

Adverse Drug Reactions for CAM and Conventional Drugs Detected in a Network of Physicians Certified to Prescribe CAM Drugs

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ABSTRACT

BACKGROUND: Within recent years, the increasing popularity of complementary and alternative medicine (CAM) has led health care authorities to focus on the safety of these drugs. One reason for the low awareness of adverse drug reactions (ADRs) associated with CAM might be that users and physicians believe that there are no risks associated with CAM drugs. Recent studies have shown that ADRs are under-reported and are considered a leading cause of morbidity and mortality. The Evaluation of Anthroposophical Medicine (EvaMed) Pharmacovigilance Network was formed in 2004 at the Havelhoehe Research Institute in Berlin and is composed of 38 CAM physicians located in 12 of the 16 federal states in Germany for the purpose of using EvaMed data to evaluate the prescribing patterns, effectiveness, and safety of CAM therapies.

OBJECTIVE: To describe and quantify the volume and severity of ADRs for CAM and conventional (CON) drugs in a proprietary database created from prescriptions and patient data of primary care CAM physicians who participate in the EvaMed Network.

METHODS: This was a prospective, multicenter, observational study based on the ADR reports and electronic prescription data of 38 individual physicians (21 general practitioners, 9 pediatricians, 4 internists, 2 gynecologists, 1 dermatologist, and 1 neurologist) participating in the EvaMed Network. In addition to standard medical education, all physicians had 5 years practical experience and an additional qualification for anthroposophic medicine, which is a subcategory of CAM. All 38 physicians documented ADRs deemed serious, defined as life threatening or resulting in death, disability/incapacity, or inpatient hospital days. Due to the time-consuming nature of documenting ADRs, only a subgroup of 7 physicians (4 in general practice and 1 each in internal medicine, pediatrics, and gynecology) agreed to report both nonserious and serious ADRs. Therefore, the incidence and frequency of ADRs were evaluated in this subgroup. The study period was January 2004 through June 2009. ADRs were documented by the physicians using an electronic case report form in the EvaMed software, which was linked to the physicians' existing electronic medical record (EMR) systems and incorporated into their daily routines to avoid missing data or double entries. The participating physicians were compensated €15 (approximately US\$20) for each ADR report. All ADR reports were monitored at the Havelhoehe Research Institute by 2 physicians who evaluated patient characteristics, present visit diagnosis, target drugs, associated drug classes and type of drugs, type of ADR, actions taken for the ADR, and outcome of the ADR.

RESULTS: There were 1,018,626 drugs (54.8% CAM) prescribed by the 38 physicians for 88,431 patients, and 412 ADRs reported for 389 patients; 124 (30.1%) ADRs were for CAM drugs. The majority were reported in children (69.2%, n=285) and females (56.3%, n=232). All serious ADRs (n=14) were associated with CON drugs. In the subgroup of 7 physicians who agreed to report all ADRs, a total of 327 serious and nonserious ADRs were reported for 392,243 prescribed drugs (0.08%) and for 308 of 25,966 patients (1.2%). ADRs were reported for 241 of 16,032 children (aged 17 years or younger; 1.5%) versus 67 of 9,934 adults (0.7%). Of the 327 total ADRs, 10 (3.1%) were serious. There were 95 ADRs for 213,900 CAM prescriptions (4.4 per 10,000) versus 232 for 178,343 CON prescriptions (13.0 per 10,000). The CAM drug with the highest frequency of ADRs was *Pelargonium sidoides* root (0.21%, 4 of 1,940 prescriptions). The most fre-

quently reported ingredient in CAM was ivy leaves with an ADR frequency of 0.17% (n=11 of 6,575 prescriptions). The most reported drug connected with ADRs was amoxicillin (1.36%, n=31 of 2,276 prescriptions). The most common ADR medical management was withdrawal of the drug (82.3% overall, 83.9% CAM, 81.6% CON).

CONCLUSIONS: A sample of 38 CAM physicians reported the occurrence of at least 1 ADR for 0.4% of treated patients in a 5.5-year study period. There were no serious ADRs reported for CAM drugs. In a subsample of 7 physicians who agreed to report all nonserious and serious ADRs, 1.2% of patients experienced at least 1 ADR; rates of ADRs per 10,000 prescriptions were 4.4 for CAM drugs and 13.0 for CON drugs.

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What is already known about this subject

- Adverse drug reactions (ADRs) related to complementary and alternative medicine (CAM) pharmacotherapies (homeopathic drugs, anthroposophic remedies, and herbal medicines) are probably not recognized and therefore under-reported because users believe that CAM products are "natural" and therefore harmless. Such assumptions have led to a discrepancy between the growing interest in CAM remedies and the limited data on their potential to cause ADRs. Compared with conventional (CON) drugs, there are only sparse data available on ADRs associated with CAM, and there is no specific safety system of ADR data collection for CAM drugs.
- A spontaneous reporting system (Federal Institute for Drugs and Medical Devices), which is used in Germany to monitor the safety of drugs after marketing, is limited by the inability to determine prevalence rates because there are no data on the number of patients being treated with a certain drug. Additionally, the number of unreported ADRs remains unclear. Compared with subjects in controlled clinical trials, patient cohorts treated in everyday conditions often present a higher prevalence of comorbidity and comedication, which have a major impact on the incidence and the types of ADRs.
- The Evaluation of Anthroposophical Medicine (EvaMed) Pharmacovigilance Network of 38 CAM physicians was formed in 2004 to evaluate the prescribing patterns, effectiveness, and safety of CAM therapies and to date has published 10 studies. For the period from January 2004 through June 2007, Tabali et al. (2009) reported an increase in the number and completeness of ADR reports following face-to-face training of the 38 participating physicians in classifying and reporting ADRs. Jeschke et al. (2009) analyzed prescribing patterns and ADRs for *Asteraceae*-containing remedies from the EvaMed reported diagnostic profiles and prescribing patterns in various diseases (e.g., dementia, hypertension, and respiratory tract infections) and patient groups (elderly and children).

