, Morris DW. Adverse cutaneous reactions to mood stabilizers. *Am J Clin Dermatol.* 2003;4(1):21–30.
28. Krasowska D, Szymanek M, Schwartz RA, et al. Cutaneous effects of the most commonly used antidepressant medication, the selective serotonin reuptake inhibitors. *J Am Acad Dermatol.* 2007;56(5): 848–853.
29. Warnock JK, Morris DW. Adverse cutaneous reactions to antidepressants. *Am J Clin Dermatol.* 2002;3(5):329–339.
30. Warnock JK, Morris DW. Adverse cutaneous reactions to antipsychotics. *Am J Clin Dermatol.* 2002;3(9):629–636.
31. van der Linden PD, van der Lei J, Vlug AE, et al. Skin reactions to antibacterial agents in general practice. *J Clin Epidemiol.* 1998;51(8):703–708.