What this study adds

- In the EvaMed Network of 38 physicians, 30.1% (n=124) of all reported ADRs (n=412) were associated with CAM drugs. All 14 serious ADRs were associated with CON drugs.
- In a subgroup of 7 physicians who agreed to record all nonserious and serious ADRs, 25,966 patients (median [interquartile range] age=11 [4-38] years; female=56.1%) received a total of 392,243 drugs; of these, 1.2% experienced at least 1 ADR. The rates of ADRs were approximately 4.4 per 10,000 CAM prescriptions and 13.0 per 10,000 CON prescriptions.

Complementary and alternative medicine (CAM) has grown increasingly popular in recent years among health care professionals.¹ One major reason for its popularity is that users believe that CAM drugs are “natural” and do not involve any risks.² Thus, adverse drug reactions (ADRs) related to CAM were not a major focus of scientific research until recently. However, in recent years, health care authorities have recognized that the lack of safety data on CAM drugs is a problem.³

The field of complementary pharmacotherapy can roughly be subdivided into homeopathic drugs, anthroposophic remedies, and herbal medicines.

Homeopathic drugs consist of diluted substances derived from plants, minerals, and animals. The principle of homeopathy is based on the theory of Samuel Hahnemann, which is that “like cures like.”⁴ This is a method of treating a disease with the materials derived from the toxic and injurious agents that cause similar signs and symptoms.

Anthroposophic medicine is a holistic medical system founded in the 1920s by Rudolf Steiner and Ita Wegman.⁵ It is regarded as an extension of conventional treatment, requiring physicians to work together with their patients, not only to cure their illnesses but to understand the meaning of the disease by carefully exploring the physical, mental, and spiritual basis for the illness. Thus, although anthroposophic physicians employ conventional medical treatments, they also seek to stimulate their patients’ capacities for self-healing by using unique anthroposophic therapies and remedies.⁵ Anthroposophic remedies include preparations of botanical, mineral, or zoological origin, as well as chemical substances that are either undiluted or based on the homeopathic principle of dilution.

Herbal medicines are made from plants or plant extracts. The raw materials are used therapeutically in various forms such as tea, juice, tincture, extract, powder, and essence. Herbal medicine labels often do not specify the concentrations of the individual substances, instead indicating the amount of the active component only.⁶

Pharmacotherapy is tightly regulated by the German health

authorities, who decide on the insurance coverage for CAM and conventional (CON) drugs. In 2010, 8,250 drugs were registered on the *Red List* of marketed drugs, CAM and/or CON in Germany, 80% of which were CON drugs. Of all marketed drugs, 83% were available only with a prescription. In 2007, approximately 44% of the expenses for CAM remedies in Germany were reimbursed by health insurance.⁷ All physicians in Germany are allowed to prescribe CAM remedies; no additional qualification in the CAM field is needed.

An outpatient survey of 1,044 women in Italy showed that the major reasons for using herbal products were to strengthen the immune system; to cure gastrointestinal, respiratory, or cardiovascular problems; and to treat anxiety/sleep disturbances.⁸ Upper respiratory tract infections (URIs) are among the leading reasons for doctor visits⁹ and a common diagnosis in primary care.¹⁰ A study by Jeschke et al. (2007) of 12,081 outpatients in Germany found that 63.0% of patients with diseases of the respiratory system were treated with CAM drugs only.¹¹ Examples of herbal ingredients for treating URIs are roots of *Pelargonium sidoides* prepared as solution,¹² syrup containing dried ivy leaf extract,¹³ thyme-ivy combination as solution,¹⁴ and thyme-primrose combination.¹⁵ A systematic review and meta-analysis of 4 randomized controlled trials (RCTs) of *Pelargonium sidoides* for acute bronchitis showed that no serious adverse events were reported, and only mild and moderate adverse events occurred.¹⁰ A placebo-controlled RCT of ivy leaves and thyme herb also found only mild adverse events.¹⁴

Data on the frequency of CAM-associated ADRs are often limited to a certain drug and/or specific disease conditions.⁹⁻¹² Although an analysis by Farah et al. (2000) of 20 years of adverse reaction reports to the World Health Organization (WHO) found “substantial evidence” that herbal medicines can cause serious ADRs,¹⁶ there is a lack of information regarding the rates of occurrence of ADRs with CAM.¹⁷

ADRs are considered to be a leading cause of morbidity and mortality.¹⁸ Recent studies have shown that ADRs are underreported.¹⁹ European countries, including Germany, have established a spontaneous reporting system (Federal Institute for Drugs and Medical Devices) for suspected serious, rare, and unexpected ADRs in order to monitor the safety of CAM and CON drugs after marketing. No prescription data are reported in this system, precluding calculation of prevalence and incidence rates for individual drugs.

Physicians are obligated under their code of medical ethics to report ADRs regardless of whether they are associated with CAM or CON drugs; however, voluntary reporting is often neglected, and there is no consequence for failure to report ADRs. Thus, the number of unreported ADRs remains unknown.²⁰ In Germany, national pharmacovigilance centers have been established in addition to the Federal Institute for Drugs and Medical Devices to collect data on ADRs that lead

to hospital admission,²¹ data on serious diseases such as toxic epidermal necrolysis,²² and data for specific groups of patients who take drugs (CAM or CON) during pregnancy and breast-feeding.²³ The international Drug Safety in Psychiatry program is also participating in the collection of ADR data. This program is a prospective, multicenter program for active and continuous assessment of ADRs of marketed psychotropic drugs in psychiatric inpatients under the naturalistic conditions of routine clinical treatment.²⁴

For CAM drugs, the Evaluation of Anthroposophical Medicine (EvaMed) Pharmacovigilance Network was founded in 2004 at the Havelhoehe Research Institute in Berlin to evaluate the use of CAM drugs with regard to prescribing patterns, efficacy, and safety in routine medical practice. There have been 10 previously published studies of the EvaMed Network of physicians including that of Tabali et al. (2009), who reported the outcomes of face-to-face training of the 38 participating physicians in classifying and reporting ADRs.²⁵

The aim of the present analysis was to describe ADRs from the EvaMed Network that were identified by 38 primary care CAM physicians related to routine daily prescribing (CAM or CON) in order to estimate ADR frequency, incidence, and severity.

Methods

Design

The present study was designed as a prospective, multicenter, observational study in the EvaMed Pharmacovigilance Network.⁹ This study used anonymized data on ADRs. For German physicians, it is mandatory to report suspected serious, rare, and unexpected ADRs regardless of the drug group (CAM or CON) to the spontaneous reporting system. As no experimental research or intervention on patients was applied, no ethical approval was needed according to Chenot and Heidenreich (2004).²⁶ Nevertheless, the present study was approved by the anthroposophical Community Hospitals Havelhoehe data security office and fulfills the criteria of Good Secondary Data Analysis.²⁷

Participants and Setting

EvaMed was founded in 2004 because of a need to document the safety of CAM drugs with scientific data for a European registration; specifically, without the data, the drugs would have been removed from the market.^{28,29} EvaMed physicians therefore understood their responsibility to collect such data and agreed to participate in this project. Physicians for the EvaMed Network were recruited through the German National Association of Anthroposophic Physicians (GAÄD). In 2004, 118,085 primary care physicians were practicing in Germany.³⁰ Of those, 626 (0.5%) primary care physicians were members of the GAÄD and were pre-screened for meeting several study requirements. Specifically, physicians were required to have a

medical practice with an existing electronic medical records (EMR) system that met a number of technical requirements in order for the data to be exported electronically to the study software Quality Assurance, Documentation, Statistic (QuaDoSta).³¹ Additional inclusion criteria were a minimum of 5 years practice experience and a medical education qualification for anthroposophic medicine of 120 hours, including 1 to 2 years of work in a mentoring practice and a final examination by the GAÄD. All 362 (57.8%) of the 626 GAÄD physicians who met these criteria based on self-reported information were contacted and informed about the EvaMed Network by standard mail and, in the event of no response, 4 weeks later by telephone. Physicians were required to give their informed consent to participate in the EvaMed Network and to report all detected serious ADRs (for definition see heading "Data Collection and Classification of ADRs") to the EvaMed Network.

A total of 38 physicians (21 general practitioners, 9 pediatricians, 4 internists, 2 gynecologists, 1 dermatologist, and 1 neurologist) from 12 of the 16 federal German states agreed to participate in EvaMed, covering 6.1% of the overall primary care physicians of the GAÄD. A subgroup of 7 physicians (4 general practitioners, 1 pediatrician, 1 internist, and 1 gynecologist) agreed to report serious and nonserious ADRs, while the documentation of nonserious ADRs was voluntary for the remaining physicians.

Data Collection and Classification of ADRs

The study period lasted from January 2004 until June 2009. ADRs were documented by the physicians using an electronic case report form in the study software QuaDoSta, which was linked to the physicians' existing EMRs and fully incorporated into their daily routines to avoid missing data or double-counting entries from routine data. Sociomedical data, such as patient age, sex, diseases, and all drugs currently taken, were exported electronically.

All physicians (N=38) mandatorily reported suspected serious ADRs associated with CAM (i.e., homeopathy, anthroposophic, or herbal drugs) or CON drugs in our software. A serious ADR was defined as life threatening or resulting in death, disability/incapacity, or inpatient hospital days. Due to the time-consuming nature of documenting ADRs, only the subgroup of 7 physicians agreed to report all ADRs (nonserious and serious), while the documentation of nonserious ADRs was voluntary for the remaining physicians (n=31). For legal reasons, all suspected serious, rare, and unexpected ADR reports from the network were transferred from the Havelhoehe Research Institute to the Federal Institute for Drugs and Medical Devices in Germany. Although vaccine-associated ADRs were recorded, they were excluded in the present study.

To improve ADR reporting, all physicians received 1.5 hours of one-on-one interactive training in the individual physician's

TABLE 1 Scheme of Adverse Drug Reaction Evaluation

ADR Evaluation	Categorization	Sources	Evaluator ^a
Seriousness	Nonserious and serious “Serious” defined as: • results in death • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • is life threatening	International Conference on Harmonization ⁴⁷	Research Institute
Severity (describe the intensity of ADR symptoms)	• Grade I (mild) • Grade II (moderate) • Grade III (severe) • Grade IV (life threatening)	World Health Organization Adverse Reaction Terminology (WHO ART) ⁴⁸	Participating physicians
System organ classes (affected organ system)	26 SOCs (e.g., gastrointestinal disorders)	Medical Dictionary for Regulatory Activities Version 13.0 ⁴⁹	Research Institute
Causality (possible confounding factors)	• Certain • Probable • Possible • Unlikely • Conditional • Unclassified • Unassessable	Uppsala Monitoring Centre ⁵⁰	Research Institute
Management	• Drug withdrawal • Reduction of the dose • Change of therapy • No change in drug and no additional treatment • Others	World Health Organization ⁵¹	Participating physicians
Outcome	• Recovered • Not yet recovered (improvement, without complete remission of the ADR but expected complete recovery) • Permanent damage (complete remission of the ADR is not expected) • Unknown • Death	World Health Organization ⁵¹	Participating physicians

^aThe Havelhoehe Research Institute (Berlin) administers the Evaluation of Anthroposophical Medicine (EvaMed) Pharmacovigilance Network for 38 participating physicians who are certified to prescribe CAM drugs.

ADR = adverse drug reaction; CAM = complementary and alternative medicine; SOC = system organ class.

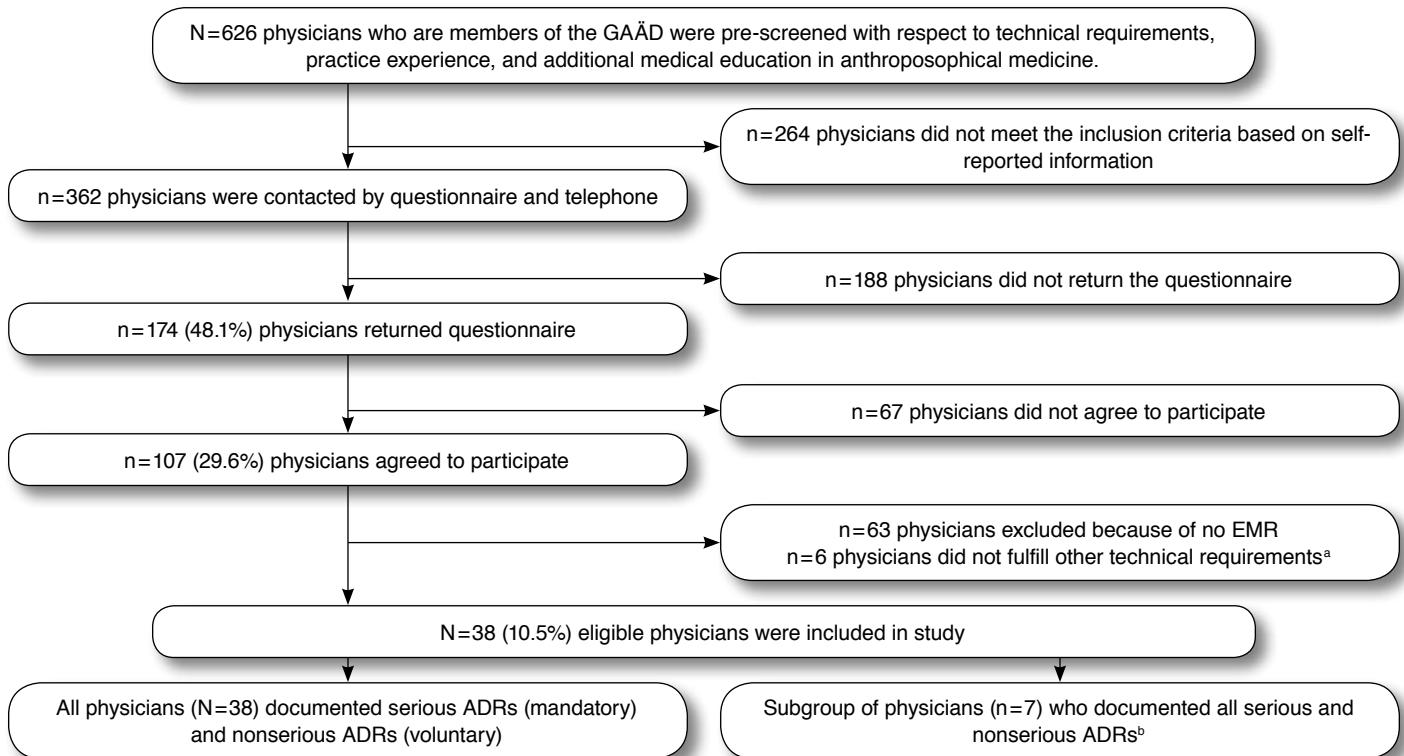
office on documenting ADRs after 21 months of participation in the EvaMed Network.²⁵ The training was divided into a theoretical and a practical component. The theoretical component consisted of a presentation on the economic and epidemiological importance of ADRs, as well as on the definition and classification of ADRs by seriousness, severity, and causality. Each physician received a manual summarizing the main points of the training session. The practical component included a problem-based learning course that provided examples of how to document ADRs using the QuaDoSta software package.

Physicians categorized the seriousness, severity, and causality of each ADR (Table 1). For the causality assessment, physicians selected relevant drugs, comedications, and present diagnoses from an electronic list generated from prescription data. In the normal routine, ADR data files were sent by the physicians to the Havelhoehe Research Institute every 2 months. In case of a serious ADR, the physicians had to inform the Research Institute within 24 hours. The physicians were compensated €15 (approximately US\$20) per reported ADR

(independent of being classified as nonserious or serious), based on a medical fee schedule to compensate for their time. No further money or incentive for participating was provided.

The Research Institute phoned each prescriber to confirm that his/her bimonthly report had been received and asked each prescriber to supply any missing data, as necessary. Each ADR was evaluated consecutively and independently by 2 physicians from the Research Institute (study contributors Lueke and Buchwald) who were trained in ADR evaluation, using a separate electronic case report verification form. Completeness, plausibility (e.g., association in time between drug administration and ADR), classification of ADR seriousness and severity, and assessment of causality were evaluated without regard to the conclusions of the participating physicians. In cases of disagreement between the 2 research physicians, a group of 3 physicians and 2 pharmacists (physician contributors Girke and Kröz and coauthor Matthes and pharmacist contributors Brüggmann and Hartmann) discussed each case until agreement was reached. The analysis is based on these verified data.

FIGURE 1 Sample Selection Flowchart



^aOther requirements included participation in local area network (LAN) connection and use of Microsoft Windows Internet Explorer software.

^bThe subgroup of 7 physicians was composed of 4 in general practice and 1 each in internal medicine, pediatrics, and gynecology.

ADR=adverse drug reaction; EMR=electronic medical record; GAÄD=German National Association of Anthroposophic Physicians (Gesellschaft Anthroposophischer Ärzte in Deutschland).

No ADR reports were rejected in this validation process. In the case of implausibility or incompleteness, the ADR was checked, and missing information was added. After that step, the ADR was transferred into the database for analysis.

Data Evaluation

Drug Characteristics. Prescribed drugs were recorded by each physician using the German National Drug Code (Pharmazentralnummer; PZN) and then were coded by the Research Institute using the Anatomical Therapeutic Chemical (ATC) classification based on the 2005 WHO-ATC index to assign the ADR reports to drug classes (e.g., psycholeptics or antibacterial for systemic use). ATC divides the active substances of each treatment into the organs or systems on which they act and their therapeutic, pharmacological, and chemical properties. Therefore, each group can include CON as well as CAM drugs.³²

Type of drug was subdivided into 2 groups, CAM and CON drugs, using the ABDA (German acronym for the Federal

Confederation of German Pharmacist Associations) database definition. The German ABDA database contains a broad range of data on all currently available medicinal drugs and substances, including information on active and nonactive ingredients, ATC, pharmaceutical form, package size, and retail price. Polypharmacy was determined according to the number of all prescribed drugs (CAM or CON) and was defined as minor (2-3 drugs), moderate (4-5 drugs), or major (more than 5 drugs), based on the method described by Veehof et al. (2000).³³

Diseases. Current diseases were recorded by the physician using the *International Classification of Diseases, Tenth Revision* (ICD-10). Multiple diseases were considered by the Research Institute if more than 2 diseases were diagnosed in the time period during which the drug that triggered the ADR was prescribed.³³

Adverse Drug Reactions. ADRs were defined, according to the WHO definition, as a response to a medicine that is noxious and unintended and that occurs at doses normally used

TABLE 2 Incidence of ADRs by Patient Age and Sex for Patients in the Prescriber Subgroup (n=7 Physicians)^a

	Number of ADRs			Number of Patients with ADRs/Total Number of Patients	Incidence
	Total	CAM	CON		
Children (aged 17 years or younger)					
All children	257	62	195	241/16,032	1.5%
Female	116	28	88	111/7,641	1.5%
Male	141	34	107	130/8,391	1.5%
Adults (aged 18 years or older)					
All adults	70	33	37	67/9,934	0.7%
Female	58	28	30	55/6,922	0.8%
Male	12	5	7	12/3,012	0.4%
Total	327	95	232	308/25,966	1.2%

^aPhysicians who agreed to report both serious and nonserious ADRs for CAM and CON therapies.

ADR=adverse drug reaction; CAM=complementary and alternative medicine; CON=conventional.

in humans.³⁴ Therefore, ADRs due to drug use in an off-label manner were excluded in the current analysis. The complete evaluation scheme for ADRs is shown in Table 1. Severity is an arbitrary scale of intensity of the ADR symptom. The severity of ADRs (mild to life threatening) shows the individual influence of the symptoms on the patient.

The source of information for verification of potential ADRs was the manufacturer's summary of product characteristics (German: "Fachinformation"). ADRs were evaluated with respect to the following:

- patient demographics, present diagnoses for which the triggering drug of the ADR were prescribed, and involved drugs, as documented in the physicians' EMR systems.
- associated drug classes and type of drugs, which were determined in the Research Institute after ADR documentation by linking the ADR report to the ATC and ABDA database.
- the kind of ADR, action(s) taken to manage the ADR, and outcome of the ADR, which were directly analyzed from the data recorded by the physicians.

Statistical Analysis. All statistical analyses were performed using SPSS for Windows, version 16.0 (IBM SPSS, Armonk, NY). Descriptive analysis was used to determine ADR rates. Means and standard deviations (SDs) were calculated for continuous, normally distributed data. For age, which had a skewed distribution, medians and interquartile ranges (IQRs) were reported. ADR incidence rates were calculated as the percentage of patients with ADRs divided by the total number of patients at risk during the study period. ADR frequencies for drug classes were calculated as the percentage of suspected ADRs for each drug class divided by the number of prescriptions for the drug class during the study period.

TABLE 3 Rates of Serious and Nonserious ADRs for Prescriber Subgroup (n=7 Physicians)^a

	CAM	CON
Total number of prescriptions (n)	213,900	178,343
Serious ADRs—rate per 10,000 prescriptions (n)	0.00 (0)	0.56 (10)
Nonserious ADRs—rate per 10,000 prescriptions (n)	4.44 (95)	12.44 (222)
All ADRs—rate per 10,000 prescriptions	4.44	13.01

^aPhysicians who agreed to report both serious and nonserious ADRs for CAM and CON therapies.

ADR=adverse drug reaction; CAM=complementary and alternative medicine; CON=conventional.

Subgroup analyses were performed for patient age groups (aged 17 years or younger vs. aged 18 years or older), gender, type of suspected drug (CAM vs. CON), ADR reaction according to system organ class (SOC), rechallenge, causality, management, and outcome of ADR. Comparisons between groups were made using Pearson's chi-square test.

Results

A total of 38 physicians (10.5% of the physicians contacted) from 12 of the 16 German states participated (21 general practitioners, 9 pediatricians, 4 internists, 2 gynecologist, 1 dermatologist, and 1 neurologist) and fulfilled the technical requirements and the inclusion criteria (Figure 1). No physician was excluded because of less than 5 years practical experience and/or additional qualification. The mean (SD) age of the physicians was 48 (6.1) years, and 55% were male. In total, 88,431 patients were treated in the study period. Median (IQR) age was 13 (4-43) years; 56.5% were female; and 53.9% were aged 17 years or younger. Overall, 1,018,626 treatments were prescribed by the whole sample of 38 physicians, 54.8% (n=558,207) for CAM.

Subgroup Analysis of Serious and Nonserious ADRs

Seven physicians from general medicine (n=4), pediatrics (n=1), internal medicine (n=1), and gynecology (n=1) agreed to report serious and nonserious ADRs. Within this subgroup, 25,966 patients (median [IQR] age=11 [4-38] years; female=56.1%) received a total of 392,243 drugs (CON=45.5%, n=178,343). One-third (36.8%) of the patients were treated by general practitioners, 46.0% by pediatricians, 16.3% by internists, and 0.9% by other practitioners.

In the subgroup of 7 physicians, 327 ADRs were reported altogether, of which 10 were serious. All serious ADRs were associated with CON drugs. According to the severity of the reported ADRs, 14.1% (n=47) were classified as grade I (mild); 78.9% (n=258) as grade II (moderate); 6.1% (n=20) as grade III (severe), and 0.6% (n=2) as grade IV (life threatening). ADR report counts and incidence rates classified by subgroup (age group, sex, and type of medication) are shown in Table 2. ADR

TABLE 4 Frequency of ADRs for Drugs with at Least 4 Reports in the Prescriber Subgroup (n=7 Physicians)

Active Pharmaceutical Ingredient ^a	ATC Code	Number of ADRs	Number of Prescriptions	ADR Frequency (%)	Severity (WHO Grade ^b)	ADR Seriousness
Cefadroxil	J01DB05	10	465	2.15	I=1, II=9	10 nonserious
Clarithromycin	J01FA09	9	559	1.61	II=8, III=1	9 nonserious
Erythromycin	J01FA01	26	1,702	1.53	I=3, II=22, III=1	25 nonserious, 1 serious
Amoxicillin	J01CA04	31	2,276	1.36	I=2, II=26; III=3	29 nonserious, 2 serious
Methylphenidate	N06BA04	6	443	1.35	II=6	6 nonserious
Sulfamethoxazole and trimethoprim	J01EE01	7	745	0.94	I=2, II=3; III=2	6 nonserious, 1 serious
Mucolytics combination	R05CB10	7	1,190	0.59	II=7	7 nonserious
Acetylcysteine	R05CB01	6	1,194	0.50	I=1, II=5	6 nonserious
Benzathine phenoxymethylpenicillin	J01CE10	5	996	0.50	I=1, II=4	5 nonserious
Cefaclor	J01DC04	17	4,559	0.37	I=1, II=16	17 nonserious
Phenoxymethylpenicillin	J01CE02	9	2,561	0.35	I=1, II=7, III=1	9 nonserious
<i>Pelargonium sidoides</i> root—CAM	R05CP05	4	1,940	0.21	I=1, II=3	4 nonserious
Drug combination of Primula root Thyme herb Drosera herb—CAM	R05CP03 R05CP01 R05DP01	4	2,203	0.18	I=1, II=3	4 nonserious
Ivy leaves—CAM	R05CP02	11	6,575	0.17	I=1, II=10	11 nonserious
Cefuroxime	J01DC02	4	404	0.99	I=1, II=3	4 nonserious
Salbutamol	R03AC02	5	5,394	0.09	II=4, IV=1	4 nonserious, 1 serious
Drug combination of Primula root Thyme herb—CAM	R05CP03 R05CP01	4	4,357	0.09	II=4	4 nonserious
Paracetamol	N02BE01	4	10,741	0.04	I=1, II=3	4 nonserious

^aAgents in the list are conventional drugs unless marked as CAM.

^bSee Table 1 for description of WHO grades.

ADR=adverse drug reaction; ATC=Anatomical Therapeutic Chemical; CAM=complementary and alternative medicine; WHO=World Health Organization.

rates per 10,000 prescriptions were 4.4 for CAM and 13.0 for CON (Table 3).

Of 232 CON ADR reports, amoxicillin (13.4%, n=31) was the most reported suspected drug; of the amoxicillin ADRs, the most frequently documented symptom was drug rash (41.9%, n=13; Table 4). Cefadroxil had the highest ADR rate per prescription (2.2%). Of 95 CAM ADRs, ivy leaves were the most reported ingredient (11.6%, n=11) with the following documented reactions: anal pain (n=2), drug rash (n=2), vomiting (n=3), inflammation of the skin (n=1), enteritis (n=1), pruritus (n=1), and abdominal pain (n=1). The ADR rate per prescription for ivy leaves was 0.17%. For the reported ADRs, ivy leaves in 9 cases were administered as suppository and in 2 cases orally as syrup.

Analysis of ADRs from the Total Sample (N=38 Physicians)

A total of 430 ADR reports was received and screened from the complete sample of 38 physicians; 18 reports were classified as “off-label use” and thus were excluded, leading to a final count of 412 reported ADRs in 389 patients. Of these, 124 (30.1%) were for CAM drugs. Most of the ADRs were reported by pediatricians (65.3%, n=269), followed by general practitioners (22.6%, n=93) and others (12.1%, n=50). The majority of the ADRs was reported in children (69.2%, n=285). In children,

75.8% (n=216) of the ADR reports were associated with CON drugs. In adults, 127 ADRs were reported, and 56.7% (n=72) were associated with CON drugs. Of 412 ADRs, 232 (56.3%) occurred in female patients.

Physicians reported mostly nonserious ADRs (96.6%, n=398); all 14 serious ADRs were associated with CON. For the 31 physicians for whom it was voluntary to report nonserious ADRs, 71 nonserious ADRs were reported. The remaining 327 nonserious ADRs were reported by the subgroup of the physicians (n=7) who reported all ADRs. The primary reason for the classification of an ADR as serious was hospital admission (n=9 of 14 [64.3%] serious ADRs).

The severity of the reported ADRs was classified according to WHO-Adverse Reaction Terminology (ART) as grade I (mild) in 15.0% (n=62) of the 412 cases, grade II (moderate) in 75.0% (n=309), grade III (severe) in 9.2% (n=38), and grade IV (life threatening) in 0.7% (n=3). Among the 124 CAM-associated ADRs, 96.0% (n=119) were classified as mild or moderate (grade I or II), and 4.0% (n=5) were severe (grade III).

Drugs Associated with ADRs

In identifying drugs associated with ADRs, we assumed that more than 1 drug could be associated with an ADR. For example, if a patient was taking 2 drugs at the time of an ADR,

TABLE 5 Medical Management and Outcome of ADRs (N = 38 Physicians)

	% (n) of Total ADRs		
	Total	CAM	CON
Management^a			
Drug withdrawal	82.3 (339)	83.9 (104)	81.6 (235)
Reduction of dose	5.3 (22)	8.1 (10)	4.2 (12)
Change of therapy	6.6 (27)	11.3 (14)	4.5 (13)
No change in drug and no additional treatment	13.6 (56)	8.9 (11)	13.9 (40)
Other	10.7 (44)	4.8 (6)	13.2 (38)
Outcome			
Recovered	88.1 (363)	92.7 (115)	86.1 (248)
Not yet recovered ^b	8.3 (34)	4.0 (5)	10.1 (29)
Permanent damage ^b	0.0 (0)	0.0 (0)	0.0 (0)
Unknown	3.6 (15)	3.2 (4)	3.8 (11)
Death	0.0 (0)	0.0 (0)	0.0 (0)
Total	100.0 (412)	100.0 (124)	100.0 (288)

^aMore than 1 entry was possible for each ADR.

^bNot yet recovered means that the patient was improved but not completely recovered at the time of evaluation, with complete recovery expected. Permanent damage means that complete remission of the ADR is not expected.

ADR=adverse drug reaction; CAM=complementary and alternative medicine; CON=conventional.

it was assumed that both drugs were potentially responsible. We found 429 individual drugs associated with 412 ADRs. For CAM, 131 individual drugs for 124 ADR reports were suspected. The drug class “antibacterial medication for systemic use” was most commonly involved in ADR reports (34.3%, n = 147 of 429 drugs), followed by “homeopathic and anthroposophical drugs” (22.1%, n = 95 of 429 drugs) without special ATC classification, “cough and cold preparations” (9.8%, n = 42 of 429 drugs), and drugs for “obstructive respiratory diseases” (3.0%, n = 13 of 429 drugs). Among the remaining drug classes (altogether 30.8%, n = 132 of 429 drugs), no drug class comprised more than 3.0% of the ADRs. It should be noted that the ATC drug classes may include both CAM and CON drugs; however, this pattern was observed only in “cough and cold preparations,” where 24 drugs were classified as CAM (e.g., ivy leaves) and 18 as CON (e.g., acetylsteine).

Types of Reactions/System Organ Classes

A total of 552 reactions for 412 ADRs were reported. The most commonly affected SOC was “skin and subcutaneous tissue disorders” (30.4%) and “gastrointestinal disorders” (28.2%) in all CAM and CON drugs, followed by “psychiatric disorders” (8.7%); “general disorders and administration site” (6.0%); “nervous system disorders” (6.0%); and “respiratory, thoracic and mediastinal disorders” (4.5%). In sum, we identified 169 reactions reported for 124 CAM-associated ADRs and 383 reactions for 288 CON-associated ADRs.

Rechallenge and Causality

The overall rechallenge rate was 10.0% (n = 41); 22 cases of CAM-associated ADRs were rechallenged with 18 cases reporting a positive rechallenge, meaning the former ADRs occurred again. For CON drugs, 19 ADRs were rechallenged with 15 being positive (associated with the former ADRs). In 37 cases, the patient recovered after rechallenge, while symptoms were still present at the time of evaluation in 4 cases of CON-associated ADRs (asthma, pruritus, and 2 cases of eczema).

Concerning causality assessment, 48.3% (n = 199) of the 412 reports were rated as probable, and 47.8% (n = 197) were rated as possible. Within CAM-associated ADRs, more than one-half of the reports were classified as possible (53.2%, n = 66), followed by probable (39.5%, n = 49), unlikely (5.6%, n = 7), and uncertain (1.6%, n = 2). In 150 of 288 (52.1%) CON-associated ADR cases, the causality assessments were classified as probable; 131 (45.5%) were classified as possible, 5 cases (1.7%) unlikely, and 2 cases (0.7%) uncertain.

Management and Outcome

The suspected drug was withdrawn for the management of the ADR in the majority of reports (82.3%, n = 339; Table 5). In 363 (88.1%) cases of the reports, the patient recovered from the reaction.

Discussion

The EvaMed Network is the only German pharmacovigilance system that evaluates prescribing patterns and CAM-related ADRs. Previously published studies included the analysis of an educational program for reporting ADRs and an observational study of prescribing patterns in patients with dementia.^{25,35} Network data were also used to report ADRs for inpatients in the Community Hospital Havelhoehe.³⁶

The present study observed ADRs in relation to the number of drugs prescribed and patients exposed by physicians in a primary care network of CAM prescribers. Due to the method of collecting the complete prescription data, both CON and CAM treatments were analyzed for all patients over the complete study period; it was not possible to build groups of CAM-versus CON-treated patients. However, we found that 30.1% (n = 124 of 412 ADR reports) were associated with CAM out of 558,207 CAM prescriptions, and no ADRs were serious.

Unlike other studies and despite a high workload for documentation, we were able to calculate an incidence rate in a group of physicians who reported both serious and nonserious ADRs.^{12,15} The overall per patient incidence of ADRs independent of CAM or CON in our study was 1.2%, which differs from those reported in other studies; in one study, the incidence rate for outpatients was reported to be 0.01%, and in another study of frail elderly patients following a hospital stay, the reported ADR rate was 1.92 per 1,000 person-days of follow-up (33% of patients).^{3,37} One reason for this result might be the setting of our study. While our study was placed in outpatient care with a

heterogenous patient sample, other studies focused on ambulatory clinic settings³⁸ or on elderly persons.^{37,39} A further reason could be the way of reporting. The EvaMed system transfers EMR data about drugs and diseases to the study database, avoiding double documentation. While documenting an ADR, physicians were able to connect relevant drugs, comedications, and diseases with ADRs. This system led to an improvement of reporting quality because ADRs attributable to multiple drugs could be recognized. The incidence for children in the present study was also identical (1.5%) to the incidence in a systematic review about ADRs in pediatric outpatients.⁴⁰

As all prescriptions in the practices were generated and automatically coded, it was possible to calculate the frequency of ADRs for CAM and CON drugs prescribed in the subgroup of the 7 physicians. It was also possible to calculate the frequency of ADRs for all prescribed single drugs, which have been calculated in only a few surveys and projects.⁴¹ For CAM-associated ADRs, the most frequently reported ingredient was ivy leaves with an ADR frequency of 0.17% of prescriptions. A study conducted in Germany of the tolerability of dried ivy leaf extract in 52,077 children found an ADR incidence of 0.22%.⁴² However, it should be noted that this result is based on the number of patients and is not a rate of ADRs for prescriptions written.

A similar study about drug complications in ambulatory care identified antibiotics as the most involved drug class.³⁸ In the present study, amoxicillin was the most frequent single drug associated with ADRs (n=31 reports). Amoxicillin was perhaps reported more often than other drugs for an ADR because it was more commonly used; cefadroxil had a higher rate of ADRs per prescription (2.2%). Similarly, comparing ivy leaves with *Pelargonium sidoides* root, ivy leaves were used more often, but *Pelargonium sidoides* root had a higher ADR frequency (0.17% of 6,575 prescriptions vs. 0.21% of 1,940 prescriptions, respectively). However, this difference in ADR frequency was small and may not be of much concern clinically.

The frequency of CAM-associated ADRs in our study was low (0.04%) compared with the rates observed in 2 studies of homeopathy and CON for respiratory and ear complaints. In those studies, the rates of adverse effects in patients treated with homeopathy were 3.1% and 7.8%, respectively.^{43,44} This result might be explained by findings of a systematic review by Thomsen et al. (2007),⁴⁵ which found that studies with a short follow-up period had a higher ADR frequency than studies with a long follow-up. Thus, the relatively low ADR frequency rate in our study, with its 5.5-year follow-up period, might not be surprising. However, the studies of Haidvogel et al. (2007) and Riley et al. (2001)^{43,44} also showed a higher frequency in the CON group (7.6% and 22.3%, respectively) compared with the homeopathic group. In our study, the reason for the difference in frequency (0.13% for CON-associated ADRs) might be due to a global, multidisease focus of our participating physicians, diverting their attention from only 1 drug class.

Organ Systems. The organ system “skin and subcutaneous tissue disorders” was most commonly affected (30.4%) independent of the type of medication. These results are similar to the studies of Jose and Rao (2006) with an ADR rate of 23.5%,³ and Honigman et al. (2001) with an ADR rate of 26.0%.⁴⁶

Causality. For 48.3% of the 412 ADRs, causality was classified as probable, which is similar to the 53.7% rate of probable causality in the study by Jose and Rao.³ In the present study, 45.5% of CON ADR reports were classified as probable. For CAM, 39.5% of ADRs were classified as probable and 53.2% as possible, perhaps because CAM ADR reactions were not mentioned in the manufacturer’s summary of product characteristics. This finding demonstrates the necessity of documenting and publicizing ADRs. However, causality results should be viewed within the context of a review of causality assessment methods for ADRs, which found that no single method is universally accepted, resulting in problems of reproducibility and validity.³⁵

Management/Rechallenge/Outcome. Drug withdrawal was the first step for the management of ADRs in both types of medication, which was also reported by Jose and Rao.³ Rechallenge, when a drug is given again to a patient after it is previously withdrawn, was higher for CAM-associated ADRs (17.7%, 22 rechallenged out of 124 CAM ADRs) compared with CON-associated ADRs (6.6%, 19 rechallenged out of 288 CON ADRs). The overall rechallenge rate was 10.0% (41 rechallenged out of 412 ADRs overall). The switch to a potentially safer alternative drug resulted in this low number. In the majority of reports (88.1%), patients completely recovered, a rate that is similar to that observed by Jose and Rao (80.6%).³ In no cases did persistent damage occur.

Limitations

This study has several important limitations. The first and foremost limitation of this study is the biased sample of physicians: all were CAM physicians who were willing to participate in this data collection and might have modified their reporting behaviors in response to the needs and settings of the study (Hawthorne Effect). In addition, the group of 38 participating physicians are not representative of physicians in general practice in Germany, including their receipt of an educational intervention to improve ADR reporting.²⁵ Second, it may also be possible that CAM physicians reported only what they expected, and thus unexpected reactions were not recognized and reported. Third, the reports of potential ADRs could be underestimated because physicians may not have been informed by their patients about the occurrence of all ADRs; it could be that mild and minimal reactions were not reported to the physician and therefore were not documented. Fourth, we do not know whether patients actually consumed the drugs or took them as prescribed (e.g., on an empty stomach or with food). Fifth, a patient may have visited another physician and received drugs that would not have been documented in the

EvaMed Network database. Sixth, payment to prescribers of €15 (approximately US\$20) for each reported ADR could have influenced the number of reports.

Conclusions

In a small sample of 7 CAM physicians who reported both serious and nonserious ADRs, there were 213,900 CAM prescriptions (54.5%) of 392,243 total prescriptions for CAM and CON drugs. The serious ADR rate was 0.6 per 10,000 prescriptions for CON drugs, and no CAM ADRs were serious. The overall ADR rates per 10,000 prescriptions were 4.4 for CAM prescriptions and 13.0 for CON prescriptions.

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